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ACUTE GASTROINTESTINAL BLEEDING: PROPOSED STUDY OUTCOMES AND NEW RANDOMIZED CONTROLLED TRIALS

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SUMMARY

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Alan Barkun: Conception and design of GI workshop presentation, analysis and interpretation of the data, recommended new RCT's, presented the findings at the NIH-NHLB Institute and reviewed and approved the manuscript.

David Cave, Ian Gralnek, Rome Jutabha, Loren Laine, James Lau, John Saltzman, Roy Soetikno, and Joseph Sung: Collected and critically analyzed the data, recommended new RCT's, and reviewed and approved the manuscript.

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AUTHORSHIP STATEMENT

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BACKGROUND—Acute gastrointestinal bleeding (GIB) remains a common cause of hospitalization. However, interpretation and comparisons of published studies in GIB have been hampered by disparate study methodology.

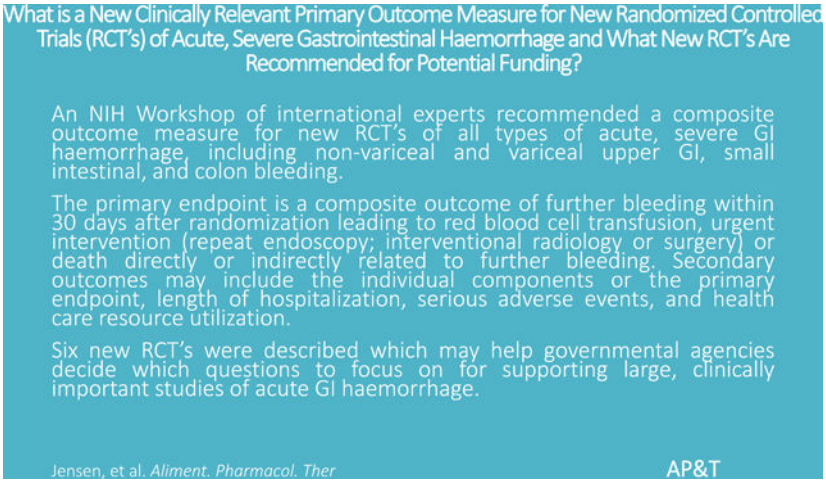
AIMS—To make recommendations about outcome measures to be used in future randomized controlled trials (RCTs) of patients with acute bleeding from any GI source (non-variceal UGI, variceal, small bowel, or colon) and suggest new RCTs in acute GIB for future peer-reviewed funding.

METHODS—As part of a National Institutes of Health conference entitled “Hemostatic Outcomes in Clinical Trials”, a group of GIB experts performed targeted critical reviews of available evidence with the goal of proposing a bleeding outcome that could potentially be applied to different disciplines. In addition, the panel sought to develop a clinically meaningful primary endpoint specifically for acute GIB, potentially allowing a more contemporary regrouping of clinically relevant outcomes.

RESULTS—The primary endpoint proposed was a composite outcome of further bleeding within 30 days after randomization leading to red blood cell transfusion, urgent intervention (repeat endoscopy; interventional radiology or surgery), or death. Secondary outcomes may include the individual components of the primary outcome, length of hospitalization, serious adverse events, and health care resource utilization.

CONCLUSION—The proposed endpoint may help move the GIB field forward by focusing on the most clinically relevant outcomes for patients with acute GIB of all types and informing study design and importance of sample size determination for future RCTs in GIB.

Graphical Abstract



Keywords

GI haemorrhage; outcomes; RCTs

INTRODUCTION

An NIH conference entitled “Hemostatic Outcomes in Clinical Trials” was held in September 2019, sponsored by the National Heart, Lung, and Blood Institute (NHLBI). Multiple disciplines of different types of acute haemorrhage and experts in each field were included. The purposes were to critically review and make recommendations about 1) what clinical outcomes (primary and secondary) to assess and compare in future randomized controlled trials (RCT’s) for management of severe acute haemorrhage, 2) what new methodologies or RCT’s to perform in each speciality or type of haemorrhage, and 3) whether there are generic outcome measures across all types of organ haemorrhage that could be utilized in RCT’s. These recommendations were made to the program directors of the NHLBI who plan to utilize them in future programmatic funding considerations and instructions to investigators. A separate manuscript of the entire proceedings has been accepted for publication. [1]

In contrast, the current manuscript focuses on the analysis and recommendations as they pertain to acute gastrointestinal (GI) bleeding by the Gastroenterology Study Group that included all co-authors of this work. Our goals were to make recommendations about primary and secondary outcome measures for future GI bleeding RCT’s with an aim of adopting a possible composite outcome that could potentially be applied to different disciplines, while allowing a more contemporary regrouping of clinically relevant endpoints. This endpoint would focus on the most clinically relevant outcome(s) for patients with GI bleeding and inform study design and statistical powering of future trials, while also providing a more standardized approach when considering new studies for future peer-reviewed funding related to acute GI haemorrhage.

BACKGROUND

Acute upper and lower GI bleeding are prevalent and remain common causes of hospitalisation, health resource utilization and morbidity. [2–7] As an example, Peery et al reported that GI haemorrhage was the most common gastrointestinal, liver or pancreatic principal diagnosis in US hospitals in 2014 with UGI haemorrhage accounting for 203,460 annual admissions and LGI haemorrhage 161,540, with aggregate national changes of $3.63 billion US dollars. [5] This is especially true as life expectancy increases and anti-thrombotic drug use grows.[8] Exceptional efforts by reputable investigators have moved the GI field forward. Yet interpretation and comparisons of many published studies - especially RCT’s that have assessed both upper and lower GI bleeding – have been hampered by disparate study methodologies. Examples include varying randomization procedures (which frequently lack blinding), different timing for allocation to study or treatment groups, heterogeneous choices of study endpoints (especially primary outcomes), co-interventions, lack of generalizability, and small sample sizes with inadequate powering for clinically important outcomes. Additionally, there exist relatively very few large prospective, collaborative, multicentre GI randomized controlled studies which further underlines the limited inferences to be drawn from underpowered studies. Limited funding for large multicentre clinical RCT’s in GI bleeding has also restricted progress. Systematic reviews and meta-analyses have also been constrained by significant differences in study

designs, including choice of patient populations, interventions, and definitions of study endpoints or outcomes.

Attempts at identifying a common, unified, primary outcome measure in non-variceal upper GI bleeding, the most common type of RCT's of acute GI haemorrhage, have been unsuccessful to date even though some investigators have, over the past 5–10 years, adopted 7-day further bleeding and/or 30-day mortality, as proposed by a previous consensus group for this type of acute UGI haemorrhage.[9] Rebleeding, re-intervention for further bleeding, surgery and angiographic treatment, RBC transfusions, hospital days and death are common primary and secondary outcomes in reports on acute severe variceal, small bowel, and colonic bleeding, but composite outcomes are rarely reported in these latter studies. As for composite outcome measures applied and reported in the field, they remain few and empirically chosen, often without respecting usual methodological criteria. [10] This is in stark contrast to some other therapeutic areas such as in cardiovascular disease where composite outcome measures have become commonplace. [11] Although defining a common primary outcome and a set of important secondary outcome measures both in upper (variceal or non-variceal) and lower GI bleeding may be difficult to achieve, there is a need for attempting to streamline this important aspect of study methodology in the hope of addressing many of the aforementioned methodological limitations while increasing the internal validity of subsequent summary analyses, such as meta-analyses. One other limitation of this effort to assess and formulate a new primary outcome for RCT's is that the preponderance of RCT's have been reported about peptic ulcer bleeding (PUB's), rather than variceal, small bowel, and colonic haemorrhage. This is despite the decreasing incidence of PUB's and increasing rate of colonic haemorrhage.[6, 12] Regardless, outcomes in clinical trials should be relevant to patient care, amenable to independent unbiased assessment, and have the potential to be influenced by the trial intervention. Because trial results inform the care of different patients, in different places and at different times, we must also consider generalizability when selecting outcomes. Wide adoption of such study endpoints will help guide peer-review committees in future funding of worthy individual site or multicentre RCT's.

LIMITATIONS OF ADOPTED METHODS AS PART OF THE NIH WORKSHOP PROCESS

a. The following report is based on narrative and targeted reviews of the available published and unpublished evidence rather than a series of formal systematic reviews coupled to rigorous grading of the certainty of all relevant evidence, as has been recently reported by some of the current authors. [4–5] This approach mirrors the aim of the recommendations that provide an informed consultative opinion for the NHLBI on primary and secondary outcomes in addition to recommendations for new multicentre randomized controlled trials (RCT's) related to acute GI haemorrhage.

b. Focus of the patient population studied: The GI committee chose to primarily focus on addressing acute variceal and non-variceal upper GI bleeding, overt small bowel bleeding, and lower GI haemorrhage (e.g. colonic), as it applies to immediate management and secondary prevention within 30 (non-variceal UGI

or colonic haemorrhage) to 42 days (variceal haemorrhage) of follow-up for important clinical outcomes including mortality. Although we discuss different sources of GI bleeding, the entry point to an RCT is symptoms of acute overt haemorrhage from all possible sources in the GI tract (haematemesis, melena, and/or haematochezia) while excluding occult GI bleeding. We also do not include prophylactic studies for primary or secondary prevention of acute or chronic GI bleeding. Although most of our analysis of publications and conclusions are focused on non-variceal UGI haemorrhage, the aim was to apply the recommendations to all severe, acute GI bleeding, including variceal, colonic, and small bowel haemorrhage.

c. Because of lack of expertise with other therapeutic areas treating acute severe haemorrhage outside the GI tract, committee members wanted to clarify that most of the recommendations pertain to GI-specific outcomes, [2–5] some of which may or not be applicable to other disease processes or therapeutic areas outside the GI track. However, where applicable, a brief discussion of advantages and disadvantages in choosing certain endpoints that could be common to another organ bleeding is included.

d. In acute GI haemorrhage, the index bleed imputes an important clinical impact. Yet most of GI trials have also looked at rebleeding over time with varying time horizons adopted. This biological phenomenon may vary according to the therapeutic areas and bleeding aetiology, yet the set of outcomes related to the natural history of GI bleeding must also be captured in any primary outcome choice.

e. The authors felt other considerations about risk factors for the study populations may influence outcomes and should be considered when thinking of adopting a single primary outcome for what are very heterogeneous GI aetiologies. These include: severity of bleeding (e.g. hemodynamic instability), endoscopic stigmata of recent haemorrhage (SRH), arterial blood flow monitoring underneath SRH, co-morbidities, concurrent medications (e.g. anti-thrombotic drugs), aetiology of bleeding, and risk assessment scores (e.g. Glasgow-Blatchford score).[2–5] It is also important to appreciate that different GI lesions follow markedly different natural histories, although the members agreed to initially consider a “generic” GI bleeding patient for the discussions, without worrying about the GI source as mentioned above.

f. The authors tried to review outcomes that might be common to all patients with acute haemorrhage from the GI tract or other origins. However, the GI group felt that recommendations could only address patients with acute GI bleeding as discussed above. This conclusion was drawn based on 4 main considerations: 1) The characteristics of patients presenting with acute GI bleeding are different than other causes of life-threatening haemorrhage from other organs. 2) The field of GI bleeding is mature with sophisticated outcomes previously assessed in RCT’s that are more focused on this therapeutic area for which there are high-quality data to inform overall assessments. 3) Mortality in patients with GI

bleeding is usually not directly related to haemorrhage and/or to hypovolemic shock, so that all-cause or bleeding-related mortality alone is not a viable primary outcome of most RCT's of acute GI haemorrhage. 4) The natural history and course of GI bleeding often differ from acute haemorrhage originating in other organs.

SUGGESTION FOR ADOPTION OF A COMPOSITE OUTCOME MEASURE

Composite outcome measures are widely used in certain therapeutic areas such as cardiovascular disease but have typically not been adopted in acute GI bleeding therapeutic studies. [11] Although criteria used to determine the validity of such endpoints are not widely accepted, the extent to which the answers to the following questions are met or not may help determine whether one needs to examine the component end points separately: a) Are the component end points of similar importance clinically (e.g. to patients)? b) Did the different endpoints occur with similar frequency? c) Are the component end points likely to have similar relative risk reductions? d) Is the underlying biology of the component endpoints similar? [11]

An example of a composite endpoint recently proposed in the non- variceal upper GI bleeding literature, and more specifically for risk score validation as it applied principally to non- interventional studies, included red blood cell (RBC) transfusions, urgent intervention for bleeding (endoscopy, interventional radiology, or surgery), and 30-day mortality. [13] Recently another composite outcome score was reported in a study of Dieulafoy's lesion bleeding which included further bleeding, salvage treatment (surgery or angiography), severe complications, and all-cause mortality within 30 days. [14]

However, in order to better understand GI outcome measures, a review of possible individual contributing endpoints follows.

ENDPOINTS IN GASTROINTESTINAL BLEEDING TRIALS THAT HAVE BEEN ASSESSED TO DATE

Although many outcomes have been proposed for GI bleeding, trials of endoscopic or pharmacological therapy in the era of proton pump inhibitors (PPI) and red-blood-cell transfusion in the last 2 decades have provided some of the most sophisticated endpoints in the context of PUB RCTs. [15] Additional attempts, especially in the field of risk stratification and risk prediction modelling have explored possible composite outcome measures with limited validation of such measures.[10] Different primary and secondary measures are listed below with relevant definitions and/or biological plausibility presented.

The goals of GI haemostasis for severe acute GI haemorrhage are control of active bleeding and prevention of rebleeding. [14, 16–23] Initial control of bleeding has traditionally been guided and defined by visual criteria on endoscopy (see next section). However, the adequacy of endoscopic haemostasis (in order to prevent rebleeding) is more difficult to define on visual criteria alone, but usually includes obliteration of the lumen and blood flow of the artery running in the bed of the bleeding lesion (such an ulcer [16–18] or diverticulum

[20, 21]) or blood flow in the varices[19]. For focal non-variceal GI lesions this may be achieved with therapies such as coaptive thermo-coagulation of the stigmata of recent haemorrhage (SRH) or mechanical therapy with placement of haemoclips (through the scope or cap-mounted) on the SRH, with or without injection of epinephrine. [14, 16–23] Additional methods (often used for variceal haemorrhage) include injection of sclerosants, application of ligating bands or haemostatic topical agents. All these clinical, visually guided endpoints that have been utilized for the last four decades have been descriptive, arbitrary, and subjective. [2–5] However, recently obliteration of arterial blood flow underneath SRH has been reported to highly correlate with prevention of rebleeding and successful, definitive haemostasis. [14, 16–21] Blood flow underneath SRH in focal non-variceal GI lesions or in varices can be readily detected by a Doppler endoscopic probe (DEP) and this technology has been recommended for further assessment and validation in future RCTs as a potential secondary endpoint to facilitate objective and standardized comparisons across RCTs with regards to risk stratification and defining definitive haemostasis. [14, 16–21]

Initial Haemostasis for Actively Bleeding Lesions

Although useful in assessing very short-term outcomes and differentiating the usefulness of certain haemostatic methods, initial or primary haemostasis (on visual endoscopic observation) as an endpoint only partially impacts subsequent clinical outcomes such as morbidity and mortality. For actively bleeding lesions, a definition for primary haemostasis (or its inverse, persistent bleeding, described below) has varied in the literature, usually being achieved after 3–5 minutes of visual observation following what the endoscopist records as the optimal attempt at endoscopic haemostasis.

More recently, the DEP has been reported as a better guide to definitive haemostasis and as a predictor of subsequent rebleeding, based upon RCT's and prospective cohort studies, principally from one research team· [14, 16–21] These findings have the potential to advance the concept of definitive endoscopic haemostasis beyond visual cues in that the persistence of residual blood flow in arteries underneath SRH or in varices after standard visually guided endoscopic haemostasis is a major risk factor and determinant of rebleeding in both for nonvariceal and variceal haemorrhage. [14, 16–21]

Persistent Bleeding

Persistent bleeding is haemorrhage that persists or is ongoing at the conclusion of index endoscopy. This may occur when active bleeding does not stop despite endoscopic intervention or when a non-bleeding lesion develops active bleeding during the index endoscopy (e.g. induced by endoscopic therapy) that is not controlled with the therapies being evaluated.[14–22] With current endoscopic haemostasis techniques for non-variceal GI bleeding (including PUB's and diverticular haemorrhage), this endoscopic outcome of failed initial haemostasis has a low incidence and thus would require very large numbers of patients if used as the sole primary outcome measure in future RCT's.

Recurrent Bleeding

This outcome has been the most commonly adopted primary outcome measure and also correlates with most other clinically meaningful endpoints. [2–5] Its timing has varied

according to aetiology. For example, 72 hours or 7 days for the highest risk period following haemostasis of peptic ulcers, [2–5] although 30 days may be more relevant for variceal [19, 24, 25] or colonic haemorrhage, [20–22] because of their different patterns of rebleeding. Rebleeding is also affected by the use or re-initiation of antithrombotic agents, that may extend the high-risk rebleeding period while healing of the lesion is incomplete. [2–5] As one example of proposed criteria, for rebleeding in NVUGIB refer to Table 1, from a prior consensus group. [9] One of the limitations of that publication was that studies of variceal or colonic bleeding were not included. [9] Nevertheless, the present NIHGIB group recommended against rebleeding as a sole primary endpoint because it ignores the efficacy of an intervention in halting active bleeding.

Further Bleeding

Further bleeding is a composite of persistent and recurrent bleeding. It was previously recommended in 2010 as the primary endpoint in new RCT's of acute non-variceal GI haemorrhage because it provides an overall assessment of the haemostatic efficacy of an intervention and because prevention of further bleeding is a primary goal in patients with GI bleeding. [9] Further bleeding also includes persistent bleeding induced by initial endoscopic therapy (e.g. induction of bleeding when treating a non-bleeding visible vessel or adherent clot) or recurrent bleeding that is due to the initial endoscopic therapy (e.g., bleeding from ligation-induced ulcer). Refer to Table 1.

However, in the last decade further bleeding has not been consistently adopted as a primary endpoint in RCT's of acute non-variceal GI haemorrhage. [26] Nevertheless, further bleeding should be considered as a clinically relevant outcome, since its biological foundations are sound, and its direction and incremental decrease evolve with therapy in the same general direction as other important outcomes such as mortality. [10]

Repeat Endoscopic Procedures

This criterion refers to the need for one or more additional endoscopic procedures done for visualization and possible repeat haemostasis of a lesion causing further bleeding after the index endoscopy. This endpoint also can include endoscopies done for complications of prior interventions (e.g. bleeding from ligation-induced ulcer).

Surgery and Angiographic Embolization as Salvage Therapies

These are performed during an index hospitalization when there is evidence of severe, clinically significant acute GI bleeding that cannot be managed by endoscopy alone. Surgery and/or angiographic embolization have been used as outcome measures when performed for management of further bleeding or for a complication of a study intervention. [14, 16, 17, 19–23] These endpoints have been included in both upper and lower GI bleeding studies but are limited by the subjectivity of the clinical criteria used to decide on such interventions in most studies. No widely accepted consensus definitions for triggering such interventions exist.

The need for surgery or transcatheter arterial embolization is uncommon in severe non-variceal UGI haemorrhage due to the natural history of some aetiologies of GI bleeding

(e.g. spontaneous resolution and low rates of rebleeding) and the current excellent success rates of modern endoscopic and medical therapy in higher-risk patients. [14, 16–18, 23] Repeat endoscopic haemostasis for recurrent peptic ulcer bleeding is also safer than emergency surgery. [27] In addition, with fewer ulcer surgeries being performed now worldwide, expertise in performance of PUB surgery is limited and not available in many medical centres. However, both angiographic therapies and surgery are more common in severe variceal or diverticular haemorrhage, where endoscopic therapy is often not as successful for definitive haemostasis. [19, 20–22, 24, 25]

Mortality: Bleeding-Related and All-Cause

Mortality is a consideration as a primary endpoint in acute GI bleeding because of its clinical relevance, but it has important limitations. Mortality of non-variceal upper and lower GI bleeding is relatively uncommon (<5% in most contemporary studies and 2% in a recent U.S. database study[28]). Therefore, all-cause mortality alone is a problematic choice as the primary end point in most studies of GI haemorrhage, unless extremely large studies are conducted.

In addition, most deaths are related to a patient's underlying comorbidities and not solely to blood loss, so mortality may not solely reflect a bleeding-related endpoint and will be diluted by non-bleeding issues, thereby potentially hindering signals of efficacy or harm. Importantly, an intervention in a trial may successfully prevent further bleeding, but patients may still die related to decompensation of their underlying illness that was precipitated by the bleeding episode. Thus, a successful intervention could be labelled as ineffective in a number of cases if all-cause mortality were employed as an endpoint. Furthermore, all-cause mortality will vary across different disease entities and populations, reducing its generalizability. [28] For non-variceal upper GI bleeding, a 30-day mortality outcome has been recommended. For assessment of mortality for variceal bleeding, a 42-day time horizon has been recently recommended owing to biological differences and disparate course of illness compared to nonvariceal upper GI bleeding.[24]

Mortality due to GI bleeding, which includes deaths related to bleeding or complications of study intervention, has also been used as an outcome. The main concern with bleeding-related mortality is that the cause of death is determined subjectively and may be subject to bias. Misclassification of the cause of death is a particular concern in un-blinded trials, where knowledge of group allocation might influence decisions about the cause of death and introduce bias.

Length of Hospital Stay (Total and Intensive Care Unit)

In RCT's of acute GI haemorrhage, the days in the hospital should begin at the time of randomization to normalize for any differences in time from presentation to randomization. This will be especially important if patients who develop GI bleeding while already hospitalized for another reason are included. The number of days spent in an intensive care unit (ICU) or in a monitored bed also should be recorded. Problems with these measures as endpoints are the subjectivity (e.g. in the decision when to discharge or consider continued hospitalization no longer related to a bleeding episode) and the fact that decisions are also

affected by many patient-related issues other than bleeding and are dependent on local practices and health-care system issues.

Red Blood Cell Transfusions

This endpoint reflects packed red blood cells (RBCs) or whole blood ordered after randomization. The subjective decision of transfusing and how much to transfuse introduces bias in adopting this outcome. Additionally, transfusion is not only an outcome but also a baseline characteristic that may reflect blood loss prior to randomization. Thus, the receipt of RBC transfusions after randomization may be related to blood lost prior to randomization and this will be increasingly important when randomization occurs closer to the time of initial presentation. Transfusions given in response to blood lost before randomization cannot be affected by the trial intervention and this will confound the assessment of efficacy.

Other Individual Endpoints

These have included, but are not limited to, finding of a clinically significant lesion (e.g., high-risk lesions in the case of PPI-pre-endoscopy trials and studies in lower GI bleeding), severe adverse events (both due to acute bleeding and rebleeding – such as a CVA or MI - as well as procedure-related – such as aspiration pneumonia or perforation), [2–5, 14, 16, 17] and quality of life measures. These endpoints are hampered by lack of standardization, subjectivity, or unclear direct relationship to some of the more commonly used aforementioned clinical outcomes. One additional outcome that has been used particularly in lower GI bleeding is diagnostic yield. [20, 22, 29] In variceal bleeding, several disease-specific outcomes have been used as well, such as use of interventional radiology and rates of pneumonia, hepatic encephalopathy, bacterial peritonitis, and other infections. [19, 24, 25] These are often less related to the acute bleeding than the exacerbation of the underlying liver disease. [19, 24, 25]

Cost Analyses Endpoints – Costs /Units of Effectiveness

Ideally, the true costs of all aspects of care for the patient should be calculated from a societal perspective. Actual costs rather than hospital charges and physician charges should also be considered. For conclusions to be useful across health care systems that include varying fee structures and different currencies, health resource utilization should be collected. Ideally, a third-party payer perspective should be adopted. As for the choice of unit of effectiveness, this measure should ideally not be associated with costs. Quality-Adjusted-Life-Years are typically recommended as the best endpoint, but data addressing this measure in GI bleeding are limited in the literature. Furthermore, the brevity of the disease condition (e.g. an acute health state usually with a 30-day time horizon) limits the interest of adopting such a measure of effectiveness.[30] Alternately, cost analyses have typically assessed effectiveness as the proportion of patients avoiding rebleeding (i.e. cost to avoid one episode of rebleeding) even though this is a choice that violates the independence required between numerator and denominator. [30, 31]

RECOMMENDATIONS FOR ACUTE GASTROINTESTINAL BLEEDING OUTCOMES

Primary Outcome

The panel sought to develop a clinically meaningful primary outcome that most practitioners would agree is an appropriate target in future trials for all types of acute GI bleeding--variceal and nonvariceal upper, small bowel, and colonic. Reduction in further bleeding which leads to clinical consequences was recommended as a new primary goal of RCTs in acute GI bleeding. Specifically, we propose a primary composite outcome of further bleeding after randomisation leading to RBC transfusion, urgent intervention (repeat endoscopy; surgery or interventional radiology), or death after randomization that is related to GI bleeding. The time period to assess the endpoint was suggested to be 30 days. Although 7 days may be appropriate for further bleeding due to peptic ulcers, the panel was concerned that longer periods might be more appropriate for other sources such as varices or colonic lesions. In addition, 30 days is generally accepted as an appropriate period for assessment of mortality for non-variceal and colonic GIB, although 42 days may be more appropriate for variceal haemorrhage. Also, a single time period for assessment of the entire composite outcome is more practical than assessment of each component of the composite at separate times or of use of different time periods for different aetiologies of GIB.

We recognize that issues of subjectivity are a potential concern with this composite endpoint, as with almost all other endpoints besides all-cause mortality, and this is especially true in unblinded trials. To reduce the possibility that transfusions may reflect blood loss related to the pre- randomization index presentation and haemodynamic resuscitation, only transfusions ordered after randomization should be included. Further refinements (e.g. only including transfusions at some study-defined time after presentation) should be considered if randomization occurs very soon after presentation. Urgent interventions are included if done for further bleeding or related to complications of initial intervention (e.g., further bleeding or perforation after initial endoscopic therapy). Death due to further bleeding is included if directly related to blood loss (e.g., haemorrhagic shock), while death from decompensation of an underlying condition not due to the effects of persistent or recurrent bleeding after randomization is not included. For example, a patient with further bleeding after randomization leading to hypotension and a myocardial infarction would be included in the composite outcome, while a patient who presented with a myocardial infarction at the time of admission and, after randomization onto a trial of acute GI bleeding, dies from complications of the infarction would not be included in the primary composite outcome. For new RCT's reporting composite outcomes with RBC transfusions and deaths directly or indirectly related to further bleeding, an independent data and safety monitoring board is recommended to assess each of these results.

Secondary Outcomes

Secondary outcomes may include the individual components of the primary outcome (red blood cell transfusions, urgent interventions, and bleeding-related death), further bleeding (with or without the resultant consequences required for the primary outcome), length of

hospitalization (total hospital days and ICU days), serious adverse events including those related to GI bleeding or interventions, and health care resource utilization.

DISCUSSION

Applying the recommendation to utilize a composite outcome for future RCT's of acute GI haemorrhage will take time, validation, education, and consensus among investigators and funding agencies. [32] The components chosen by the GI haemorrhage group were carefully assessed and selected while respecting methodologic criteria. [10] When these criteria and processes for development and utilization of composite outcomes are not followed, limitations may occur in interpreting the results of RCT's, such as suggested for a recent report of stress ulcer prophylaxis in which an overall effect related to proton pump inhibitors (PPI) was difficult to interpret as the components of the composite measure included some outcomes that may increase and others that decrease with PPI use. [33] Meanwhile, reporting both the primary composite outcome and other secondary outcomes will facilitate interpretation and comparisons of results with both new RCT's and past studies of acute GI haemorrhage. For GI haemorrhage as in cardiovascular RCT's, adoption of composite measures as a primary outcome will be a work in progress and some may still question the importance and relevance. [32]

RECOMMENDATIONS ON NEW RCTS FOR ACTIVE GASTROINTESTINAL HAEMORRHAGE

The study group also discussed and recommended several, large new studies of acute GI haemorrhage which are clinically important and could move the field forward if adequately funded. Refer to Table 2 for a list of clinically relevant large RCT's that should be considered for funding by governmental agencies as multicentre RCT's. Included are the lesion types of bleeding, hypotheses, specific primary and secondary clinically related outcomes, potential sample sizes to consider, and selected references of related studies or methodologies. When possible, treatments should be masked and the healthcare workers managing the patients after the randomization should be blinded as to the treatment allocated. At the very least data collection, data entry, and analysis should be carried out by personnel blinded to treatment group allocation. If endoscopic or interventional radiology/surgical treatments are included, standardization among the investigators of lesion types, stigmata of recent haemorrhage, indications, inclusion criteria, transfusion criteria and timing, techniques are recommended prior to initiation of the RCT. All RCT's should be registered with ClinicalTrials.gov. The list of studies is not meant to be all inclusive but may help US (e.g. federal agencies such as the NIH or Veterans Administration) and other international governmental funding agencies (e.g. National Health Service agencies in UK, Canadian Institutes for Health Research in Canada, and equivalent peer-review funding government organizations in the European Union) decide which questions to focus on for supporting new large, clinically important GI studies of acute GI haemorrhage.

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Table 1.

Criteria for Rebleeding in Acute Non-Variceal Upper GI Haemorrhage

When haematemesis or bloody NG aspirate is documented more than 6 hours after endoscopy,
After normalization of stool color, when new melaena or haematochezia is witnessed
After more than 1 hour of hemodynamic stability, when tachycardia (110 beats/min or higher) develops in the absence of another cause such as sepsis, cardiogenic shock, or a medication effect
After two stable haemoglobin levels (within 0.5 gm/d) at least 3 hours apart, when a decrease of haemoglobin of 2 or more gm/dl is documented
When ongoing melaena or haematochezia is documented along with persistent tachycardia and/or hypotension that do not resolve within 8 hours of the endoscopy in spite of ongoing resuscitation
When there is persistent melaena or haematochezia and the haemoglobin decreases 3 or more gm/dl within 24 hours

Modified from Ref 9.

Table 2.

Six New Proposed Randomized Controlled Studies for Acute Gastrointestinal Haemorrhage

Proposed RCT	Lesion Type	Specific Aims	1^0 Outcome	2^0 Outcome	Hypothesis	SS estimate	Comments	Reference
1. DEP assisted haemostasis of severe NVUGIB compared to standard haemostasis as initial treatment	NVUGIB Stratify by: a) 1^0 Initial treatment b) 2^0 Treatment of further bleeding c) Ulcers vs. Dieulafoy's d) SRH	Compare clinical outcomes of patients with NVUGIB treated with DEP Monitoring vs. Standard haemostasis (hemoclips &/or MPEC)	Composite Outcome	Further bleeding Need for post-EGD intervention Complications Transfusions Length of Stay Surgery Mortality Cost Analysis	DEP assisted treatment will improve outcomes of patients with severe NVUGIB because arterial blood flow underneath is obliterated DEP assisted haemostasis will be more cost effective than visually guided treatment	≥ 100 patients/ treatment group	+ Hospitalized patients + Major SRH only + Multicentre RCT + 30 day F/U	+Jensen DM (14) +Jensen DM (15–18) + Barkun A (30) +McCarty TR (31)
2. Haemostatic Powder Spray as initial treatment for severe UGIB. (EV, PUB's, DL's)	EV's/PHTN lesions and Non-Variceal UGI lesions (Ulcers, DL, MWT) Stratify by: a) NV vs. Variceal b) SRH include FI (A & B) FII (A & B)	Comparison of haemostatic powder spray with standard haemostasis for EV's or NVUGI lesions with major stigmata of haemorrhage + oozing Standard treatments: EV's (RBL/Sclero therapy Rx) Ulcers/ Dieulafoy's (Haemoclips or MPEC)	Composite Outcome	Further bleeding Need for post-EGD Rx Blood transfusions Complications TIPS (EV) Surgery (Non-V) Angio (Non V) Mortality Cost Analysis	Haemostatic powder spray will result in high rates of initial haemostasis for active bleeding but patients will have more bleeding, higher rates of intervention, and higher costs than standard haemostasis	Probably large: 1° – ≥ 75 – 100/group 2° – 50- ≥ 75/group	+ Hospitalized patients + Major stigmata only (active bleeding - FIA, visible vessel - FIIA/platelet plug - FIIB, or adherent clot) + Oozing (FIB) + 90 day F/U + Large (100 patients/group) Multicentre + RCT-International	+ DeFrancis (24) + Villanueva (25) + Sung JJY (34) + Lau JYW (35) + Barkun A (30) + McCarty TR (31)
3. Haemostatic powder spray as endoscopic treatment for neoplastic & diffuse mucosal bleeding compared to standard endoscopic haemostasis or medical treatment	Colon or UGI neoplasms or diffuse lesions with active bleeding (focal or diffuse) Stratify by: + Neoplasia UGI Colon + Diffuse Bleeding + Angioma syndromes + Ischemia + PHTN lesions + RBL ulcers + Gastropathy	Comparison of 3 treatment groups: haemospray, standard endoscopic treatment (APC, MPEC, &/or haemoclipping) and medical treatment for control of neoplastic and diffuse lesion GI bleeding	Composite Outcome	Further bleeding Need for post endoscopy intervention Blood transfusions LOS Angiography Surgery Radiation Cost analysis	Haemostatic powder spray and standard endoscopic haemostasis will control active bleeding but not reduce RBC transfusions, further tests, length of stay, proportion of neoplastic patients receiving definite treatments or costs compared to medical treatment alone	≥ 75 patients/ group	+ Inpatients or outpatients + Only active bleeding (FIA or IB) + RCT International study + 90 day F/U	+ Chen Y-I (36) + Chahal D (37) + Barkun A (30) + McCarty TR (31)
4. RBC scanning or Angiography (CT or Standard Angio) vs. Colon Capsule	Severe LGIB – Haematochezia (Not melaena or haematemesis)	Compare sensitivity, specifically, and accuracy of lesion localisation and/or	Sensitivity, specifically, and	+ Time to diagnosis + # Other tests to Dx + LOS +Cost Analysis	Colon capsule will be more accurate and more cost effective than RBC scan and/or	≥ 75–100 patients/ Group	+ Inpatients + Gold standard for final diagnosis is other tests	+ Camus M, (38) + Marya N (39)

Proposed RCT	Lesion Type	Specific Aims	1^0 Outcome	2^0 Outcome	Hypothesis	SS estimate	Comments	Reference
Endoscopy for lesion localization and diagnosis in patients with severe haematochezia		Dx of RBC/Angio vs. Colon Capsule Endoscopy	Accuracy of tests	+Role of telemedicine (Capsule & scan groups)	angiography for lesion localization and/or early diagnosis		(such as urgent colonoscopy, push or deep enteroscopy, histology, &/or surgery) + Multicentre RCT + 30 day F/U	
5. VCE vs. Standard of care (SOC) Endoscopy (EGD and/or push enteroscopy) for ICU patients with severe UGIB	Haematemesis or melaena and suspected UGIB from EV/PHTN or NVUGI lesions	Compare accuracy for lesion localisation/Dx of VCE vs. SOC Endoscopy	Rates of Lesion localisation &/or diagnosis	+ Time to Dx and Rx + Re-admission rates + RBC & other transfusions + # of other interventions for Dx +Complications + LOS + Cost analysis	Time to diagnosis will be faster with VCE and VCE will be more cost effective than SOC endoscopy	≥ 50 patients/ group	+ ICU inpatients + Multicentre RCT + Exclusion - intubated patient not able to swallow capsule + 30 day F/U	+ Marya N (39) + Barkun A (30) + McCarty TR (31)
6. OTSC vs. Haemoclipping for definitive diverticular haemorrhage as primary Rx	Hospitalised patients with definitive diverticular bleeding (SRH on urgent colonoscopy) + stratify by SRH – active bleeding, NBVV, clot, or spot (DEP +)	Compare rebleeding rates of OTSC vs. standard haemoclipping for definitive diverticular bleeding	Composite Outcome	+ Recurrent diverticular haemorrhage + RBC transfusion + Early rebleeding + Re-admission rates for TIC bleeding + Rates of arterial blood flow under SRH detected by DEP + Other interventions + Complications + Angio embolisation + Surgery + Mortality +Cost analysis	OTSC of definitive diverticular bleeding will reduce further bleeding acutely and long term costs will be less compared to through the scope haemoclipping	≥ 75 patients/ treatment	+ Inpatients + Multicenter + Blinded + RCT + International experts on diverticular haemostasis (US, Japan, EU, etc) + ≥ 24 months F/U	+ Jensen DM (20–22, 29) + Kaltenbach (40) + Ishii N (41) + Barkun A (30) + McCarty TR (31)

Legend:

APC = Argon plasma coagulation

Angio = Angiography

DEP = Doppler endoscopic probe

Dx = Diagnosis

EGD = Esophagogastroduodenoscopy

EV = Esophageal varices

FFP = Fresh frozen plasma

F/U = Follow-up (time)

ICU = Intensive care unit

Lesser SRH = Oozing bleeding (FIB) or spot (FIIC) DEP + Major SRH = active pulsatile arterial bleeding, NBVV, or adherent clot.

LGI = Lower gastrointestinal (bleeding)

LOS = Length of (hospital) stay

MPEC = Multipolar electrocoagulation

NVUGIB = Non-variceal upper gastrointestinal bleeding

NBVV = Non-bleeding visible vessel

OTSC = Large over-the-scope clip

PHTN = Portal hypertension (lesion)

PPIU = Post polypectomy induced ulcer (bleeding)

RBC = Red blood cell

RCT = Randomised controlled trial

Rx = Treatment

SOC = Standard of care

SRH = Stigmata of recent haemorrhage

SS = Sample size (estimate)

VCE = Video capsule endoscopy