Harnessing the power of clinician judgement. Identifying risk of deteriorating and dying in people with a haematological malignancy: A Delphi study

Title

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Running head

Identifying dying hematology

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Acknowledgements

N/A

Conflict of interest statement

No conflict of interest has been declared by the author(s).

Funding statement

The lead author (EB) was funded by the following bodies to complete this study as a Doctor of Philosophy Candidate: National Health and Medical Research Council Centre for Research Excellence in End-of-Life Care, Queensland University of Technology, the Royal Brisbane and Women's Hospital, and Centaur Memorial Fund for Nurses.

Author contributions

All authors have agreed on the final version and meet at least one of the following criteria (recommended by the ICMJE*): 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content. * http://www.icmje.org/recommendations/

Abstract

Aim: To provide expert consensus on the clinical indicators that signal a person with a hematological malignancy is at high risk of deteriorating and dying.

Background: Identification of people who are at risk of deteriorating and dying is essential to facilitate patient autonomy, appropriate treatment decisions, and effective end-of-life care.

Design / methods: A three-step modified Delphi approach was conducted over a six-month period (September 2015 – March 2016) to gather opinion from an international panel of experts (n=27) on the clinical indicators that signal a person with a hematological malignancy is at high risk of deteriorating and dying. The first round was informed by a systematic review of prognostic factors present in the final months of life for people with a hematological malignancy. Consensus was achieved if 70% of responses fell within two points on a seven-point Likert-type scale.

Findings: Consensus was achieved on the following 11 clinical indicators: 1) advancing age; 2) declining performances status; 3) presence of co-morbidities; 4) disease status; 5) persistent infections (bacterial and viral); 6) fungal infections; 7) severe graft versus host disease; 8) requiring high care; 9) signs of frailty; 10) treatment limitations; and 11) anorexia and/or weight loss. Consensus was also achieved on associated themes and statements for each indicator.

Conclusion: The findings of this study indicate that subjective clinician-assessed indicators that are contextually relevant to the nature of hematological malignancies are markers of risk. This study has provided valuable preliminary findings on the topic and will inform future research.

Key words: Hematological malignancies; identifying dying; end of life; palliative care; clinical indicators; Delphi approach; mixed-methods; nursing.

SUMMARY STATEMENT

Why is this research needed?

- A significant gap in knowledge exists regarding prognosticating near the end of life for people with a hematological malignancy.
- Few studies have explored prognostic factors or prognostic tools to inform timely integration of palliative care provision and transitioning to end-of-life care in the specialty area of clinical malignant hematology.

What are the key findings?

- This study used the Delphi approach to gather expert consensus regarding the clinical indicators that signal a person with a hematological malignancy is at risk of deteriorating and dying.
- Consensus was achieved on the following 11 clinical indicators: 1) advancing age; 2) declining performances status; 3) presence of co-morbidities; 4) disease status; 5) persistent infections (bacterial and viral); 6) fungal infections; 7) severe graft versus host disease; 8) requiring high care; 9) signs of frailty; 10) treatment limitations; and 11) anorexia and/or weight loss.
- Clinical indicators included in the final results were a combination of subjective and objective markers of deterioration due to the heterogeneity of people with a hematological malignancy.

How should the findings be used to influence policy/practice/research/education?

- The clinical indicators identified in this study can be used to highlight an appropriate time for clinicians to engage in: 1) sensitive person-centered discussions with patients and their families regarding the possibility of deterioration; 2) a collaborative reassessment of the goals of care; 3) an assessment of current and potential palliative care needs; and 4) proactive planning for end-of-life care.

- This work has started the conversation regarding an anticipatory approach to deteriorating and dying for people with a hematological malignancy.
- Further research is warranted to investigate the findings of this study in the clinical setting.

Word count 4,932

INTRODUCTION

Hematological malignancies are a collection of heterogeneous neoplasms that originate in cells of the bone marrow and lymphatic system (Rodriguez-Abreu, Bordoni, & Zucca, 2007). This includes diseases such as acute and chronic leukaemia, Hodgkin and non-Hodgkin lymphoma and multiple myeloma. Collectively, hematological malignancies are the sixth most commonly diagnosed cancers in the world (Ferlay et al., 2015).

Background

A significant body of international literature highlights there are challenges providing palliative and end-of-life care in the specialty area of clinical malignant hematology (Moreno-Alonso et al., 2017). People with a hematological malignancy often experience a fluctuating and unpredictable illness trajectory, and can deteriorate rapidly to a terminal event (Hung et al., 2013; Manitta et al., 2010; McGrath & Holewa, 2007). There can be hope for long term survival or cure in the presence of critical illness or advanced disease (LeBlanc et al., 2015; Odejide, Salas Coronado, Watts, Wright, & Abel, 2014). For these reasons, prognosticating is difficult for people with a hematological malignancy, leading to delays in identification of dying and problems transitioning to a palliative approach (Auret, Bulsara, & Joske, 2003; Manitta et al., 2010; McGrath & Holewa, 2007). Hematologists have cited lack of prognostic tools near the end of life as a hindrance to optimal end-of-life care (Auret et al., 2003).

A significant gap in knowledge exists regarding predicting survival near the end of life for people with a hematological malignancy (Button, Chan, Chambers, Butler, & Yates, 2017a; Button, Chan, Chambers, Butler, & Yates, 2017b). A recent systematic review of prognostic factors present in the final three months of life revealed that the body of knowledge is predominantly focused on people who are admitted to the intensive care unit (ICU), or are treated aggressively (Button et al., 2017b). Few studies have explored prognostic factors or prognostic tools to inform transitioning to end-of-life care for people with a hematological malignancy (Button et al., 2017a; Chou et al., 2015; Corbett, Johnstone, McCracken Trauer, & Spruyt, 2013; Kripp et al., 2014; Ohno, Abe, Sasaki, & Okuhiro, 2017).

Identifying when a person is at risk of deteriorating and dying is vital to facilitate appropriate treatment decisions, patient autonomy, resuscitation planning, advance care planning and best practice care at the end of life (Highet, Crawford, Murray, & Boyd, 2013). Accurate identification of risk can allow clinicians (medical, nursing and allied health) to have honest sensitive conversations with patients and their families around the potential for deterioration and death, whilst continuing current appropriate care (Dalgaard, Thorsell, & Delmar, 2010; Highet et al., 2013). This has been referred to as ‘raining day thinking’ or ‘insurance policy health care’ where patients are encouraged to ‘hope for the best, but prepare for the rest’ (Gold Standards Framework, 2011). This concept has a subtle yet important difference to prognosticating, which typically focuses on predicting time frames of survival (Christakis, 1999; Glare & Sinclair, 2008; Highet et al., 2013). In contrast, identifying risk of deteriorating and dying focuses on planning for potential needs (Gold Standards Framework, 2011).

Terminology

The term ‘deteriorating and dying’ was used in this study to align with internationally used language around risk of death for the purposes of palliative care integration

(Highet et al., 2013). Although widely used, this term is poorly defined in the literature. In this study, the term 'deteriorating and dying' refers to when a person is at risk of dying within three to six months. This is a shorter timeframe than other research focusing on identifying risk of dying which looks at the last six to 12 months (Maas, Murray, Engels, & Campbell, 2013). This shortened time frame was considered appropriate for people with a hematological malignancy, who often deteriorate rapidly (McGrath & Holewa, 2007). Additionally, this terminology was used as it is difficult to separate deterioration and death without the benefit of hindsight, particularly for people with a hematological malignancy who often experience episodes of sudden deterioration in their clinical condition, followed by periods of recovery and stability (McGrath & Holewa, 2007). People who experience clinical deterioration are likely to have physical, psychosocial or spiritual palliative care needs, regardless of the outcome of the deterioration. For these reasons, the term 'deterioration and dying' has been used.

Conceptual framework

The transdisciplinary model of evidence-based decision-making was the broad conceptual framework that guided this study as it acknowledged the range of appropriate research methods to address a complex clinical question, the contextual nature of decision-making, and the importance of the individual or population (Satterfield et al., 2009). The model provides a clear and rationale process for clinical decision-making by incorporating the three following domains: 1) best available research evidence; 2) clinical expertise; and 3) the population's characteristics needs, values and preferences (Satterfield et al., 2009). This was the appropriate model to guide this research and to facilitate the translation of evidence into practice.

Aim

This study aimed to use the Delphi approach to identify clinical indicators that signal a person with a hematological malignancy is at risk of deteriorating and dying by confirming, rejecting and expanding on the findings of a systematic review of prognostic factors present near the end of life for people with a hematological malignancy.

DESIGN

We conducted a three-step international modified Delphi approach between September 2015 and March 2016. The Delphi method is an iterative structured process designed to gather opinion from a panel of geographically dispersed expert participants, via a series of surveys (Keeney et al., 2001). The approach is an accepted and widely used research method (Hsu & Sanford, 2007) and is said to be growing in popularity, particularly in the area of health sciences due to its ability to explore complex topics (Keeney et al., 2001). Although there is no set rule on the number of rounds necessary to achieve consensus, it is often reached within three rounds (Hasson, Keeney, & McKenna, 2000). Participant anonymity among the panel reduces the influence of persuasive leaders in the group (Hasson et al., 2000).

The approach was appropriate for this study as it is a validated mixed-method technique for measuring and achieving consensus of opinion on a complex topic where there is limited scientific evidence available (Keeney et al., 2001). This study was needed to strengthen and expand on the current body of knowledge regarding predicting survival near the end of life. A systematic review of prognostic factors present in the final three months of life demonstrated that the majority of studies were focused on patients treated aggressively in the acute care setting, and explored objective or laboratory based factors (Button et al., 2017b). The iterative rounds of surveys with expert clinicians, and the combination of qualitative and quantitative data, facilitated for the refinement of clinical indicators, and a more complete and clinically relevant understanding of the topic being studied.

This study aimed to identify clinical indicators rather than prognostic factors as the latter are often focused on estimating the chances of disease recovery, recurrence or death. In this study, clinical indicators were defined as patient outcomes that are markers of risk and improve the quality of patient care, support services and organizational functions (Mainz, 2003). Clinical indicators are used to monitor the quality of health care and to create the basis for improvement and prioritisation in health care.

Participants

An international panel of hematology and palliative care medical specialists and advanced practice nurses were selected to participate. Purposive sampling, which was criteria based, was utilized to select the panel. Panel members had to have a minimum of five years of experience in a currently held advanced clinical role caring directly for people with a hematological malignancy.

Potential participants were recruited by contacting: 1) positional leaders and key authors of publications in the peer reviewed literature; 2) local stakeholders at the researcher's health care facility or local region; and 3) members of relevant professional bodies. The Haematology Society of Australia and New Zealand, Palliative Care Australia, Palliative Care Nurses Australia and the European Association for Palliative Care assisted with recruitment by advertising for the study via e-mails, newsletters or blogs. American clinicians were contacted as position leaders and seminal authors. A fine balance exists to select experts who will be relatively impartial on the topic, yet also be interested enough in the research topic to participate to completion (Hasson et al., 2000). Variation in our sampling techniques enhanced the representativeness of the sample and reduced bias associated with a non-random sample, which is a key criticism of the method (Hasson et al., 2000; Keeney et al., 2001).

A participant nomination resource document was developed and the research team recorded names and details of all potential participants including years of experience, current

role and other relevant information (i.e. publications in the field). If a person expressed interest in participating in the study, they were then contacted by the researcher for further information to ensure they met the selection criteria.

Analysis and statistical methods

Opinions of participants were captured using a seven-point Likert-type scale which ranged from '1 = entirely disagree' to '7 = entirely agree'. Consensus on an item was defined *a priori* and was considered to be achieved if at least 70% of participants' responses fell within two side-by-side points on a seven-point Likert-type scale (i.e. 1 and 2), which is a modified version of Ulschak's definition of consensus (Ulschak, 1983). Themes and statements emerged from the open-ended text to qualify each of the clinical indicators and provide context. These were then rated quantitatively. A theme was defined as a subject or central idea, and a statement was a clear expression of a particular point. An item (clinical indicator, or associated theme or statement) was included in the following round (or final results) if the consensus rating fell on 'entirely agree / mostly agree' (6/7) or 'mostly agree / somewhat agree' (5/6).

Quantitative data were extracted from the data collection tool, entered into Microsoft Office Excel spreadsheets and then imported into IBM SPSS Statistics version 23 (SPSS). Descriptive statistics were analysed to identify missing data and to assess for consensus. Data reporting the collective judgement of the panel were analysed via median and inter quartile range (IQR), and consensus rating (including percentage of vote on rating) to represent the collective judgement of the group (Keeney et al., 2011).

Open-ended data were transcribed into a Microsoft Office Excel spreadsheet to allow for movement and filtering. Open-ended data in the Delphi method are best analysed via a simple process of content analysis (Keeney et al., 2011). Therefore, open-ended data were subjected to a process of content analysis using a modified version of Burnard's 14 step process (Burnard, 1991). Not all steps in Burnard's process were relevant to this study. Hence,

qualitative analysis was modified to meet the specific needs of this study and was justified accordingly. An outline of the content analysis is presented in Table 1 with comparison to Burnard's process. This method of content analysis was followed consistently and rigourously. Themes and statements to emerge from open-ended data provided context and allowed each indicator to be modified, collapsed or excluded. Between rounds, each clinical indicator was also explored in light of the relevant literature and critically reviewed according to the study aims.

Rigour

Implementation of the Delphi method requires a high level of 'methodological precision' (Hasson et al., 2000). The key weaknesses, potential issues and limitations include a low response rate of the panel, consumption of large blocks of time, the lack of validity and reliability, the inappropriate selection of experts, the anonymity of participants, a rigid questionnaire design, subjective data analysis, and the potential for consensus of general statements rather than specific information (Hsu & Sanford, 2007; Keeney et al., 2001; Keeney et al., 2006). These issues were carefully considered by the research team, and recommendations published by seminal authors in the field were followed when designing the protocol and undertaking this study (Hasson et al., 2000; Hsu & Sanford, 2007; Keeney et al., 2006). Steps were taken to enhance the rigour of the approach. Selection of participants was performed judiciously as it is a crucial step in the Delphi approach (Hsu & Sanford, 2007). A second reviewer (NG) independently performed the steps of content analysis (Burnard, 1991). All decisions made in the study were reviewed by a second member of the research team. A detailed decision-making trail was kept by the research team to enhance the transparency and rigor of the approach.

Methodology of the Delphi process

The methodology of the Delphi approach used in this study is displayed in Figure 1.

Round 1: The panel was asked to review and expand on the findings of a systematic review of prognostic factors present in the final three months of life for people with a hematological malignancy (Button et al., 2017b). Twenty-seven indicators were presented to the panel who was asked to provide a numerical rating on the extent they felt these indicators were associated with deteriorating and dying within three to six months. They were also asked to provide open-ended responses regarding each indicator and suggest new clinical indicators.

Round 2: The panel was informed of the results of the Round 1 survey including the median score, IQR, the consensus rating, and the associated themes and statements related to each indicator. All new indicators suggested in Round 1 were also displayed. The panel was asked to review their previous opinion in light of the new data, re-rate each clinical indicator, and rate the importance of the themes and statements associated with each clinical indicator, in addition to the new clinical indicators suggested. Space was provided for open-ended responses. Indicators that achieved consensus for inclusion were included in the final results while undecided indicators were taken into Round 3.

Round 3: The panel was informed of the results of Round 2 including the median score, IQR, and the consensus rating and percentage for all clinical indicators and associated themes that were rated in Round 2. Participants were asked to review any clinical indicators and themes or statements that had not achieved consensus or been excluded in the previous round. This was the last opportunity for participants to review their previous opinions. No open-ended data were elicited.

Ethical considerations

The study was approved by the appropriate hospital ethics committees: HREC/15/QRBW/289 and received administrative approval by the university ethics committee. Participants provided informed consent and anonymity was ensured throughout the study and on completion.

RESULTS

Participants

During the recruitment phase 31 individuals returned signed consent forms. All participants had over five years experience in advanced roles working directly with people with a range of hematological malignancies (i.e. leukemia, lymphoma, myeloma, stem cell transplantation) throughout the illness trajectory. Only one participant worked solely with one tumor stream (lymphoma). Many participants had published widely around palliative care for people with a hematological malignancy. Characteristics of the panel are displayed in Table 2.

Delphi process

Throughout the three rounds of survey distribution, response rates were maintained at 84% (n=27). A flow chart of the Delphi processes of achieving consensus is displayed in Figure 2.

Round 1: Of the 27 clinical indicators presented in Round 1, 11 achieved consensus for inclusion (+/- modifications), one achieved consensus for exclusion and the remaining were collapsed as they were similar to other indicators. The surveys contained a significant amount of open-ended data relating to the clinical indicators, which allowed for modification and refinement of indicators in conjunction with study aims and the literature. Twenty-four themes and statements emerging from the open-ended text were identified. Eleven new clinical indicators were suggested. Themes and statements relating to current indicators, and new indicators were suggested by the participants in open-ended text, which was analysed by two independent reviewers according to Burnard's 14 step process as described above (Burnard, 1991). The modified clinical indicators, themes and statements identified in the open-ended responses and new clinical indicators were carried into Round 2 for the panel to rate. All data that emerged from the open-ended text were (anonymously) carried into Round 2 to be voted on by the group, regardless of who suggested it, or how frequent it was suggested. This was

done to ensure all comments from the panel were treated with equal importance and were given the opportunity to be reviewed.

Round 2: Of 22 clinical indicators presented in Round 2, 10 achieved consensus for inclusion in the final results. A number of themes and statements also achieved consensus for inclusion in the final results and served as qualifiers for the associated clinical indicators. Participants provided a minimal amount of open-ended data and no new themes or statements were identified. Clinical indicators were modified, collapsed or excluded based on the themes and statements that achieved consensus for inclusion. Following on from this analysis, two clinical indicators and two themes and statements were taken into Round 3 as they had not yet achieved consensus for inclusion or exclusion.

Round 3: One clinical indicator and two themes and statements achieved consensus for inclusion in the final results. One indicator did not achieve consensus and remains undecided as being associated with deteriorating and dying; distress. Supporting Information Table 3 displays the clinical indicators that were presented in each round, and those that achieved consensus for inclusion in each round.

Final results

Three iterations of surveys resulted in consensus of opinion merging on 11 clinical indicators that covered personal characteristics of patient (older age, co-morbidities, anorexia / weight loss), disease status (relapsed, refractory, persistent disease), complications (persistent infections [bacterial and fungal], invasive fungal infections, graft versus host disease), performance and care level (declining performance, requiring high care, signs of frailty), and treatment (treatment limitations). A range of themes and statements also associated with these clinical indicators also achieved consensus. One clinical indicator, distress, did not achieve consensus despite being modified according to associated themes and statements. This was the only indicator that was deliberated on by the panel. The collective response, degree of

agreement, consensus score and rating of all clinical indicators and associated themes and statement included in the final results are displayed in Table 4.

Additional findings

Several key findings were made in addition to the identification of clinical indicators. These findings value-added to the aims of the study by providing context and a more complex understanding of the clinical indicators and identifying risk of deteriorating and dying in the specialty area of clinical malignant hematology. During the three iterations of surveys, participants' opinions moved to favor more subjective clinical indicators (such as declining performance status), or those with subjective clinician-assessed qualifying statements (as presented in Table 4), to identify risk of deteriorating and dying. This was in contrast to the prognostic factors identified in the systematic review that informed the Round 1 survey (Button et al., 2017b). These studies predominantly focused on objective or laboratory based indicators derived from blood test results or definitions of organ failure (Button et al., 2017b). This move is reflected well in one participants' comment following the Round 1 survey: *"More specific clinical criteria that are disease-based and situation-based are probably more useful…… compared to the more lab-oriented and organ-based things"* - Participant #24, dual trained (hematology and palliative care) medical specialist.

The participants also repeatedly expressed the importance of relationships between indicators, and contextual aspects of the clinical indicators. For example, one participant noted: "*I think it's difficult to comment on individual clinical indicators as how indicative they are depends on the clinical context and what other indicators that the patient has. Some suggestions as individual indicators may be reversible, whereas others in the presence of other co-morbidities may be catastrophic"* - Participant #23, hematology medical specialist.

Participants also expressed that certain clinical indicators were strongly interlinked and were more significant in the context of another indicator being present. For example, age and

presence of co-morbidities, and disease status and treatment limitations. Another concept that was highlighted was the importance of the underlying cause and potential for reversibility of a clinical indicator, particularly around complications of treatment. Participants felt certain clinical indicators were important but only if they were not related to an acute and reversible cause, for instance bone marrow suppression following chemotherapy, which is an expected complication. These indicators were deemed more serious if they were associated with refractory, relapsed, progressive disease: *"We expect this"* (in response to question about anemia) - Participant #31, hematology advance practice nurse, and "*Neutropenia may be a transient clinical situation during chemotherapy"* - Participant #15, hematology advanced practice nurse.

DISCUSSION

Eleven clinical indicators and several themes and statements relating to the clinical indicators achieved consensus as being associated with deteriorating and dying for people with a hematological malignancy. The clinical indicator, distress, did not achieve consensus, therefore remains an undecided indicator that requires further investigation as being associated with deteriorating and dying. The most significant finding of this study is a shift away from objective, quantitative, laboratory based indicators that were identified in the systematic review of prognostic factors that informed the Round 1 survey (Button et al., 2017b). As the rounds progressed, the mixed-methods Delphi process facilitated the panel to merge opinion on more subjective, qualitative, and clinician assessed indicators, with free-text comments highlighting that indicators should be considered in the broader context of the patient's clinical situation. This was keeping in line with similar work in this area in which clinical indicators that identify risk of dying in the cancer and non-cancer population are also subjective in nature and harness the power of clinician judgement (Maas, et al., 2013). This is the first study to take this approach to identifying risk of deteriorating and dying in the haematology setting.

A key strength of this study, is that the expert panel refined the clinical indicators over the three rounds with their knowledge of the specific diseases, the fluctuating illness trajectory of hematological malignancies, and reversible nature of many complications. This is an important finding in this study as previous studies on prognosticating for people with a hematological malignancy near the end of life have tested variables that are somewhat blunt measures if not adequately contextualised for the hematology population (Button et al., 2017b). For example, some studies measured signs of bone marrow suppression (anemia, thrombocytopenia or neutropenia) without noting if it was related to recent chemotherapy, and would therefore likely resolve in the short-term or progressive disease. We believe the 11 indicators and associated themes and statements that achieved consensus in this study adequately address the heterogeneity in the hematology population and between individuals, and are clinically and contextually relevant. For example, final results accounted for people with high risk and low risk disease, the elderly population with co-morbidities and treatment limitations, and younger people treated aggressively who may die from infection of GVHD post stem cell transplant. Further testing is required to confirm this.

This work significantly adds to the body of knowledge as the findings of this study confirm and build upon the few studies that have explored prognosticating near the end of life for people with a hematological malignancy to inform palliative and end-of-life care. Chou and colleagues (2015) found that the Palliative Prognostic Index (PPI) was a useful prognosticator of life expectancy in 'terminally ill' people (in-patients and out-patients) with hematological malignancies known to a specialist palliative care service (median survival of 16 days, IQR 4-4.75 days) in Taiwan. The core components of the PPI include performance status, dyspnoea, delirium, oral intake and edema (Chou et al., 2015). Our findings corroborate performance status and oral intake, but not the remaining components of the PPI. Ohno and colleagues (2017) reported that the PPI was predictive of mortality in people with a hematological

malignancy admitted to a hematology unit (median survival of 6.4 weeks) in Japan. Additionally, these authors found a prognostic model developed by Kripp and colleagues (2014) was also significantly predictive of mortality for people in a palliative care unit (in-patient hospice) in Germany categorised in a 'high risk' group (Ohno et al., 2017). This model included low performance status, requiring opioid analgesia, low platelet count, low albumin levels, and high lactate dehydrogenase levels (Kripp et al., 2014). This study significantly builds upon previous work as neither of these two studies assessed the importance of advanced or relapsed disease. While performance status and oral intake were present in final results of this study, dyspnea, delirium, edema, lactage dehydrogenase, platelet count and albumin levels were excluded, modified or collapsed following on from Round 1. This could be attributed to the Chou et al. (2015) and Ohno et al. (2017) studies having shorter time frames of survival in their populations (16 days and 6.4 weeks respectively) than was the aim of this study, to identify risk of deteriorating and dying within three to six months. Our study provides valuable findings that can facilitate anticipatory care planning prior to the final days to weeks of life.

To date, limited literature has explored an appropriate time to plan and prepare patients with a hematological malignancy for potential deterioration and death, and their carers (Button et al., 2017a). This study has created new knowledge on this topic to inform clinical practice. Additionally, this work has started the conversation regarding an anticipatory approach to deteriorating and dying for people with a hematological malignancy. This approach is appropriate for this population due to the fluctuating and unpredictable illness trajectory they often experience with potential for rapid deterioration to a terminal event (Hung et al., 2013; Manitta et al., 2010; McGrath & Holewa, 2007).

This study is a stand-alone piece in a larger program of work that has begun to address a gap in knowledge. Limited literature has explored predicting survival near the end of life for people with a hematological malignancy to inform palliative care provision and transitioning

to end-of-life care (Manitta et al., 2010). This Delphi approach was conducted following a systematic review of prognostic factors in the final three months of life for people with a hematological malignancy which identified significant gaps and limitations in the body of knowledge (Button et al., 2017b). Following on from this Delphi, a case-control study was conducted to test the clinical indicators identified by the expert panel (currently under review). The findings of the case-control study will inform the development of a clinical tool to identify risk of deteriorating and dying for people with a hematological malignancy. This work will require prospective testing in the clinical setting and will be the next phase of this program of research.

Strengths and limitations

It is acknowledged that this study has limitations. Although international experts participated, clinicians from countries outside of Australia were under-represented. Only medical and nursing clinicians were included. The opinions of other health care professionals, and patients and families would provide valuable data on this topic. It is acknowledged that the findings of this study are the opinions of a group of expert clinicians in the field. Our findings require testing in a clinical context. Although individual clinicians can be overly optimistic when prognosticating near the end of life (Christakis & Lamont, 2000), there is evidence that supports clinician judgement as a valuable method of identifying risk of dying to inform palliative and end-of-life care planning (Maltoni et al., 2005; Mitchell et al., 2017). The iterative group process of the Delphi approach strengthened individual clinician judgement through the three iterations and group 'discussion'. Additionally, the Delphi approach was an appropriate method for this study as limited literature existed on this complex topic (Keeney et al., 2001; Keeney et al., 2006). It was a valuable method to use to create preliminary knowledge. Although preliminary, the findings of this study are valuable as they are the best available evidence to date regarding identifying risk of dying within three to six months for

people with a hematological malignancy and can be used in combination with clinical judgement.

CONCLUSION

Eleven clinical indicators associated with deteriorating and dying for people with a hematological malignancy have been identified via an international Delphi panel of expert hematology and palliative care clinicians. These clinical indicators can help guide clinicians on an appropriate time to engage in sensitive person-centered conversations with patients and their families around the potential for deteriorating and dying. This can lead to collaborative discussions around goals of care, resuscitation planning, advance care planning, referral to specialist palliative care services (if this has not already occurred), and planning for possible death; and ultimately increase patient autonomy (Highet et al., 2013; Maas et al., 2013; Nightingale, Monsell, Wong, & Cheung, 2011).

This study has provided valuable preliminary findings on an important and underexplored topic. Further research is needed to validate the indicators in the clinical setting and explore what type of palliative care intervention would be appropriate for people identified at risk. As this patient cohort have an unpredictable and fluctuating and illness trajectory with potential for rapid deterioration, appropriate palliative care interventions must be timely, efficient and individualised. Patients should be encouraged not to delay doing the things that are important to them.

Although further work is required to test the findings of this study can be used by clinicians in combination with their clinical judgement. Clinicians often have a ‘gut feeling’ or intuition regarding potential deterioration in patients. This research can help to validate that intuition. Our findings could be incorporated into screening of patients in the in-patient or out-patient setting for patients with any hematological malignancy, and act as a prompt for clinician intuition. The findings of this Delphi can inform discussions around risk of deteriorating and

dying and anticipatory care planning as they present the best available expert opinion on the topic. The findings of this study can help to guide clinicians on how to give patients more control over their death, and the time they have remaining.

REFERENCES

Auret, K., Bulsara, C., & Joske, D. (2003). Australasian haematologist referral patterns to palliative care: Lack of consensus on when and why. *Internal Medicine Journal, 33*, 566-571. doi: 10.1111/j.1445-5994.2003.00490

Burnard, P. (1991). A method of analysing interview transcripts in qualitative research. *Nurse education today, 11*(6), 461-466. doi: http://dx.doi.org/10.1016/0260-6917(91)90009-Y

Button, E., Chan, R. J., Chambers, S., Butler, J., & Yates, P. (2017a). Lack of palliative mortality prediction tools for people with a hematological malignancy: Call to action. *Journal of Palliative Medicine, 20*(8), 802-803. doi: 10.1089/jpm.2017.0024

Button, E., Chan, R. J., Chambers, S., Butler, J., & Yates, P. (2017b). A systmatic review of prognostic factors in the final three months of life for popele with a hematological malignancy. *BMC Cancer, 17*(213). doi: 10.1186/s12885-017-3207-7

Chou, W.-C., Kao, C.-Y., Wang, P.-N., Chang, H., Wang, H.-M., Chang, P.-H., . . . Hung, Y.-S. (2015). The application of the palliative prognostic index, charlson comorbidity index, and Glasgow prognostic score in predicting the life expectancy of patients with hematologic malignancies under palliative care. *BMC Palliative Care, 14*(18), 1-7. doi: 10.1186/s12904-015-0011-5

Christakis, N. (1999). *Death foretold: Prophecy and prognosis in medical care*. Chicago: University of Chicago Press.

Christakis, N. A., & Lamont, E. B. (2000). Extent and determinants of error in doctors' prognoses in terminally ill patients: Prospective cohort study. *British Medical Journal, 320*, 469-472.

Corbett, C., Johnstone, M., McCracken Trauer, J., & Spruyt, O. (2013). Palliative care and hematological malignancies: Increased referrals at a comprehensive cancer centre. *Journal of Palliative Medicine, 16*(5), 537-542. doi: 10.1089/jpm.2012.0377

Dalgaard, K., Thorsell, G., & Delmar, C. (2010). Identifying transitions in terminal illness trajectories: A critical factor in hospital-based palliative care. *International Journal of Palliative Medicine, 16*(2), 87-92.

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., . . . Bray, F. (2015). Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer, 136*(5), E359-E386. doi:10.1002/ijc.29210

Glare, P., & Sinclair, C. (2008). Palliative medicine review: Prognostication. *Journal of Palliative Medicine, 11*(1), 84-102. doi: 10.1089/jpm.2008.9992

Gold Standards Framework. (2011). Prognostic Indicator Guidance. Retrieved 19th May, 2014 from www.://www.goldstandardsframework.org.uk

Hasson, F., Keeney, S., & McKenna, H. (2000). Research guidelines for the Delphi survey technique. *Journal of Advanced Nursing, 32* (4), 1008-1015. doi: 10.1046/j.1365-2648.2000.t01-1-01567.x

Highet, G., Crawford, D., Murray, S., & Boyd, K. (2013). Development and evaluation of the Supportive and Palliative Care Indicators Tool (SPICT): A mixed method study. *Supportive and Palliative Care, 1*, 1-6. doi: 10.1136/bmjspcare-2013-000488).

Hung, Y.-S., Wu, J.-H., Chang, H., Wang, P.-N., Kao, C.-Y., Wang, H.-M., . . . Chou, W.-C. (2013). Characteristics of patients with hematologic malignancies who received palliative care consultation services in a medical center. *American Journal of Hospice & Palliative Medicine, 30*(8), 773-780. doi: 10.1177/1049909112471423

Keeney, S., Hasson, F., & McKenna, H. (2001). A critical review of the Delphi technique as a research methodology for nursing. *International Journal of Nursing Studies, 38*, 195-200. doi: http://dx.doi.org/10.1016/S0020-7489(00)00044-4

Keeney, S., Hasson, F., & McKenna, H. (2006). Consulting the oracle: Ten lessons from using the Delphi technique in nursing research. *Journal of Advanced Nursing, 53*(2), 205-212. doi: 10.1111/j.1365-2648.2006.03716.x

Keeney, S., Hasson, F., & McKenna, H. P. (2011). The Delphi technique in nursing and health research. from http://lib.myilibrary.com?id=294450

Kripp, M., Willer, A., Schmidt, C., Pilz, L., Gencer, D., Buchheidt, D., . . . Hofheinz, R. (2014). Patients with malignant hematological disorders treated on a palliative care unit: Prognostic impact of clinical factors. *Annals of Hematology, 93*, 317–325. doi: 10.1007/s00277-013-1861-7

LeBlanc, T. W., O'Donnell, J. D., Crowley-Matoka, M., Rabow, M. W., Smith, C. B., White, D. B., . . . Schenker, Y. (2015). Perceptions of palliative care among hematologic malignancy specialists: a mixed-methods study. *Journal of oncology practice, 11*(2), e230-e238.

Maas, E., Murray, S., Engels, Y., & Campbell, C. (2013). What tools are available to identify patietns with palliative care needs in primary care: A systematic literature review and survey of European practice. *Supportive and Palliative Care, 3*, 444-451. doi: :10.1136/bmjspcare-2013-000527

Mainz, J. (2003). Defining and classifying clinical indicators for quality improvement. *International Journal of Quality in Health Care, 15*(6). doi: https://doi.org/10.1093/intqhc/mzg081

Maltoni, M., Caraceni, A., Brunelli, C., Broeckaert, B., Christakis, N., Eychmueller, S., . . . Larkin, P. (2005). Prognostic factors in advanced cancer patients: evidence-based clinical recommendations—a study by the Steering Committee of the European Association for Palliative Care. *Journal of Clinical Oncology, 23*(25), 6240-6248.

Manitta, V., Philip, J., & Cole-Sinclair, M. (2010). Palliative care and the hemato-oncological patient: Can we live together? A review of the literature. *Journal of Palliative Medicine, 13*(8), 1021-1025. doi: 10.1089/jpm.2009.0267

McGrath, P., & Holewa, H. (2007). Special considerations for haematology patients in relation to end-of-life care: Australian findings. *European Journal of Cancer Care, 16*, 164-171. doi: 10.1111/j.1365-2354.2006.00745.x

Mitchell, G., Senior, H., Rhee, J., Ware, R., Youn, S., Teo, P., . . . Clayton, J. (2017). Using intuition or a formal palliative care needs assessment screening process in general practice to predict death within 12 months: A randomised controlled trial. *Palliative Medicine, 1*([Epub ahead of print]). doi: doi: 10.1177/0269216317698621

Moreno-Alonso D, Porta-Sales, Monforte-Royo M, Trelis-Navarro J, Sureda-Balarí A and De Sevilla-Ribosa A. Palliative care in patients with haematological neoplasms: An integrative systematic review. *Palliative Medicine*. 2017; Article first published online: November 13, 2017 1-27

Nightingale, L., Monsell, M., Wong, W., & Cheung, C. (2011). How to give haematology patients better end-of-life care. *European Journal of Palliative Care, 18*(3), 114-117.

Odejide, O. O., Salas Coronado, D. Y., Watts, C. D., Wright, A. A., & Abel, G. A. (2014). End-of-life care for blood cancers: A series of focus groups with hematologic oncologists. *Journal of oncology practice, 10*(6), e396-e403. doi: http://dx.doi.org/10.1200/JOP.2014.001537

Ohno, E., Abe, M., Sasaki, H., & Okuhiro, K. (2017). Validation of 2 prognostic models in hospitalized patients with advanced hematological malignancies in Japan. *American Journal of Hospice and Palliative Medicine,* 1049909115615567. doi: 10.1177/1049909115615567

Satterfield, J. M., Spring, B., Brownson, R. C., Mullen, E. J., Newhouse, R. P., Walker, B. B., & Whitlock, E. P. (2009). Toward a transdisciplinary model of evidence-based practice. *Milbank Quarterly, 87*(2), 368-390, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2698591/pdf/milq0087-0368.pdf

Ulschak, F. (1983). *Human resource development: The theory and practice of needs assessment*.

Table 1. Burnard's process of content analysis used in this study.

Step	Burnard's process	Modification for this study
1	Make notes post interview	Interviews were not conducted. Data were entered from the data collection tools directly into a Microsoft Excel spreadsheet.
2	Read transcripts and note general themes	Nil change – conducted as recommended
3	Note as many headings as required	Nil change – conducted as recommended
4	Categories are grouped together	Nil change – conducted as recommended
5	Remove repetitive headings.	Nil change – conducted as recommended
6	Two researchers independently generate categories from data	One researcher generated categories and an independent reviewer confirmed or challenged the decisions.
7	Transcripts re-read alongside list of categories	Nil change – conducted as recommended
8	Each transcript worked through and coded	Nil change – conducted as recommended
9	Coded sections cut and collapsed together	Nil change – conducted as recommended
10	All collapsed sections organised under headings	Nil change – conducted as recommended
11	Some participants asked to check	This did not occur as participants were asked to re-review results in the subsequent round.
12	All sections filed for write up	Nil change – conducted as recommended Write up occurred via the development of next round of survey.
13	Access to original transcripts – write up	Nil change – conducted as recommended.
14	Use of literature (separate or integrated)	Nil change – conducted as recommended Findings were informed by the relevant literature and study aims.

Table 2. Characteristics of consented participants

Variable	Numbers (%)
Total participants	**31 (100)**
Specialty training	
Hematology	16 (51.6)
Palliative care	11 (35.5)
Hematology and palliative care	4 (12.9)
Profession	
Medical specialist (consultant, senior physician)	16 (51.6)
Advanced practice nurse (nurse practitioner, clinical nurse consultant, clinical nurse specialist)	15 (48.4)
Gender	
Female	18 (58)
Country of residence	
Australia	21 (67.7)
United States	5 (16.1)
Switzerland	1 (3.2)
Germany	1 (3.2)
United Kingdom	1 (3.2)
Hong Kong, China	1 (3.2)
New Zealand	1 (3.2)
Professional title	
Professor / Associate Professor (Medical or Nursing)	9 (29)
Clinical Nurse Consultant / Specialist / Researcher	8 (25.8)
Nurse Practitioner	6 (19.3)
Medical Specialist	8 (25.8)
Years of experience in specialty area	Median 20 (IQR 14.65-26.75)

Table 3. Clinical indicators presented and included in each Delphi round

Round 1		Round 2		Round 3	
Clinical indicators presented	Clinical indicators that achieved consensus for inclusion and new indicators – carried into Round 2	Clinical indicators presented	Clinical indicators that achieved consensus for inclusion – included in final results	Clinical indicators presented*	Clinical indicators that achieved consensus for inclusion – included in final results
1. Older age 2. Transfusions 3. Opiates 4. Artificial feeds 5. Performance status 6. Infection 7. Cytomegalovirus 8. Pneumonia 9. Fungal infection 10. Multi-morbidity 11. Liver dysfunction 12. Liver enzymes 13. Renal dysfunction 14. Urea creatinine	1. Older age 2. Performance status 3. Co-morbidities 4. Disease status 5. Blood transfusion support 6. Infection 7. Fungal infection 8. Organ damage 9. Acute disease 10. Graft versus host disease 11. Bone marrow suppression	1. Older age 2. Performance status 3. Co-morbidities 4. Disease Status 5. Blood transfusion support 6. Infections 7. Fungal infection 8. Organ damage 9. Acute disease 10. Graft versus host disease 11. Bone marrow	1. Older age 2. Performance status 3. Co-morbidities 4. Multi-relapse, progressive or treatment refractory disease 5. Infections 6. Fungal infection 7. Graft versus host disease (GVHD) 8. High care 9. Frailty 10. Treatment	1. Anorexia and / or weight loss 2. Distress	1. Anorexia and / or weight loss

15. Renal replacement 16. Respiratory dysfunction 17. Cardiac dysfunction 18. Relapse / refractory disease 19. Acute leukemia 20. History of stem cell transplant 21. Anemia 22. Neutropenia 23.Thrombocytopenia 24. Coagulopathy 25. Lactate dehydrogenase 26. C-reactive protein 27.Hypoalbuminemia	**New clinical indicators:** 1. Prolonged hospitalization 2. Frequent hospitalization 3. Admission to intensive care unit 4. High care 5. Symptom based treatment 6. Frailty 7. Anorexia, weight loss 8. Uncontrolled pain 9. Patient choice 10. Distress 11. Treatment limitations	suppression 12. Prolonged hospitalization 13. Frequent hospitalization 14. Admission to intensive care unit 15. High care 16. Symptom based treatment 17. Frailty 18. Anorexia, weight loss 19. Uncontrolled pain 20. Patient choice 21. Distress 22. Treatment limitations	limitations		

* Clinical indicators that achieved consensus for inclusion in Round 2 were included in final results and were not re-rated in Round 3

Table 4. Collective response, degree of agreement, consensus rating and associated themes and statements for clinical indicators included in final results

Items rated by expert panel	Median (1-7)	IQR	% of scores on rating	Consensus rating *
Clinical indicators				
Older age	6	6-7	84.6	6/7
Declining performance status	7	6-7	91.6	6/7
Presence of co-morbidities	7	6-7	86.3	6/7
Disease status (relapse, refractory, persistent investigator)	7	6-7	100	6/7
Persistent infections (bacterial and viral)	6	5-6	77.8	5/6
Invasive fungal infection	6	5-6	73	5/6/7
Graft versus host disease (GVHD)	5	5-6	80.8	5/6
High care	6	6-7	80	6/7
Signs of frailty	6	6-6.25	84.6	6/7
Anorexia and/or weight loss	6	5-6	84.2	5/6
Treatment limitations	7	6-7	92.6	6/7
Distress	4	3-5	65.4	N/A
Themes and statements related to each of the clinical indicators				
Older age				
• Older patient ≥70 years of age diagnosed with high risk/acute disease (i.e. difficult to treat, rapidly accelerating, requires aggressive treatment)	7	6-7	92.6	6/7

Performance status				
• Progressive and likely irreversible decline in performance status (observed by clinician or documented in patients' records)	7	6-7	96.3	6/7
• Spending more than 50% of time in bed/lying down/sitting, needs help with personal care, and/or dependence in 2 or more activities of daily living	7	6-7	93	6/7
Co-morbidities				
• Concurrent complex conditions (2 or more), which are progressing or advanced and likely irreversible, including: 1) liver disease; 2) cardiac disease; 3) kidney disease (including patient on renal replacement therapy); 4) respiratory disease; 5) neurological disease; 6) dementia; or 7) cancer (solid tumour diagnosis).	6	6-7	85.2	6/7
Disease status				
• Relapse of high risk/acute disease (i.e. difficult to treat, rapidly accelerating, requires aggressive treatment)	7	6-7	88.9	6/7
• Persistent, progressive anemia, neutropenia and/or thrombocytopenia, related to disease progression, (likely irreversible rather than short term response to treatment) with associated increase in transfusion or colony stimulating factor support	6	6-7	70.7	6/7
• Progressive liver, renal, respiratory or cardiac dysfunction associated with disease progression	7	6-7	88.9	6/7
• If relapsed post allogeneic stem cell transplant with two of the following conditions: 1) within 12 months of transplantation; 2) poor response to or treatment limitations for salvage therapy; and/or 3) with aggressive high risk disease.	6	5-7	70.3	6/7

Infections (bacterial and viral)				
• Persistent and/or drug resistant infections – including multi-resistant organisms	6	5-6	77.8	5/6
Fungal infection				
• Persistent/recurrent fungal infections – unresponsive to treatment	7	6-7	80	6/7
• If patient immunocompromised due to progressive disease, requires ongoing active treatment or on immunosuppressant medications	6	5-7	72	6/7
• Invasive fungal infection	6	5-6	92.3	5/6
GVHD				
• Stage 3 – 4 acute graft versus host disease that is steroid refractory	6	5-6	73.1	6/7
• Severe chronic graft versus host disease (National Institute of Health definition)	5	5-6	80.8	5/6
High care				
• Need for ongoing high level of care at home or in nursing home or other high care facility (excluding short stay for rehabilitation)	6	6-7	80	6/7
Signs of frailty				
• Signs of frailty in last 6 months (not related to an acute cause) including: 1) incontinence: 2) breakdown in skin integrity (pressure injuries, skin tears, incontinence associated dermatitis); 3) falls; 4) recurrent infections; 5) persistent dysphagia; or 6) delirium.	6	6-6.25	84.6	6/7
Anorexia and/or weight loss				
• Anorexia and/or unexplained progressive weight loss, likely irreversible including: 1) BMI <18.5; 2) weight loss >5% in 1 month or >15% in 3 months; or 3) or food	6	5-6	84.2	5/6

intake less than required in past week **				
Treatment limitations				
• 1) Due to inability to tolerate treatment (poor physiological reserve, age, performance status, infections, co-morbidities, organ damage); 2) no curative or life-prolonging treatment available or effective; or 3) initiation of treatment limitations by patient or next of kin and/or medical team.	7	6-7	92.6	6/7
Distress				
• Ongoing significant psychological distress as indicated by an elevated score on a distress thermometer or another psychological symptom questionnaire, not related to acute concurrent condition	4	3-5	65.4	N/A

* consensus rating from 1 = entirely disagree to 7 = entirely agree

** based on European Society for Clinical Nutrition and Metabolism (ESPN) Guidelines for Nutrition Screening, 2002.

Figure 1. Flow chart of the Delphi process used in this study.

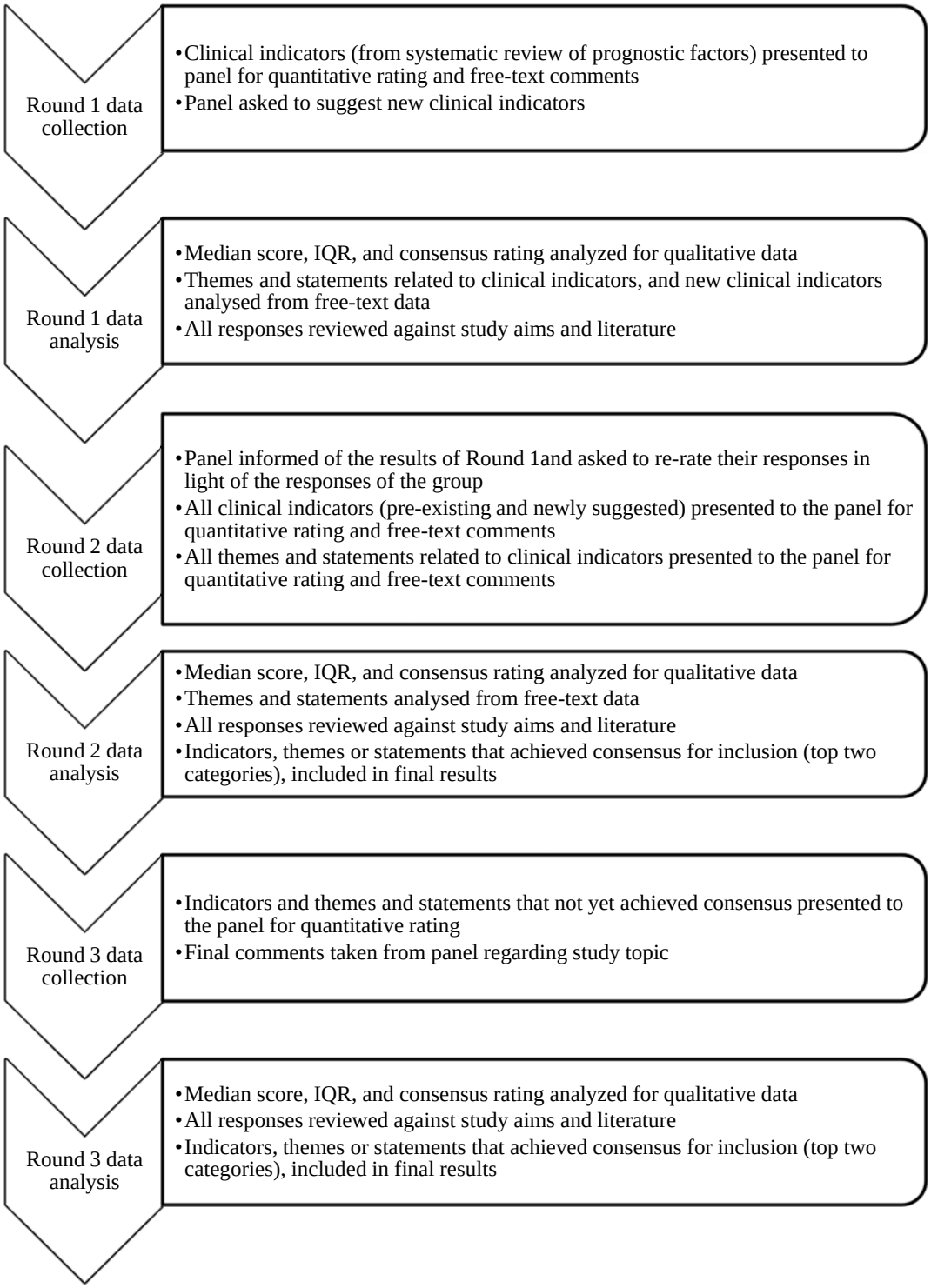

Figure 2. Flow chart of Delphi process to reach consensus