CLINICALLY IMPORTANT BLEEDING IN HEMATOLOGICAL MALIGNANCIES

HEALTHCARE PROVIDER PERCEPTIONS OF CLINICALLY IMPORTANT BLEEDING IN HEMATOLOGICAL MALIGNANCIES: A QUALITATIVE STUDY

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LAY ABSTRACT

Acute leukemia (AL) and its treatments cause patients to bleed more easily. In clinical trials, bleeding is often used as an outcome of studies looking at ways to treat AL. Whether a bleeding event is considered significant or not is determined using a definition developed by the World Health Organization (WHO). However, the criterion for clinically significant bleeding has some limitations, such as adequately differentiating minor bleeds from major bleeds, perhaps reflecting the lack of input from healthcare providers and patients themselves. To understand and identify the components of clinically significant bleeding, we conducted interviews with physicians, nurse practitioners and registered nurses who care for AL patients undergoing chemotherapy in Canada. We found that healthcare providers consider various factors, such as the site and amount of bleeding, management approach, need for intervention, recurrence of bleeding, and changes in vital signs, to determine whether a bleed is significant. Using these characteristics, we grouped bleeds into three groups: clinically significant, potentially clinically significant, and lacking clinical significance. These provide an overview of healthcare providers' perspectives and must be combined with patients' perspectives to develop a comprehensive definition of clinically important bleeding in the AL population that is informed by evidence, clinicians, and patients alike.

ABSTRACT

Introduction: Acute leukemia (AL) is a rapidly progressive disease. AL and induction chemotherapy lead to an increased risk of bleeding. Bleeding is measured in clinical trials using the World Health Organization (WHO) bleeding scale. The scale defines a clinically significant bleed as a composite outcome of a grade 2 bleed or higher. The use of this composite outcome is problematic, as it does not distinguish minor bleeds, signs or symptoms of bleeding, does not consider the total burden of bleeding and lacks input from healthcare providers and patients. Given this, our objective was to identify healthcare providers' perspectives on the components of clinically important bleeding in AL patients.

Methods: Using qualitative description, we conducted 19 interviews with physicians (n=12), nurses (n=3), and nurse practitioners (n=4) who provide care to AL patients undergoing induction chemotherapy in Canada. Participants were recruited from professional organizations, networks, and social media. Interview data were analyzed using an inductive approach for conventional content analysis.

Results: Healthcare providers identified various factors that were considered to determine the significance or severity of a bleed. Participants assessed factors including the location and amount of blood, the management strategy, the need for intervention, multiple bleeds, changes in vital signs and other patient-specific factors. We developed three categories to

differentiate bleeds: those with clinical significance, those with potential for clinical significance, and those without clinical significance.

Conclusion: Healthcare providers considered various characteristics when determining the significance and or severity of a bleed. These characteristics were assessed in conjunction with other factors such as the patient's medical condition, bleeding history, and clinical intuition to predict the likelihood of a serious bleed. Future research should explore AL patients' perspectives of clinically important bleeding to create a definition that is informed by evidence, clinicians, and patients.

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LIST OF ABBREVIATIONS AND SYMBOLS

AL	Acute leukemia
AML	Acute myeloid leukemia
ALL	Acute lymphocytic leukemia
CLL	Chronic lymphocytic leukemia
CML	Chronic myelogenous leukemia
HCP	Healthcare provider
UBS	Utility-based bleeding scale
ST	Shipra Taneja
MV	Meredith Vanstone
CH	Chris Hillis
NH	Nancy Heddle
SL	Shannon Lane
MK	Meera Karunakaran
BSMS	Bleeding Severity Measurement Scale
WHO	World Health Organization
BAT	Bleeding Assessment Tool
RCT	Randomized Control Trial
RBC	Red blood cells
DCIBO	Defining Clinically Important Bleeding Outcomes

DECLARATION OF ACADEMIC ACHIEVEMENT

This study was conceptualized, and funding secured by Dr. Christopher Hillis, Professor Nancy Heddle, Dr. Meredith Vanstone, and members of the DCIBO steering committee as part of a larger study aiming to develop a bleeding measurement tool by combining a secondary analysis of RCT data, and qualitative interviews of healthcare providers and patients. The study described in this thesis developed one of these types of data: healthcare provider perspectives. This study was designed by Shipra Taneja, Dr. Meredith Vanstone, Dr. Christopher Hillis and Professor Nancy Heddle. It was operationalized by Shipra Taneja, with co-ordination, interviewing, and coding assistance from Shannon Lane and Meera Karunakaran, under the guidance of Dr. Meredith Vanstone, Dr. Christopher Hillis, Professor Nancy Heddle, and members of the DCIBO steering committee. Shipra Taneja led data collection and analysis for this study. The thesis manuscript was written independently by Shipra Taneja, with critical revision and suggestions from Dr. Meredith Vanstone, Dr. Christopher Hillis, and Professor Nancy Heddle.

INTRODUCTION

Acute leukemia (AL) is a rapidly progressive disease that is fatal if not treated. Each year, approximately 7000 Canadians are diagnosed with AL. (1) The AL cancer cells (blasts) slow the production of red blood cells and platelets, which can lead to anemia (low hemoglobin) and thrombocytopenia (low platelets). Induction chemotherapy removes the cancerous cells from the body. However, the use of induction chemotherapy reduces platelet counts (thrombocytopenia). Thrombocytopenia is one factor that can increase a patient's risk of bleeding during their disease and treatment. (2,3) Given this, patients require numerous blood product transfusions to increase their platelet counts which will treat bleeding.

In clinical trials of AL, researchers use bleeding as an outcome to test new products and find better ways to treat bleeding. They currently use the World Health Organization (WHO) bleeding scale to measure bleeding outcomes, which categorizes signs and symptoms from grade 0 (no bleeding) to 4 (bleeding that can cause death). (4) The WHO bleeding scale defines a clinically significant bleed as grade 2, 3, or 4, but the use of this composite outcome is problematic. Grade 2 bleeding events are more frequent and milder but are grouped with bleeding events that are less frequent and severe. Additionally, it is unknown whether grade 2 bleeding events predict future more severe (grade 3 or 4) bleeding events. (5–7) Other evidence-based tools have been developed to evaluate clinically significant bleeding more precisely, but these tools do not distinguish minor bleeds, the signs and symptoms of bleeding, and the total burden associated with

multiple or recurring bleeding events. (8) A qualitative study describing patient and provider perspectives has not been conducted when developing these tools or the WHO scale. As patients experience these bleeds, they may find particular bleeds to be distressing, worrisome, or burdensome, but their concerns may not always be acknowledged in scale development. Healthcare providers also know the bleeds that patients are concerned about, which may influence their clinical management. (9) Healthcare providers may be concerned about particular bleeds or may be aware of bleeds that are concerning to patients, which may influence their clinical management. These experiences have not been captured in bleeding tools as they are designed using data from RCTs. The Core Outcome Measures in Effectiveness Trials group has highlighted the need for outcomes that are relevant to patients and those involved in their care. (10) Given these considerations, there needs to be a new bleeding tool that identifies the signs and symptoms associated with bleeding and that is relevant to AL patients and others involved in their care. (10) Developing a new bleeding tool in clinical research can aid in evaluating new therapies that have the potential to enhance patient outcomes in clinical practice.

LITERATURE REVIEW

Overview of Acute Leukemia

Acute leukemia (AL) is a rapidly progressive disease that develops in the bone marrow and is fatal if not treated. AL occurs due to several genetic alterations or mutations that occur during the formation of blood cell components (hematopoiesis). (11) The main types of acute leukemia include acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL). (12) AML is the most common type of leukemia in adults with a predicted incidence rate of about 2.79 cases per 100,000 person-years in Canada. (13) AML patients are classified into one of three disease groups (favourable, intermediate and adverse). (14) These groups help clinicians predict treatment responses and overall survival rates. (14)

The standard of care for patients with AML is induction chemotherapy and post-remission therapy (consolidation). Induction chemotherapy is used to destroy as many cancer cells as possible to achieve complete remission. (14) After induction chemotherapy, patients enter post-remission therapy which is to prevent any recurrence of the disease. Previous studies have found that patients with the intermediate disease have a 50-60% complete response to induction chemotherapy and up to 80% response for those that have a favourable risk. (14)

Risk of Bleeding

At diagnosis of AML and following induction chemotherapy patients experience anemia (low hemoglobin) and thrombocytopenia (low platelets). Low platelet and low

hemoglobin levels cause an increased risk of bleeding, which can lead to serious complications, including death. (2,3) Clinical factors such as coagulopathy, chemotherapy-induced damage to the mucosal lining, and hospital-acquired infections may increase the likelihood of bleeding. (15) During the course of treatment, patients may encounter a range of bruising and bleeding. This can range from minor bleeds (e.g., nosebleeds (epistaxis) or stool occult bleeds) to severe bleeds (e.g., retinal bleeds with vision loss or intracranial hemorrhage with neurologic deficits). Platelet transfusions are used to help increase platelet counts to decrease the risk of bleeding or stop active bleeding. (16,17) Given these risks, AML patients undergo numerous platelet transfusions during induction and consolidation chemotherapy to increase their platelet counts. Red blood cell transfusions are given to prevent severe anemia and to provide hemostatic support to patients as they experience bleeding. (18) However, there is a need to identify why some patients are more likely to experience severe bleeding and find alternative methods of preventing and treating bleeding. (2) The potential utility of a tool to grade bleeding in clinical trials can support the research of finding interventions which treat bleeding.

Bleeding Tools

Researchers measure bleeding as a clinical outcome in trials to test new products and find better ways to treat bleeding in AML patients. This is often measured using a measurement tool, which is an instrument that evaluates the phenomenon of interest. (19) One of the most common tools used to classify bleeds in clinical trials is the World

Health Organization (WHO) bleeding tool. (4) This tool was developed in 1981 to help clinicians and researchers assess and standardize the reporting of bleeding during cancer treatment. (4) This tool has been widely used in platelet transfusion trials to test new therapies but has never been validated for transfusion clinical trials. (4,20) As seen in Figure 1, the grading tool categorizes the bleeds to a grade based on severity. (4,6) It ranges from grade 0 (no bleeding) to grade 4 (debilitating blood loss). Transfusion researchers have adopted and adapted the WHO bleeding criteria, which characterize a clinically significant bleed as grade 2 or higher and may encompass signs and symptoms of bleeding. The use of the WHO bleeding criteria in transfusion trials has been critiqued for methodological weaknesses. (6) Firstly, the scale claims to classify bleeds into a grade based on increasing levels of severity, but instead, the grades categorize different types of bleeding (e.g., hematuria = mild blood loss). (6) In transfusion clinical trials, bleeding is measured as a composite outcome where grades 2,3 and 4 are grouped as one clinical outcome. The use of this composite outcome is problematic, as grade 2 bleeds are defined as minor blood loss and occur frequently during induction chemotherapy. (5,21) They are grouped into this composite outcome with grades 3 and 4 bleeds which are less frequent but have greater clinical relevance. The inclusion of grade 2 bleeds in the composite outcome improves study feasibility as it allows for an attainable sample size for trials. (6) Despite the improvement of feasibility for the trial, the importance of the clinical bleeding outcome is reduced. There is also a lack of literature identifying whether grade 1 or 2 bleeds (minor bleeds) are appropriate surrogate outcomes which may predict more severe bleeding events. (2,6) Additionally, the WHO bleeding scale does not consider the

duration of the bleeding. (6) This is essential information as minor bleeds could occur for a long time (hours or days), which may cause severe blood loss. In clinical trials, the bleeding outcome is reported as one outcome classified as grade two or higher, even though they could have experienced other significant or non-significant bleeds during the study. There is no description indicating the associated symptoms, the total amount of bleeding or the duration of the bleeding for each subject (total burden of bleeding). The inclusion of these variables could support the evaluation of interventions to treat bleeding in AL patients.

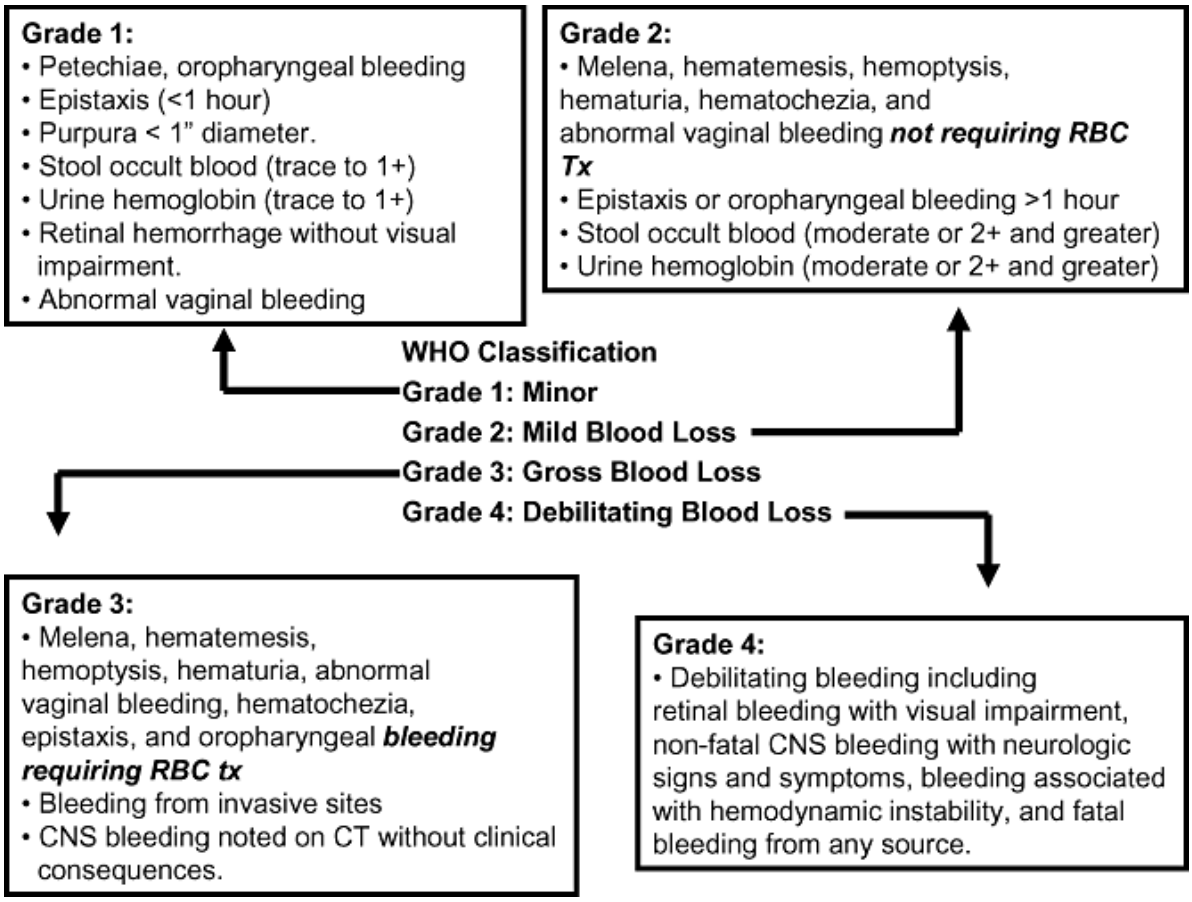

Figure 1 *- WHO Bleeding Scale as described by Heddle et al. (5)*

Other measurement tools for assessing bleeding have been created for hematological malignancies. In 2012, Webert et al. developed the Bleeding Severity Measurement Scale (BSMS) for patients with chemotherapy-induced thrombocytopenia. (8) The items for the measurement scale were developed from a literature review, existing bleeding scales in other disciplines, and surveys with healthcare providers who work with patients with chemotherapy-induced thrombocytopenia. (8) Clinically significant bleeding in the BSMS was defined as a) any bleeding with pain or bleeding that required intervention (e.g., transfusion, surgery, invasive procedures, administration of

medication); b) serious bleeding with significant morbidity (e.g., all central nervous system bleeding, hemodynamic instability such as tachycardia or hypotension, vision loss, other significant morbidities); and c) fatal bleeding. (8) The BSMS was evaluated for content validity, criterion validity, and intra- and inter-rater reliability and demonstrated good validity and reliability. (8) The BSMS has some limitations, as the scale does not consider some important minor bleeds (e.g., hematuria), or patient perspectives on the bleeding items. (8) The BSMS was not widely used in studies, and the reason for the lack of uptake is unknown.

In 2018, the Bleeding Assessment Tool (BAT) was developed by Dyer et al to capture all bleeding events and translate them into a clinically relevant grade. (22) This assessment tool was developed using bleeding assessments from an observational cohort study of patients with hematologic malignancies in four countries. (22) The BAT tool was designed to assess the severity and location of the bleeding. However, the bleeding episodes were defined using the WHO bleeding criteria. (22) In using the BAT, bleeding is first assessed using one form, but additional assessments are involved depending on if the bleed was categorized as non-severe or severe. (22) Despite the good reliability concordance between assessors looking at the bleed, the use of the tool requires additional training for assessors to record some types of bleeds (skin). Additionally, the tool was evaluated by a small number of bleeding assessors indicating the reliability may change in a larger population. (22)

All three bleeding tools that are used in transfusion clinical trials for AL patients to categorize bleeding have limitations. They have never been analyzed to measure the total burden of bleeding, consider important minor bleeds, and both patient and health care providers' perspectives. Bleeding is typically reported as a binary outcome in RCTs at a single time point, omitting details such as the duration or grade severity of the bleed. Additionally, these tools may contain bleeding that is not clinically significant to increase the overall frequency of bleeding to obtain a feasible sample size. The use of these bleeding tools in clinical trials poses a challenge to the validity of the studies and outcomes. If the measurement tool is not measuring the intended construct or grading the bleeds accurately, then it is difficult to confirm that the study results are valid. (19) A weak measurement tool can directly impact the ability to detect statistical relationships between the treatment and outcome. (19) This can pose a threat to the study results as they may not be valid or generalizable to the AL population. The study's validity could improve if they used a measurement tool and analytical approach that included the total burden of bleeding, patient and provider perspectives and information on minor bleeds. For instance, identifying the total burden of bleeding may help identify future bleeds or the impact of the bleeding on treatment. Minor bleeds may also develop clinical importance and a tool which doesn't adequately categorize minor bleeds may miss important distinctions. A few studies have been published exploring the relationship between minor bleeds and severe bleeding events. In two studies, minor bleeds were not found to be associated with more severe bleeding. (17,23) However, the data in both studies were categorized by the WHO bleeding scale and then analyzed.

A recent study by Balitsky et al. found hematuria (a minor bleed as per WHO) was associated with severe bleeding when looking at RCT data at the level of signs and symptoms rather than a grade category. (24) Due to these findings, more data are needed to identify whether minor bleeds have clinical importance. Patients' and providers' perspectives are crucial to identify as they may emphasize clinical relevance. There may be some bleeds during chemotherapy that are deemed clinically irrelevant or minor but are distressing and worrisome to patients and their families. They may not require a specific intervention, but it is unknown if they predict additional bleeding events in the future. Healthcare providers may be concerned about a specific type of bleeding based on their experience and practice. They might be aware of bleeding that leads to additional patient distress. Patient-reported outcomes for other bleeding conditions (e.g., menstrual bleeding, hemophilia) have begun to incorporate patient and provider perspectives in the instrument development phase to better understand the nuances of bleeding. (25–27)

Bleeding Definitions

In some cases, researchers have already developed a definition or criteria for bleeding. A clinical definition is used to describe a particular condition and is based on set criteria. For instance, Stalfelt et al. conducted a retrospective study on the final phase of AML to increase knowledge and describe clinical problems. (28) They created a definition to categorize bleeding as either slight or severe. (28) The researchers identified that at the time, there was no guidance or criteria to describe bleeding in this population.

They created two definitions but did not provide insight into how these definitions were generated. Slight bleeding was identified as bleeding with no far-reaching measures taken (e.g., transfusions, referral to specialists), while severe was defined as bleeding that needed these measures. (28)

In other instances, particular bleeds that AML patients may experience have definitions of what constitutes a severe or clinically important bleed. These definitions have been created through the evaluation of clinical studies and consensus from experts in the field. (29–31) For example, epistaxis (nosebleed) is a type of bleeding that AML patients may experience during their treatment. A clinical practice guideline created for the general adult patient population identifies that severe bleeding includes a posterior nosebleed, hemodynamic instability due to blood loss and a decrease in hemoglobin of ≥ 2g/dL or required ≥2 units of RBCs. (29) Similar definitions or criteria of severe or clinically important bleeding also exist for upper gastrointestinal bleeding and hemoptysis. (30,31) However, these guidelines have not been validated in the AL population and due to the pathophysiology of the disease, they may not be transferable to this population.

Health Care Provider's Knowledge of Bleeding during Induction Chemotherapy

There is currently no published literature exploring healthcare providers' knowledge or attitudes toward bleeding during induction chemotherapy. However, some published work has explored the experiences of bleeding in other types of cancers and conditions.

In 2013, Zheng et al. completed a qualitative descriptive phenomenology study exploring nurses' experiences of upper gastrointestinal bleeding in patients with hepatocellular carcinoma. (32) The interviews focused on how nurses felt about catastrophic bleeding in hepatocellular carcinoma patients. Nurses described being fearful, stressed and confused when patients experienced catastrophic bleeding. (32) Often, witnessing this traumatic bleeding negatively impacted the nurses' work and made them think about their own life. (32) Although this study did not explore healthcare providers' knowledge about bleeding, they identified nurses need training for handling catastrophic bleeding events. (32)

In 2009, McGrath et al. led a similar qualitative descriptive phenomenology study with hematologists, hematological nurses, and palliative care nurses. (9) They explored the experiences of managing catastrophic bleeds for hematology patients. McGrath et al. highlighted that some nurses believed there was some unpredictability in knowing who is likely to bleed, while others could easily predict. (9) Some nurses had a general idea of who would bleed based on their disease (AML patients) and who would not (myelomas). Also, they identified clinical predictors of bleeding, which included blood counts, low platelets, thrombocytopenia or neutropenia. (9) Hematologists elaborated that catastrophic bleeding was predictable in patients with leukemia, lymphoma, and myelomas, but some patients won't experience it even if predicted. (9) McGrath et al. also described that healthcare providers felt distressed when witnessing external catastrophic bleeding in patients. (9) A hematologist indicated that witnessing these bleeds is also emotionally distressing for carers and their families, especially when it is a visible (external) bleed. (9)

As this study focused on hematology in general, the healthcare providers did not specify if there were additional predictors besides disease that led to catastrophic bleeding.

Significance of the proposed study

As identified in the literature, there currently is an unmet need for a bleeding outcome that identifies future bleeding and is relevant to healthcare providers involved in the care of AL patients. This qualitative study will explore the components of clinically significant bleeding identified by physicians and nurses who care for patients with AL. The qualitative findings will be combined with a secondary analysis of three RCTs. The integration of these results will allow for a deeper understanding of clinically important bleeding and offer new insights that go beyond results obtained by only one of the two analyses. My MSc thesis will focus on identifying the components of clinically significant bleeding from qualitative interviews with healthcare providers. The identified constructs from the qualitative interviews and results from a secondary analysis of RCT will aid in the development of a utility-bleeding score.

METHODS

Objective

This study aimed to identify the components of clinically important bleeding from the perspective of healthcare providers. While the current project stops after describing what healthcare providers think marks clinically significant bleeding and why, the identified components will be used along with other data sources in a larger project to develop a utility-bleeding score.

The guiding research question was "What do physicians and nurses who treat patients with AL believe are the components of clinically important bleeding for AL patients receiving induction chemotherapy"?

Setting

This qualitative study was specifically focused on healthcare providers that treat AL patients in Canada. This study was led by a team of researchers at McMaster University in the Departments of Medicine and Oncology with collaborators in Canada, the United Kingdom, and the United States. The study team included clinicians (hematologists and clinical nurse specialists) who care for AL patients, biostatisticians, methodologists, a patient partner, a research coordinator, a research assistant, and a graduate student.

Methodology

A qualitative descriptive methodology was used to understand healthcare providers' perspectives of relevant and important bleeding in patients undergoing induction chemotherapy for AL. (33,34) Qualitative description is a methodology outlined by Dr. Margarete Sandelowski that is used to discover and describe participants' perspectives and views on the world and a particular phenomenon. (33–35) Qualitative description allows researchers to undercover a rich and concise description of a phenomenon that closely aligns with participants' views. (36) Qualitative description is mainly used to answer applied health research questions as it captures the voice of those experiencing the phenomenon with minimal interpretation from the researcher. (35) It is often used to transform clinical practice and health services and make policy recommendations. (35)

Qualitative description methodology was selected for this study, as we aimed to understand and describe healthcare providers' perspectives of relevant and important bleeding in the AL population. The use of this methodology allowed us to explore a clear and concise description of bleeding and understand its meaning and relevance through analysis and interpretation. (33,34) We were able to capture data which closely resembled the participants' views with little interpretation from the research team. Additionally, the rich and concise descriptions of important bleeding will enable us to accurately incorporate participant views into a utility-bleeding score. A more interpretive methodology would have been inappropriate because it would be reliant on the research

team's assumptions or preconceived notions of clinically significant bleeding. It would also move away from the participant's voice, providing less valuable information on clinically important bleeding. Similarly, a quantitative approach such as a survey to measure provider views would have been inappropriate because it would include assumptions and preconceived notions by the research team. Moreover, it would have lacked information on why a bleed was clinically significant and how providers arrived at their decision for each bleed.

Philosophical stance

This qualitative descriptive study followed the mode of naturalistic inquiry with a philosophical underpinning of post-positivism. (33) Qualitative description takes a post-positivist and naturalistic philosophical underpinning. Post-positivism is a philosophy that proposes that reality can be measured, understood, and observed using a rigorous approach. (37) However, the "post" indicates an acknowledgment that the researcher's experiences and interpretations will influence the outcome. While this emphasis on research influence is stronger in other paradigms, such as constructivism or interpretivism, post-positivism does acknowledge that knowledge is influenced by social and cultural factors. (37) Naturalistic inquiry aims to understand and describe humans in their natural setting to capture subjective experiences. (35,38) Given our study aims, this approach has allowed us to explore the perspectives of healthcare providers in their natural setting, which is a hospital unit in which they care for AL patients. Additionally, this approach to inquiry acknowledges the role of the researcher in the research study and

their preconceived understanding and knowledge of the topic. (35,38) It also acknowledges that our clinician co-investigators have their own preconceptions and perspectives on clinically important bleeding, which are considered during data collection and interpretation.

Theoretical lens

Theoretical frameworks are used in qualitative health research to guide the research process. This includes choosing the appropriate methodology, collecting, and analyzing data and shaping the findings. (39) Theoretical frameworks may generate richer qualitative findings which can be used to support knowledge or action. (39) For this study, we did not employ a theoretical framework as there is a lack of literature exploring bleeding perspectives.

Even without a theoretical framework, we can still acknowledge that our understanding of the phenomenon is shaped by theories that form a background context to the study. For example, in this study of clinician perceptions, we are influenced by frameworks such as the CanMEDS framework, which places medical expertise at the centre of physician competence, with scholarship, health advocacy, communication, collaboration, and leadership mentioned as secondary competencies shaping medical practice. (40) We are also informed by critiques of this framework such as the lack of focus on social and humanistic aspects of medical practice. (40) We understand nurses to be trained in a different way, which focuses not just on clinical evidence but also

emphasizes the importance of the relationship between nurse and patient. This often leads to the development of clinical intuition about the patient's needs and health status. (41)

Study Design

Healthcare providers (physicians, nurse practitioners and nurses) were invited to participate in one individual interview. We chose this method of data collection instead of a focus group for several reasons. Firstly, we wanted to ensure all participants had enough time to provide insight into each question. Focus groups sometimes lead to unequal speaking times for participants. Secondly, due to the COVID-19 pandemic, many healthcare providers are overworked and have limited availability, making it difficult to coordinate focus group times with multiple participants. Lastly, healthcare providers would not experience any influence power dynamic, especially if focus groups contained nurses and physicians with varying experiences from the same institution. As there is a lack of robust knowledge and insight on this topic, an interview would provide greater insights while considering each participant's experiences.

Participants were asked open-ended questions about bleeding during the interview. The questions covered clinically significant bleeds, how bleeding was assessed and documented, less significant bleeds, and patients' worries about bleeding. A separate study will be conducted to gather patients' perspectives and incorporate them into the final bleeding tool.

Population

Our population of interest is registered nurses, nurse practitioners and physicians who care for AL patients in Canada. There were no geographic, clinical practice settings, or experience limits.

To participate, healthcare providers had to be registered to practice in Canada, be able to provide informed consent and complete the interview in English. Our interview team did not have members with French expertise, participants had to complete the interview in English.

Sampling and Recruitment

We used a combination of purposeful sampling, maximum variation, and snowball sampling to recruit HCPs. (42,43) Purposive sampling involves selecting participants who are informed or experienced about the phenomenon of interest (bleeding). Maximum variation sampling is where participants are selected based on different factors to ensure diversity. (42,43) We used maximum variation sampling to ensure that we interviewed participants with varying professional designations, experience levels, geographical locations, and gender. We asked clinician participants to identify their gender, as socialized differences in clinical care may impact the way they relate to patients. At the end of the interview, participants were asked to circulate an email about our study to their professional networks, also known as snowball sampling. The combination of these sampling approaches allowed us to gather a diverse number of clinicians with varying experiences and perceptions of bleeding.

Initially, we recruited eligible HCPs (e.g., physicians, nurse practitioners, nurses) who have direct experience providing care to patients with AL during induction chemotherapy. We recruited HCPs through the Canadian Hematology Society, the Canadian Leukemia Study Group, from those known to members of the steering committee, and from the participants' professional networks. When recruitment from these sources was not sufficient to reach potential individuals who were interested in participating, we completed an ethics amendment and received approval to recruit participants from the network of other clinicians who may know someone in hematology and on social media. Our social media advertisements were shared on Twitter and Facebook by members of our study team and by professional organizations including the Canadian Nurses Association of Oncology and the Canadian Hematology Society. These recruitment methods allowed potential participants to receive an email or view a link which led them to a REDCap form to collect contact information and fill out the informed consent form.

Sample Size

We aimed to recruit 15-20 healthcare providers; to reach data sufficiency. We defined data sufficiency as the point where no new information emerges from the study participants during data collection. (44) We anticipated that 15-20 would be enough to reach sufficiency based on Malterud et al.'s model on sample size qualitative interviews. (45) This model outlines five points (aim, specificity, theory, dialogue, and analysis) that are used to determine whether a large or small sample is needed based on the research

question. (45) Based on this model, the study aim was identified as broad because it focuses on HCPs' perception of important bleeding. The eligibility criteria were sparse as participants must be physicians or nurses who provide direct care to patients with AL during induction chemotherapy. (45) The interviews could provide strong dialogue, but this was dependent on the clinical expertise and availability of the participant. Additionally, there was no established theory on HCPs' perceptions of bleeding during induction chemotherapy. We aimed to compare nurses' and physicians' perspectives on bleeding, so the use of a cross-case required more participants. Given the considerations for each criterion in the model, we anticipated that the sample size of 15-20 participants would allow for diverse perspectives to help describe and understand clinically relevant and important bleeding. (45)

We confirmed that data sufficiency was met when no additional characteristics of significant bleeding were mentioned and the rationale for those bleeds was rich in information and sufficient to adequately answer the research question. However, a few additional nurses, specifically male identifying nurses from other geographical regions may have confirmed that data sufficiency was reached and provided any missing perspectives. Given the challenges of recruiting nurses in other provinces in Canada, this was not feasible in our timeframe.

Data generation procedures

We invited HCPs (physicians and nurses) who provide care for patients with AL to participate in one semi-structured interview with one of three female interviewers (SL,

MK, ST). None of the interviewers are clinicians and were not previously known to the participants. After participants received information on our study, via email or on social media, they completed a REDCap form that collected informed consent and contact information. After receiving a completed informed consent form, ST connected with potential participants by email and sent them a signed PDF of their consent form and booked a mutually agreeable time for a virtual interview (phone or on Zoom). Participants were also sent another REDCap form to complete a short demographic survey with questions about their gender, hospital site location, position, years of experience, and the number of AL patients they treat per year.

Interviews were conducted between October 28, 2022, and February 28, 2023. Interviews were audio-recorded and transcribed verbatim. Interviews were transcribed by research assistants at McMaster Centre for Transfusion Research and two members of the study team (MK and ST).

During the interviews, participants were asked open-ended questions about their perceptions and clinical knowledge of bleeding and bruising. Two interview guides (one for nurses and one for physicians) [Appendix 1 and 2] were developed by the research team consisting of clinicians, methodologists, a biostatistician, research staff and students, and a patient partner. The interview guides were piloted with two HCPs on the study team and were revised based on feedback. As more interviews were conducted, the interview guides evolved as new theoretical insights developed throughout the study. These changes were shared with members of the large study team at regular monthly meetings and via email to CH, NH and MV.

At the end of the interview, participants were given a $20 gift card to Tim Hortons or Starbucks as an honorarium in appreciation for their time and insight.

Ethics

We obtained ethics approval from the Clinical Trials Ontario streamline review process with the Hamilton Integrated Research Ethics Board acting as REB of record. All data collection and management procedures followed the Tri-Council Policy Statement of Ethical Conduct for Research Involving Humans. HCPs provided written consent for participating in the interviews. They were informed of the potential risks associated with the study, such as data privacy. All identifiable data were protected and stored using a unique study identifier. All data were password-protected and stored on an institutional drive. Only members of the study team had access to these files. Participants were provided with informed consent in plain language, had opportunities to ask questions throughout the study, and could withdraw at any time.

Ethical challenges in this study were unlikely to be a concern as the healthcare provider participants were not discussing a deeply personal or emotional issue. Although they could mention past cases involving clinically significant bleeding that was distressing, our interview questions do not specifically ask for this. The participant would only provide that information if they felt it was applicable. Additionally, there was little concern about a power imbalance between the interviewer and the participant due to the clinician status of the participant and there was no prior or existing relationship between them. (46)

Data Analysis

Data collection and analysis occurred concurrently. After the first few interviews with HCPs, the transcripts were reviewed by the research team to ensure the interview guide elicited data relevant to the research objectives. Some questions were revised with input from CH, MV and NH to help better understand HCPs' views on bleeding. After each interview, interviewers were encouraged to write memos identifying any developing insights or analytic ideas during data collection.

Data from the interviews were analyzed following an inductive approach to conventional content analysis. (47,48) Content analysis is an analytical technique for interpreting the content of the text. (48) Conventional content analysis is used specifically when there is a lack of theory or research on the phenomenon being studied. (48) We employed an inductive approach, wherein categories and codes were generated from the data, rather than existing knowledge. (47) The use of conventional content analysis in the qualitative description methodology enabled us to moderately interpret the data but define it in a manner that closely mirrored the participant's description. (33)

The analytic team (ST, MK, SL) began open coding nine of the initial transcripts. Open coding involved reading and re-reading the transcripts to identify common aspects of the content. Analysts were encouraged to think about how the participant described important bleeding as they did multiple close reads of the transcripts. The analysts met to compare their open coding and develop a codebook. This codebook contained a list of categories, each with a definition that described the content, allowing similar pieces of

text to be grouped. (47) This codebook was then applied to the remaining transcripts, evolving as some categories were collapsed or parsed out. The findings from each category were written into analytic memos, which highlighted and captured the key components in that category. (47,48)

We used the constant comparison method outlined by Boeije to compare physicians, nurse practitioners, and registered nurses' perspectives on clinically important bleeding. (49) Additionally, we investigated similarities and differences between early-career physicians and early-career nurses. (49) These comparisons were made to determine whether there were different interpretations of what clinically important bleeding meant and was defined as. For example, a nurse described a specific type of bleeding as very distressing, but physicians did not consider it clinically relevant. These comparisons will provide important insight for the development of the utility-bleeding score.

Role

The analysis was conducted by a small analytic team. ST took the intellectual lead by designing the codebook, coding transcripts, and writing analytic memos of the findings. MK and SL played a supportive analytic role by collaborating on the codebook, coding transcripts, and providing feedback on the analytic findings. Also involved were CH, NH, and MV who provided thorough feedback and revisions at each stage of the

coding process and the broader interdisciplinary team who provided feedback on the interpretations of the analytic findings.

Rigour

There are many approaches to achieving rigour within qualitative research. Rigour is used to ensuring that the findings reflect the true nature of the phenomenon. (50) It is a method used to establish trust and confidence in the findings and to confirm they are reproducible. (50)

In this project, we were guided by Milne et al.'s framework for enhancing rigour using qualitative description methodology. This framework included four key strategies: authenticity, credibility, criticality, and integrity. (51)

Authenticity and credibility refer to the researcher's ability to accurately capture the participant's point of view. It was achieved by ensuring participants described what type of bleeding was important to them in their own way. (51) Participants were asked open-ended questions about what clinically important bleeding meant to them, and they could describe their perspective by mentioning specific bleeds and characteristics or providing examples of cases. This helped establish comfort between the researcher and the participant. Additionally, interviewers probed participants for clarification and more detail. This involved re-iterating their responses and offering opportunities to elaborate on their answers. (51) We employed an inductive approach to conventional content analysis to confirm that our codes were participant-driven, not researcher-driven. To further confirm this, we engaged in analyst triangulation, meaning multiple analysts coded and

interpreted the data, instead of a single analyst. These findings were regularly shared with a wider team to incorporate their interpretations within the data. This ensured that the findings were participant-driven and not interpretations of a single researcher. (51) Criticality and integrity refer to the researcher's ability to minimize any potential influence on the research. (51) We achieved this by having non-clinician researchers conduct the interviews and be the primary data analysts. This helped minimize any influences or assumptions that the clinician-researchers on our team would have during data collection and analysis. Our analysts were able to further probe participants' responses to engage in a deeper understanding of bleeding due to their lack of clinical expertise. To ensure the accuracy and integrity of the data, we shared these primary interpretations with our clinical research team to confirm we had an accurate understanding of the data. We opted for this instead of member-checking, which is where findings are shared back with the participants. (51) This decision was made as the next phase of our utility-score development will be integrated with other data from healthcare providers and patients.

RESULTS

Participant characteristics

Nineteen healthcare providers, including twelve physicians, four nurse practitioners, and three registered nurses, provided informed consent and completed a semi-structured interview. Tables 1 and 2 describe the participants' characteristics. During the interview, the participants explained their understanding of clinically important bleeding in the acute leukemia population. They provided details on the components of clinically important bleeding, their ability to predict severe bleeds, how they assessed patients for bleeding, and patients' concerns regarding bleeding.

Table 1 *- Nurse (Registered Nurses and Nurse Practitioner) Characteristics*

Characteristics	n
Gender	
Female	7
Province	
Ontario	7
Number of years practicing as a nurse	
0-5	3
6-10	1
21-25	2

31+	1
Number of years practicing in AL	
0-5	2
6-10	3
21-25	2
Number of inpatients seen per year	
0-50	3
51-100	1
101-150	2
201-250	1

Table 2 *- Physician Characteristics*

Table 2: Physician Characteristics	n
Gender	
Female	5
Male	7
Province	
Alberta	3
British Columbia	2
Ontario	6
Quebec	1

Number of years practicing as an attending physician	
0-5	6
6-10	1
11-15	1
16-20	2
21-25	1
31+	1
Number of years practicing in AL (including fellowship)	
0-5	5
6-10	2
16-20	3
21-25	1
31+	1
Number of inpatients seen per year	
0-50	9
51-100	1
101-150	1
No response	1

Characteristics of clinically significant bleeds

Participants identified a variety of characteristics that distinguished whether a certain bleed was worrisome and/or clinically significant. This was discovered when they spoke about particular bleeds or when they described what clinical significance meant. We developed criteria to determine whether a bleed is clinically significant, based on the provided information. Since there were varying perspectives on the clinical significance of a given finding, the term "potentially clinically significant" captures that some participants found it concerning, while others felt it was very concerning and deemed it clinically significant. The following criteria differentiates between bleeds those that are clinically significant, ones that are potentially clinically significant and those that lack clinical significance.

Table 3 *- Criteria for differentiating bleeding*

Not clinically significant	Bleeding is not clinically significant if it meets one or more of the following: • Bleeding resolves on its own or with minimal intervention (e.g., applying light pressure) • Small volume bleed (e.g., streaks of blood, microscopic blood on urine dip, slight oozing) • Petechiae or bruises (smaller than a fist) or caused by known trauma (e.g., line insertion)
Could be clinically significant	Bleeds that could be clinically significant or may become a clinically significant bleed. These bleeds should be monitored if it meets one or more of the following:

	• A bleed that signifies the potential for a severe bleed (e.g., melena, hemoptysis, hematuria, purpura, mucosal bleeding, epistaxis, rectal bleeding) • Multiple or recurring small bleeds (e.g., streaks of blood, slight oozing) • Bleeds that are unresponsive to treatment or had delayed treatment. • Unexpected bleeding with no changes in blood work (e.g., no changes in hemoglobin, but bleeding occurs)
Clinically significant bleeding	Bleeding is clinically significant if it meets one or more of the following: • Bleeding that cannot be controlled even after 10 minutes. • Bleeds that require intervention (e.g., diagnostic testing, medications, specialist consults, transfusion, surgery) • Drop in hemoglobin by 10-20 points in a day • Changes in vital signs or blood work (e.g., drop in BP, increases in HR or RR, neurologic signs) • Bleeding in particular sites (e.g., brain, rectum, thoracic or abdominal cavity)

Not clinically significant:

Participants described the features of bleeds and bruises that made them less worried, such as those that resolved on their own or minor bleeds that stopped within a

few minutes of applying pressure. For instance, P03 described how post-procedural bleeding that resolved on its own was less worrisome:

> "I would say, yeah again, like post-procedural bleeding, things like after a bone marrow, biopsy site or a skin biopsy that resolves with a few minutes of pressure is not as significant to me."

A few others have also noted that the significance of certain bleeds and bruises depends on the context in which they occur. If the reason for the bleeding is known and not concerning, then it may not be clinically significant or worrisome.

> "I mean, it's all sort of context, dependent. So often, so as I said, often people will have petechiae at diagnosis, and not that you're not worried about it, but you often kind of know why they're having it. You know their platelets are low, or you know, while they're getting chemo, their platelets are low. They might have some, you know, they might have minor epistaxis or that resolves. They might have gums bleeding, especially at diagnosis. Sometimes their gums can be inflamed and infiltrated." P05

There was a consensus amongst participants that minor bruising, hemorrhoidal bleeding, cutaneous bleeding, subconjunctival bleeding, epistaxis or gingival bleeding that resolved on its own, and vaginal bleeding that was a typical menstrual flow for

female patients was not significant. Participants described bruises and petechiae that were smaller than a fist as not worrisome but did not further elaborate on whether larger bruises were concerning.

Potentially clinically significant:

Participants described that there were characteristics that raised their suspicion of a potentially serious bleed. Some of these characteristics included low blood counts persisting for a few days or a drastic change within a day, changes in heart rate or blood pressure, multiple small bleeds, bleeds that are unresponsive to treatment or delayed treatment, unexpected bleeding with no changes in blood work, and speed of blood loss.

> "[…] I think that sometimes it's a constellation of symptoms that go together that make you more concerned about, you know, "Hmm, I wonder if something is happening". So, you know, we could think about the brain bleed again, you know, people that drop their pressure or, you know, their level of consciousness drops and you can't really quite explain it. You know, you start thinking broadly about what this could represent. […]" N05

Some participants noted minor bleeds such as mucosal bleeding, purpura, petechial rash, bruising, epistaxis, hematuria, or rectal bleeding on their own could serve as a signal that worse or more significant bleeding could occur.

> "So I mean, if people have for recurrent small bleeds or if they're having abnormal clotting, or if they- I mean, I'm not generally concerned about minor bruising, but if bruising is extending or requiring repeat compression or anything like that, then yeah, it would be concerning." P04

For instance, while most participants did not consider petechiae to be clinically significant, a few believed that it could indicate changes in platelet levels and therefore warranted clinical attention.

> "I think petechiae is clinically significant. I think it often kind of gets pushed to the wayside as a rash, and they're not quite sure what it is in the beginning. Especially with newer staff that might not be as experienced with their assessments. I think it's just a sign that there's something going on with the platelets and need to keep a closer eye on their coags." N08

A few participants described that microscopic hematuria or genitourinary bleeding could be concerning, but instead of implementing an intervention, they suggested continuing to monitor it. This suggests that participants recognized that such bleeding could be serious but opted for a watchful approach.

> "I guess we don't see that a lot, significant genitourinary bleeding. But if we did, I think it would be concerning. I again don't think that it would usually be enough

> to cause a lack of blood pressure or a concern about organ function. But it's something that shouldn't happen, so then it becomes a matter of figuring out why it's happening. It's not something we see often, and if there's something bleeding, then there's probably again a lesion or something that needs to be investigated. So, it's worrisome in that way, not so much the amount of blood or the blood loss being the issue." P08

In other instances, bleeding from particular sites would signal to participants that significant bleeding could occur, such as melena or hematochezia.

> "Well, starting from the top, I would say that spotting, coughing, or spitting up blood could – it could be only a small amount, but that coming from inside that certainly would be concerning. You wouldn't know whether – because it could be coming from the lungs or the throat – so, that's a type of bleeding that, minor bleeding that could be of concern. I think any gastrointestinal bleeding, bleeding with bowel movements, although it's most often from hemorrhoids and fissures around the bottom end that are not going to be that serious, but any sort of bleeding that comes at all even if it's minor – patient reports, "I went to the bathroom, and there was some blood in the toilet", then that is definitely a warning. That is definitely a warning." P09

There were many cases where participants had differing opinions on the clinical significance of certain bleeds. Some believed that certain bleeds, such as melena, petechiae, mucosal bleeding, epistaxis, bruising, and hematuria, could potentially predispose individuals to clinically significant bleeding, while others felt that they met the criteria for a clinically significant bleed. These varying perspectives seemed to be influenced by healthcare providers' level of knowledge and experience in treating acute leukemia. For instance, physicians with experience ranging from 2 to 17 years were less likely to consider petechiae as clinically significant compared to a registered nurse with 22 years of experience who viewed it as clinically significant.

The type of bleeding was also a determining factor in whether other healthcare team members were notified. Some bedside nurses reported informing nurse practitioners of every new type of bleed and documenting new bruises in the patient's chart for other team members to review. Other nurse participants indicated that they would notify the team if there was active bleeding that could be potentially concerning, such as melena or hematochezia, signs of intracranial bleeding, overt bleeding, hematuria, petechiae, uncontrolled bleeding, or changes in vital signs that warranted a physician's attention.

> “I think anything that is, but it’s probably old-I don’t know it’s sometimes also an inkling-it's hard to really pinpoint, but anything that's over-excessive. Like, if there's actually frank blood like this is just lots and lots of amounts of it in the stool or in their urine. That's definitely something that requires like a definite call,

> like right quickly type. And anything that would kind of put them at risk for—their well-being, like I don't know. I feel like a lot of times, it's really just that an inkling I have. Like sometimes you just look at them, and you know that they're not doing well, and the fact that they're bleeding too, just makes you feel a little bit worried and concerned. So that's when you would actually do that and like give physician the call. Versus let's say you see a small bruise on the arm, or like a bruise on the leg, that probably won't warrant something that is particle as an escalation versus somebody who's like over-excessively bleeding." N01

One nurse practitioner participant shared the types of bleeds that she was frequently notified about:

> "So they would tell me if there was some overt bleeding such as hemoptysis or hematemesis with their bleeding through in- when they cough up frank blood, and when they throw up frank blood; if there's blood in their urine, hematuria; if there's blood in their stool, either melena, which is black GI bleeding, or hematochezia, which is frank blood from the lower bowel. If there's pain, that's weird, and it's a really good in-tune nurse that knows that maybe a lower back pain might be intraperitoneal bleed. If there's a headache, that, or visual changes that they think are new, that the patient hasn't talked about before that they want to make me aware of. If they have conjunctival bleeding or bleeding in the sclera of the eye. Basically bleeding anywhere that is worrisome, not just a little ooze from

somewhere that's well controlled. Or if they have a really bad nosebleed that's not being controlled. So basically any bleeding that is worrisome." N04

Clinically significant bleeds

Participants often based their assessment of whether a bleed was clinically significant on specific characteristics, such as the amount of blood, the duration and ability to gain control of the bleeding, the level of intervention required, the impact on vital signs, and the location of the bleed in areas that posed a risk to the individual's life.

For instance, when P02 described why hematuria was significant, they emphasized how concerning the volume of blood being lost was:

"And, so to me, whenever I see hematuria in the context of thrombocytopenia that, you know, that association, it, you know, is concerning the, you know, other things that, you know, if you're requiring a transfusion, you're losing a significant volume of blood which is concerning as a function that you know, just general."

Similarly, participants identified that continuous or uncontrolled bleeding indicated that the bleeding was clinically significant.

> "I think, just in general, if you, wherever it is, if you just, if you have bleeding that's uncontrolled, then that would be clinically significant to me just because then it requires prompt intervention and monitoring." N10

Many participants reported that clinically significant bleeds were the ones that necessitated "significant" interventions. These interventions included diagnostic testing (e.g., endoscopy for a GI bleed), medications (e.g., tranexamic acid), specialist consults (e.g., ENT, gastroenterology, urology), a blood or platelet transfusion, or surgical intervention to stop the bleeding.

> "So, for me, clinically significant bleeding would be anything that requires intervention. So, either with blood product administration, or administration of other medications to prevent bleeding, or intervention like using pressure bandages, requiring like an endoscopy to look in the stomach if there's bleeding from the stomach or the bowels, so anything that really requires us to intervene." P03

However, not all healthcare providers assigned the same weight to these interventions. For instance, most physicians had a strong consensus that the use of transfusions was indicative of significant bleeds. One physician participant with 24 years of experience in acute leukemia noted that only interventions beyond tranexamic acid or transfusion were significant.

> "Well, I think if you have to do anything beyond tranexamic acid or a platelet transfusion, so if the patient needs an intervention from someone else. If you have to call in a surgeon or a GI person to scope them or ENT to cauterize or, you know, a neurosurgeon to do a burr hole. Those things, I think, would be, would be concerning." P08

In general, there was moderate agreement that the need for transfusion, surgical intervention, specialist consult, and diagnostic testing indicated a significant bleeding event. Some participants also considered the use of tranexamic acid or pressure bandages/packing as indicative of significant bleeding.

Participants noted that these interventions may pose additional risks to acute leukemia patients, such as issues with other organs, like the kidneys or the gastrointestinal tract which could lead to other medical events.

Key indicators of potentially clinically significant bleeding identified by healthcare providers include changes in vital signs, blood work, and physical changes. Participants noted changes in platelet count, skin texture, hemoglobin, blood pressure, heart rate, respiratory rate, and neurological and psychological signs that raised concern. For example, P14 stated that a change in their vitals indicated that there were experiencing severe bleeding:

> "So, I mean, first of all, the clinical exam, you know, like if you see a large amount of blood, or if you're seeing a change in their vital signs, you know, that's a major thing, a change in level of consciousness, production in their hemoglobin as well, which indicates that they're losing significant amounts of blood."

Visible bleeding was another sign of concern for a clinically significant bleed. N04 noted that patients would alert her if they saw "frank blood" defined as fresh red blood. Some particular areas would be of particular concern:

> "So they would tell me if there was some overt bleeding such as hemoptysis or hematemesis with their bleeding through in-when they cough up frank blood, and when they throw up frank blood; if there's blood in their urine, hematuria; if there's blood in their stool, either melena, which is black GI bleeding, or hematochezia, which is frank blood from the lower bowel."

Some participants expressed that a clinically significant bleed included any bleeding that was life-threatening. P06 described a clinically significant bleed as:

> "I think any bleeding which can put the patient's life at risk, it's considered serious or fatal. Any bleeding which can cause significant organ damage, for example, intracranial bleed, like massive GI bleed, which can affect their vital signs and

make them, for example, clinically in a hypovolemic or hemorrhagic shock. I think it's serious".

These bleeds were mentioned as bleeds that could cause death or permanent damage (e.g., neurologic damage). For instance, all participants identified that intracranial bleeds were life-threatening and clinically significant. Some participants mentioned that other life-threatening bleeds also included gastrointestinal bleeding, retroperitoneal bleeding and pulmonary bleeding.

The healthcare participants' years of experience working in acute leukemia did not appear to have a significant impact on how they identified significant bleeds. Physicians identified a broad range of bleeds that were particularly worrisome and clinically significant, whereas bedside nurses and nurse practitioners may have had a narrower focus. For instance, physicians mentioned bleeds such as post-procedural bleeding with significant blood flow, hematemesis, joint bleeding, hematomas, and mucosal bleeding were areas of concern. Despite differences in the types of bleeds that participants found concerning, there was a general consensus that any bleeding in the brain, abdominal, or thoracic areas was particularly worrisome.

The perspectives on the characteristics of clinically significant bleeds varied by healthcare providers. For example, there was little agreement between bedside nurses on characteristics that defined clinical significance. In their interviews, they each mentioned

different features that could indicate a clinically significant bleed, such as the need for critical care intervention, the presence of overt blood, significant blood loss, drops in hemoglobin levels, the need for transfusions, uncontrolled bleeding, the use of tranexamic acid, and the need for diagnostic testing.

In contrast to the bedside nurses, the nurse practitioners had a stronger agreement with each other on the characteristics of clinically significant bleeds. All participants described changes in vital signs, the need for transfusions, and specialist consultations as indications of significant bleeding. Some participants also noted that the amount of blood, uncontrolled bleeding, diagnostic testing, and the presence of overt blood were also factors that suggested significant bleeding.

There was moderate agreement among physicians regarding indicators including life-threatening bleeding, uncontrolled and prolonged bleeding, the amount of blood loss, damage to other organs, and the use of interventions such as tranexamic acid, diagnostic testing, surgery, or specialist consultations. A few physician participants also mentioned that the presence of overt or visible blood and changes in the level of consciousness were indicators of concern.

Predicting a serious bleed

Participants acknowledged that several factors could influence the prediction of a serious bleed. They explained that prediction is closely tied to the assessment of the

patient's condition and bleeding characteristics but is also subject to a degree of randomness and unpredictability. A few participants mentioned their clinical intuition, or subconscious insights based on past knowledge and experience, played a role in their prediction and assessment strategies.

For instance, when asked about their level of confidence in predicting a serious bleed, many participants described that it is often challenging, as it is dependent on the patient's disease and presentation. In some cases, bleeds could occur if a patient falls, making it difficult to predict.

> I think it's actually pretty difficult to predict a serious bleed, you know that's the thing, these are semi-random events, especially things, you know, a lot of cases significant bleeds will happen after a bit like, you know, after a fall, you know, and I've seen intracranial bleeding in an AL patient occurring after a fall. It's difficult to predict the fall, and some of the falls that I've seen happened in people who are you know, mid 40's no pathology suspect, but they trip on bed clothing or something. P12

Two bedside nurses mentioned that predicting the severity of a bleed often relied on their nurse's "inkling" or "gut feeling". They explained that despite a patient's normal vital signs or lab results, they could sense that something was not right, often through

subtle changes in the patient's behaviour. This intuition frequently prompted additional assessments to determine if a bleed was occurring.

> "Yeah, you know this, it's funny, because we really do talk about this whole gut feeling in hematology like if you sense that something is off. Sometimes you can't even explain it. Sometimes the vital signs may seem completely normal and um but you just know that there's something not right with the patients with their lengthy stays at the hospital. We know we do know our patients very well and you can usually sense that something's not quite right, even if you're not seeing it right away. Or even if you're not seeing it through like labs or vital signs just yet, or obvious blood loss. So yeah, it's whether putting your finger on it or just having that gut instinct, you can- there is a sense that something not great is happening whether it's a bleed or it's something else going on. […]" N08

Many participants described that there were factors that predisposed patients to a higher risk of bleeding and bruising. These factors included the use of blood thinners, high white blood count, thrombocytopenia, and concurrent health conditions (e.g., ulcers or other malignancies).

Other Types of Leukemia

Some participants highlighted the increased risk of bleeding for patients presenting with acute promyelocytic leukemia (APL), due to their disease manifestation,

which makes them more susceptible to clinically significant bleeding events with disseminated intravascular coagulation. They noted that APL patients are more likely to bleed with trauma, such as from their line insertions. A few participants described bleeds that are common and potentially concerning in APL patients, including such as epistaxis, hematuria, melena, mucosal bleeding, intracranial hemorrhage, retroperitoneal bleeding, and joint bleeding.

> "I mean, they, they just bleed more with trauma. They bleed more with – so their line insertions, or bone marrows. They can have more mucocutaneous bleeding, so a bit more epistaxis but these are all the same bleeds we see in the other patients, so yeah." P08

Patients' concerns about bleeding

The participants discussed the involvement of patients in their own care, which encompassed addressing their concerns regarding bleeding, providing them with an educational overview of their disease and associated bleeding risk, as well as engaging them in clinical assessments.

For instance, patients would alert the healthcare team about their worries about some bleeds including petechiae, gum bleeding, epistaxis, melena, hemoptysis or hematemesis, heavy menses, hematuria, bruises, intracranial bleeding, and subconjunctival hemorrhages. Some participants noted that patients tend to mention their

concerns about signs and symptoms of bleeding when they are visible or causing distress. Several physician participants noted that for patients, the cosmetic aspect of bleeding was most alarming.

> "Yeah, I would say, it's interesting, you know, when we're having this discussion that I think that some patients can be really focused on the cosmetic aspect of the bleeding, and it can be really distressing to them. Not just like from a, you know, it doesn't look nice, but from a worry – it it's a reminder on your skin of like having a disease when you have a bruise from the disease, so I think that they tend to bring it up. The bleeding that we would consider maybe more nuisance bleeding, but to the patient is still very bothersome." P03

Accordingly, patient concerns that were reported to healthcare providers did not always equate to a judgement that the bleeding was clinically significant. Participants reported that bleeding that causes pain or is particularly irritating for the patient (e.g., epistaxis that won't stop) were concerns mentioned by patients.

A few participants stated that patients would ask questions when the bleeding occurred, which would lead to opportunities for them to provide education about their disease.

> "I find that they only would do that if it's actually happening at that moment. So if, again, they ring their call bell, and they see that they have new blood in the stool, or if they have blood in their urine, I think that's when they would ask questions, and they're- they'll be a little bit more anxious and concerned. And then, that's when we kind of do our education piece." N01

Educating patients about bleeding

Some healthcare providers provided a comprehensive overview of bleeding to their patients. Others felt that patients were already overwhelmed with information at the time of diagnosis and chose to be more general in their discussions about bleeding.

Several healthcare provider participants described providing patients with information about bleeding when describing their overall disease diagnosis. These conversations often revolved around why patients may experience bleeding, the risk of bleeding, types of bleeds they may experience, and which bleeds to notify the healthcare team about.

For instance, according to P13, patients were informed that they would experience bleeding as a result of both their disease and its treatment:

> "Hmm- So usually the discussion would be around the fact that because of leukemia, their counts might be low including the platelets in particular, or also

> dysfunctional. And along with the fact that induction chemotherapy will cause myelosuppression and drop their counts, there's a chance for platelets to be affected as well, and that increases their risk of bleed."

Others informed patients about bleeding when they were receiving blood products:

> "So, we usually tell our patients that chemotherapy will, or the treatment that they receive will often lower their platelet count, which can also increase their bleeding risk and the need for blood transfusion support. So sometimes patients have questions about why they're receiving blood products so often, what kind of blood products they're receiving." N01

Some healthcare providers informed patients of specific bleeding they may experience, including gastrointestinal bleeds, hematuria, scleral hemorrhages, rectal bleeding, epistaxis, intracranial bleeding, petechiae, melena, bleeding in the thoracic or abdominal cavity, pulmonary bleeding, heavier menses, mucocutaneous bleeding, and DIC for APL patients. N05 mentioned that healthcare providers specifically mentioned certain types of bleeds to patients, in order to make them aware of the potential risks:

> "Well, because those are typically, you know, somebody's platelets are low, which is what's going to happen with any of these leukemias – it just puts them at risk of bleeding. So, we lower the platelets by virtue of treatment, and that's just going to

> immediately put them at risk for bruising, bleeding. You know, all of those types of things that can happen with low platelets. And so, I think that it's important for people to know that right up front, that these are the things that could happen, so."

Additionally, nurses described educating patients on specific types of bleeds or signs and symptoms to encourage them to alert the healthcare team if any of those bleeds occurred:

> "Maybe some education around what melena looks like, when to call their nurse, or report this through like their provider at the bedside. And similarly, like reporting symptoms like headaches or neurological symptoms. Those are the common sites for bleeding that they would really need to be aware of those possibilities, and then to if- they're having things like epistaxis that won't stop, letting us know." N03.

As part of patient education, nurses emphasized the importance of careful personal hygiene activities to reduce the risk of bleeding.

> "I talk to them right from 'don't use a straight razor or a razor to shave your legs because you may bleed, or a hard toothbrush because you may have bleeding from the gums' all the way to, 'If you do cut yourself that you're going to bleed for a long period of time' […]" N04.

Assessment and documenting bleeding & bruising

During the interviews, healthcare providers described their process of identifying, assessing, and documenting new bleeds and bruises in AL patients.

Physician, nurse and nurse practitioner participants affirmed potential challenges in identifying bruising and bleeding on darker skin tones, emphasizing the importance of involving patients in clinical assessments. Nurses assessed patients daily for bleeding risk by checking their blood work and inquiring about any new bleeding, rashes, or bruises. Some nurses specifically asked patients if they experienced any pain, changes in stool, vomiting, headaches or visual disturbances.

> "So, usually for me, it's daily per shift. We do our assessment head to toe, which is also daily. However, if we do notice that there's something that's changed, or if the patient actually reports that something is different, we might do our assessments more frequently. I wouldn't give it an actual like hourly mark type thing. But if let's say they're reporting that there's blood in the urine or stool, we might have them actually go into the collection hat, and we may look at it at every void to see what it's looking like. And how that, I guess, progresses throughout the shift." N01

N08 described involving patients in these clinical assessments by requesting them to keep the evidence or write bleeds down.

> "I make sure that they're writing things down. So, I'll make sure that there's a piece of paper in the bathroom, so if they're having a GI bleed that they're writing that down. I tell them that if they're having like menstrual bleeds, GI bleeds, nosebleeds anything like that, to let me know, and to keep the like, the Kleenexes, the pads, or the stool in the toilet that they've had. So I tell them to keep those things because I need to see them. I ask them about headaches. If they have worsening headaches, then they need to let me know of that, and to let me know how bad the headaches are on a scale of one to ten. So I'm checking those pain scales. Hmm. Yeah. So basically having them record things down to as best as they can, and sort of like keeping the evidence- the stool in the toilet- because it's one thing for me to see it, and then I have to make sure I document it. But if it's relevant, then I need to also let the nurse practitioner or doctor know."

While most bleeds or bruises were documented in patient charts, this practice was dependent on the clinician. Some physicians acknowledged omitting notes about superficial bleeding, such as petechiae because they aren't "really serious" (P06) or were common in AL patients due to low platelets.

> "I would say that certainly any clinically significant bleeding is usually pretty consistently documented. I would say the more superficial bleeding, like bruising or ecchymosis and petechiae are not always consistently documented." P14

DISCUSSION

In this study, we aimed to investigate healthcare providers' perceptions of the components of clinically important bleeding in AL patients receiving induction chemotherapy. After conducting interviews with 19 healthcare providers, we identified several characteristics that are considered when determining whether a bleed was worrisome and/or clinically significant. The participants reported assessing the site of the bleed, the amount of blood, the management approach, the need for intervention, the recurrence of the bleed, and changes in vital signs to determine the significance of a bleed. Based on the description of bleeding characteristics, we established criteria to determine whether a type of bleeding was clinically significant.

Our analysis led to the creation of three categories to differentiate bleeds based on their clinical significance: those that were clinically significant, those that were potentially clinically significant, and those that lacked clinical significance. The category of potentially clinically significant bleeds reflected varying opinions among healthcare providers about the severity of the bleed and the presence of signs, such as melena, that were not definitive but required more investigations as they may indicate or lead to a significant bleeding event. The components of clinically significant bleeding events (e.g., the site of the bleeding, the amount of blood, and interventions needed) influenced healthcare providers' assessment strategies and the information they conveyed to patients. For example, bleeding from a site that has the potential to become clinically significant

would require closer monitoring before considering intervention. Healthcare providers also emphasized the importance of involving patients in this monitoring process by educating them on signs/symptoms to look out for and when to alert the team. Although patients often expressed their concerns or distress regarding specific bleeds, healthcare providers did not always consider this to be indicative of a clinically significant bleed. Instead, healthcare providers relied on their understanding of these characteristics and other factors that could influence the likelihood of a serious bleed. These additional factors included the assessment of the patient's condition, bleeding history and clinical intuition based on past knowledge and experience.

Although this is the first study to report on healthcare providers' perceptions of clinically important bleeding in AL patients, our findings resemble the Bleeding Severity Measurement Scale (BSMS) items by Webert et al. (8) The BSMS was developed through consultation with 48 experts who identified key determinants of clinically significant bleeding in chemotherapy-induced thrombocytopenia patients. The purpose of our study was to better understand the reasoning behind participants' perceptions of clinically significant bleeding, whereas Webert et al.'s intention was to create a scale that could be used to measure bleeding severity. Our findings align with the BSMS in that bleeding requiring interventions (e.g., transfusion, surgery, administration of medication) invasive processes or investigations, or increased monitoring were considered clinically significant. Webert et al. also identified central nervous system bleeding as a significant site of clinical significance, as well as significant pain, hemodynamic instability, vision

loss, significant morbidity, or bleeding contributing to a patient's death. (8) However, in contrast to Webert et al.'s study, our participants did not identify significant pain as a characteristic of clinically significant bleeding. This difference in findings may reflect that pain is an infrequent symptom associated with bleeding in this patient population. Webert et al. used several sources to generate items for their scale, including a literature review, reviewing existing bleeding measurement scales, and surveying healthcare providers. (8) It is possible that the difference in our findings regarding the role of significant pain in determining clinically significant bleeding could be attributed to differences in the expertise of healthcare providers and the sources of information used to develop the measurement scales. It is also possible our participants did not consider significant pain as meaningful or important when describing clinically significant bleeding. Additionally, the most frequent bleeds experienced by AL patients include skin, eye, epistaxis, gingival and gastrointestinal bleeding. (52) However, the healthcare providers may not perceive these bleeds to be painful, if not communicated by the patient. It's worth noting that the differences in the questions asked of participants in our study and Webert et al.'s study may have also contributed to the different findings regarding the role of significant pain in determining clinically significant bleeding. In our study, we asked participants to describe what they considered to be clinically significant bleeding, while Webert et al. asked participants to identify symptoms and signs of bleeding. (8) In contrast to Webert et al., who asked participants for specific aspects of bleeding, our study employed a broader question to explore the characteristics of clinically significant bleeding as perceived by healthcare providers. We asked, "What are the characteristics of

a clinically significant bleed?" This broader question may explain why participants did not report significant pain as a symptom of significant bleeding, as our question did not specifically inquire about symptoms and signs.

Two participants in our study described that their clinical intuition or subconscious insights played a role in predicting the severity of bleeding. They found it difficult to explain these intuitive judgements. We also saw implicit mention of intuition from participants who used phrases, such as a patient “not looking quite right” in terms of behaviour or remarking on other tacit signs of distress. Clinical intuition is a concept that has been recognized in medical and nursing education, described as a sense of knowing that something is true despite a lack of evidence. (53,54) Clinical intuition is understood as the rapid, subconscious formation of judgment that draws upon the clinician’s knowledge and expertise in a way that they cannot articulate. It should not be understood as a paranormal or “extrasensory” phenomenon. Clinical intuition also referred to as gut feeling, inkling or a hunch, is a concept that practitioners rely on and develop over time with encounters of their patients. (55) Nurses have reported that intuition is grounded in their knowledge, experience, and relationship with the patient. (53,54) This aligns with the discussions from the two nurses in our study, who described a hunch that helped them identify or predict a severe bleed. Both nurses who described this institution are bedside nurses, which may reflect the close relationship that bedside nurses form with their patients over time. (56) Interestingly, these nurses had varied experience as registered nurses, but relatively less experience working in acute leukemia, with less than 10 years

of experience in this specialty. This demonstrates that spending extended periods with patients allows these nurses to develop a strong sense of the patient's normal patterns and behaviours, which can help them recognize when something is amiss. This relationship between bedside nurses and patients is contrasted with the relationship that patients have with their physicians and nurse practitioners, who are not often physically present for extended periods. The nurses in our study emphasized that they do not rely solely on their intuition, but also look for signs of evidence. In situations where the evidence was lacking, they communicated their concerns to the healthcare team for further input and guidance. Additionally, clinical intuition has been widely discussed in the nursing literature in contrast to medicine. Research has suggested that physicians often struggle with articulating their intuition and tend to focus on easily identifiable components. (57,58) This could explain why only the nurse participants mentioned their clinical intuition explicitly in comparison to the physician participants. These findings also align with reports in the literature that suggest that clinical intuition is not a substitute for evidence-based practice, but rather an additional tool for healthcare providers to consider. (53) Although the concept of clinical intuition in the context of hematology has not been extensively discussed in the literature, the findings from our study suggest that bedside nurses' intuition may play a role in identifying and predicting severe bleeds in AL patients. Given the potential significance of this finding, clinical intuition in the context of hematology should be explored.

Participants in our study reported that there were factors that influenced the prediction of a serious bleed, including the patient's condition and bleeding characteristics. However, they also noted that there was an element of unpredictability. These findings align with those of McGrath et al. who conducted a study on Australian healthcare providers' experiences with catastrophic bleeding during end-of-life care in hematology. (9) Healthcare providers in the study by McGrath et al. suggested that while it was sometimes possible to predict the patients that were likely to bleed based on clinical predictors (e.g., blood counts) there was a level of unpredictability. (9) McGrath et al. also noted variability between healthcare providers and the factors that they considered when predicting a serious bleed. Healthcare providers in their study listed a variety of factors that could indicate whether a patient at end of life would bleed, such as their blood count, their diagnosis or type of hematologic disorder, and additional risk factors. (9) This list resembles the factors that our participants described for predicting a serious bleed in leukemia patients. Participants noted that the use of anticoagulation, changes in blood counts, concurrent health conditions, and different types of leukemia alerted them to the possibility of severe bleeding. These similarities in factors used for predicting bleeding severity suggest that there may be common factors that healthcare providers rely on across different patient populations and clinical contexts.

Implications for utility-based bleeding scale

The results of this study provide valuable insights that can inform the development of a utility-based bleeding scale, which has the potential to be used in acute

leukemia or transfusion clinical trials. Typically, measurement instruments are developed using a combination of qualitative and quantitative data. Qualitative interviews are often used to generate items or considerations for a tool, as well as to assess content validity. (19,59) In this study, we utilized semi-structured interviews to explore the components of clinically important bleeding. The use of qualitative description methodology enabled us to capture the participants' perspectives in their own words, which will be valuable in the development of the utility-based bleeding score. Revicki et al. conducted similar work by utilizing data from the literature, patient interviews, and discussions with physicians to generate items for their scale on asthma outcomes in patients. (60) However, their approach focused on asking participants to rank items for their scale. (60) In contrast, our study used an exploratory approach to identify what healthcare providers consider important before ranking and assessing for content validity. The exploratory findings from healthcare providers' interviews will also enhance the reliability and validity of the scale, as it captures what is clinically meaningful to providers and important to patients. Moving forward, we plan to integrate the healthcare provider data with patient interviews and results from a secondary analysis to generate items for the utility-based bleeding scale. We will then conduct short interviews or a Delphi process with healthcare providers and patients to assess content validity. The use of the Delphi process can help to obtain consensus and content validation on the components of clinically significant bleeding, through a series of surveys. (61) Similarly, the use of short interviews with experts can validate or provide additional insight towards the structure and content of the items.

Significance

Research has shown the value of conducting qualitative interviews or focus groups for the development of clinical outcome assessments in clinical trials. (62) Interviews with patients, caregivers, and clinicians provide insights beyond identifying that a change is clinically important, but also shed light on why it is important and how new blood products may improve patient care. (62) By complementing quantitative analyses and findings on clinical significance with qualitative data from those involved in patient care, we gain a deeper understanding of the meaningfulness of clinical outcomes. This holistic approach enriches our knowledge and inform the development of more patient-centred clinical assessments that reflect the perspectives and needs of all individuals involved in the patient's care.

Implications for Education, Clinical Practice, and Research

The results of this study have important implications for education, clinical practice, and research. Firstly, our findings revealed differences among healthcare providers in how they view and understand the characteristics of significant bleeding. While there was some consensus on bleeds that were clinically significant, there were others that fell into a grey area, where some healthcare providers believed they were significant while others did not. This highlights the need for more concise definitions, education, or resources to help healthcare providers consistently identify the signs and symptoms of clinically important bleeding.

Our study also revealed that only some participants provided a rationale for significant bleeds based on research evidence, indicating the need to further encourage healthcare providers to engage with research evidence to inform and improve clinical practice. These findings underscore the importance of ongoing education, knowledge translation, and evidence-based practice to ensure optimal care for patients undergoing induction chemotherapy for acute leukemia.

The differences identified in how healthcare providers perceive and define clinically significant bleeding highlight the need for further investigation into the factors that contribute to these differences and the establishment of guidelines for bleeding assessments. Additionally, the explicit mention of clinical intuition by nurses compared to physicians suggests a potential area of research on the role of clinical intuition in bleeding assessments and its integration into clinical decision-making. This could help advance our understanding of evidence-based medicine and clinical intuition in hematology. Furthermore, the focus of our study was on healthcare providers who provide care for AL patients undergoing induction chemotherapy. Future research could explore the perspectives of patients and caregivers on their experiences and perceptions of bleeding during induction chemotherapy and consolidation. This could help develop a definition of clinically important bleeding that is informed by evidence, clinicians, and patients and provide a comprehensive understanding of bleeding in the context of patient care.

Strengths and Limitations

To our knowledge, this is the first qualitative study that explored healthcare providers' perceptions of the components of clinically important bleeding in the acute leukemia population. This study is unique as it included perspectives from a wide range of physicians with varying expertise and different geographical regions. The components of clinically important bleeding can be represented when developing a utility-based bleeding score that accounts for the perspectives of those treating the disease, as well as clinical evidence. By incorporating the perspectives of healthcare providers who treat acute leukemia patients with other sources of information, a score can reflect the characteristics that are most relevant to the clinical decision-making process. Thus, the score can lead to more effective and tailored interventions for patients with acute leukemia who are at risk of bleeding.

This study has a few limitations that need to be considered. This study was limited by the sample of nurses we were able to obtain. We were not able to recruit nurse practitioners and registered nurses beyond two institutions in the same geographical region. The perspectives of the nurses in this study may not represent those of all nurses in similar or different geographical regions. However, we also acknowledge the distinctions in the clinical roles of NPs and RNs, and how their experiences and knowledge may elicit different perspectives of clinically important bleeding. Additionally, the interpretations are bound to the historical and geographical context in which the study was conducted and may not apply to all settings.

CONCLUSION

Healthcare providers identified several characteristics are considered when determining whether a bleed was worrisome and/or clinically significant. Through our analysis, we created three categories: clinically significant, those that were potentially clinically significant, and those that lacked clinical significance. Healthcare providers relied on their understanding of these characteristics and other factors such as the patient's condition, bleeding history and clinical intuition to predict the likelihood of a serious bleed. Future research should explore AL patients' perspectives of clinically important bleeding to create a definition or utility-based bleeding score that is informed by evidence, clinicians, and patients.

REFERENCES

1. Lee S. Canadian Cancer Society. [cited 2023 Apr 6]. Leukemia statistics. Available from: https://cancer.ca/en/cancer-information/cancer-types/leukemia/statistics

2. Chai KL, Wood EM. What is clinically significant bleeding? Transfusion. 2021;61(2):340–3.

3. Wilson NR, Khan M, Cox TM, Nassif M, Qiao W, Garg N, et al. Bleeding outcomes in thrombocytopenic acute leukemic patients with venous thromboembolism. eJHaem. 2020;1(2):448–56.

4. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981 Jan 1;47(1):207–14.

5. Heddle NM, Cook RJ. Composite outcomes in clinical trials: what are they and when should they be used? Transfusion. 2011 Jan;51(1):11–3.

6. Heddle NM, Arnold DM, Webert KE. Time to rethink clinically important outcomes in platelet transfusion trials. Transfusion. 2011 Feb;51(2):430–4.

7. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite Outcomes in Randomized TrialsGreater Precision But With Greater Uncertainty? JAMA. 2003 May 21;289(19):2554–9.

8. Webert KE, Arnold DM, Lui Y, Carruthers J, Arnold E, Heddle NM. A new tool to assess bleeding severity in patients with chemotherapy-induced thrombocytopenia (CME). Transfusion. 2012;52(11):2466–74.

9. McGrath P, Leahy M. Catastrophic bleeds during end-of-life care in haematology: controversies from Australian research. Support Care Cancer. 2009 May 1;17(5):527–37.

10. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. Trials. 2017 Jun 20;18(3):280.

11. Rose-Inman H, Kuehl D. Acute Leukemia. Hematology/Oncology Clinics. 2017 Dec 1;31(6):1011–28.

12. Lee S. Canadian Cancer Society. [cited 2022 May 3]. What is leukemia? Available from: https://cancer.ca/en/cancer-information/cancer-types/leukemia/what-is-leukemia

13. Shysh AC, Nguyen LT, Guo M, Vaska M, Naugler C, Rashid-Kolvear F. The incidence of acute myeloid leukemia in Calgary, Alberta, Canada: a retrospective cohort study. BMC Public Health. 2017 Aug 3;18(1):94.

14. Pelcovits A, Niroula R. Acute Myeloid Leukemia: A Review. :3.

15. Wang TF, Makar RS, Antic D, Levy JH, Douketis JD, Connors JM, et al. Management of hemostatic complications in acute leukemia: guidance from the SSC of the ISTH. J Thromb Haemost. 2020 Dec;18(12):3174–83.

16. Heddle NM, Cook RJ, Sigouin C, Slichter SJ, Murphy M, Rebulla P, et al. A descriptive analysis of international transfusion practice and bleeding outcomes in patients with acute leukemia. Transfusion. 2006;46(6):903–11.

17. Stanworth SJ, Hudson CL, Estcourt LJ, Johnson RJ, Wood EM. Risk of bleeding and use of platelet transfusions in patients with hematologic malignancies: recurrent event analysis. Haematologica. 2015 Jun;100(6):740–7.

18. Cannas G, Thomas X. Supportive care in patients with acute leukaemia: historical perspectives. Blood Transfus. 2015 Apr;13(2):205–20.

19. Streiner DL, Norman GR, Cairney J. Health Measurement Scales: A Practical Guide to Their Development and Use. Oxford University Press; 2015. 415 p.

20. Estcourt LJ, Heddle N, Kaufman R, McCullough J, Murphy MF, Slichter S, et al. The challenges of measuring bleeding outcomes in clinical trials of platelet transfusions. Transfusion. 2013;53(7):1531–43.

21. Stanworth SJ, Dyer C, Choo L, Bakrania L, Copplestone A, Llewelyn C, et al. Do All Patients With Hematologic Malignancies and Severe Thrombocytopenia Need Prophylactic Platelet Transfusions?: Background, Rationale, and Design of a Clinical

Trial (Trial of Platelet Prophylaxis) to Assess the Effectiveness of Prophylactic Platelet Transfusions. Transfusion Medicine Reviews. 2010 Jul 1;24(3):163–71.

22. Dyer C, Alquist CR, Cole-Sinclair M, Curnow E, Dunbar NM, Estcourt LJ, et al. A multicentred study to validate a consensus bleeding assessment tool developed by the biomedical excellence for safer transfusion collaborative for use in patients with haematological malignancy. Vox Sanguinis. 2018;113(3):251–9.

23. Webert K, Cook RJ, Sigouin CS, Rebulla P, Heddle NM. The risk of bleeding in thrombocytopenic patients with acute myeloid leukemia. Haematologica. 2006 Nov;91(11):1530–7.

24. Balitsky AK, Liu Y, Van der Meer PF, Heddle NM, Arnold DM. Exploring the components of bleeding outcomes in transfusion trials for patients with hematologic malignancy. Transfusion. 2021;61(1):286–93.

25. Matteson K, Scott D, Raker C, Clark M. The menstrual bleeding questionnaire: development and validation of a comprehensive patient-reported outcome instrument for heavy menstrual bleeding. BJOG: An International Journal of Obstetrics & Gynaecology. 2015;122(5):681–9.

26. Pike M, Chopek A, Young NL, Usuba K, Belletrutti MJ, McLaughlin R, et al. Quality of life in adolescents with heavy menstrual bleeding: Validation of the Adolescent Menstrual Bleeding Questionnaire (aMBQ). Research and Practice in Thrombosis and Haemostasis. 2021;5(7):e12615.

27. Germini F, Debono VB, Page D, Zuk V, Kucher A, Cotoi C, et al. User-Centered Development and Testing of the Online Patient-Reported Outcomes, Burdens, and Experiences (PROBE) Survey and the myPROBE App and Integration With the Canadian Bleeding Disorder Registry: Mixed Methods Study. JMIR Human Factors. 2022 Mar 2;9(1):e30797.

28. Stalfelt AM, Brodin H, Pettersson S, Eklöf A. The final phase in acute myeloid leukaemia (AML): A study on bleeding, infection and pain. Leukemia Research. 2003 Jun 1;27(6):481–8.

29. Tunkel DE, Anne S, Payne SC, Ishman SL, Rosenfeld RM, Abramson PJ, et al. Clinical Practice Guideline: Nosebleed (Epistaxis). Otolaryngol Head Neck Surg. 2020 Jan 1;162(1_suppl):S1–38.

30. Cook D, Heyland D, Griffith L, Cook R, Marshall J, Pagliarello J, et al. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. Critical Care Medicine. 1999 Dec;27(12):2812.

31. Ketai LH, Mohammed TLH, Kirsch J, Kanne JP, Chung JH, Donnelly EF, et al. ACR Appropriateness Criteria® Hemoptysis. Journal of Thoracic Imaging. 2014 May;29(3):W19.

32. Zheng R, Dong F, Qiang W, Wang Y. Nurses' experiences with catastrophic upper gastrointestinal bleeding in patients with hepatocellular carcinoma: A qualitative study. European Journal of Oncology Nursing. 2013 Aug 1;17(4):408–15.

33. Sandelowski M. Whatever happened to qualitative description? Research in Nursing & Health. 2000;23(4):334–40.

34. Sandelowski M. What's in a name? Qualitative description revisited. Research in Nursing & Health. 2010;33(1):77–84.

35. Bradshaw C, Atkinson S, Doody O. Employing a Qualitative Description Approach in Health Care Research. Global Qualitative Nursing Research. 2017 Jan 1;4:2333393617742282.

36. Neergaard MA, Olesen F, Andersen RS, Sondergaard J. Qualitative description – the poor cousin of health research? BMC Medical Research Methodology. 2009 Jul 16;9(1):52.

37. Petty NJ, Thomson OP, Stew G. Ready for a paradigm shift? Part 1: Introducing the philosophy of qualitative research. Manual Therapy. 2012 Aug 1;17(4):267–74.

38. Lincoln YS, Guba EG. Naturalistic Inquiry. SAGE; 1985. 422 p.

39. Giacomini M. Theory Matters in Qualitative Health Research. In: The SAGE Handbook of Qualitative Methods in Health Research [Internet]. 1 Oliver's Yard, 55 City Road, London EC1Y 1SP United Kingdom: SAGE Publications Ltd; 2010 [cited 2023 Feb 16]. p. 125–56. Available from: https://methods.sagepub.com/book/sage-hdbk-qualitative-methods-in-health-research/n8.xml

40. Whitehead CR, Austin Z, Hodges BD. Flower power: the armoured expert in the CanMEDS competency framework? Adv Health Sci Educ Theory Pract. 2011 Dec;16(5):681–94.

41. R. N. SHP, Stern PN. Discovery of Nursing Gestalt in Critical Care Nursing: The Importance of the Gray Gorilla Syndrome. Image: the Journal of Nursing Scholarship. 1983;15(2):51–7.

42. Patton MQ. Qualitative evaluation and research methods, 2nd ed. Thousand Oaks, CA, US: Sage Publications, Inc; 1990. 532 p. (Qualitative evaluation and research methods, 2nd ed).

43. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. Adm Policy Ment Health. 2015 Sep;42(5):533–44.

44. Sandelowski M. Sample size in qualitative research. Research in Nursing & Health. 1995;18(2):179–83.

45. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. Qual Health Res. 2016 Nov 1;26(13):1753–60.

46. Richards HM, Schwartz LJ. Ethics of qualitative research: are there special issues for health services research? Family Practice. 2002 Apr 1;19(2):135–9.

47. Elo S, Kyngäs H. The qualitative content analysis process. Journal of Advanced Nursing. 2008;62(1):107–15.

48. Hsieh HF, Shannon SE. Three Approaches to Qualitative Content Analysis. Qual Health Res. 2005 Nov 1;15(9):1277–88.

49. Boeije H. A Purposeful Approach to the Constant Comparative Method in the Analysis of Qualitative Interviews. Quality & Quantity. 2002 Nov 1;36(4):391–409.

50. Morse JM. Critical Analysis of Strategies for Determining Rigor in Qualitative Inquiry. Qual Health Res. 2015 Sep 1;25(9):1212–22.

51. Milne J, Oberle K. Enhancing rigor in qualitative description: a case study. J Wound Ostomy Continence Nurs. 2005;32(6):413–20.

52. Franchini M, Frattini F, Crestani S, Bonfanti C. Bleeding Complications in Patients with Hematologic Malignancies. Semin Thromb Hemost. 2013 Feb;39(01):094–100.

53. Melin-Johansson C, Palmqvist R, Rönnberg L. Clinical intuition in the nursing process and decision-making—A mixed-studies review. Journal of Clinical Nursing. 2017;26(23–24):3936–49.

54. Vanstone M, Monteiro S, Colvin E, Norman G, Sherbino J, Sibbald M, et al. Experienced physician descriptions of intuition in clinical reasoning: a typology: Diagnosis. 2019 Sep 1;6(3):259–68.

55. Stolper E, Van de Wiel M, Van Royen P, Van Bokhoven M, Van der Weijden T, Dinant GJ. Gut Feelings as a Third Track in General Practitioners' Diagnostic Reasoning. Journal of General Internal Medicine. 2011 Feb;26(2):197–203.

56. Gobet F, Chassy P. Towards an alternative to Benner's theory of expert intuition in nursing: A discussion paper. International Journal of Nursing Studies. 2008;45(1):129–39.

57. Peters A, Vanstone M, Monteiro S, Norman G, Sherbino J, Sibbald M. Examining the Influence of Context and Professional Culture on Clinical Reasoning Through Rhetorical-Narrative Analysis. Qual Health Res. 2017 May 1;27(6):866–76.

58. Cristancho S, Bidinosti S, Lingard L, Novick R, Ott M, Forbes T. Seeing in Different Ways: Introducing "Rich Pictures" in the Study of Expert Judgment. Qual Health Res. 2015 May;25(5):713–25.

59. Keszei AP, Novak M, Streiner DL. Introduction to health measurement scales. Journal of Psychosomatic Research. 2010 Apr;68(4):319–23.

60. Revicki DA, Kline Leidy N, Brennan-Diemer F, Sorensen S, Togias A. Integrating Patient Preferences Into Health Outcomes Assessment: The Multiattribute Asthma Symptom Utility Index. Chest. 1998 Oct 1;114(4):998–1007.

61. Bull C, Crilly J, Latimer S, Gillespie BM. Establishing the content validity of a new emergency department patient-reported experience measure (ED PREM): a Delphi study. BMC Emergency Medicine. 2022 Apr 9;22(1):65.

62. Staunton H, Willgoss T, Nelsen L, Burbridge C, Sully K, Rofail D, et al. An overview of using qualitative techniques to explore and define estimates of clinically important change on clinical outcome assessments. Journal of Patient-Reported Outcomes. 2019 Mar 4;3(1):16.

APPENDIX 1 – PHYSICIAN INTERVIEW GUIDE

Bleeding Perceptions Questions

Now I'm going to ask you some questions about your personal perceptions of bleeding. We are interested in hearing about your experience and your understanding based on your clinical experience working with and treating patients with acute leukemia.

1). What do patients with newly diagnosed AL need to know about the potential for bleeding when they are first diagnosed and ready to start induction chemotherapy?

1a). Do you tell patients about the risk of bleeding and how it may present?

1b). Are there particular bleeds you mention and why?

1c). Do you differentiate between bleeding as a disease manifestation or a treatment side effect?

2). Do patients discuss their concerns about signs and symptoms of bleeding? If YES, what are they?

a) Do patients discuss their concerns about bruising? If YES, what are they?

3). When caring for patients with AL undergoing chemotherapy, what bleeding is clinically significant?

3a). What about this bleed is concerning?

3b). What is this bleed a sign or symptom of?

3c). Is there any bruising that is clinically significant?

4). What bleeding are you less worried about?

5). Thinking about patients with APL, do they experience the same types of clinically significant bleeds as other AML patients and ALL patients?

5a) Are there certain types of clinically significant bleeds that primarily tend to occur, or only occur in patients with APL? Which ones?

6). What are the characteristics of a clinically significant bleed (i.e. serious bleed)?

6a). When you see bleeding in a patient, what signs or indications tell you whether or not this bleeding is severe? Probes: For example, these could be signs and symptoms, impacts on the patient, or tests/treatments that might have to be ordered.

6b). Sometimes bleeding might be significant enough to need treatment. Are there particular interventions that would make you think that a bleed was significant?

6c) Of the treatments and tests you just mentioned, which ones might have a large impact on the patient?

6d). Are there types of minor bleeding that based on your experience serve as a cue or hint or that tip you off that a worse, more significant bleed may develop? P

6e) In your DCF, you mentioned ___ serious bleeding event. Can you tell me a little more about that?

6f) What do you perceive to be the impact or clinical significance of a patient experiencing multiple bleeds, occurring on the same day?

7). Are signs and symptoms of bleeding documented when they occur? If YES, are all types of bleeding documented? (i.e., mild bleeding, like petechiae, or only more severe bleeding)?

8). How do you assess bruising? Is it the same for darker skin tones or do you do something different?

9). How well do you think you are able to predict a serious bleed?

9a). Are you able to put your finger on signs or symptoms that give you the signal of a serious bleed developing in the future?

10). Do you have any other perceptions or comments about bleeding in this patient population that we have not discussed during this interview that you would like to share?

11). Would you be willing to be contacted to again about this study?

12). Would you be willing to circulate an email invitation about the study through your professional networks?

APPENDIX 2 – NURSE INTERVIEW GUIDE

Bleeding Perceptions Questions

1). What do patients with newly diagnosed AL need to know about the potential for bleeding when they are first diagnosed and ready to start induction chemotherapy?

1a) We know that clinical life is very busy in an ideal world what do you teach your patients about bleeding?

1b) Is there anything you think your patients should know that you don't usually teach them?

1c). Do you tell patients about the risk of bleeding and how it may present?

Probes:

Are there particular bleeds you mention, and why?

1d). When speaking with patients do you differentiate between bleeding as a disease manifestation or a treatment side effect?

2). As a nurse caring for patients with AL do you assess bleeding? If YES, ask 2a-d. If NO, proceed to question 3.

2a). How often do you assess bleeding?

2b). How do you perform that assessment?

2c). What is the clinical purpose of the assessments?

2d). Do you involve patients in assessments? Why or why not?

2e). Are there certain signs/symptoms of bleeding that you would notify other members of the healthcare team about immediately? If yes, which ones and why?

3). Do you document bleeding? YES/NO

3a). If YES, are all types of bleeding documented? (i.e., mild bleeding, like petechiae, or only more severe bleeding)

4). Do patients discuss their concerns about signs and symptoms of bleeding with you? If YES, what are they?

a) Do patients discuss their concerns about bruising? If YES, what are they?

5). How do you assess bruising? Is it the same for darker skin tones or do you do something different?

6). When caring for patients with AL undergoing induction chemotherapy, what bleeding is clinically significant?

6a). What about this bleed is concerning?

6b). What is this bleed a sign or symptoms of?

6c). Is there any bruising that is clinically significant?

6d) What do you perceive to be the impact or clinical significance of a patient experiencing multiple bleeds, occurring on the same day?

7). What bleeding are you less worried about?

8.) Thinking about patients with APL, do they experience the same types of clinically significant bleeds as other AML patients and ALL patients?

8a) Are there certain types of clinically significant bleeds that primarily tend to occur, or only occur in patients with APL? Which ones?

9). What are the characteristics of a clinically significant bleed (i.e. serious bleed)?

9a). When you see bleeding in a patient, what signs or indications tell you whether or not this bleeding is severe? Probes: For example, these could be signs and symptoms, impacts on the patient, or tests/treatments that might have to be ordered.

9b). Sometimes bleeding might be significant enough to need treatment. Are there particular interventions that would make you think that a bleed was significant?

9c) Of the treatments and tests you just mentioned, which ones might have a large impact on the patient?

9d). Are there types of minor bleeding that based on your experience serve as a cue or hint or that tip you off that a worse, more significant bleed may develop?

9e) In your DCF, you mentioned ___ serious bleeding event. Can you tell me a little more about that?

10). How well do you think you are able to predict a serious bleed?

10a). Would you be able to put your finger on the symptoms or signs that give you the signal that this may be a serious bleed?

11). Do you have any other perceptions or comments about bleeding in this patient population that we have not discussed during this interview that you would like to share?

12). Would you be willing to be contacted to again about this study?

13). Would you be willing to circulate an email invitation about the study through your professional networks?

APPENDIX 3 – NURSE DATA COLLECTION FORM

Confidential

Defining Clinically Important Bleeding Outcomes Study - Nurse Demographic Information Survey

Thank you for agreeing to participate in an interview for the Defining clinically important bleeding outcomes for clinical trials in hematological malignancies: perceptions of patients and health care providers, study.

Prior to the interview we would like to collect some demographic information from you using this survey.

Note: As specified in the study informed consent form, records identifying you will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in the consent document.

Please contact the study coordinator using the contact information provided below if you have any questions:

Study coordinator: Shannon Lane

Email: lanesj@mcmaster.ca

Phone: 905 525 9140 ext. 21788

Thank you!

Defining Clinically Important Bleeding Outcomes Study

Nurse Demographic Information Survey

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1. What is your gender identity? (choose all that apply)
   - ☐ Woman
   - ☐ Man
   - ☐ Transgender
   - ☐ Non-binary
   - ☐ Prefer not to respond
   - ☐ Other

2. What is the name of the hospital in which you provide care for inpatients with acute leukemia? _____

3. What is your position? _____

4. How many years have you been practicing? _____

5. How many years of experience do you have working with inpatients with acute leukemia? _____

6. What is the approximate number of acute leukemia inpatients that you care for in a year? _____

7. Have you ever cared for an acute leukemia inpatient who experienced a severe bleeding event?
   - ○ Yes
   - ○ No

7a. If yes, please describe the type of severe bleeding event and approximately when this took place (i.e. what year?) _____

Defining Clinically Important Bleeding Outcomes Study Nurse Demographic Information Data Collection Form v2.0_4FEB2022

Thank you for providing this information.

APPENDIX 4 – PHYSICIAN DATA COLLECTION FORM

Confidential

Defining Clinically Important Bleeding Outcomes Study - Physician Demographic Information Survey

Thank you for agreeing to participate in an interview for the Defining clinically important bleeding outcomes for clinical trials in hematological malignancies: perceptions of patients and health care providers, study.

Prior to the interview we would like to collect some demographic information from you using this survey.

Note: As specified in the study informed consent form, records identifying you will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in the consent document.

Please contact the study coordinator using the contact information provided below if you have any questions:

Study coordinator: Shannon Lane

Email: lanesj@mcmaster.ca

Phone: 905 525 9140 ext. 21788

Thank you!

Defining Clinically Important Bleeding Outcomes Study

Physician Demographic Information Survey

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1. What is your gender identity? (choose all that apply)
   - ☐ Woman
   - ☐ Man
   - ☐ Transgender
   - ☐ Non-binary
   - ☐ Prefer not to respond
   - ☐ Other

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2. What is the name of the hospital in which you provide care to patients with acute leukemia? _____

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3. What is your position? _____

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4. How many years have you been practicing? _____

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5. How many years of experience do you have working with patients with acute leukemia? _____

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6. What is the approximate number of acute leukemia patients that you care for in a year? _____

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7. Have you ever cared for an acute leukemia patient who has experienced a severe bleeding event?
   - ◯ Yes
   - ◯ No

7a. If yes, please describe the type of severe bleeding event and approximately when this took place (i.e., what year?). _____

Defining Clinically Important Bleeding Outcomes Study Physician Demographic Information Data Collection Form v2.0_4FEB2022

Thank you for providing this information.

APPENDIX 5 – PHASE 1 CODEBOOK

Defining Clinically Important Bleeding Outcomes - Codebook

Name	Description
1. Clinically Significant Bleeds (CSB)	Clinically significant bleeds identified by the participant
a. Type of Bleed/Bruising	The specific type of bleed mentioned (e.g., intracranial, GI bleed, etc) will be made as a code, with the rationale and cause as a child code.
i. Rationale	
ii. Cause or Sign & Symptoms	
b. Characteristics of CSB	The characteristics that participants identify make the bleed significant (e.g., duration of the bleed)
i. Amount or duration of the bleed	
ii. Continuous or uncontrolled bleeding	
iii. Significant drop in vital signs	e.g., haemoglobin, tachycardia, low blood count, hypotension (low blood pressure), hemodynamic instability, changes in IRT
iv. Visible bleeding	e.g., overt blood, fresh blood
v. Life-threatening bleed	e.g., bleed that can lead to death
vi. Bleed that can cause morbidity	e.g., bleed that can impact quality of life or damage/injury
vii. Bleeds that require interventions	e.g., blood transfusion, consult with ENT or other specialities, lab work, endoscopies, bronchoscopy, fibrinogen replacement
viii. Bleeds that can cause other medical events	
2. Predicting a serious bleed	
a. Bleeds that progress into worse bleeding/bruising	
b. Clinical intuition	
3. Less significant bleed	Bleeds that are not clinically significant or less worrisome to participants

a. Characteristics of LSB	
b. Type of Bleed/Bruising	The specific type of bleed mentioned (e.g., intracranial, GI bleed, etc) will be made as a code, with the rationale and cause as a child code.
i) Rationale	
ii) Cause	
4. Patients	
a. Information provided to patients	Information that patients are given when they are about to begin induction-chemotherapy or information provided by the care team.
b. Patient's concerns about bleeding	This include the signs or symptoms that they are concerned about
5. Assessing & Documenting Bleeding	Provider's description of how they document and assess bleeding in AL patients
a. Documenting the bleeding	
b. Assessing the patient for bleeding/bruising	
c. Detecting bleeding/bruising on different skin tones	
6. Risk Factors for Bleeding/Bruising	Risk factors that may influence bleeding or bruising in patients with AL
a. Different types of leukemia	e.g., APL
b. DIC	
c. Concurrent health conditions	e.g., thrombocytopenia
d. Blood Thinners/Aspirin	
7. Guidance on Bleeding	Guidance for providers for managing bleeding in AL patients