

Bleeding during critical illness: A prospective cohort study using a new measurement tool

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Abstract

Purpose: To estimate the incidence, severity, duration and consequences of bleeding during critical illness, and to test the performance characteristics of a new bleeding assessment tool.

Methods: Clinical bleeding assessments were performed prospectively on 100 consecutive patients admitted to a medical-surgical intensive care unit (ICU) using a novel bleeding measurement tool called *HE*morrhage *ME*asurement (*HEME*). Bleeding assessments were done daily in duplicate and independently by blinded, trained assessors. Inter-rater agreement and construct validity of the *HEME* tool were calculated using ϕ . Risk factors for major bleeding were identified using a multivariable Cox proportional hazards model.

Results: Overall, 90% of patients experienced a total of 480 bleeds of which 94.8% were minor and 5.2% were major. Inter-rater reliability of the *HEME* tool was excellent ($\phi = 0.98$, 95% CI: 0.96 to 0.99). A decrease in platelet count and a prolongation of partial thromboplastin time were independent risk factors for major bleeding but neither were renal failure nor prophylactic anticoagulation. Patients with major bleeding received more blood transfu-

sions and had longer ICU stays compared to patients with minor or no bleeding.

Conclusions: Bleeding, although primarily minor, occurred in the majority of ICU patients. One of five patients experienced a major bleed which was associated with abnormal coagulation tests but not with prophylactic anticoagulants. These baseline bleeding rates can inform the design of future clinical trials in critical care that use bleeding as an outcome and *HEME* is a useful tool to measure bleeding in critically ill patients.

Keywords: Hemorrhage, critical care, intensive care, measurement tool, reliability testing

Bleeding is a feared complication of critical illness. A true or perceived increase in the risk of bleeding can lead to diagnostic or therapeutic interventions such as endoscopies and blood transfusions, and to the omission of effective preventative therapy such as anticoagulant thromboprophylaxis or cardioprotection with anti-platelet agents. Although bleeding itself is considered an adverse outcome, the clinical importance and functional consequences of bleeding among criti-

cally ill patients have not been well described. In patients with acute coronary syndrome¹ and in patients undergoing bone marrow transplantation², bleeding has been shown to adversely affect prognosis.

Bleeding is an important outcome measure of efficacy and/or safety in many randomized trials in critically ill patients including stress ulcer prophylaxis trials³ and thromboprophylaxis trials⁴. However, the interpretation of these data is often difficult because of the lack of a reference or 'control' rate of bleeding across all anatomical sites in a heterogeneous ICU population. Furthermore, many such trials exclude patients who are bleeding or at high risk of bleeding, generating lower bleeding rates than would be expected in observational studies. To evaluate rigorously the efficacy of interventions designed to prevent bleeding, or the safety of interventions that may predispose to bleeding, a baseline reference is needed for comparison.

Not only are accurate estimates of the frequency and severity of bleeding in critically ill patients lacking, there is also no validated method of measuring bleeding in this population.⁵ Several bleeding measurement tools have been designed to capture treatment-related bleeding complications in stable cancer patients including the National Cancer Institute Common Toxicity Criteria⁶, the Eastern Cooperative Oncology Group Common Toxicity Criteria⁷, and, probably the most widely used among cancer patients⁸, the World Health organization (WHO) bleeding scale.⁹ Other tools have been designed for use in patients on anticoagulant therapies.^{10,11} None of these tools were designed for complex critically ill patients.

The objective of this study was to estimate the prevalence and incidence of bleeding from all anatomical sites, and to describe the severity, duration and consequences of bleeding in a prospective observational study of critically ill medical-surgical patients. The secondary objective was to test the performance characteristics and construct validity of a new bleeding assessment tool we developed called *HEME* (*HE*morhage *ME*asurement).

Materials and Methods

Patients

This study was approved by, and carried out according to the instructions of the institutional Research Ethics Board (REB). Other than daily bleeding assessments, there was no intervention performed, and therefore the REB waived the need for informed consent for this prospective audit which had no influence on patient care. One hundred consecutive patients admitted to a 15 bed medical-surgical university-affiliated ICU with a projected length of stay of 24 hr or more were enrolled between July 2005 and October 2005. Every day, patients were prospectively assessed for bleeding for the duration of their ICU admission until discharge, death or the end of 90 days, whichever came first. Weekend assessments were done retrospectively on Mondays. Bleeding assessments were performed in duplicate and independently by two of four trained research coordinators blinded to each other's ratings using the HEME tool and the WHO scale. Assessors were trained on the use of both tools which were piloted prior to starting the study. After canvassing bedside nurses each morning for new or ongoing bleeding events, additional data were obtained from each patient's medical chart and physiological and laboratory data were obtained from a computerized clinical information system (Carevue, Phillips, Andover, Minn).

HEME bleeding measurement tool

HEME was designed to describe the site, severity, duration and clinical consequences of discrete bleeding events (Figure 1). Given the lack of an existing relevant tool to measure bleeding in patients with critical illness, items for the HEME tool were collected from instruments used in prior critical care studies.^{4,12,13} Item generation and item reduction were not performed analytically; instead, items were finalized from the candidate items by consensus among our critical care (DC) and hematology (DA and KW) group members with clinical and research experience. Bleeding severity was graded as fatal, major or minor based on the degree of physiological impairment and

Instructions for assessors: Complete this form daily. Use a separate form for each bleeding site.

BLEEDING SITE

- ☐ 1. **Vascular catheter or insertion site**, Specify side: ☐ Right ☐ Left
- Specify site: ☐ a. peripheral vein-arm ☐ d. PICC line ☐ f. jugular
☐ b. peripheral vein-leg ☐ e. femoral ☐ g. subclavian
☐ c. other: _____
- ☐ 2. **Other skin bleeding** (not CVC-related): ☐ a. bruising ☐ b. petechiae ☐ c. non-surgical wound
- ☐ 3. **Gastrointestinal**: ☐ a. NG blood ☐ b. Hematemesis ☐ c. melena ☐ d. hematochezia
- ☐ 4. **Respiratory**: ☐ a. tracheostomy ☐ b. ETT aspirate ☐ c. hemoptysis ☐ d. chest tube
- ☐ 5. **Surgical Site**: ☐ a. incision ☐ b. drain
- ☐ 6. **Genitourinary**: ☐ a. gross hematuria ☐ b. vaginal ☐ c. bleeding around a urinary catheter
- ☐ 7. **Retroperitoneal** ☐ 11. **Pericardial**
- ☐ 8. **Intracranial** ☐ 12. **Intraarticular (non-traumatic)**
- ☐ 9. **Intraspinal or epidural** ☐ 13. **Other (describe)**
- ☐ 10. **Intraocular (not subconjunctival)**

BLEEDING SEVERITY

☐ **Fatal Bleeding** description: _____

☐ Major Bleeding

1. Overt bleeding with ANY ONE of the following in the absence of other causes:

- ☐ Decrease in hemoglobin of 20g/L or more
☐ Transfusion of 2 or more units of RBCs with no increase in Hg
☐ Decrease in systolic BP by 10mmHg or more while patient sitting up
☐ Spontaneous decrease in systolic BP of 20mmHg or more
☐ Increase in heart rate by 20 bpm or more

2. Bleeding at ANY ONE of the following critical sites:

- ☐ Intracranial ☐ Intraspinal
☐ Intraocular (not subconjunctival) ☐ Pericardial
☐ Retroperitoneal ☐ Intraarticular (non-traumatic)

3. Wound related bleeding requiring an intervention:

☐ Specify intervention: _____

☐ **Minor Bleeding** ☐ Bleeding that did not meet criteria for major or fatal bleeding

TIMING

☐ New ☐ Ongoing ☐ Recurrent bleed at same site

Start date: _____ Stop date: _____
 Start time: _____ Stop time: _____

Started prior to study day? ☐ Yes ☐ No

FIGURE 1. HEME bleeding assessment tool. A separate form was completed in duplicate daily for all patients (n=100).

the anatomical site of the bleed. A bleed was considered *fatal* if the patient died while bleeding and only if the bleed was believed to be the cause of death; *major*, if it resulted in severe physiologic derangements, occurred at a critical site (e.g., intracranial, retroperitoneal, pericardial) or resulted in the need for major therapeutic interventions; and *minor*, if bleeding did not meet criteria for major bleeding (e.g., epistaxis, wound-related bleeding, subconjunctival bleeding, ecchymoses, etc). HEME relied on physiological indicators of hemodynamic instability to identify major bleeding (including a decrease in blood pressure or and increase in heart rate). Recognizing that in complex ICU patients, such derangements are common and not necessarily attributable to bleeding, assessors were asked to consider such physiologic changes only if they occurred in the absence of other causes. Start and end times of each bleeding event were recorded. Discrete bleeds were those that occurred at distinct anatomical sites (even if they occurred simultaneously) or recurrent bleeds at the same sites. Finally, if a major bleed was identified, the attending intensive care unit physician was asked to describe any clinical consequences that were considered attributable to the major bleeding event such as myocardial, neurological, renal, hepatic or soft tissue ischemia.

The WHO bleeding scale

Bleeding assessments were also performed by each assessor using the WHO bleeding assessment scale.⁹ By this ordinal scale, bleeds are graded from 0 to 4, where grade 0 is no bleeding; grade 1 is petechiae; grade 2 is mild blood loss; grade 3 is gross blood loss; and grade 4 is debilitating blood loss. By convention in most cancer trials, bleeding that is WHO grade 2 or higher is considered clinically important; however, to adapt the criteria so they are relevant to critically ill patients, we classified major bleeding as WHO grade 3 or higher.

Analysis

We summarized continuous data using means and standard deviation (SD) or medians and interquartile ranges (IQR) when data were skewed. We used t tests

to compare continuous data and Chi-square tests to compare proportions. The phi (ϕ) statistic provided a chance-independent measure of inter-rater agreement for both the HEME tool and of the WHO scale assuming non-independence of observations.¹⁴ Agreement of the HEME tool and the WHO scale was also determined using ϕ . A Cox proportional hazards model¹⁵ was used to assess the effect of both fixed and time-varying risk factors on the hazard rate of major bleeding over time and on the hazard rate of minor bleeding over time. Risk factors included in this model were: admission diagnosis, APACHE II score¹⁶, platelet count, coagulation parameters, use of prophylactic or therapeutic doses of unfractionated heparin or low molecular weight heparin in the two days preceding a bleed, use of antiplatelet agents in the seven days preceding a bleed, the need for dialysis and other events and exposures representing premorbid bleeding risk factors. Only the independent predictor variables identified by backwards selection are reported ($P < 0.05$ in the multivariable regression analysis). Mortality among patients with non-fatal major bleeds and among patients with minor bleeds or no bleeding was compared using a 2-sided Fisher's exact test and length of ICU stay was compared using a 2-sided Wilcoxon test.

Results

One hundred consecutive patients were enrolled over the three month study period, aged 63.3 (18.3) yr [mean (SD)]; and 60.0% were female. APACHE II score was 24.8 (9.2) and most admissions were medical (71.0%). The median length of ICU stay was five days (interquartile range [IQR] 2 – 12) and ICU mortality for the entire cohort was 15.0%. Patient characteristics are shown in Table 1.

There were 480 discrete bleeding events (both major and minor) among 90 patients who experienced 1,905 days with bleeding. Based on the severity of their worst bleed, 70 of 100 patients had minor bleeding only, 20 had at least one major bleed (25 in total) and ten patients had no bleeding events. Of 480 bleeds, 25 (5.2%) were major lasting for a median of four days (IQR 2 – 9) and 455 (94.8%) were minor

TABLE 1. Patient demographics.

	n=100
Age [mean (SD)]	63.3 (18.3)
Females [(n, %)]	60 (60)
APACHE II [mean (SD)]	24.8 (9.2)
Primary admission diagnosis [n (%)]	
Cardiovascular	15 (15)
Pulmonary	19 (19)
Gastrointestinal	28 (28)
Neurological	4 (4)
Sepsis	13 (13)
Metabolic	8 (8)
Hematologic	1 (1)
Renal	6 (6)
Other	6 (6)
Admission type [n (%)]	
Medical	71 (71)
Surgical	29 (29)
ICU length of stay in days [median (IQR)]	5 (2-12)
ICU mortality [n (%)]	15 (15)

lasting for a median of two days (IQR 2 – 4). Patients experienced a median of three bleeds each (IQR 2 – 6) (Figure 2). There were 11 prevalent major bleeding events (present on admission to ICU) and 14 incident major bleeding (acquired during ICU admission). The anatomical sites and laboratory features of bleeding by severity (major or minor, based on the most serious bleed) are shown in Table 2. Over half of all major bleeds (52.0%) were gastrointestinal in origin, while minor bleeds were mostly from vascular catheter insertion sites (40.4%), endotracheal tubes (16.3%) and surgical wounds (14.3%).

Agreement between raters on bleeding severity assessments using the HEME tool was excellent ($\phi = 0.98$, 95% CI: 0.96 to 0.99). Inter-rater agreement for the WHO scale was also very high ($\phi = 0.99$, 95% CI: 0.97, 0.99). There was excellent agreement on the designation of major bleeding by the HEME tool and the WHO scale ($\phi = 0.98$, 95% CI: 0.96, 0.99).

Risk factors for major bleeding that were identified in the Cox regression analysis were a prolongation of partial thromboplastin time (PTT) at any time (HR= 1.2, 95% CI: 1.1 to 1.3, for every 10 sec increase) and a reduction in platelet count (HR= 1.7, 95% CI: 1.2 to 2.3, for every $50 \times 10^9/L$ decrease) (Ta-

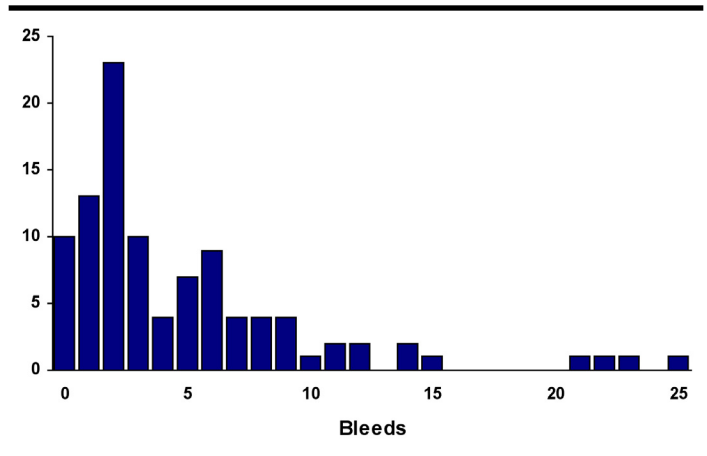


FIGURE 2. Histogram of number of bleeds (major or minor) per patient (n=100).

ble 3). APACHE II score and surgical admission were predictors of minor bleeding (HR= 1.3, 95% CI: 1.0, 1.6; and HR= 2.0, 95% CI: 1.2, 3.3 respectively). Neither prophylactic heparin nor antiplatelet agents (such as acetylsalicylic acid, clopidogrel, ticlopidine) were significant risk factors for major or minor bleeding. No patients receiving therapeutic heparin experienced a major bleed.

To examine outcomes associated with major bleeding, we compared the proportion of patients requiring blood transfusions that were temporally related (within 3 days) to bleeding events (Table 4). Significantly more patients with major bleeding received platelet, red blood cell and fresh frozen plasma transfusions compared with patients with minor or no bleeding. The duration of ICU stay was longer for patients with major bleeds than for patients with minor or no bleeds [11 days (IQR 4 – 42) versus 4 days (IQR 2 – 11), $p = 0.019$]. However, there was no difference in mortality [5/20 (25%) vs. 10/80 (13%) respectively, $P = 0.17$]. In the opinion of the attending ICU physician, 13 complications occurred as a result of major bleeding in 12 of 20 patients. Complications were myocardial ischemia or other cardiovascular complications (n=8), the need for surgical packing (n=2), or exploratory laparotomy (n=1) and renal and neurological impairment (n=1 each). The eight remaining patients with major bleeds suffered no clinical sequelae as a result. No patients were classified as

TABLE 2. Features and anatomical locations of major (n=25) and minor (n=455) bleeds observed in 90 of 100 consecutive medical-surgical ICU patients. Discrete bleeds were those that occurred at distinct anatomical sites or recurrent bleeds at the same sites.

	Major bleeds (n=25)	Minor bleeds (n=455)	All Bleeds (n=480)
Days with bleeding (median, IQR)	4 (2-9)	2 (2-4)	2 (2-4)
Location of bleeds, n (%)			
Vascular catheter/ insertion site	0	184 (40.4)	184 (38.3)
Endotracheal tube	3 (12.0)	74 (16.3)	77 (16.0)
Surgical Site	6 (24.0)	65 (14.3)	71 (14.8)
Other skin bleeding	1 (4.0)	61 (13.4)	62 (12.9)
Oral secretions	2 (8.0)	32 (7.0)	34 (7.1)
Gastrointestinal	13 (52.0)	16 (3.5)	29 (6.0)
Genitourinary	0	17 (3.7)	17 (3.5)
Nasopharyngeal	0	4 (0.9)	4 (0.8)
Other	0	2 (0.4)	2 (0.4)
Laboratory features on the first day of bleeding (mean, 95% CI)			
INR, highest*	1.7 (1.5, 1.9)	1.4 (1.3, 1.4)	1.4 (1.3, 1.5)
PTT, highest* (seconds)	68.4 (50.8, 85.9)	46.3 (43.8, 48.8)	47.6 (45.0, 50.2)
Platelets, lowest* (x10 ⁹ /L)	93 (66, 120)	170 (157, 179)	164 (153, 175)
Creatinine, highest (μ/L)	126 (84, 168)	166 (151, 181)	164 (149, 178)

* $P < 0.05$ for major versus minor bleeds.

IQR = interquartile range; CI= confidence interval; PTT= partial thromboplastin time

“Other” refers to bleeding at the epidural catheter site and subconjunctival hemorrhage

having fatal bleeding, though ultimately some of these critically ill patients died.

Discussion

In this prospective study, bleeding, although primarily minor, occurred in the majority (90%) of consecutive medical-surgical critically ill patients. Major bleeds were mostly from the gastrointestinal tract and were associated with a prolonged PTT and a low platelet count compared with previous values at any time, but not with the use of prophylactic anticoagulants or anti-platelet agents. Patients with major bleeds had longer ICU stays and required more blood products than patients with minor or no bleeds. No patients had fatal bleeding and no difference in mortality was observed between patients with and without major bleeding. The performance characteristics of HEME, a new bleeding assessment tool for critically ill patients, were highly satisfactory.

To our knowledge, this study is the first to prospectively describe the frequency of bleeding from all anatomical sites among heterogeneous critically ill patients. Major bleeding is an important cause of morbidity in the ICU and knowledge of the frequency of all bleeding events helps distinguish expected from unexpected bleeding rates in future clinical trials. The measurement of bleeding in this study and the design of the HEME tool addressed key methodological challenges including the need for standardized population-specific definitions of bleeding severity, the need for independent adjudication of bleeding assessments, and the need for careful analytic methods to reflect clinical importance.^{8,17} HEME is superior to existing bleeding scales including WHO, because it provides descriptive detail on the site and severity of bleeding, and reflects the clinical importance of major bleeding specific among ICU patients. It also captures the duration and recurrence of bleeding which can aid in the interpretation and analysis of trial data. Other strengths of this study were the use of rigorous methods to assess the

TABLE 3. Predictors of major and minor bleeding identified using multivariable regression analysis.

	Hazard Ratio	95% CI	P
Time to First Major Bleed			
PTT (per 10 second increase)	1.2	(1.1, 1.3)	0.004
Platelets (per 50 x10 ⁹ /L decrease)	1.7	(1.2, 2.3)	0.002
Time to First Minor Bleed			
APACHE II Score (per 10 unit increase)	1.3	(1.0, 1.6)	0.039
Surgical Admission	2.0	(1.2, 3.3)	0.009

APACHE= Acute Physiology and Chronic Health Evaluation;

ASA= acetylsalicylic acid; INR= international normalized ratio;

PTT= partial thromboplastin time

performance characteristics of the tool including prospective, paired, independent assessments by trained assessors and the use of the ϕ statistic to estimate chance-independent agreement.

Limitations of this study were the lack of a population-specific reference standard to assess construct validity of HEME, and uncertainty about the ease of use of HEME in routine clinical practice. Given that risk factor analyses depend on the distribution of risks in the population of interest, it is possible that other risk factors and risk factor combinations

may be more predictive of major bleeding in different ICU populations. HEME does not differentiate between minor and trivial bleeding, which are generally not documented in health records in the ICU setting and generally not associated with adverse consequences. Also, since none of the patients with a major bleed were receiving therapeutic doses of anticoagulants, this variable could not be evaluated in our risk factor model, and the single centre design of this study limits the applicability of these data to specialized trauma or neurosurgical ICUs, for example.

The most precise estimates of bleeding among critically ill patients have previously been derived from randomized clinical trials in which bleeding (or avoidance thereof) was an outcome or an adverse event. In a randomized controlled trial comparing ranitidine and sucralfate stress ulcer prophylaxis among 1,200 mechanically ventilated patients, the frequency of clinically important upper gastrointestinal bleeding was 1.7% in the ranitidine group and 3.8% in the sucralfate group.³ In a randomized controlled trial evaluating the efficacy and safety of nadroparin thromboprophylaxis among 223 mechanically ventilated medical ICU patients, the rate of major bleeding in the placebo group was 2.7%.¹⁸ The observed frequency of major bleeding in our study was higher (20%) likely because bleeding was the

TABLE 4. Outcomes associated with major bleeding. Patients were characterized as having *major* or *minor* bleeding based on their worst bleed. Transfusions were captured if they were administered between the first day of bleeding and 3 days after the last bleeding day.

	Patients with major bleed(s) (n=20)	Patients with minor bleed(s) only (n=70)	Patients with no bleeding (n=10)	P*
Transfusions, n (%)				
Platelets	10 (50)	8 (11)	1 (10)	<0.001
RBC	19 (95)	32 (46)	0 (0)	<0.001
FFP	17 (85)	20 (29)	1 (10)	<0.001
Cryoprecipitate	1 (5)	1 (1)	0 (0)	0.362
ICU length of stay (days; median, IQR)	11 (4 – 42)	5 (3 – 12)	2 (1 – 4)	0.019
ICU mortality N (%)	5 (25)	9 (13)	1 (10)	0.17

* P-values for major versus minor or no bleeding

RBC= red blood cell; FFP= fresh frozen plasma

primary outcome, all anatomical sites were considered and prospective bleeding assessments were performed by dedicated and trained assessors. In addition, the generalizability of data from previous trials is limited by case mix and stringent trial eligibility criteria.

Until now, there has not been a bleeding measurement tool for patients with critical illness. In a review of the literature, Koreth and colleagues identified over 16 published bleeding scales⁵ none of which was designed to capture clinically important bleeding in critically ill patients. Even among existing tools, there is a lack of standardized definitions, as demonstrated in a systematic review by Raskob and colleagues which identified 18 different definitions of 'severe bleeding' among 62 eligible studies of thromboprophylaxis following hip surgery.¹⁹ A clinically useful bleeding measurement tool must be population specific and must use definitions that can be standardized across studies.

Bleeding in the ICU is perceived to be an important problem, yet few studies have addressed its clinical impact. We found that patients with major bleeds were more likely to receive blood transfusions and had longer ICU admissions; however, ICU mortality was not higher than in patients with minor or no bleeding. Conversely, an association between bleeding and death has been observed in other patient populations. Data from over 34,000 patients with acute coronary syndrome enrolled in 2 prospective registries and 2 randomized controlled trials were recently re-analyzed to examine the association between major bleeding and death.¹ Patients with a major bleed had a 5-fold higher incidence at death during the first 30 days and a 1.5-fold higher incidence of death between 30 days and 6 months. Similarly, in a retrospective analysis of 1,402 patients undergoing bone marrow transplantation at one center, bleeding was associated with lower overall survival.² The lack of association between bleeding and ICU mortality in the current study does not exclude the possibility that bleeding can lead to death in some circumstances. Our sample size may not have been large enough to detect a difference in mortality; moreover, among critically ill patients, bleeding may not be as important a risk factor for death as in other populations because of the

complex comorbidities that influence mortality in this setting. We did not observe any fatal bleeds, although in the ICU setting, if a bleed preceded death, the label of fatal bleeding may be insensible, since such patients invariably die *with* bleeding (e.g., a patient with renal failure and ongoing melena has a hyperkalemic cardiac arrest) and rarely *due to* bleeding (e.g., a patient dies from hypovolemic shock due to massive uncontrolled upper gastrointestinal hemorrhage).

Conclusions

Bleeding in the ICU is common and is mostly minor. Major bleeds were associated with a prolonged PTT and a low platelet count and resulted in increased use of blood products and longer ICU stays. These data establish a control rate of bleeding among heterogeneous patients with critical illness which can be used to inform the design of future clinical trials. Although it requires further clinimetric evaluation, the HEME tool would allow standardized comparisons of bleeding complications among clinical studies in critical care medicine.

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Author Contributions

Donald M. Arnold (guarantor)- Conceived and planned the research, interpreted the results, wrote the paper and approved the final version.

Laura Donahoe- Planned the research, performed bleeding assessments, substantively reviewed the paper and approved the final version of the manuscript.

France J. Clarke- Planned the research, performed bleeding assessments, substantively reviewed the paper and approved the final version of the manuscript.

Andrea J. Tkaczyk- Planned the research, performed bleeding assessments, substantively reviewed the paper and approved the final version of the manuscript.

Diane Heels-Ansdell- Planned the research, performed the analysis, interpreted the results, substantively reviewed the paper and approved the final version.

Nicole Zytaruk- Planned the research, performed bleeding assessments, substantively reviewed the paper and approved the final version of the manuscript.

Richard Cook- Conceived and planned the research, interpreted the results, substantively reviewed the paper and approved the final version.

Kathryn E. Webert- Conceived and planned the research, substantively reviewed the paper and approved the final version.

Ellen McDonald- Conceived the research, substantively reviewed the paper and approved the final version.

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