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: Data Safety Monitoring Board Charter

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Data and Safety Monitoring Board Charter

Protocol for the use of the EC-10 capsule in the Emergency Department for acute non-hematemesis gastrointestinal bleeding

1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for the project entitled: ***A randomized trial comparing video capsule first versus standard of care for acute gastrointestinal bleeding (hematemesis and non-hematemesis) in the clinical decision unit at UMass Memorial Healthcare- University campus***

This Charter defines the primary responsibilities of the DSMB, its relationship with other Program components, its membership, and the nature, purpose and timing of its meetings. It also provides the procedures for ensuring confidentiality and proper communication, the approach to statistical monitoring guidelines to be implemented and an outline of the reports to be provided to the DSMB. The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

2. Overview of the Study

There is accumulating evidence that the conventional approach to the assessment of hematemesis and non-hematemesis gastrointestinal bleeding could be improved by early deployment of a video capsule (VCE) [1,2]. In patients with hematemesis, data suggests that at least 30% of patients do not require in-patient upper endoscopy [1]. This can be done shortly and safely after discharge. VCE can provide direct evidence of active bleeding or whether it has ceased. Patients with melena and hematochezia may benefit from early capsule endoscopy, since both signs provide poor localization of the origin of bleeding. Non-hematemesis GI bleeding [NHGIB] represents 64% of patients with gastrointestinal bleeding [3]. Data suggests that with the ingestion of a video capsule in the emergency department there could be a shortened time to diagnosis, and a reduction in numbers of procedures and /or admissions [1, 2]. These observations suggest that the early deployment of a video capsule could result in better quality of care and cost containment. Several studies now suggest that the closer VCE is performed to the time of bleeding, the higher the likelihood of locating the source and the higher the therapeutic intervention rate and shorter length of stay[4,5]. The use of capsule endoscopy in patients with non-hematemesis bleeding has a higher diagnostic yield than does upper endoscopy and colonoscopy[2].

3. Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the studies.

The DSMB is an independent group advisory to the Project Director and is required to provide recommendations about starting, continuing, and stopping the studies. In addition, the DSMB is asked to make recommendations, as appropriate, to the study about:

- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Participant safety
- Notification of and referral for abnormal findings
- Efficacy of the study intervention

The DSMB will monitor the study for the occurrence of adverse events (both serious and otherwise) in the treatment arms. A significant increase in the rate of adverse events in one treatment group would be cause for concern for the safety of participants in the study. Information on adverse events will be presented in several ways: (1) listings of serious adverse events in the two treatment groups with accompanying narrative summary by the investigator; (2) summaries of adverse events by body system and type of event. This information will be presented by blinded treatment group (i.e., Treatment A and Treatment B) to the DSMB for each group.

The investigators reserve the right to discontinue the study for any reason at any time.

The study will be stopped if the DSMB determines a need to do so.

4. Organization and Interactions

The following description illustrates the relationship between the DSMB and other entities in this study.

Communication with DSMB members will be primarily through the study statistical investigator, Dr. Bruce Barton PhD. It is expected that study investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

The performance site will report all fatal events, unanticipated problems and other serious adverse events (AEs) and suspected adverse reactions (SAEs) to the DSMB, Study Sponsor, and IRB by secure email within 5 days of first knowledge of the event. Additionally, all on-going study data for that particular subject will be entered to allow for Adverse Event Follow-up.

Reporting email addresses:

1. DSMB
    a. Dr Bruce. Barton@umassmed.edu
2. Local IRB (use internal reporting process)

5. DSMB Members

The DSMB will consist of three experienced investigators, including clinicians and a biostatistician/epidemiologist, to exercise oversight of the safety of trial participants and of the conduct of the study. The DSMB members are:

1**. Bruce Barton, PhD**
Professor of Quantitative Health Sciences and Director Quantitative Methods Core

University of Massachusetts Medical School
Worcester MA

2. Robert Goldberg, Ph.D.
Professor of Quantitative Health Sciences and Section Chief, Epidemiology of Chronic Diseases and Vulnerable Populations
University of Massachusetts Medical School
Worcester MA

3. Benjamin Hyatt MD
Attending Physician
Emerson Hospital
Concord MA

Anupam Singh MD
Assistant Professor of Medicine
UMass Memorial Healthcare
Worcester MA

The DSMB will review periodic data and safety monitoring reports with schedule and content as indicated below. The DSMB Reports will be prepared by study staff, under the direction of the trial biostatistician (Dr. Sharina Person). The initial contents of the DSMB report (outlined below) will be discussed with the DSMB prior to the first data review meeting. As deemed necessary by the DSMB, it may request additional data/information for reports and advise study director regarding continuation/discontinuation of the study. The study will provide staff to act as the DSMB Secretary to record the deliberations and decisions of the DSMB.

6. Scheduling, Timing, and Organization of Meetings

The DSMB will meet at least twice per year and possibly more frequently if the speed of recruitment warrants it. The DSMB may request more frequent reports of selected information, such as recruitment or adverse events, and, if one or more members requests, a meeting will be arranged as soon as possible. Minutes of the DSMB meetings and communications from the DSMB to the PI will also be filed with the UMMS IRB and Office of Research.

Meetings and conference calls will be scheduled by the DCC.

- For this DSMB, meetings will be held as needed (with a minimum of twice per year).
- Review of interim safety analyses will occur quarterly (between meetings) and, if a member has any concerns, a conference call will be arranged promptly.

The agenda for DSMB meetings and calls will be drafted by the study. The study statistician will finalize the agenda after consultation with the DSMB Chair. The agenda and meeting materials should be distributed by the study two weeks before each meeting or call.

Before each meeting, when the agenda is sent out, the study will ask all DSMB members to state whether they have developed any new conflicts of interest since the last formal annual report. If a new conflict is reported, the Chair and study statistician will determine if the conflict limits the ability of the DSMB member to participate in the discussion. The DSMB also will review adverse event data, other safety data, quality and completeness of study data, and

enrollment data at each meeting to ensure proper trial conduct. At intervals, as requested by the DSMB, the DSMB will also review formal interim analyses of the primary end point.

Monitoring reports for the DSMB will include, but will not be limited to, such tabulations both overall (open meeting) and by blinded treatment arm (closed meeting) as:

1. Recruitment by week/month;
2. Baseline characteristics of the patients;
3. Completeness of data;
4. Summary of adverse events by type;
5. Summary of adverse events by body system;
6. Listing of adverse events (including duration, severity, seriousness, relatedness, action taken, resolution);
7. Descriptive information for each endpoint without statistical testing except at designated interim monitoring points if requested by the DSMB; and
8. Quality control analyses.

It is expected that all DSMB members will attend every meeting and call. However, it is recognized that this may not always be possible. Because of the small number of DSMB members, the DSMB may wish to establish a procedure for review and voting on acceptance of the DSMB report without meeting attendance. All standing DSMB members are voting members.

7. Discussion of Confidential Material

DSMB meetings and calls will be organized into open, closed, and executive sessions.

- During the **open sessions**, information will be presented to the DSMB by the study investigators, with time for discussion.

- During the **closed sessions**, the DSMB and study statistician (without study investigators present) will discuss confidential data from the studies, including information on efficacy and safety by treatment arm. The DSMB will decide whether to remain masked to the treatment assignments at each meeting. If the closed session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session.

At the conclusion of the closed sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators to ask questions to clarify the recommendations. The meeting is then adjourned.

8. Reports of DSMB Deliberations

- Action plan: If the DSMB's recommendations require significant changes or follow-up, study investigators will prepare an action plan outlining the steps required to implement the recommendations.

- Formal minutes: The Study Statistician or her designee, acting as the DSMB secretary, is responsible for the accuracy of the formal DSMB minutes and will be produced within 30 days of the meeting or call. These minutes are prepared to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. These minutes will be reviewed by Study Staff before being forwarded to the DSMB Chair for final review and approval. The DSMB Chair may sign the minutes or indicate approval electronically via email. Subsequently, the minutes are sent back to the study investigators, and included in the materials for the subsequent DSMB meeting to be approved by voice vote at that meeting. Once they have been voted and approved by the Board, they are considered Final.

9. Statistical Monitoring Guidelines

Prior to the first meeting where data will be presented, a review of the statistical analysis plan (SAP) will be conducted. The DSMB should discuss the adequacy of that plan including what statistical monitoring procedure to follow to guide their recommendations about termination or continuation of the trial. The SAP will include not only the statistical analysis procedures, but also the definition of all calculated variables, including the calculation of change for the endpoints. These procedures could include guidelines for early termination for benefit, termination for futility, and termination for safety reasons. The SAP will also include definitions of the tables and figures for the DSMB reports. Any changes to the SAP will be forward to the DSMB for review and approval.

Formal statistical stopping boundaries will be proposed for this study for both safety and efficacy (including futility). Continuing enrollment will be determined and approved at each DSMB meeting. The DSMB will receive a report on all reported AEs and SAEs as well as the proportion of subjects with any specific event of interest. The DSMB will make the final recommendation for early termination versus continuation of the study after reviewing the available data. The decision will be guided by safety. In addition to the planned evaluations, the DSMB can request to receive quarterly safety summary reports of enrollment, baseline demographics, withdrawals from treatment and/or all AEs and SAEs with information on relation to study procedure.

References.

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4.Pennazio M, Santucci R, Rondonotti E, Abbiati C, Beccari G, Rossini FP, De Franchis R. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases.Gastroenterology. 2004 Mar;126(3):643-53.PMID:14988816

5. Singh A, Marshall C, Chaudhuri B, Okoli C, Foley A, Person SD, Bhattacharya K, Cave DR.Timing of video capsule endoscopy relative to overt obscure GI bleeding: implications from a retrospective study. Gastrointest Endosc. 2013 May;77(5):761-6. PMID:23375526