PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	What counts as Patient-Important Upper Gastrointestinal Bleeding in the ICU?: A Mixed-Methods Study Protocol of Patient and Family Perspectives
AUTHORS	Cook, Deborah; Swinton, Marilyn; Krewulak, Karla; Fiest, Kirsten; Dionne, Joanna; Debigare, Sylvie; Guyatt, Gordon; Taneja, Shipra; Alhazzani, Waleed; Burns, Karen; Marshall, John; Muscedere, John; Gouskos, Audrey; Finfer, Simon; Deane, Adam M; Myburgh, John; Rochwerg, Bram; Ball, Ian; Mele, Tina; Niven, Daniel; English, Shane; Verhovsek, Madeleine; Vanstone, Meredith

VERSION 1 – REVIEW

REVIEWER	Levi, Riccardo Humanitas University, Biomedical Sciences
REVIEW RETURNED	24-Dec-2022

GENERAL COMMENTS	In the protocol entitled “Patient Important Gastrointestinal Bleeding in the ICU:A Mixed-Methods Study of Patient and Family Perspectives”, the Authors provided a protocol to investigate the belief on tests and treatments of UGIB patients and their families. Even though the work could provide important insights for future research studies in UGIB, there are some concerning points that still need to be clarified: 1) Even though the research is mainly qualitative, statistical analysis should be performed to correct for possible underlying bias. Please be more specific in which variables will be tested in the quantitative analyses section and how qualitative analyses will be summed up to be integrated with quantitative ones. 2) Will patients be evenly stratify across each institution?

REVIEWER	Skurzak, Stefano Ospedale San Giovanni Battista, Dipartimento di Anestesia e di Medicina degli Stati Critici
REVIEW RETURNED	01-Feb-2023

GENERAL COMMENTS	The study by Dr. Cook is intended to obtain a novel definition of “patient important gastrointestinal bleeding” through the engagement of ICU patients and relatives. This new definition has several ambitious potential aims: a general purpose definition to be used in future research a definition that could be used as a secondary outcome of the ongoing multicentre study REVISE

	With regard to a “general purpose” definition the study protocol suffers from some apparent limitations: The type of gastrointestinal bleeding may have several different etiologies beyond the so called “stress related bleeding”. Do the authors have considered these non stress-ulcers related bleeding in ICU in their informative materials? For example, is there a chapter dedicated to variceal bleeding in chronic liver disease and their treatments including TIPS (and consequences on the patient long term)? Applying the exclusion criteria adopted in the Previse study in this case is clearly inappropriate. There is no effort in the selection of patients and relatives with a documented history of ICU gastrointestinal bleeding. This limits the possibility to catch relevant aspects of patients perspectives on this topic. This is far more likely with an initial estimation of a sample size of 50 patients. As to the definition useful to “inform” the secondary outcome of the REVISE trial, it is completely unclear to me on how the new definition could be adapted to already recorded data according to specific CRF. How investigators could code the response of patients and relatives in a definition that could be retrospectively applied to the REVISE. The risk of conditioning and biasing an open approach to “what most matters to patients and families” is outstanding in my view. The complex process of transforming qualitative data of patients perspective into definitions or ranking of treatments options should be completely free of previous study influences. In the protocol I can’t find reassurance on this crucial point. A worked-simulated example of how coding has been applied should be provided from pilot experience. In any case the detailed process should be included as supplementary material in order to make the pathway from patients to definition trackable and inspectable (and debatable) at any time (in the final publication of results). The “data saturation” steps should also documented. Data regarding compensation of patients and relatives should be included in the final manuscript. In conclusion This is an interesting and tremendously complicated work. The large academic consortium proposing this study should be commended for this effort. However, the relation with the Revise trial seems more toxic than beneficial in my view. The study protocol should more extensively address this source of bias.

REVIEWER	Marmo, Riccardo Hospital L.Curto, Division of Gastroenterology
REVIEW RETURNED	08-Feb-2023

GENERAL COMMENTS	This is a sequential mixed-methods, qualitative-dominant, multi-center study with an instrument-building aim ;the study is patients, and family oriented, The pilot work began in 2021 and trial completion is anticipated in 2023. The overall objective of this study is to elicit the views of patients

	and families regarding features, tests and treatment for gastrointestinal bleeding that are important to them. Definition : Clinically important gastrointestinal bleeding is defined as overt bleeding in the absence of other causes with one of the following features: 1)spontaneous decrease in systolic (SBP) or diastolic (DBP) blood pressure of >20 mmHg within 24 hours of upper GI bleeding, 2) an orthostatic increase in HR >20 beats/minute and a decrease in SBP of >10 mmHg, 3) initiation of vasopressors or increase in their infusion rate of >20%, 4) a decrease of haemoglobin of >2 g/dl (20 g/l) in 24 hours, or 5) transfusion of >2 units of red blood cells within 24 hours of bleeding. Please clarify by whom and when clinically important gastrointestinal bleeding is defined. In the Participants section I suggest detailing the inclusion and exclusion criteria. Do you exclude patients who developed gastrointestinal bleeding during the ICU stay? Do you exclude patients clinically important gastrointestinal bleeding but not in ICU admitted? Provide information regarding the criteria admission to the ICU, more exactly who was the decision maker and the reason behind his/her choice. Include the time elapsed by ICU admission to the interview Literature suggests that 80% of gastrointestinal bleeding patients are elderly and with comorbidities; 30% are in ASA III or IV condition. Mortality is directly related to the bleeding episode in 20% of cases, while in 80% of cases it is due to the deterioration of comorbidities. Such a difference in the mortality risk (bleeding related and non-bleeding related) could be taken into account. There is a risk that you include patient with clinical important bleeding but needing intensive care by comorbities deterioration In the Orientation and Education Tools section the authors focused on the slide deck containing presentations of upper gastrointestinal bleeding, mainly stomach. This is a subgroup of patients with gastrointestinal bleeding and probably it is related to patients who require less intensive treatment compared to those affected by variceal haemorrhage, small bowel and colon haemorrhage. I believe this study suffers of a selection bias risk which could mislead focus group participants and interviewees.

REVIEWER	Qi, Xingshun General Hospital of Shenyang Military Region
REVIEW RETURNED	10-Feb-2023

GENERAL COMMENTS	1. The authors use the definition of patient important bleeding as a secondary outcome. How to verify its significance and validity in clinical practice? Can it predict the death? 2. “patient important bleeding” or “patient-important bleeding”? 3. In the “Participants” section, the inclusion of participants regardless of the experience of bleeding is not rigorous. In my opinion, eligible participants should be restricted to those with previous bleeding. 4. In the “Quantitative Data Collection” section, the authors said “For this reason, we will not objectively verify whether the patient developed bleeding”. Since the authors could not guarantee the patient’s bleeding experience, the authors should discuss this in the Discussion part. 5. In the sentence “The research question is ‘What are the most concerning tests and treatments to patients and families in the event of an upper gastrointestinal bleed?”, the event of an upper

	gastrointestinal bleed should occur in the setting of ICU. 6. In the sentence "…enrolled in an international RCT of stress ulcer prophylaxis", the full name of RCT should be given. 7. In the sentence "We elicited feedback on the clarity, comprehensiveness and redundancy of the questions…", a comma should be added after the word "comprehensiveness".

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Mr. Riccardo Levi, Humanitas University, IRCCS Humanitas Research Hospital
Comments to the Author:

In the protocol entitled "Patient Important Gastrointestinal Bleeding in the ICU: A Mixed-Methods Study of Patient and Family Perspectives", the Authors provided a protocol to investigate the belief on tests and treatments of UGIB patients and their families. Even though the work could provide important insights for future research studies in UGIB, there are some concerning points that still need to be clarified:

1) Even though the research is mainly qualitative, statistical analysis should be performed to correct for possible underlying bias. Please be more specific in which variables will be tested in the quantitative analyses section and how qualitative analyses will be summed up to be integrated with quantitative ones.

We are pleased to provide more detail and clarify. Descriptive statistical analysis will be performed to describe the sample (e.g. proportion of participants identifying as men, spouses etc.). We will use measures of central tendency and dispersion, as well as proportions. This information is described in lines 376-77, and the data (patient and family member characteristics) is described in lines 329-337. We have added a small revision to make this link clear:

Data describing patient and family member characteristics, as described in the Quantitative Data Collection section, will be analyzed using descriptive statistics, measures of central tendency and dispersion, and proportions.

We have added additional description of how the qualitative data from this study is translated into an instrument for use in the REVISE RCT in lines 379-388:

Data Integration
The current study is designed with an instrument-building aim. Qualitative data will be translated into a measure for use as a secondary outcome of the ongoing REVISE trial. The planned translation of qualitative data into a secondary trial outcome will involve the creation of a binary variable for "patient-important bleeding". The qualitative data analysis will inform a list of tests, treatments, or clinical outcomes which if experienced, constitute patient-important bleeding. If REVISE trial participants have had bleeding which led to the use of one of those tests or treatments, they will be deemed to have experienced patient-important gastrointstinal bleeding. In the absence of bleeding or absence of bleeding leading to test or treatment of concern to patients or family members, REVISE trial participants will be classified as not to have experienced patient-important gastrointestinal bleeding. If REVISE trial participants have had bleeding which directly resulted in death, and participants state that death this is deemed to be a patient-important outcome, they will be deemed to have experienced patient-important gastrointestinal bleeding.

The current protocol does not describe any quantitative data beyond participant demographics, so there are no quantitative variables to describe or analyze in the current study. When the data from this

study are integrated in the REVISE trial as a secondary outcome, additional statistical analysis (e.g., adjustment for stratification variables as specified a priori) will certainly be performed.

2) Will patients be evenly stratify across each institution?

In this qualitative study, patients are not recruited solely from institutions, but also from patient and family organizations that are extra-institutional (described lines 213-231 in the original text). Accordingly, institutional stratification does not align with this study design or participant sampling methodology.

Reviewer: 2
Dr. Stefano Skurzak, Ospedale San Giovanni Battista
Comments to the Author:
Dear Editor and authors

The study by Dr. Cook is intended to obtain a novel definition of "patient important gastrointestinal bleeding" through the engagement of ICU patients and relatives.

This new definition has several ambitious potential aims: 1) a general purpose definition to be used in future research; 2) a definition that could be used as a secondary outcome of the ongoing multicentre study REVISE

With regard to a "general purpose" definition the study protocol suffers from some apparent limitations:

The type of gastrointestinal bleeding may have several different etiologies beyond the so called "stress related bleeding". Do the authors have considered these non stress-ulcers related bleeding in ICU in their informative materials? For example, is there a chapter dedicated to variceal bleeding in chronic liver disease and their treatments including TIPS (and consequences on the patient long term)? Applying the exclusion criteria adopted in the Previse study in this case is clearly inappropriate.

Thank you for this question. Of course we acknowledge the many different etiologies of upper gastrointestinal bleeding, which are important in practice, but peripheral to this study. This study is designed to inform practice and research related to upper gastrointestinal bleeding relevant to stress ulceration. Our study's educational materials need to focus on the topic aligned with the objective of our study.

There is no effort in the selection of patients and relatives with a documented history of ICU gastrointestinal bleeding. This limits the possibility to catch relevant aspects of patients perspectives on this topic. This is far more likely with an initial estimation of a sample size of 50 patients.

The research question for this study is best answered by a mix of both types of participants who are considering bleeding for the first time (ICU survivors and families of ICU patients), and those who have experienced (patients) or witnessed (families) such bleeding – all of whom have familiarity with the context of critical illness. We are explicitly avoiding a sampling strategy to include <u>only</u> those who are familiar with gastrointestinal bleeding in the ICU, as this represents the minority of admitted ICU patients. Therefore, we are intentional in our decision not to recruit only patients and relatives with a documented history of ICU-acquired gastrointestinal bleeding, in order to elicit a range of rich perspectives that offers verisimilitude (Patton, 2014) to the experiences of patients and family members first encountering gastrointestinal bleeding in the ICU. As the reviewer astutely points out, we are likely to recruit some people with a personal history of gastrointestinal bleeding with our sample size of 50. We are also likely to recruit many people without this experience, reflecting the generally low incidence of upper gastrointestinal bleeding during critical illness. Respectfully, this latter group of participants is more representative of the population of interest: ICU patients and family members experiencing bleeding for the first time in the ICU, and those who are likely to receive prophylactic acid suppression. If we recruited only participants who had personally experienced gastrointestinal bleeding while in the ICU, their views would be informed by that specific experience and t*heir data may be biased by the specific outcome of their bleeding event. This would be appropriate if our research question concerned actual <u>experiences</u> of*

upper gastrointestinal bleeding, but is not appropriate to ascertain which types of upper GI bleeding are concerning to critically patients and families of critically ill patients more generally. We have also added some relevant methodological references to our revised manuscript.

We are purposeful in our decision not to make personal experience with upper gastrointestinal bleeding an inclusion criterion; most patients and families who encounter this type of bleeding do so for the first time and will make judgments about the importance of that outcome from that perspective. By recruiting participants who have not experienced or witnessed bleeding, but who imagine themselves in this situation, we will identify a participant population most similar to patients and families who will encounter this clinical scenario. However, personal experience with gastrointestinal bleeding from a patient's perspective, ad bearing witness to gastrointestinal bleeding from a family perspective is not an exclusion criterion, to reflect a range of perspectives for this study.

As to the definition useful to "inform" the secondary outcome of the REVISE trial, it is completely unclear to me on how the new definition could be adapted to already recorded data according to specific CRF. How investigators could code the response of patients and relatives in a definition that could be retrospectively applied to the REVISE. The risk of conditioning and biasing an open approach to "what most matters to patients and families" is outstanding in my view.

To avoid conditioning, participating in this qualitative study is not conditional on enrolment in a trial and we thus we agree, and we have, an open stance. Just to underscore, this study design does <u>not</u> involve identifying each patient in the REVISE trial who bleeds, then interviewing them real time or shortly thereafter, to elicit their specific views (or views of their family members). This is stated in the manuscript at lines 200-201, where we describe that patients enrolled in REVISE are excluded from the current study. Our investigative group considered it important to exclude REVISE participants in order to avoid methodologic concerns and logistic barriers.

Thank you for the chance to clarify our approach to use results of this study in the REVISE trial. For every patient in the REVISE trial who has any gastrointestinal bleeding, we are capturing which tests and treatments they receive. Our qualitative data will help delineate the perceptions of these tests and treatments, each of which will be classified as indicative of patient-important bleeding or not. When the trial is over, this information will be applied to each bleeding event in the REVISE trial. Each patient will be categorized as having, or not having, patient-important bleeding. We have added a section describing how this qualitative data will inform the development of a binary outcome of patient-important bleeding based on which tests and treatments were administered to treat GI bleeding in critically ill patients. Our approach, which we hope is more clear, has been added at lines 379-388 and has been excerpted above in response to Reviewer 1.

The complex process of transforming qualitative data of patients perspective into definitions or ranking of treatments options should be completely free of previous study influences. In the protocol I can't find reassurance on this crucial point.

We agree on the need to incorporate patient and family input into randomized trials. We developed this study in the absence of pre-existing studies on this topic of patient and family-informed outcome definitions on bleeding. To our knowledge, this is the first study of what matters to critically ill patients and family members about upper gastrointestinal bleeding.
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To study a phenomenon or topic, a research team needs to have familiarity with other studies on the topic, and understand where the gaps are in the literature are. This helps to design and implement the protocol, and interpret results in lightf existing studies on this topic. Here are the methods used to maximize the separation of this study from previous study influences, with a note about where they appear in the manuscript, when relevant:

- *An ICU survivor and family member of a critically ill patient who have not experienced or witnessed bleeding are co-investigators on this study to help ensure that their constituent views are the focus of this study.*

- *Our research team is composed of a variety of scholars, clinicians, and patients who are not affiliated with any bleeding studies.*
- *Our research team is also comprised of intensivists, some of whom have additional training in surgery, trauma, or gastroentology, a hematologist, and some other researchers familiar with bleeding studies in various settings, to help understand how this study fits with, and extends, existing literature within and outside the ICU.*
- *Pilot work involved extensive input from patients and family members with lived experience in the ICU, unrelated to any other studies on gastrointestinal bleeding (line 273-280).*
- *Participants in this study will include patients and family members regardless of whether or not they had bleeding; however, enrolment in REVISE is an exclusion criterion (line 181-182).*
- *The physician presenter who will communicate the explanation of tests and treatments is the PI of the REVISE trial and will leave the data collection session after this information is presented, before the focus group or interview begins. (line 283).*
- *The interviewers and fieldnote taker are not involved in the REVISE study. (line 269).*
- *Of the 5 lead data analysts, 4 are not involved in the REVISE trial.*

Our findings will be shared with a sample of participants in a member-checking exercise to ensure that the results resonate and reflect the views of patients and family members (line 353).

A worked-simulated example of how coding has been applied should be provided from pilot experience. In any case the detailed process should be included as supplementary material in order to make the pathway from patients to definition trackable and inspectable (and debatable) at any time (in the final publication of results). The “data saturation” steps should also documented.

As described in the protocol manuscript, the pilot work was completed to create the education materials, and create and refine the focus group guide. The conversations in this pilot work were focused on instrument and tool development and refinement. These conversations as part of the pilot work were not analyzed per se. The description of qualitative analyses (e.g. potential patient-important considerations) are exemplars, only. They do not represent the creation of an analytic framework, as this study will use an inductive analytic approach, where analysis is derived from the data and will necessarily evolve as more data is collected. Accordingly, it is methodologically infeasible to provide details about the coding framework at this protocol stage, but it will be described as refined in the final manuscript.

The determination of data saturation will also be documented, as described at line 245-247.

Data saturation will be assessed periodically by 5 investigators through a review of transcripts and coding reports, and audit trail examination; a description of this process will be included in the final manuscript. (line 217-219)

Data regarding compensation of patients and relatives should be included in the final manuscript.

Thank you. We have added this information at line 311 in this protocol paper, and will also include it in the final manuscript:

All participants will receive a $25 gift card to thank them for their time.

In conclusion

This is an interesting and tremendously complicated work. The large academic consortium proposing this study should be commended for this effort. However, the relation with the Revise trial seems more toxic than beneficial in my view. The study protocol should more extensively address this source of bias.

We appreciate the time taken to offer these comments and the acknowledgement of the complexity of this work. If other investigators had studied this issue and obtained patient and family input to create a

*useful definition, we would have been pleased to consider adopting that definition. As such, we were surprised to read the word 'toxic' regarding our study designed to inform the REVISE trial. We hope that our approach as described above is more explanatory.*span style="font-family:'Times New Roman'; font-style:italic"> We *have added some useful clarifying material in response to these suggestions, thank you. We also would like to cite this thoughtful peer-reviewer in the acknowledgements section of our paper if agreeable, and if the journal allows, and do so for all peer-reviewers.*

Reviewer: 3

Dr. Riccardo Marmo, Hospital L.Curto
Comments to the Author:
This is a sequential mixed-methods, qualitative-dominant, multi-center study with an instrument-building aim; the study is patients, and family oriented, The pilot work began in 2021 and trial completion is anticipated in 2023.

The overall objective of this study is to elicit the views of patients and families regarding features, tests and treatment for gastrointestinal bleeding that are important to them.
Definition: Clinically important gastrointestinal bleeding is defined as overt bleeding in the absence of other causes with one of the following features: 1)spontaneous decrease in systolic (SBP) or diastolic (DBP) blood pressure of >20 mmHg within 24 hours of upper GI bleeding, 2) an orthostatic increase in HR >20 beats/minute and a decrease in SBP of >10 mmHg, 3) initiation of vasopressors or increase in their infusion rate of >20%, 4) a decrease of haemoglobin of >2 g/dl (20 g/l) in 24 hours, or 5) transfusion of >2 units of red blood cells within 24 hours of bleeding. Please clarify by whom and when clinically important gastrointestinal bleeding is defined.

In the Participants section I suggest detailing the inclusion and exclusion criteria. Do you exclude patients who developed gastrointestinal bleeding during the ICU stay? Do you exclude patients clinically important gastrointestinal bleeding but not in ICU admitted? Provide information regarding the criteria admission to the ICU, more exactly who was the decision maker and the reason behind his/her choice. Include the time elapsed by ICU admission to the interview. Literature suggests that 80% of gastrointestinal bleeding patients are elderly and with comorbidities; 30% are in ASA III or IV condition. Mortality is directly related to the bleeding episode in 20% of cases, while in 80% of cases it is due to the deterioration of comorbidities. Such a difference in the mortality risk (bleeding related and non-bleeding related) could be taken into account. There is a risk that you include patient with clinical important bleeding but needing intensive care by comorbities deterioration

Assuming that participants in this study indicate that dying from bleeding is patient-important, we will definitely incorporate this into the definition. We did not indicate this plan specifically, but now have done so, if this is a finding during interviews and focus groups. This revision is visible at lines 284-289 excerpted below:

While the guide focuses on asking questions about how participants evaluate particular tests and treatments, it also includes many open-ended questions about what aspects or consequences of upper gastrointestinal bleeding matter most to participants. We anticipate that participants may raise concerns about bleeding-associated morbidity and mortality here (e.g., death is likely to be identified as a patient-important outcome if it occurred due to bleeding).
We outline the inclusion criteria for participant characteristics on lines 174-182. We will not involve persons with gastrointestinal bleeding who are not admitted to the ICU. Our focus is on patients who were admitting to the ICU, and family members of patients who were admitted to the ICU. We will not retrospectively ask who the decision-maker was endorsing the *ICU admission and the reason(s) for that admission. Please see the response to Reviewer 1 regarding why we are not purposefully recruiting only participants who have personal experience with gastrointestinal bleeding, copied below:*

We are explicitly avoiding a sampling strategy to include only those who are familiar with gastrointestinal bleeding in the ICU. This is the minority of admitting ICU patients, reflecting the event rate of 2-6% of patients. The research question for this study is best answered by a mix of both types of participants who are considering bleeding for the first time (ICU survivors and families of ICU patients), and those who have experienced (patients) or witnessed (families) such bleeding – all of whom have familiarity with the context of critical illness. We are explicitly avoiding a sampling strategy

to include only those who are familiar with gastrointestinal bleeding in the ICU, as this represents the minority of admitted ICU patients. Therefore, we are intentional iour decision not to recruit only patients and relatives with a documented history of ICU-acquired gastrointestinal bleeding, in order to elicit a range of rich perspectives that offers verisimilitude (Patton, 2014) to the experiences of patients and family members first encountering gastrointestinal bleeding in the ICU. As the reviewer astutely points out, we are likely to recruit some people with a personal history of gastrointestinal bleeding with our sample size of 50. We are also likely to recruit many people without this experience, reflecting the generally low incidence of upper gastrointestinal bleeding during critical illness. Respectfully, this latter group of participants is more representative of the population of interest: ICU patients and family members experiencing bleeding for the first time in the ICU, and those who are likely to receive prophylactic acid suppression. If we recruited only participants who had personally experienced gastrointestinal bleeding while in the ICU, their views would be informed by that specific experience and their data may be biased by the specific outcome of their bleeding event. This would be appropriate if our research question concerned actual experiences of upper gastrointestinal bleeding, but is not appropriateo ascertain which types of upper gastrointestinal bleeding are concerning to critically patients and families of critically ill patients more generally.

In the Orientation and Education Tools section the authors focused on the slide deck containing presentations of upper gastrointestinal bleeding, mainly stomach. This is a subgroup of patients with gastrointestinal bleeding and probably it is related to patients who require less intensive treatment compared to those affected by variceal haemorrhage, small bowel and colon haemorrhage.

We have revised the title, abstract, and main text to make clear that this study focuses on upper gastrointestinal bleeding. We have limited this study to focus on upper gastrointestinal bleeding purposefully due to our objective of designing an instrument to label upper gastrointestinal patient-important bleeding in the REVISE trial, and for possible use in practice and other research on this topic.

I believe this study suffers of a selection bias risk which could mislead focus group participants and interviewees.

Qualitative research participants are recruited and sampled on the basis of their ability to provide rich and relevant data to answer the research question (Patton, 2014). Qualitative research does not use probabilistic sampling nor does it strive for representative samples (Maxwell & Chmiel, 2014). Sampling prioritizes participants who have the most relevant data to contribute, making no claim that their perspectives are representative of the entire population's experience. While an explanation of the epistemological foundations of qualitative research is beyond the scope of this response letter, the reviewer may be interested in the following resource, which we have added to the references of this protocol:

Maxwell JA, Chmiel M. Generalization in and from qualitative analysis. The SAGE handbook of qualitative data analysis. 2014;7(37):540-53.

Reviewer: 4
Dr. Xingshun Qi, General Hospital of Shenyang Military Region
Comments to the Author:

1) The authors use the definition of patient important bleeding as a secondary outcome. How to verify its significance and validity in clinical practice? Can it predict the death?

The current protocol is not designed to elicit data that contributes to clinical predictions of morbidity or mortality. Instead, we strive to design a secondary outcome which supplements the main REVISE trial efficacy outcome (clinically important upper gastrointestinal bleeding) to offer information about whether and how upper gastrointestinal bleeding matters to patients, outside of its relation to morbidity and mortality. Of course, if morbidity or mortality is mentioned as a patient-important consequence of bleeding (which is anticipated), that will be incorporated into the measure (lines 287). Rigorous qualitative research is marked by originality, usefulness, credibility, trustworthiness *(Cope, 2014). The concept of verification is not used as proposed by the*

researcher in qualitative research which operates in a constructivist or interpretivist paradigm (Crotty, 1998).

2) "patient important bleeding" or "patient-important bleeding"?

Thank you. This has been standardized and we added a hyphen throughout.

3) In the "Participants" section, the inclusion of participants regardless of the experience of bleeding is not rigorous. In my opinion, eligible participants should be restricted to those with previous bleeding.

We are methodologically concerned about restricting participants to those who have experienced or witnessed bleeding. Please see our response to Reviewer 1 on this matter:

We are explicitly avoiding a sampling strategy to include only those who are familiar with gastrointestinal bleeding in the ICU. This is the minority of admitting ICU patients, reflecting the event rate of 2-6% of patients. Therefore, we are intentional in our decision not to recruit patients and relatves with a documented history of ICU gastrointestinal bleeding, in order to elicit a range of rich perspectives that offers verisimilitude (Patton, 2014) to the experiences of patients and family members first encountering gastrointestinal bleeding in the ICU. As the reviewer astutely points out, we are likely to recruit some people with a personal history of gastrointestinal bleeding with our sample size of 50. We are also likely to recruit many people without this experience, reflecting the generally low incidence of upper gastrointestinal bleeding during critical illness. Respectfully, this latter group of participants is more representative of the population of interest: ICU patients and family members experiencing bleeding for the first time in the ICU. If we recruited only participants who had personally experienced gastrointestinal bleeding while in the ICU, their views would be informed by that specific experience and their data may be biased by the specific outcome of that bleeding. This would be appropriate if our research question concerned <u>experiences</u> of upper gastrointestinal bleeding, but is not appropriate to ascertain which types of upper gastrointestinal bleeding are concerning to patients and families. This current research question is best answered by a mix of both types of participants who are considering bleedng for the first time, and those who have experienced such bleeding – all of whom have familiarity with the context of critical illness.

We are purposeful in our decision not to make personal experience with upper gastrointestinal bleeding an inclusion criterion; most patients and families who encounter this type of bleeding do so for the first time, and will make judgments about the importance of that outcome from that perspective. By recruiting participants who have not experienced or witnessed bleeding, but who imagine themselves in this situation, we will identify a participant population most similar to patients and families who will encounter this clinical scenario. However, personal experience with gastrointestinal bleeding from a patient's perspective, and bearing witness to gastrointestinal bleeding from a family perspective is not an exclusion criterion, to reflect a range of perspectives for this study. (line 203-210)

4) In the "Quantitative Data Collection" section, the authors said "For this reason, we will not objectively verify whether the patient developed bleeding". Since the authors could not guarantee the patient's bleeding experience, the authors should discuss this in the Discussion part.

We have both a topic-related and methodological reason for making this research decision. As described at line 333,

Given that experiencing or witnessing a bleed may inform participant perspectives on bleeding, documenting a bleeding event is only relevant *if the participant was aware of the bleeding*.

Therefore, verifying whether or not patients experienced a bleed in the ICU would not yield useful information - if the research participant was not aware that they (or their family member) experienced a bleed they will not be able to represent that experience in the perspectives and opinions they will share in this study.

Second, in designing this study we would not mandate that participants 'prove' their bleeding status on ethical or logistic grounds. Such methodology could be viewed as insensitive and inappropriate, potentially causing emotional suffering without provisions in place to help interpret any questions that might arise when participants read their records or those of their critically ill loved one. This possible consequence would be especially concerning for those asked to obtain the medical records of a deceased loved one. Further, if pursued, requesting this type of clinical documentation weeks, months or years since a bleed would require nagivating institutional regulations across a variety of institutions, which would be unsuitably burdensome to research participants in this context. Further, such detailed information about bleeding severity is inconsistently part of retrievable excerpts of medical records. In summary, requiring proof of bleeding status would not be supported in ethics review in this jurisdiction.

We have no reason to believe that participants would deliberately mislead a research team about having had (for patients) or witnessed (for families) bleeding. However, we acknowledge that some misinterpretation may affect the classification of our participants, however. We have added this point briefly at line 198 (excerpted below) and in lines 333 (excerpted immediately above).

> All experiential data will be self-reported, consistent with best practices in qualitative research.

5) In the sentence "The research question is 'What are the most concerning tests and treatments to patients and families in the event of an upper gastrointestinal bleed?", the event of an upper gastrointestinal bleed should occur in the setting of ICU.

We have made this revision. Thank you for suggesting the specificity which was implied.

6) In the sentence "…enrolled in an international RCT of stress ulcer prophylaxis", the full name of RCT should be given.

We appreciate this suggestion and have made this revision.

7) In the sentence "We elicited feedback on the clarity, comprehensiveness and redundancy of the questions…", a comma should be added after the word "comprehensiveness".

Thank you. We have made this revision.

We are grateful for these reviews and appreciate the chance to improve this manuscript.

The literature on patient and family-informed research design in critical care is modest but growing. We are glad that our study will add to this focus. We have added 4 citations to our revised manuscript, to alert readers to current literature on this topic, pertaining to issues of the importance of, and strategies for operationalizing meaningful engagement with patients in research.

> Sacristán JA, Aguarón A, Avendaño-Solá C, Garrido P, Carrión J, Gutiérrez A, et al. Patient involvement in clinical research: why, when, and how. Patient preference and adherence. 2016:631-40.
>
> Domecq JP, Prutsky G, Elraiyah T, Wang Z, Nabhan M, Shippee N, et al. Patient engagement in research: a systematic review. BMC health services research. 2014;14(1):1-9.
>
> Burns KE, McDonald E, Debigaré S, Zamir N, Vasquez M, Piche-Ayotte M, et al. Patient and family engagement in patient care and research in Canadian intensive care units: a national survey.
> Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2022:1-10
> IAP2 Spectrum of Public Participation. International Association for Public Participation. Louisville, CO: International Association for Public Participation; 2018.

Also, to familiarize readers with qualitative research methods as relevant to this protocol, we have added 4 additional methodologic citations which we hope are useful.

Cope DG. Methods and meanings: credibility and trustworthiness of qualitative research. In Oncology nursing forum 2014 Jan 1 (Vol. 41, No. 1).

Crotty MJ. The foundations of social research: Meaning and perspective in the research process. The foundations of social research. 1998:1-256.

Patton MQ. Qualitative research & evaluation methods: Integrating theory and practice. Sage publications; 2014 Oct 29.

Maxwell JA, Chmiel M. Generalization in and from qualitative analysis. The SAGE handbook of qualitative data analysis. 2014;7(37):540-53.

Thank you for the chance to sharpen this protocol report.

VERSION 2 – REVIEW

REVIEWER	Levi, Riccardo Humanitas University, Biomedical Sciences
REVIEW RETURNED	14-Apr-2023

GENERAL COMMENTS	I have received the revised manuscript of the protocol entitled "What counts as Patient-Important Upper Gastrointestinal Bleeding in the ICU?: A Mixed-Methods Study Study Protocol of Patient and Family Perspectives". The Authors addressed my concerning points, which increased the clarity of the protocol.

REVIEWER	Skurzak, Stefano Ospedale San Giovanni Battista, Dipartimento di Anestesia e di Medicina degli Stati Critici
REVIEW RETURNED	21-Apr-2023

GENERAL COMMENTS	first of all, let me apologize for the unfortunate and not appropriate use of the word “toxic” in my first review of your manuscript. I am grateful for your extensive and detailed replies. I, here, summarise what I consider open issues of your proposal: 1 If the focus of the study is stress ulceration related upper gastrointestinal bleeding (GI) and no other types of GI bleeding this should be clearly stated all across the manuscript (eg. Stress related upper GI vs upper gastrointestinal bleeding) “This study is designed to inform practice and research related to upper gastrointestinal bleeding relevant to stress ulceration.” 2 Patient and family members selection Ok clarified 3 Influences of REVISE study on the present study. Patients and relatives without any specific knowledge or previous experience of GI bleeding will be largely influenced by the initial presentation which will be held by a physician involved in the Revise study. “The physician presenter who will communicate the explanation of tests and treatments is the PI of the REVISE trial…”

	In the PIB two pages summary (In the table in page 2 of the summary) Diagnostic endoscopy is associated with a common adverse effect “drowsiness related to sedation” which is clearly inadequate to describe the complex scenario of urgent endoscopy in the ICU (need to intubate a frail critically ill patient, need to prolong intubation vs no discomfort in a patient already sedated for other reasons). I acknowledged that these aspects will be filtered by patients/relatives memories of ICU stay but I think that the initial presentation together with session interaction with the interviewers have a major role in the responses obtained. In conclusion the authors clarified many of the points raised in the first round of review. I still have the sensation that the profound interaction with the REVISE trial is a source of inevitable bias while looking for a new definition of “patient important bleeding”. The efforts of the authors to keep this bias as low as possible have been thoroughly described in the reply and in the protocol manuscript and I will be interested in reading the results of the study itself. I think that a full access to the patients/family members interviews should be available with the final paper through a specific link as a base for future discussion on this complex argument.

REVIEWER	Marmo, Riccardo Hospital L.Curto, Division of Gastroenterology
REVIEW RETURNED	24-Apr-2023

GENERAL COMMENTS	The authors improved the text as suggested, however some concerns still remain. The authors investigated the experience of family members and patients who developed upper gastrointestinal bleeding while being admitted to ICU. Patients who survive intensive care and digestive bleeding represent a particular sample for having passed a relevant experience but with a doubly positive outcome; positive for having overcome the criticality of intensive care and the additional criticality of digestive bleeding. To assess the impact of the lived experience related to digestive bleeding it may be helpful to consider also patients in ICU admitted without AUGIB (Acute upper Gastrointestinal Bleeding). It is possible that the sample used represents the group of patients who had the best experience. The authors state that "The overall objective of this study is to elicit the views of patients and families regarding features, tests and treatment for upper gastrointestinal bleeding that are important to them." The study design should collect information about the diagnostic and therapeutic process. The authors use an (unvalidated) tool to define the severity of digestive bleeding; it is possible that within this definition there are patients who have more elements of severity or on the contrary no element at all. How do they intend to stratify this covariate? The stated goal of the study is to evaluate the experience of family members, probably the most frustrating experience for family members is to have lost a beloved one, this experience could be considered. The estimated sample size may not detect patients who have needed more invasive treatment such as repeating a second endoscopy, needing radiological or surgical treatment; These events affect approximately 3-5% of patients with upper gastro intestinal bleeding. The authors must describe the process followed to enroll the

	patients and include those with upper gastrointestinal bleeding.