INVESTIGATOR STUDY PLAN - H00015196

NCT03955055

Study Title: A randomized comparison of early deployment of a video capsule (Endocapsule EC-10: Olympus Tokyo. Japan) in Clinical Decision Unit versus conventional work-up of hematemesis [H] and non-hematemesis gastrointestinal bleeding [NHGIB]

Document Title: Study Protocol

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1. TITLE

A randomized comparison of early deployment of a video capsule (Endocapsule EC-10: Olympus Tokyo. Japan) in Clinical Decision Unit (CDU) versus standard of care (SOC) work-up of hematemesis [H] and non-hematemesis gastrointestinal bleeding [NHGIB].

2. EXTERNAL IRB REVIEW HISTORY*

Not applicable.

3. PRIOR APPROVALS:

This is an inter-departmental study with the Emergency Department and Division of Gastroenterology. Dr. Cave and Dr. Sabato are the principal investigators.

Conflict of Interest (COI):

PI has discussed the project with Dr. Stuart Levitz, chair of the COI committee. Neither investigator has any financial conflicts of interest.

Clinical Engineering Department:

The project will require placement of a computer workstation on wheels (WOW) in the CDU and another in the GI Research Office. These, as well three recorder systems, will be installed with the help of the clinical engineering department and cleared by them prior to use.

Biohazardous Agents:

Not applicable.

Radiation:

The 'Questions for PI Checklist' from the Subcommittee on Human Uses [SHU] of the Radiation Safety Committee [RSC] has been reviewed and there is no requirement for pre-approval by the subcommittee. A copy of this checklist has been added to attachments. A KUB is only performed on those patients whose capsule does not reach the cecum before the battery runs out and who do not see the capsule excreted in their feces in the 2 weeks following the procedure. This is standard of care.

4. OBJECTIVES*

1) The objectives of this study are to compare the efficacy of video capsule endoscopy (VCE) as first line vs the standard of care workup of H [upper endoscopy] and NHGIB by endoscopy [upper, lower and other tests] in the rate of detection of active bleeding in patients admitted to the clinical decision unit (CDU). We propose to examine differences in time to detection of active bleeding, diagnosis, reduction in numbers of procedures, hospital costs and length of stay between a conventional workup protocol and our proposed protocol of early capsule endoscopy deployment**.** All patients in the SOC group will be admitted to the

hospital. These will be compared to those in the VCE first group who are stable and may be discharged from the CDU directly.

5. BACKGROUND*

After 40 years of considering gastrointestinal bleeding as upper or lower and largely ignoring the small intestine, there is accumulating evidence that the conventional approach to the assessment of NHGIB could be improved by early deployment of a video capsule as the first diagnostic test. Currently, video capsule endoscopy is considered the gold standard diagnostic test for small intestinal bleeding after upper and lower endoscopy. However, we feel that video capsule endoscopy is an underutilized, minimally invasive tool that can improve rates of detection, minimize patient discomfort, and shorten the length of hospital stay for many patients. In a recent study at UMass of 336 patients who presented to the ED with complaints of gastrointestinal bleeding only 36 patients (10.7%) were given a video capsule during their stay.[1]

Traditionally, in patients with hematemesis, upper endoscopy has been the diagnostic and therapeutic modality of choice. However, recent data from a randomized clinical trial by Sung et al suggests that when video capsule endoscopy is used as the primary diagnostic tool, the investigators were able to safely define those patients that require admission from those that can be discharged for later follow-up [2]. In this cohort, 30% of patients could be safely discharged and undergo endoscopy, if necessary within 48 hours, as an outpatient. This data is consistent with our internal epidemiological data from UMass where nearly 30% of patients who were admitted did not receive any endoscopic evaluation as in-patients.

Similarly, in a randomized controlled trial, we have recently shown that patients with NHGIB may benefit from early VCE. In this population, the detection of active bleeding with video capsule as the first procedure was 63% compared with 27% for the standard of care approach. We did not demonstrate a significant reduction in length stay since this was not part of the trial design. No attempt was made to change physician behavior. The study was too small to demonstrate a reduction in procedures, but there was a modest reduction in healthcare costs despite the addition of the video capsule. We encountered no adverse events in the study. Readmission rates were not significantly reduced but there were no readmissions in the capsule group for G.I. bleeding where there were four in the standard of care group.

Our hypothesis is that both signs and symptoms provide poor localization as to the origin of bleeding in NHGIB. Data from our previous study suggests that the ingestion of a video capsule in the emergency department could quickly and non-invasively provide clinicians accurate data as to the origin of the bleeding. This information could provide a guide to further management of the patient. Video capsule endoscopy is able to visualize bleeding in the esophagus, stomach, duodenum, small intestine and right colon, thereby eliminating the guess work of deciding which endoscopic approach to use.

We plan to use the clinical decision unit for two reasons. This unit provides an ideal site for the early safe deployment of a video capsule or initiation of a standard of care workup for either or NHGIB. Second, in those patients who are demonstrated not to be bleeding

in either group by capsule endoscopy or standard of care workup may be discharged home safely without being admitted, thereby saving significant costs. It is known that 80% of patients stop bleeding spontaneously. Thus, the earlier they are examined the more likely the origin of the bleeding is likely to be found and appropriate management instituted

The use of capsule endoscopy has been approved by the FDA since 2001 for small intestinal bleeding obscure GI Bleeding. It is very safe, no deaths associated with its use have been reported. More than 3 million capsules have been deployed and obstruction and perforation are extremely rare.

Interest in the broader use of VCE is .accumulating. In 2004 Sachdev et al reported a pilot study on the use of early use of VCE in acute NHGIB. This showed a 50% reduction to time to diagnosis in 24 patients. More recently studies of VCE deployed in the ED, in patients with upper GI bleeding showed improved management. Our group recently demonstrated that the closer a video capsule is performed to the time of bleeding the higher the likelihood of locating the sources and the higher the therapeutic intervention rate.[3]

This protocol is logical step to prospectively examine this concept in a large randomized prospective trial for both H and NHGIB. The questions are, can early capsule intervention decrease time to diagnosis, numbers of procedures, admission rate and hospital length of stay in patients with H and NHGIB.

References:

1. Jawaid S GB, Singh, A, Marshall C, and Cave D. . The epidemiology of gastrointestinal bleeding in an academic emergency department as a basis for reconfiguring the conventional approach to its diagnosis and management. . Gastrointestinal Endsocopy 2019;89:33-43.e4

2. Jawaid S MN, Gondal B, Maranda L, Marshall C, Charpentier J, Singh A, Foley A, and Cave D. . A reconsideration of the diagnosis and management of gastrointestinal bleeding based on its epidemiology and outcomes analysis. Dig Dis Sci. 2018 Dec;63(12):3448-3456.. Epub 2018 Aug 22.

3. Singh A, Marshall C, Chaudhuri B, et al. Timing of video capsule endoscopy relative to overt obscure GI bleeding: implications from a retrospective study. Gastrointest Endosc 2013;77:761-6.

6. INCLUSION AND EXCLUSION CRITERIA*

Inclusion Criteria:

- Age greater than 18 years old

- New onset of hematemesis, melena or hematochezia
- Able to sign consent
- Hemodynamically stable (i.e. blood pressure >100/60 or pulse <110 at the time of consent)
- ED must plan to admit patient to the hospital or Clinical Decision Unit.
- If patients have pacemakers and/or ICD they will be placed on telemetry.

Exclusion criteria:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners
- Prior history of gastroparesis
- Prior history of gastric, or small bowel surgery
- Prior history of inflammatory bowel disease
- Concern for infectious colitis
- Evidence of dysphagia at the time of presentation
- Presence of small amounts of bright red blood per rectum
- Allergy to metoclopramide or erythromycin
- Code status of DNR/DNI or CMO
- Prior history of abdominal radiation
- Abdominal pain suggesting an acute abdomen or obstruction. In clinical practice, only patients with crampy abdominal pain due to Crohn's disease, previous intestinal surgery and a previous history of radiation therapy require a patency capsule or CT enterography, before capsule endoscopy.
- Patients who cannot undergo surgery

Subjects who do not speak English may be included if an IRB-approved short form is available for use in their language and interpretation services are available.

7. STUDY-WIDE NUMBER OF SUBJECTS*
See #25.

8. STUDY-WIDE RECRUITMENT METHODS*
See #24.

9. STUDY TIMELINES*

- The participation of individual subjects in this study will be approximately 31-40 days (the length of their hospitalization plus an additional thirty days for follow up).
- The duration anticipated to enroll all study subjects is about 24 months.

- The estimated date for the investigators to complete this study and for data analysis is 3 years.

10. STUDY ENDPOINTS*

- The primary endpoint will be time to detection of active bleeding or stigmata of recent bleeding [blood clot or visible vessel].
- Secondary endpoints will include, admission rate, hospital length of stay, number of invasive procedures, blood product transfusions, number of therapeutic procedures, complication rates, costs of admission, and readmission rates

11. PROCEDURES INVOLVED*

Screening

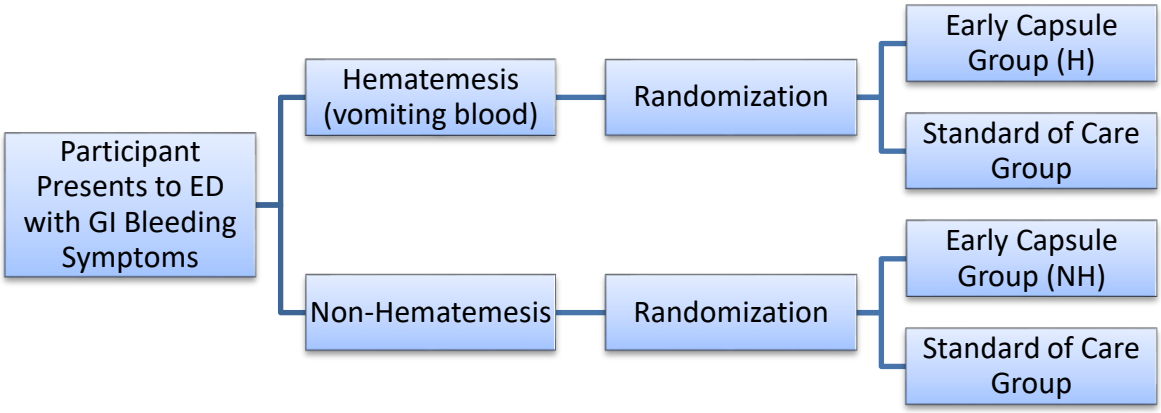
- Patients presenting to the Emergency Room with H or NHGIB (defined as hematemesis, or melena or hematochezia respectively or severe anemia) will be identified by a member of the ED staff and triaged to the CDU for stable patients or ICU for unstable patients.

  Once a subject is identified a page will be sent to a member of the research team (i.e, research staff member, GI fellow on call, or GI attending on call) from the CDU. In addition to this, the clinical research coordinator and or GI fellow will screen the Emergency Department triage software for patients who are listed as having NHGIB. Based on prior experience of our randomized trial we expect for every 3 patients asked to participate in the study, there will be 1 patient who agrees to participate. In the Emergency Department study already cited, the Emergency Department at UMass sees about 350 patients annually for GI bleeding. Of these patients, approximately 230 patients have NHGIB and 120 have hematemesis. Given the 3:1 screening ratio, we would expect approximately 40 to be enrolled for the H and 40 patients for the NHGIB patients every year who agree to participate in the study. In 24 months, we would expect to recruit up to 160 patients to our study, 80 for the H and NHGIB respectively. Once a subject is identified the subject will then be seen and examined by the GI fellow and attending as per standard of care and asked to participate in the study.

Randomization;

- If inclusion/exclusion criteria are met, the consent discussion takes place and only if the subject agrees and consent is obtained, then the subject is randomized to the "Early Capsule Group" or "Standard of Care Group." All patients in the "Early Capsule group" will receive the video capsule. A few of the patients in the "Standard of Care Group" may receive the capsule as indicated by what is considered the standard workup.

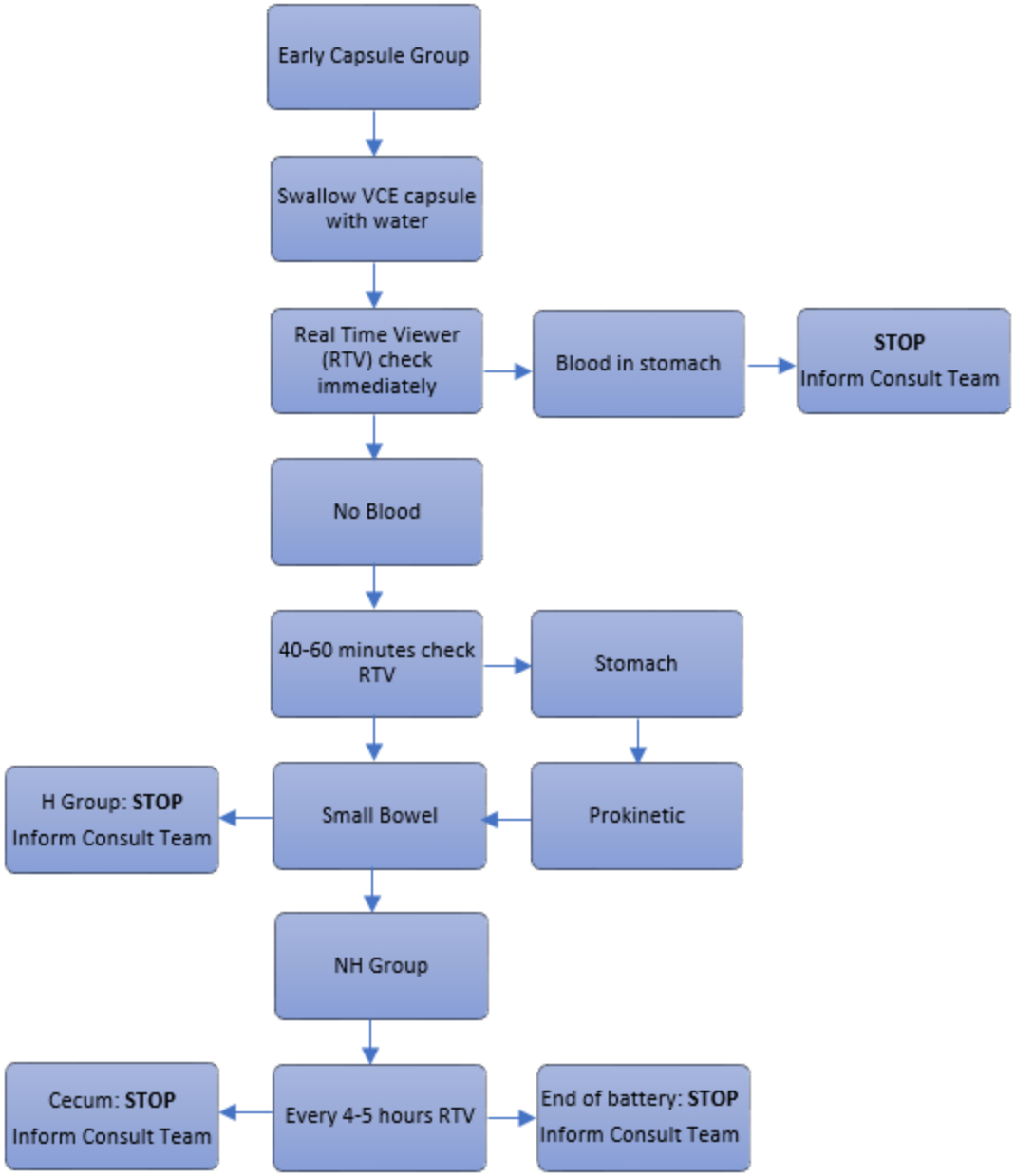
- We will assign patients to study ID numbers consecutively by the order of which they are enrolled in our study. For the Randomization Process we will be utilizing a random sorting generator to assign integers in a random order, corresponding to study IDs which allows researchers to randomly assign study participants into specific study groups. The same process would apply to the H and NHGB groups, but each of these groups will have separate randomizations. Assignments are put into a mail merge, locked with a password, and printed, then put into a sealed, security envelope, which is sealed with a Study ID sticker. The Randomization Scheme will allow us to attach particular Study ID numbers randomly to particular groups based on our criteria to have 40 subjects in the early capsule group and a comparable number in the Standard of Care SOC workup arm for both the H and NHGIB groups. The envelope is only opened once all entry criteria have been met and the subject will be assigned a group/arm. Subjects with a Study ID ending in 1-80 will be enrolled in the H group. Subjects with a Study ID ending in 100-180 will be enrolled in the NHGIB group.
- We plan to enroll up to 160 subjects in our study. 40 subjects will be randomized to the "early capsule" deployment group and 40 in the SOC arm for H patients. A similar allocation will apply to the NHGIB group with 40 patients in each arm. This means that this group of subjects will have a VCE deployed as soon as possible after presentation to the ED and CDU, once the consent process has taken place, eligibility has been confirmed, and the subject has met the standard of care guidelines for preparation before capsule ingestion. Standard preparation for capsule ingestion means that a patient cannot eat for 10 hours prior to deployment of the capsule. Therefore, patients in our study will be asked when they had last eaten. If patients report that they have not eaten anything over the past 10 hours we will deploy the capsule immediately. If, however, patients say that they have eaten something over the past 8 hours we will take note of when they believe they last ate and will deploy the capsule 8 hours after the time that they last ate. In our previous ED study, no patients in the early capsule arm had food in the stomach on capsule examination.



All medications in the study, erythromycin and metoclopramide and those used for conscious sedation during endoscopy are FDA approved

All procedures in the study are used in a conventional manner and are devices are all FDA approved. Risks of endoscopy include sore throat, bleeding, perforation and infection. Conscious sedation risks are hematoma during placement of an IV, over sedation, aspiration and pneumonia.

Procedures



Capsules are swallowed with a small [4-12 oz.] amount of water. As noted above, patients will not have the capsule deployed until it has been confirmed that 10 hours have passed since the patient had last eaten. Patients are allowed to take medications up to two hours prior to ingesting the capsule (which is standard of care).

Immediately following ingestion of the VCE a research staff member will use the capsule's Real-Time Viewer (RTV) to inspect for blood in the stomach. If blood is found in the stomach, the recording will be stopped. At 40-60 minutes following VCE

ingestion, a staff member will again use the RTV to confirm that the capsule has entered the small bowel. If the capsule at that time is still in the stomach a prokinetic agent (either metoclopramide or erythromycin, [these agents are commonly used in patients with upper GI bleeding to help get blood clot out of the stomach prior to upper endoscopy to help clear the stomach to improve the chance of finding the source of bleeding]. Based on experience the need for either prokinetic agent is in approximately 1 out of 8 patients. If a prokinetic agent is required a staff member will check within another 40-60 minutes to again verify that the capsule has moved to the small intestine. No further prokinetic will be given. For the H group the recording will be stopped after the small bowel has been entered. For the NHGIB group four to 5 hours after ingestion, a staff member will use the RTV to again check for blood. This is the mean small intestinal transit time of the small intestine. If the VCE is in the cecum, the recording will be stopped and data will be downloaded to the workstation and processed into a video. If the VCE has not reached the cecum, at four and eight hours after ingestion, a staff member will again check the RTV to see if blood is present and/or the ileocecal valve has been passed. Data from the capsule recorder will be downloaded to a workstation as soon as possible. Battery life for the EC-10 capsule is now >12 and up to 20 hours

The PI or sub-investigator will then view the video of the capsule recording [it takes about 5 minutes to establish if there is bleeding and where it is coming from. More detailed analysis will take about 15-20 minutes]. As soon as the capsule recording has been reviewed, the PI or sub-investigator will inform the patient's attending gastroenterologist on the consult service as to where the bleeding is coming from or that bleeding is not seen, as soon as possible after the video has been reviewed. Depending on the findings a recommendation will be made as to the next most appropriate test. See attached Figure 1. If blood is found in the esophagus, stomach or duodenum an upper endoscopy is recommended. If blood is seen in the small intestine, it will be recommended that the subject next have a push enteroscopy, deep enteroscopy, or angiography. If blood is found in the right colon, colonoscopy may be performed or deferred to colonoscopy as an outpatient, if active bleeding has ceased. If the capsule study is not diagnostic and no blood is seen in the GI tract and there is no ongoing hematochezia, the subject will be placed in ED observation for up to 23 hours and evaluated for potential discharge and follow-up by gastroenterology as an outpatient. If, and as appropriate an EGD or colonoscopy will be performed as an outpatient within 72 hours.

For most subjects, the capsule will pass in a bowel movement within 24 -72 hours of ingestion.

An equal number of subjects [up to 40] will be randomized to the "SOC group." For NHGIB workup may include upper endoscopy, colonoscopy, and additional capsule or small bowel enteroscopy depending on the subject's presentation and the results of the workup performed by the gastroenterology team. For some subjects, the VCE would be done as part of standard of care. We estimate that 4-10% of patients will have small intestinal bleeding. For patients requiring a video capsule endoscopy as part of "SOC workup" the patients will be given the same Olympus video capsule that is used in the "Early Capsule" group. Further management would be as standard of care which requires

admission. These subjects will be discharged on the recommendation of the attending hospitalist after completion of treatment.

Review and Follow-Up

During hospitalization, data will be recorded from ED pulse check, and EPIC regarding fluid administration, transfusion of pRBC, initial hematocrit, times and types of procedures (e.g. upper endoscopy, enteroscopy, colonoscopy etc), time from entry to ED and CDU, to time to localization of source of bleeding, admission disposition discharge from CDU, regular floor, ICU), time of discharge. The procedures involved in the hospitalization (i.e. upper endoscopy, enteroscopy, and colonoscopy) will be done as part of standard of care. All of this information will be linked to the subject's study ID number as described above. This data collection is for research purposes only.

In addition, the costs of the procedures will be collected through financial services. The costs that will be collected are both the fixed and variable costs associated with each patient in the study. We will also collect the direct and indirect costs allocated to each patient. All charges associated with the admission for each patient in the study will have costs allocated. This will be evaluated as an additional data point to compare the two arms of the study. No additional PHI will be collected.

Telephone Follow-Up

Those subjects discharged from the CDU will be contacted the following day by phone by a research staff member to make sure that they are doing well and that the appropriate follow up procedure has been arranged. Each patient will be called 30 days after discharge to check to see if bleeding has recurred. Please see attached form for telephone script that staff member will read along with particular questions that will be asked.

No more than three attempts will be made at each time point to reach the subject. If a message is left, it will be "Hello, this is [name] calling from UMass looking to speak with [subject]. Please call back at [number] at your earliest convenience. Thank you."

12. DATA AND SPECIMEN BANKING*

Not applicable.

13. Data Analysis and Management*

- Data analysis plan: As discussed above, data will be obtained through review of medical records. Specifically, we will be looking at time to detection of active bleeding or visualization of stigmata of recent bleeding such as adherent blood clot or a visible vessel, laboratory values, number of blood products transfused procedures performed, along with additional measures as described above. Once we have separated our two cohorts we will perform chi-square and standard t-tests to compare the different dependent variables in the two cohorts. We will also perform a Kaplan-Meier curve analyses to compare length of stay and time to diagnosis which is the primary metric of this study.

- Steps that will be taken to secure data: All clinical data from individual subjects will be de-identified and given a study number. The study number will serve as a link between the data and the subject's identifiable information. RedCAP online encrypted database will be used to store the dataset. The database will only be accessed by the primary investigator and research assistants.
- Data will be exported for analysis as a de-identified data set. The de-identified dataset (which would be absent of any PHI) will remain at UMass under password access by the PI and sub-investigators.
- Identifier keys will be destroyed once primary data analysis is complete.
- No identifying information will be used in any report or publication generated from this study.
- Power analysis: Based on our recent randomized trial of NHGIB of VCE v SOC, we were able to detect a very significant difference in the rate of active bleeding with 36 patients in each arm, Hazard ratio 2.7. J Sung et al. used the same sample size in their randomized trial for H bleeding to similar effect We thus plan on using 40 patients in each arm for each group. The increase to 40 from 36 is used to cover ant technical failures or incompletely studied patients.

14. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS*

Throughout course of a study subject's participation in the study they will be followed for signs of adverse events to medication administration or for complications of capsule endoscopy. Adverse events will be documented as part of initial data analysis. This data analysis will be performed by the residents and fellows who are part of the study staff for this project. Given that we anticipate minimal adverse events, any adverse events that occur will be reviewed by the study staff and the Primary Investigator within one week. This would include a complete analysis of the how the adverse event occurred in order to help prevent further events going forward. At that time the Primary Investigator will also assess cumulative reports.

We will set up a DSMB to review the adverse events and the primary aim. Risk associated with early discharge will be monitored closely, e.g. bleeding immediately after discharge

- A statistician at the UMass Medical School, a clinician inside and one outside UMass
- Review of data will be performed at the mid-point of the study
- See attached charter.

15. WITHDRAWAL OF SUBJECTS WITHOUT THEIR CONSENT*

If the patient is unable to swallow the capsule we would remove them from the study.

Patients will be withdrawn from study if the bleeding source is found to be outside of the stomach or intestines.

A subject can withdraw from the study at any time per their request.

16. RISKS TO SUBJECTS*

This study is investigating the benefits of re-ordering the process of the current care algorithm for H and NHGIB. Video capsule endoscopy is already part of standard of care for many GI bleeding workups. This is not a new diagnostic modality and no new risk is being introduced from this technology itself. There are no anticipated risks to subjects who are randomized to the early deployment of the capsule and the detection of active bleeding is expected to be at least comparable to the standard deployment.

One anticipated risk is a breach of confidentiality and to minimize this risk all identifiers will be destroyed. In order to minimize this risk, as described in Question 13, identifiers will be destroyed. Data collected will be analyzed using study ID numbers only.

The most significant risk of VCE is capsule retention. This risk is the same for both groups and there is no anticipated unforeseen risk with early deployment. The risks do not change based on timing. Capsule retention is when the video capsule does not complete its transit throughout the GI tract. Studies have varied in their reports of the frequency of capsule retention with rates of about 1%, ranging from 1-13% of total cases. The latter figure is for a study on Crohn's disease patients. If capsule retention occurs, subjects may require radiologic imaging. This usually consists of a plain film of the abdomen taken 2 weeks after the capsule was swallowed to localize the capsule. They will not be kept in hospital for this. If the patient sees the capsule in their feces, this test is not needed. The recently extended battery life of the capsule almost eliminates incomplete transit. If there is long term retention then this is likely to provide information on a previously undetected health issue that the patient has and this will be managed as is required.

Removal of a capsule may be achieved by deep enteroscopy or at the time of surgery which is usually performed to remove the cause of the retention e.g. a tumor or stricture. The capsules may be left in place, Patients have been known to safely retain the capsule for years without ill effects.

It is not expected that there is any risk that the subjects assigned to the early capsule group will require more diagnostic procedures than the conventional work-up group. The hypothesis of this study is that the early deployment group may, in fact, undergo fewer procedures and have a shorter hospitalization compared to those having a conventional work-up.

Another potential risk to the subjects in the study relates to the prokinetic medications (metoclopramide and erythromycin) which would be given if the capsule is slow to leave the stomach. Risks associated with the use of metoclopramide include allergic reactions (e.g., skin rash or difficulty breathing), extrapyramidal reactions, central nervous system effects (e.g. insomnia, headache, confusion), neuroleptic malignant syndrome, endocrine disturbances (e.g. galactorrhea, amenorrhea, gynecomastia), and cardiovascular effects (e.g. hypotension, tachycardia, bradycardia, heart failure, and AV block). The adverse effects of metoclopramide are directly correlated to the duration and dose of the drug given, so we expect the incidence of adverse effects to be minimal, given that we are giving one dose only for the purpose of this study. For erythromycin, adverse effects

include allergic reactions (e.g., skin rash or difficulty breathing), gastrointestinal effects (including nausea, vomiting, abdominal pain, diarrhea, and anorexia), hepatic dysfunction, pseudomembranous colitis, QT prolongation, and ventricular tachycardia.

These drugs are frequently used in patients with upper GI bleeding to help empty the stomach of clot prior to endoscopy to enhance visualization of the bleeding site(s). Single doses of these drugs have very low risk.

Risks of endoscopy are of bleeding, perforation and infection. Risks of conscious sedation in these patients is hypoxia, aspiration, pneumonia and very rarely death. None of the procedures used in the trial are outside the stand of care for gastrointestinal bleeding.

17. POTENTIAL DIRECT BENEFITS TO SUBJECTS*

Subjects who receive the early capsule deployment may have a quicker diagnosis of the source of GI bleeding and may be able to receive a more definitive treatment of their bleeding source which could lead to a decreased length of hospital stay as well as fewer procedures.

18. VULNERABLE POPULATIONS*

No vulnerable populations are expected to be enrolled.

19. MULTI-SITE RESEARCH*

N/A

20. COMMUNITY-BASED PARTICIPATORY RESEARCH*

N/A

21. SHARING OF RESEARCH RESULTS WITH SUBJECTS*

Study results are not expected to be shared with individual subjects and subjects will not be identified in any publications; however, de-identified results may be published in publicly-available journals. Patients will be informed of their endoscopic or capsule findings

22. SETTING

Initial screening of subjects will be performed in the Emergency Room at the UMass Memorial Medical Center – University Campus-Patients – if hemodynamically stable will be transferred to the CDU. Review of video capsule recordings will occur in the GI endoscopy clinic on the same campus. Endoscopic procedures will either be performed in the CDU or adjacent endoscopy unit.

23. RESOURCES AVAILABLE

- The Principal Investigator is a board-certified gastroenterologist with extensive experience at reading video capsules. He will oversee all aspects of the research to ensure it is conducted correctly and that all staff are properly trained on their roles and responsibilities.
- PI will be assisted by a co-investigator, who is head of the CDU, sub-investigators who are physicians (attendings, fellows, and/or residents) in the Department of Medicine and Emergency Medicine.

- Gastroenterology fellows and Medicine residents will all be used to screen potential candidates for this study once they are notified by the paging process described previously. All fellows and residents will have the appropriate CITI training and will be added to the list of project personnel prior to interacting with or obtaining consent from subjects. They will be responsible for reviewing the inclusion and exclusion criteria with the subject and with obtaining consent for the capsule endoscopy if the subjects agree to take part in the study.

- For subjects who agree to take part in the study, Gastroenterology fellows, Medicine residents and or nurse practitioners trained to deploy video capsules will also be tasked with administering the capsule and with following the results on the RTV as described previously. The Principal Investigator will personally oversee the training of the fellows and residents and personally demonstrate to them how to administer the capsule. The Principal Investigator will be available for any questions that may come up if a fellow or resident has difficulty initiating the capsule. Fellows and residents may also order prokinetic agents such as metoclopramide and erythromycin as described above. The decision to order prokinetics comes after the fellows and residents have discussed using those agents with the Principal Investigator, who is a world-renowned authority on capsule endoscopy and the use of prokinetic agents for the purpose of their use.
- Endoscopic procedures needed in any of the arms of the study will be performed by the GI attending on the GI service with a GI fellow as part of routine care.

- Trained attendings and fellows will have the responsibility to upload videos to the ShareFile environment using the capsule workstation as described. They will also communicate capsule findings from the Primary Investigator and Sub-investigator to the primary team members regarding recommendations of further workup and procedures based on the recordings. Other responsibilities will include data collection, and data analysis.

- A study coordinator in this study will have a primary role of maintaining IRB communications. All individuals will be added to the Project Personnel tab prior to participation in research activities.

- All members of the research staff will be available to the subjects for any consequences that may occur secondary to this research.

- All persons who are part of this study and listed as study personnel will meet and be trained prior to initiation of the research and will be made aware of the study protocol, procedures, and the individual duties and functions. Throughout the research project we will have frequent meetings to discuss updates on the research.

  The PI and an endoscopy nurse will provide hands on training for the attendings and fellows for the use of the video capsule including setting up the recorder sensor belt, and how to get the patient to swallow the capsule. They will also be shown how to use the real time viewer and what to look for. Instruction as to how to download the data into the workstation will be provided. NPs- medical staff will page the GI fellow for any issues related to the study. The PI pager and cell phone number will be available to staff involved with the study.

24. LOCAL RECRUITMENT METHODS

As mentioned in Section 11, subjects with H and NHGIB will be identified by a member of the Emergency Department staff, CDU staff or one of the study staff members. Based on prior experience of our randomized trial we expect for every 3 patients asked to participate in the study, there will be 1 patient who agrees to participate. In the emergency department study already cited, the Emergency Department at UMass sees about 350 patients annually for GI bleeding. Of these patients, approximately 230 patients have NHGIB and 120 have hematemesis. Given the 3:1 screening ratio, we would expect approximately 40 to be enrolled for the H and NHGIB patients every year who agree to participate in the study. In 24 months, we would expect to recruit up to 160 patients to our study, 80 for the H and NHGIB respectively. Once a subject is identified the subject will then be seen and examined by the GI fellow and attending as per standard of care and asked to participate in the study. They will be offered an opportunity to ask any questions they have regarding this study. Subjects will be notified of the risks and benefits of participating in this study. They will not be offered financial compensation for their participation. No identifying information will be collected for study purposes until patient has agreed to participate in the study. Any identifying information obtained after enrollment in the study will be de-identified/de-linked from the subject as described above.

25. LOCAL NUMBER OF SUBJECTS

Based on prior experience of our randomized trial we expect for every 3 patients asked to participate in the study, there will be 1 patient who agrees to participate. In the emergency department study already cited, the Emergency Department at UMass sees about 350 patients annually for GI bleeding. Of these patients, approximately 230 patients have NHGIB and 120 have hematemesis. Given the 3:1 screening ratio, we would expect approximately 40 to be enrolled for the H and NHGIB patients every year who agree to participate in the study. In 24 months, we would expect to recruit up to 160 patients to our study, 80 for the H and NHGIB respectively. This is consistent with our power calculations based on our prior study that showed

a very significant difference in the rate of active bleeding with 36 patients in each arm Hazard ratio 2.7. J Sung et al. used the same sample size in their randomized trial for H bleeding to similar effect We thus plan on using 40 patients in each arm for each group. The increase to 40 from 36 is used to cover anticipated technical failures or incompletely studied patients.

26. CONFIDENTIALITY

Study data and information will be stored securely at the study center. All data and information will be considered confidential. No identifying information will be used in any report or publication generated from this study. All information gathered will be placed directly into an online encrypted database (i.e. RedCAP). This will include identifier information (i.e. medical record numbers) as well as study data. The data from this database will then be exported from RedCAP and will be de-identified. Data analysis on the exported data set will then be performed. See section #13 for additional information.

Paper records, including signed consent forms and authorizations, will be kept for a minimum of 6 years after completion of the study.

27. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

The subjects will first be asked about participating in the study by their attending physician, resident or fellow before any contact is made with the study staff. Subjects will be introduced to all members of the study staff who will be performing evaluations. They will be asked only to provide personal information to the study coordinator and physician investigators.

A HIPAA Waiver will be requested for prescreening potential subjects.

The research team will obtain detailed medical history information through the medical record, including Epic and Provation. This will be accessed after the subject agrees to participate in the study and signs the HIPAA authorization included in the consent form.

Patients will swallow video capsule with the help and guidance of a trained study staff who will walk patients through the process. Study staff will be available to answer any questions at any time during the study. All patients at UMass CDU are in private rooms allowing further privacy for set up device.

28. COMPENSATION FOR RESEARCH-RELATED INJURY

In the unlikely event of a research-related injury, subjects or their insurance will be responsible for coverage.

The only complication of capsule endoscopy, apart from inability of the patient to swallow the device, is true capsule retention [> 2 weeks of retention] with or without obstruction. In this case it is the underlying disease causing the problem and the management would be covered by the patient's insurance.

29. Economic Burden to Subjects

None is anticipated from participating in the study. All costs associated with the emergency department stay, hospital admission and associated testing (including but not limited to endoscopy procedures) will be paid by the subject or insurance and the subject will be responsible for all co-pays, deductibles, etc. These are all standard of care procedures.

The patients recruited to be subjects in this study will require admission to the clinical decision unit for up to 24 hours. Before the 24 hour limit a decision will be made by the GI attending, PI and /or sub-investigators as to whether the patient should be admitted to the hospital or be discharged for outpatient follow-up and work up as needed**.** Admission to the CDU and hospital admission for GI bleeding is covered by most insurances.

For those in the early capsule group, the cost of using the prokinetic medications (if necessary) will also be paid by the subject or insurance as this is part of the standard of care procedures for their emergency department admission and assessment. Any subsequent intervention will be billed to the subject or insurance.

The cost of the video capsule and its reading, both for the early capsule group and any subject in the standard of care group who receives a video capsule, will be paid for by the study and not billed to the subject or insurance.

30. Consent Process

Consent will take place in the Emergency Department or the Clinical Decision Unit. Study staff will follow HRP-802 INVESTIGATOR GUIDANCE: Informed Consent. Subjects will be given as much time as they require before making a decision to participate in the study. The time provided for discussing the consent process with subject will be 15 minutes or greater as the subject requires. Only the listed study staff members will be involved in the consent process.

In order to minimize the possibility of coercion during the consent process, potential subjects will be notified that their care will not be altered in any way if they choose to provide or not provide consent.

If a potential participant does not speak English, but both an IRB-approved short form and appropriate interpreter services are available, non-English speaking subjects may be recruited for this study.

31. Process to Document Consent in Writing

Study staff will document consent in writing, following HRP-803 INVESTIGATOR GUIDANCE: Documentation of Informed Consent. A consent form has been attached to this submission.

32. DRUGS OR DEVICES

The video capsule that will be used in this study is the Olympus small intestinal capsule endoscopy system (EC-10 System). This system has been cleared by the FDA under 510(k) approval number K123421. This is a capsule imaging system intended for visualization of the small intestine mucosa. This is the FDA cleared labeling. There is no requirement for timing in the FDA labeling. The video capsules will be locked in our study coordinator's office. Handling and administration of the capsules will be performed by study staff members who have been trained and have experience in the tasks related to the video capsules.

A copy of the clearance document and a product manual have been added to the attachments for this study.

The two prokinetic agents that will be used as part of this study if capsule retention occurs are metoclopramide and erythromycin. Package inserts for both medications are included as attachments to this study. Metoclopramide is labeled for use in gastroparesis and not gastrointestinal bleeding. Erythromycin is not approved as a prokinetic agent; however, both drugs are often used in the hospital setting for the purposes of emptying the stomach of blood in patients with gastrointestinal bleeding.

eIRB Section 7.0 Attachments Upload Checklist

Follow How to Manage Files in eIRB and upload the following items as applicable to your submission. This checklist is provided for your convenience and is not a requirement for review.

	Investigator Study Plan
	Sponsor protocol
	Research portion of the grant
	Human subjects portion of the grant
	Written approvals from ancillary reviews (Clinical Engineering, COI, IBC, PRC, RSC, Students as Subjects, etc.)
	Recruitment materials such as flyers, brochures, posters, scripts of radio ads, etc.
	Data collection sheets, case report forms, etc.
	Surveys, measures, instruments, etc.
	Measures to assess capacity to consent
	DMC or DSMB charter
	Data safety monitoring plan
	Adverse event log
	Investigator brochure or package insert for drugs
	Instructions for use or approved FDA labeling for devices
	Sponsor justification or FDA documentation for non-significant risk device study
	IND or IDE documentation
	Patient information sheet for Humanitarian Use Device
	Approval order for Humanitarian Use Device
	Product labeling for Humanitarian Use Device
	HIPAA waiver
	HIPAA authorization
	Authorization to contact form
	Consent form(s)
	Assent forms(s)
	Fact sheet(s)
	Multi-site communication plan
	Study staff training plan
	SOPs or Manuals of Operations
	Screening log
	Compensation log
	Certificates of translation or translator attestations
	Data use agreements, memoranda of understanding,
	Documentation of data/specimen anonymity (i.e., provider will never break the code)