

# Does bleeding affect patient reported outcome measures in patients with myelodysplasia or hematologic malignancies: a systematic review.

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## **Abstract (235 words)**

### *Background*

Relatively minor bleeding (e.g. bruising/petechiae) may cause patient distress. This systematic review's objective was to assess whether bleeding affects health-related quality of life (HRQoL) or illness perceptions/representations (IPs) in patients with hematologic malignancies or myelodysplasia.

### *Study Design and Methods*

We searched, in full, 12 electronic databases (including CENTRAL; MEDLINE; EMBASE) up to 7<sup>th</sup> January 2013 for eligible randomised-controlled trials (RCTs), prospective cohort, and cross-sectional studies.

### *Results*

6247 studies were initially identified, 5945 studies were excluded on the basis of the abstract. 302 full text articles were evaluated independently by 2 reviewers, of these, 6 studies within 7 citations were eligible for inclusion. Two studies are still in progress, 4 studies within 5 citations were included in this review (1 RCT; 1 prospective observational study; 1 interview study; and 1 web-based survey). None of the included studies were designed to assess the impact bleeding had on HRQoL or IPs. The web-based survey and observational study used two new patient-reported outcome scales which specifically assessed patient distress/concern due to bleeding. The majority of patients within these two studies either did not experience bleeding or were not severely thrombocytopenic.

### *Conclusion*

There is insufficient evidence to demonstrate whether bleeding is a significant clinical problem that affects patients' HRQoL or IPs in either patients with myelodysplasia or patients with hematologic malignancies. Rigorously designed studies to assess the scale of this problem in both these groups of patients are required.

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**Keywords:**

Bleeding; Quality of life; Thrombocytopenia; Myelodysplasia; Hematologic malignancy, Illness

Perceptions/Representations

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## Background

Clinicians may not realise that relatively minor bleeding could cause patient distress. Petechiae are seen by doctors as a relatively trivial manifestation of thrombocytopenia but patients could see them as an outward sign of their illness and therefore distressing.

Any type of supportive care should explicitly assess quality of life.<sup>1</sup> The majority of platelet transfusions (69%) given to patients with hematologic malignancies or myelodysplasia (MDS) are to prevent bleeding (i.e. supportive care),<sup>2</sup> usually when their platelet count is  $< 10 \times 10^9/L$  unless they have other risk factors for bleeding.<sup>2,3</sup> There have been two recent large randomized-controlled trials (RCTs) that compared the use of prophylactic platelet transfusions versus therapeutic-only platelet transfusions.<sup>4,5</sup> Both showed that prophylactic platelet transfusions reduced bleeding (WHO grade 2 bleeding or above 43% vs. 50%,<sup>5</sup> but this strategy required significantly more platelet transfusions (mean number/patient 3 vs. 1.7;  $P < 0.001$ ).<sup>5</sup> It is essential to determine whether any benefits of platelet transfusions (e.g. reduced bleeding and patient distress) are outweighed by their costs (e.g. risks of transfusion). One way to measure patient distress would be via measurement of health-related quality of life (HRQoL) or illness perceptions/representations (IPs).

Recent data from the EXTEND<sup>6</sup> and RAISE<sup>7</sup> RCTs has shown that bleeding has a significant impact on HRQoL in patients with immune thrombocytopenia (ITP).<sup>8</sup> However, no platelet transfusion study within two recent systematic reviews assessed patients' HRQoL or IPs as an outcome measure.<sup>9,10</sup> The majority of bleeding seen within these platelet transfusion studies is considered minor or moderate by researchers and clinicians (World Health Authority (WHO) Grade 1 or 2).<sup>4,11,12</sup> Also, skin bleeding is often not considered clinically significant.<sup>4,12-15</sup> These trials used bleeding scales to produce a more objective assessment of bleeding, however these scales do not take into account the impact bleeding may have on the patients' 'quality of life'. For example, a new bleeding grading system (Bleeding Severity Measurement Scale (BSMS)) did not consider a nosebleed that did not require nasal packing or a transfusion as clinically significant.<sup>12</sup> However, for patients with hematologic malignancies or myelodysplasia we do not know what effect this minor or moderate bleeding has on patients' symptom distress or HRQoL. Patients with ITP differ significantly from patients with hematologic malignancies or MDS. The main

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symptom patients with ITP will have is bleeding, whereas patients with hematologic malignancies or MDS often have a plethora of other symptoms due to their diagnosis or treatment. The incremental impact of bleeding (usually WHO grade 1 or 2) on HRQoL or symptom distress in patients with hematologic malignancies or MDS may be minimal.

Health Related Quality of Life (HRQoL) refers to how an individual's well-being (all emotional, social, and physical aspects of the individual's life) may be impacted over time by a disease, a disability, or a disorder.<sup>16</sup> It is inherently subjective and is best measured from the patient's perspective.<sup>1</sup> Because it is multidimensional, its measurement requires the investigator to ask about a range of areas of the patient's life; including physical, emotional, and social well-being as well as functional ability.<sup>1</sup> HRQoL is now usually measured quantitatively using questionnaires (patient-reported outcome measures (PROMS)).<sup>16</sup> These questionnaires should meet certain quality criteria regarding their reliability and validity in the patient population being studied.<sup>17</sup> They can be divided into two main types: generic instruments (e.g. SF-36, 36-Item Short Form Health Survey);<sup>18</sup> and disease or disorder specific instruments (e.g. FACT-BMT, Functional Assessment of Cancer Therapy – Bone Marrow Transplantation).<sup>19</sup>

Illness representations/perceptions are patients' beliefs and expectations about an illness or physical symptom. They are central to Leventhal's Common-Sense Model (CSM) of Illness Representation (also called Self-Regulation Theory).<sup>20-22</sup> The CSM identifies the factors involved in the patient's processing of information regarding their disease or illness, how this information is integrated to provide a 'lay' view of the illness and how this 'lay' view guides coping behaviours and outcomes (Figure 1).<sup>23</sup> Research has identified six cognitive components of illness representations/perceptions (these will be referred to as perceptions throughout the rest of the review).<sup>21,22,24</sup>

A popular quantitative tool used to elicit illness perceptions is the Illness Perception Questionnaire (IPQ).<sup>25</sup> This has been revised to include emotional representations and illness coherence (IPQ-R, Quality of life and bleeding

Revised Illness Perception Questionnaire).<sup>26</sup> Across the questionnaires, high scores on Consequences, Identity, Emotional Representations, Timeline Acute/Chronic and Timeline Cyclical dimensions typically represent more negative beliefs. Conversely, high scores on the Coherence, Personal Control and Treatment Control dimensions represent more positive beliefs.<sup>27</sup>

### *Why it is important to do this review*

There is a need to understand the effect, if any, of bleeding on patient's illness perceptions/representations (IPs) and HRQoL, and ultimately upon clinical outcomes. This would enable a more robust evaluation of platelet transfusion strategies and disease treatments in the future.

### *Objectives*

Primary: To assess whether bleeding affects HRQoL or IPs in patients with hematologic malignancies or myelodysplasia (MDS).

Secondary: To determine: methodological quality of included studies and explore any difference in patient reported outcomes with regards to bleeding; whether quantitative measures of HRQoL or IP have been developed specifically related to bleeding; and whether any studies have used interventions to reduce symptom distress.

## **Methods**

### *Protocol and registration*

Full details of the inclusion criteria and methods for the analysis were pre-specified and documented in a protocol [PROSPERO (CRD 42011001446) and published on-line (<http://www.crd.york.ac.uk/prospero/>)].

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## *Criteria*

### *Types of studies:*

Randomized controlled trials (RCTs), prospective cohort studies and prospective cross-sectional studies were included in this review. These studies could be quantitative or qualitative in nature. Retrospective studies, case reports, animal studies, laboratory studies, and reviews were excluded from the review.

### *Types of participants*

Patients of any age were included if they had MDS or a hematologic malignancy and were severely thrombocytopenic ( $\leq 50 \times 10^9/l$  for at least 5 days) or expected to become severely thrombocytopenic due to their treatment. HRQoL or illness perception evaluation and bleeding had to be primary or secondary outcomes in the original study.

Studies were excluded if patients had other hematologic disorders; patients were not thrombocytopenic; or only family members/care-givers were asked about HRQoL. If studies consisted of mixed populations of patients, with diagnoses of solid tumors or non-malignant hematologic disorders, only data from the hematologic malignancy/MDS sub-groups were included. If sub-group data was not provided (after contacting the study authors), the study was excluded if fewer than 80% of participants had hematologic malignancies/MDS.

### *Types of outcome measures*

#### Primary outcomes

- HRQoL or IPs and its relation to bleeding.

#### Secondary outcomes

- Number and severity of bleeding episodes
- Mortality (all cause and secondary to bleeding)

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### *Search methods*

Nine electronic databases (including MEDLINE (1948 to 2013); EMBASE (1980 to 2013); CINAHL (1982 to 2013); Transfusion Evidence Library (1980 to 2013)), as well as three electronic trials databases were searched in full up to 7<sup>th</sup> January 2013. There was no restriction on language or publication period. (See Appendix 1 for Search strategies). Database searching was augmented by hand-searching reference lists of all included studies, relevant review articles, and current treatment guidelines.

### *Data collection and analysis*

#### *Selection of studies*

All electronically derived citations and abstracts of papers identified by the review search strategy were initially screened by one reviewer (CD) and duplicates were removed. The abstracts were then screened for relevancy by another reviewer (LE, AK or DP). Twenty per cent of these abstracts were selected randomly and these were then screened independently by a third reviewer (LE, AK or DP): any disagreements were resolved by discussion. Studies not meeting the inclusion criteria were excluded at this stage. The full texts of all potentially relevant studies were formally assessed for eligibility by any two out of four independent reviewers (LE, AK, DP, ES): any disagreements were resolved by discussion. Further information was sought from the study authors when the study reports contained insufficient data to enable a decision to be made about eligibility for this review. All studies that failed to meet our eligibility criteria were detailed in a table of excluded studies. Methodological quality was not an exclusion criterion.

#### *Data extraction and management*

Data extraction was conducted according to the guidelines proposed by The Cochrane Collaboration,<sup>28</sup> by two authors working independently (DP, ES). Disagreements between the review authors were resolved by consensus. A third review author (LE) gave her opinion if the first two authors could not

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reach a consensus. The review authors were not blinded to names of authors, institutions, journals, or the outcomes of the studies. Data were extracted using a standardised data extraction form designed specifically for use in this review (Appendix 2). When study reports did not provide sufficient information, authors and study groups were contacted for additional details.

### *Assessment of risk of bias*

Any thorough systematic review needs to assess the methodological quality of the included studies. In systematic reviews, the main issue is whether the effect seen in the primary studies is the true effect or whether a defect in study design (internal validity) has led the result to be over or under-estimated (biased).<sup>29</sup>

All included studies were assessed by two review authors (LE, DP) for possible risk of bias. For RCTs this was conducted as described in the Cochrane Handbook of Systematic Reviews of Interventions.<sup>30</sup> The assessment included information about the design, conduct, and analysis of the trial.

For non-randomised trials no validated critical appraisal or risk of bias tool was available for use.<sup>31-33</sup>

Therefore, the risk of bias was assessed using the domains defined by Sanderson et al<sup>31</sup> as critical for the assessment of study quality of observational studies. Sanderson and colleagues developed a tool for assessing whether critical appraisal tools within their systematic review contained the essential information for appraising the conduct of observational studies based on the STROBE guidelines<sup>34</sup> (Appendix 2).

Information from relevant reporting guidelines (CHERRIES, COREQ, STROBE)<sup>34-36</sup> were used to aid the decision on whether an aspect of a particular study design would affect the internal validity of the study. The types of bias were then rated within each category as high, low or unclear risk of bias. This system of reporting bias is obviously flawed and so the reasons why studies were categorised as low, high or unclear risk of bias were documented to enable readers to come to their own conclusions about the degree of bias inherent within each study and to aid transparency of the review process.<sup>29</sup>

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### *Measures of treatment effect*

When available we recorded dichotomous outcomes as the numbers of outcomes and continuous outcomes as means and standard deviations. No relative effect measures were calculated. Qualitative information was transcribed from the study report and quoted verbatim.

### *Dealing with missing data*

Three of the four included study authors were contacted by e-mail in order to obtain information that was missing or unclear in the published reports.<sup>37-39</sup> Two authors responded and provided further unpublished information.<sup>37,38</sup> The author of one of the on-going studies confirmed that this has not yet been published in full.<sup>40</sup>

Two trials included patients with hematologic malignancies as well as patients with solid tumours or non-malignant hematologic disorders. The authors were contacted because data could not be extracted for a malignant hematology 'subgroup' from the reported information. In both studies, **patients with hematologic malignancies constituted only a minority of all study patients** and the authors were unable to provide additional information on the hematology sub-group, these studies were therefore excluded **from the review**.<sup>41,42</sup>

### *Data synthesis*

We provided a narrative synthesis of the findings from the included studies, structured around the type of study design and type of outcome. No meta-analyses were performed because the studies were not homogeneous in their study design.

No formal assessments of heterogeneity or reporting biases were performed because no meta-analyses were performed.

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## Results

### *Description of studies*

#### *Results of the search*

(See Figure 2 – PRISMA Flow Diagram). 6247 studies were initially identified after duplicates were removed, 5945 studies were excluded on the basis of the abstract by one review author (LE, AK or DP) and 20% of these abstracts were randomly selected and independently assessed by a second review author (LE, AK or DP). 302 full text articles were assessed for eligibility by any two of four review authors (LE, AK, DP, ES).

#### *Included studies*

**Study Type.** There were six studies within seven citations eligible for inclusion within this review. One of these studies is due to start recruiting patients,<sup>43</sup> and the other has not yet been published in full<sup>40</sup> (Table S1 Appendix 5). Of the completed studies, there was one RCT;<sup>39</sup> one prospective observational study;<sup>38</sup> one interview study;<sup>44</sup> and one web-based survey<sup>37,45</sup> (Table 1: Characteristics of Included Studies). In total four studies were included in this review.

**Participants.** The four included studies contained 450 participants. One study consisted of only patients with MDS,<sup>37</sup> the other three studies consisted of patients with a mixture of diagnoses (Table 1). The mean age of patients within the studies ranged from 49 to 70 years of age.

**Interventions.** There was only one interventional study,<sup>39</sup> and this was an RCT. This examined the effects of a computer-assisted, interactive tailored patient assessment (ITPA) tool on patient care, symptom distress, and patients' need for symptom management during treatment and rehabilitation.

**Outcomes.** None of the four studies were designed to study the effect of bleeding on HRQoL or IPs. All of the studies reported overall symptom distress, disease burden or HRQoL related to their disease or its treatment as their main outcome measure.<sup>37-39,44</sup> Assessment of symptom distress or disease burden

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was assessed as a one-off measure in two studies.<sup>37,44</sup> It was assessed over 30 days in one study<sup>38</sup> and for up to one year in the final study<sup>39</sup> (Table 1).

### *Excluded studies*

There were 295 studies excluded on the basis of a full text review (Appendix 3: Screening Algorithm). The reasons for exclusion were: no bleeding reported (n=204); no patient-related outcome reported (n=42); review rather than primary study (n=29); retrospective study (n=15); and wrong patient group (i.e. not patients with haematological malignancies or myelodysplasia) (n=5). (For a list of excluded studies see Appendix 4).

### *Risk of bias*

All included studies were assessed by two review authors (LE, DP) as previously described and all four studies were found to be at significant risk of bias (See Table 2 for the separate risk categories and reasons why each study was rated as high, low or unclear risk).

### *Patient reported Outcome Measures (PROMS)*

#### *Illness Perception (IPs) Questionnaires*

No IP questionnaires were used to assess patients' IPs within any of the four studies.

#### *HRQoL Questionnaires*

A wide number of established and novel tools were used to assess the patients' HRQoL within the four included studies (Table 1 & Appendix 5 Table S2). The number of HRQoL assessment tools used in each study varied between one<sup>39</sup> and three.<sup>37,38,44</sup>

The Functional Assessment Cancer Therapy (FACT) was the only tool used in more than one study.<sup>37,38</sup>

Other widely used and validated HRQoL tools within the studies included: SF-36;<sup>39</sup> EORTC QLQ-C30;<sup>44</sup>

Profile of Mood States (POMS);<sup>38</sup> and EuroQol EQ-5D.<sup>37</sup>

### *Quality of life and bleeding*

Two of the studies used novel HRQoL tools which included specific questions relating to bleeding.<sup>37,38</sup> (Table 1 & Appendix 5 Table S2).

*Timing of HRQoL assessments.* (Table 1) All studies completed a minimum of one HRQoL assessment, with the two cross-sectional studies only completing a single assessment.<sup>37,44</sup>

#### *Other PROMs*

The RCT<sup>39</sup> used their novel interactive tailored patient assessment (ITPA) tool to assess symptom distress, and patients' need for symptom management prior to inpatient and outpatient assessments for up to 365 days.

#### *Assessment of bleeding*

(See Table 1)

#### *Formalized bleeding assessments*

None of the studies reported using a specific bleeding assessment tool.<sup>37-39,44</sup>

#### *Effects of interventions*

(See Table 3)

#### *Primary Outcome: Health related Quality of life (HRQoL)/Illness Perception(IP) and its relation to bleeding*

None of the studies reported a quantitative relationship between IP and bleeding or between HRQoL and bleeding.<sup>37-39,44</sup>

The RCT only reported a combined outcome measure of bleeding and infection as one of their symptom distress measures.<sup>39</sup> The authors were contacted for further information but did not respond.

#### *Quality of life and bleeding*

In the prospective observational study (autologous stem cell transplant patients) only 3% of patients had moderate or severe bleeding during the study.<sup>38</sup> The authors did not analyse separately patients who bled and patients who did not bleed it was therefore not possible to assess whether bleeding caused symptom distress [unpublished information from authors].<sup>38</sup>

The on-line survey of MDS patients assessed concern about bleeding but did not relate it to whether patients had experienced recent bleeding or not.<sup>37</sup> Only 68.5% of patients (137/200) answered this section of the survey, and only 20% of these patients (28/137) had a platelet count less than  $50 \times 10^9/L$  (Table 4). Significant differences in platelet count groups were obtained on worry about serious bleeding, pinpoint bleeding and vaginal bleeding, patients within the 30 to 49 platelet count group (7% of patients (9/137) reported the most problems [unpublished information provided by the author].<sup>37</sup> The 14% (19/137) of patients with platelet counts below 30 reported far fewer concerns about bleeding. None of the platelet count groups showed differences in concern about bleeding from the mouth and gums, nose or seeing blood in the urine or stool.

In the interview study (leukemia and lymphoma patients), bleeding was only mentioned as part of the open-ended interview, no quantitative assessment was performed.<sup>44</sup> Two of the five patients had nosebleeds (during the interview)<sup>44</sup> and neither participant felt this was important. However, the interviewers noted that all the patients downplayed all their physical symptoms significantly despite objective evidence of significant weight loss, hair-loss, mucositis or bleeding.

#### *Secondary Outcome: Number and severity of bleeding episodes*

Three of the four studies reported bleeding<sup>37,38,44</sup> (See Table 3). The prospective observational study reported bleeding at platelet count nadir in only 3% of patients.<sup>38</sup> The interview study reported epistaxis in two patients and bruising was noted by the interviewers but there was no comment about the severity of the bleeding.<sup>44</sup> The on-line survey asked about bleeding present in the preceding week however the answers were poorly completed. Overall, only 55% of patients (76/137 with a known

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platelet count) reported whether they had had spontaneous bleeding, bruising, blood blisters in the mouth or blood in the urine or stool within the previous week [unpublished data provided by the author] (Table 4).<sup>37</sup>

#### *Secondary Outcome: Mortality (All-cause or secondary to bleeding)*

This outcome was only relevant to two of the four studies<sup>38,39</sup> (longitudinal studies). The other two studies were of a cross-sectional design and all patients had to be alive to participate in the studies.<sup>37,44</sup> Of these two studies, only one study reported all-cause mortality.<sup>39</sup> 11 patients died in the intervention arm and eight patients died in the control arm during the first 100 days. Neither study reported mortality due to bleeding.

## **Discussion**

The main objective of this review was to determine **whether bleeding affects HRQoL or Illness Perception (IP)** in patients with hematologic malignancies or myelodysplasia. Other objectives were to: determine whether a HRQoL tool had been developed that specifically assessed patient distress/concern in relation to bleeding symptoms; determine whether any studies had used interventions to reduce symptom distress; and assess the methodological quality of included studies.

#### *Summary of key findings*

Six studies were identified and two of these studies have not been completed. There were therefore four studies included in this review.

This review found no studies that evaluated the differences in HRQoL or IPs between patients who did or did not experience bleeding. Thus we are unable to establish the extent to which bleeding affects HRQoL or illness perceptions. Nor were we able to establish whether patients with myelodysplasia had a

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different perception of bleeding to those patients with transient bone marrow failure (e.g. after chemotherapy or stem cell transplantation).

The web-based survey<sup>37</sup> and observational study<sup>38</sup> used two new patient-reported outcome (PRO) scales FACT-Th (MDS patients) and MDASI-BMT (stem-cell transplant patients), respectively which specifically assessed patient distress/concern in relation to bleeding symptoms. However, these tools were not used within these studies to assess differences in HRQoL due to bleeding.

The RCT<sup>39</sup> did use an ITPA tool to assess symptom distress and feedback information to the nurses and doctors but they did not analyse bleeding separately from infection and therefore effectiveness of this tool for reducing symptom distress due to bleeding is unknown.

### *Quality of the evidence*

Overall the quality of the evidence is poor. The four studies identified in the systematic review were all at a significant risk of bias.

There is no universal validated and well used patient reported outcome measure which could be used to assess the impact of bleeding on quality of life in patients with haematological malignancies and MDS.

The two HRQoL tools which included an assessment of bleeding (MDASI-BMT and FACT-Th) have not been validated in this patient group. Furthermore the remaining HRQoL tools used in these studies were not designed to assess the impact of bleeding upon HRQoL (Table S2 Appendix 5).

In addition the two studies that assessed patient reported outcome measures to evaluate HRQoL prospectively over time, were undertaken over very different time periods. Both studies reported high attrition rates and losses to follow-up.<sup>38,39</sup> The remaining two studies only performed a single assessment (Table 1). HRQoL assessments are more likely to provide meaningful information to healthcare professionals when they are reported sequentially to provide a representation of changes over time.<sup>46,47</sup>

### **Quality of life and bleeding**

Patients with hematologic malignancies and MDS often have many other symptoms including side effects of complex and variable treatments, in addition to the psychological impact of fear, insecurity and carer/hospital dependence; all of which are important to patients. Indeed, within the four identified studies patients often rated symptoms other than bleeding as more problematic. However, whether this is due to the underlying study design; in that investigators failed to acknowledge the potential impact of bleeding through direct patient questioning or whether other symptoms are more concerning to patients is unclear. Certainly, the incidence of bleeding (3%) was much lower in the prospective observational study<sup>38</sup> than rates seen in recent well-conducted platelet transfusion trials of similar patients (45 to 59%).<sup>5,48</sup> In these platelet transfusion studies formalized daily bleeding assessments were performed and the rates of severe or life-threatening bleeding were similar to the overall incidence of bleeding (2 to 9%) reported in the cohort study.<sup>38</sup>

### *Strengths and Limitations*

We know of no previous reviews on this subject and within this review found four low quality studies that were not specifically designed to answer the question posed by this systematic review. There were no obvious biases within the review process: a protocol was pre-specified, a wide search was conducted, the relevance of each paper identified was carefully assessed, and no restrictions were made for the language in which the paper was originally published.

Excluding studies that only reported bleeding as an adverse event did not limit this review's findings.

Any study that only reported bleeding as an adverse event would not separate patients with bleeding and those who did not in to two separate groups and compare patient reported outcome measures between the two groups.

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Limiting this review to only patients with hematologic malignancies or MDS may have limited the generalizability of this review to patients with other types of cancer. However, patients with hematologic disorders have more profound and prolonged thrombocytopenia than patients with other types of cancer. This is reflected by the fact that hematology patients use up to 60% of all platelet transfusions issued.<sup>49</sup> We chose to limit our review to patients with hematologic malignancies or MDS because if there is a true difference in symptom distress or HRQoL due to bleeding it is more likely to be detected within this high risk patient group.

It is important to distinguish between quality of reporting and quality of what was actually done in the design, conduct and analysis of a study. A high quality report ensures that all relevant information is available to the reader but does not guarantee it is free of bias.<sup>50</sup>

The assessment of methodological quality and risk of bias was limited by the lack of a 'gold-standard' critical appraisal tool (CAT). Several systematic reviews have assessed tools for assessing quality and susceptibility to bias in non-randomised studies.<sup>31-33</sup> All these reviews have concluded that there is no currently agreed 'gold standard' critical appraisal tool; the majority of tools did not undergo a rigorous development process and that there are many tools to choose from. Katrak and colleagues<sup>32</sup> identified 121 critical appraisal tools and Sanderson and colleagues identified 86 tools.<sup>31</sup> Quality scales and resulting scores tend to combine aspects of reporting quality and aspects of trial quality which can lead to a flawed assessment, and therefore these types of assessments should be avoided.<sup>51,52</sup>

Due to these problems we tried to make our risk of bias assessment as transparent as possible. We used categories that had been previously recognised as critically important for assessing methodological quality,<sup>31</sup> provided the reasons we classified a study as at high, unclear, or low risk of bias as well as our summary decision for each domain.

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### *Implications for Practice and Research*

There is a lack of evidence to establish if bleeding is a significant clinical problem that affects patients' HRQoL or illness perceptions. The four studies identified in the systematic review did not focus primarily on bleeding. This review will therefore not affect current clinical practice because we found no evidence on which to base a change in practice.

The main implications of this review are the research agenda, as well as awaiting the results of the two on-going studies in patients with MDS (Table S1 Appendix 5). Studies are required to assess whether bleeding causes patients distress, and if so, to what extent this occurs and whether this differs between patients with prolonged periods of thrombocytopenia e.g. MDS or patients with reversible thrombocytopenia (e.g. after chemotherapy or a stem cell transplant). Different research approaches may be required, including the development of a validated patient-reported outcome measure, as well as independently verified documentation of the presence or absence of bleeding.

### **Contributions of authors**

Lise Estcourt: protocol development, searching, selection of studies, eligibility and quality assessment, data analysis and content expert.

Debbie Pinchon: protocol development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis and content expert.

Emily Symington: selection of studies, eligibility and quality assessment, data extraction and analysis.

Anne Kelly: protocol development, selection of studies, eligibility assessment.

Susan Brunskill: protocol development and methodological expert.

Carolyn Doree: protocol development, searching and selection of studies.

Liz Glidewell: protocol development and content expert.

Simon Stanworth: protocol development and content expert.

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Lise Estcourt drafted the paper and all review authors contributed to the preparation of the final review article.

## **Conflicts of interest**

None known

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**Figure 1: Leventhal's Common Sense Model of Illness Representation**

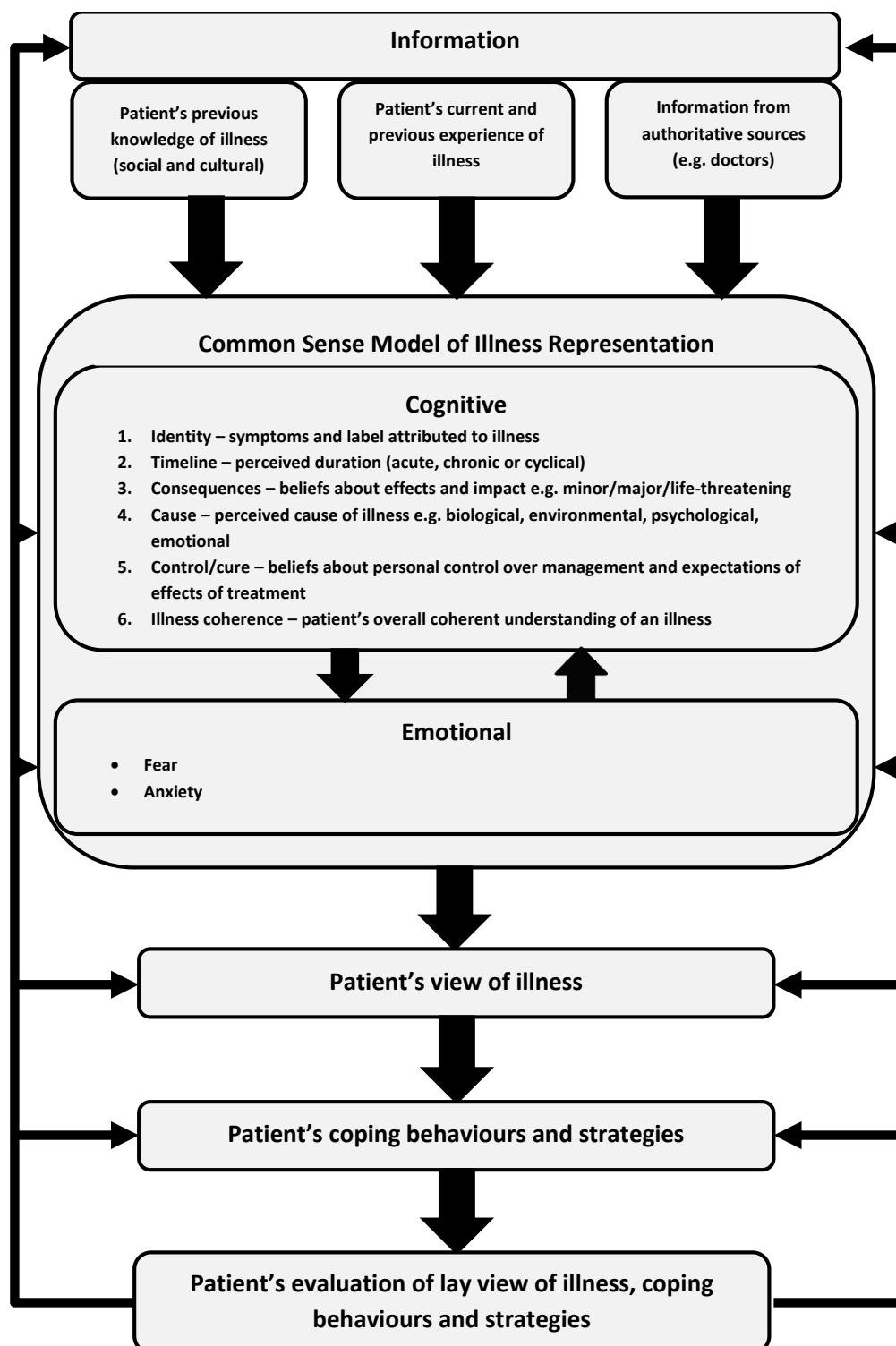
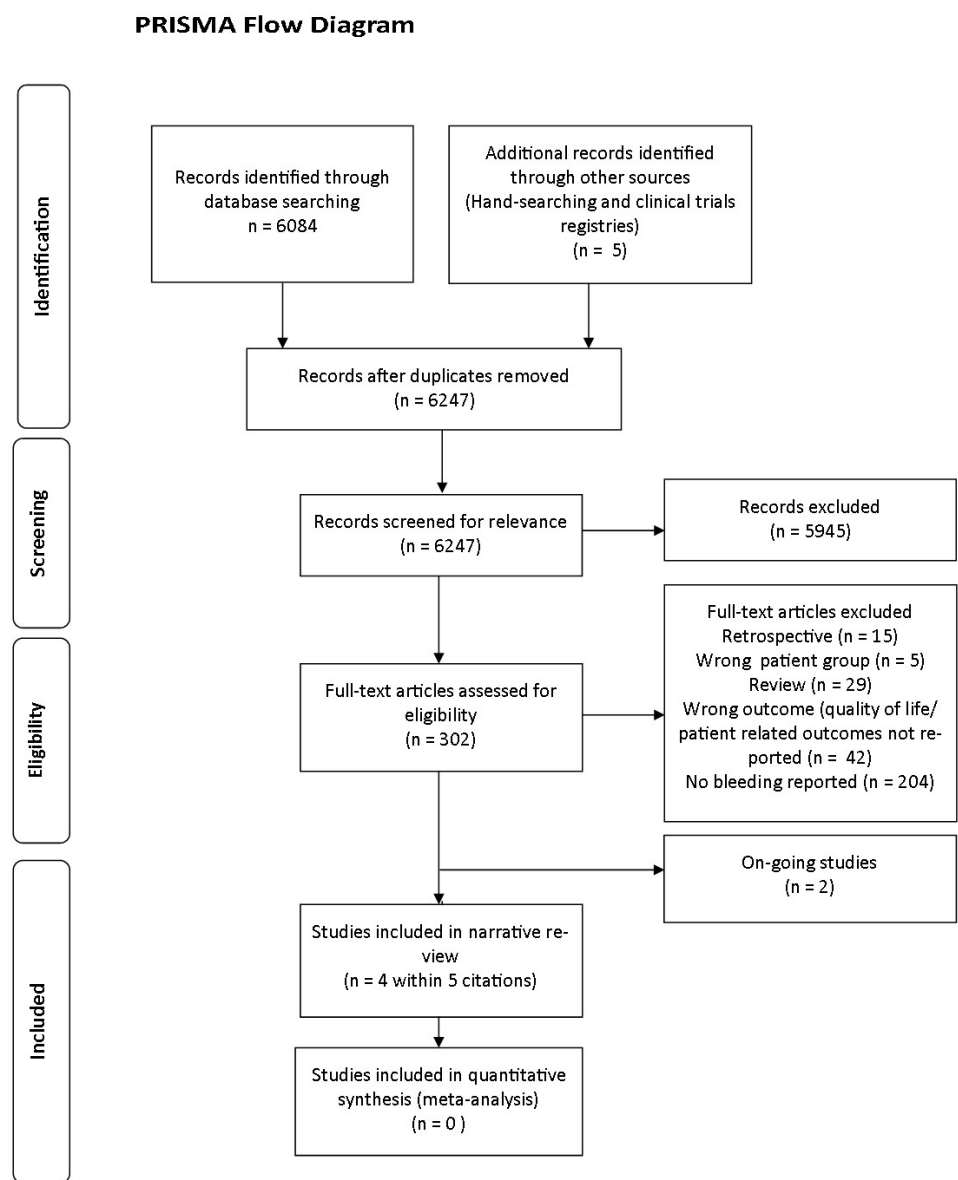


Figure 2: PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews

**Table I Characteristics of included Studies**

Study & country	Study design	No. of participants	Main aim of study	Assessment of patient-related outcomes	Assessment of bleeding	Haematological diagnosis and treatment of participants	Mean age participants (yrs)
<b>Ruland 2010</b> <sup>39</sup> Norway	RCT Multi-centre	145 (75 intervention 70 control) 100 followed up for 100 days [19 (13%) died, 10 (7%) dropped out, 16 (11%) lost to follow-up] 51 followed up for 365 days	Does use of a novel ITPA reduce symptom burden	SF-36 (baseline only) ITPA* (Prior to inpatient and outpatient assessments for up to 365 days)	Self-reported using ITPA and retrospective review of the notes to confirm symptoms reported by patient.	Leukaemia (28) Lymphoma (111) Myeloma (6) Chemotherapy (98) SCT (47)	49.5
<b>Anderson 2007</b> <sup>38</sup> USA	Prospective observational study Single centre	100 12 lost to follow-up (12%)	Assess symptom burden of patients undergoing autologous stem cell transplant	MDASI-BMT* (5x baseline to D30) FACT-BMT (Baseline & D30) POMS (Baseline & D30)	Method not reported	Non-Hodgkins lymphoma (34) Myeloma (66) SCT (100)	53.6
<b>Persson 1995</b> <sup>44</sup> Sweden	Open-ended interview Single centre	5	Explore patients experience of physical	Open-ended interview. EORTC QLQ-C30	Noted by interviewer. No systematic assessment of	Acute leukaemia (4) Lymphoma (1)	70.4

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			and psychological problems during active phase of disease and treatment	SOC LGC (Single assessment)	bleeding	Active treatment (5), type of treatment not reported	
List 2009 <sup>37</sup>  USA	Web-based survey  Multi-centre	200†  137 included in analysis of bleeding and platelet count†	Explore the patient burden associated with MDS disease and treatment	Bespoke measure* included† EQ-5D FACT-Th FACT-G Other items from questionnaires used in clinical studies MDS (Single assessment)	Self-reported	MDS  Only 28 had platelet count < 50 x 10 <sup>9</sup> /L†  Chemotherapy (39/70)**†	64.7

\*Patient related outcome measure devised for this study

†Unpublished data

\*\* Only 70 of the 200 study patients reported whether or not they were currently receiving any chemotherapy treatment

EORTC = European Organization for Research and Treatment of Cancer; FACT-BMT = Functional assessment of Cancer Therapy – Bone Marrow Transplantation; FACT-G = Functional assessment of Cancer Therapy – General; FACT- Th = Functional assessment of Cancer Therapy –Thrombocytopenia; IPSS = International Prognostic Scoring System; ITPA = Interactive Tailored Patient Assessment; LGC = Lund Gerontology Centre; MDASI-BMT = MD Anderson Symptom Inventory- Bone Marrow Transplant; POMS = Profile of Mood States; SCT = Stem cell transplant; SF-36 = Short Form 36; SOC = Sense of Coherence Scales

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**Table 2: Risk of Bias Table**

Study Name	Ruland 2010 <sup>39</sup>	Anderson 2007 <sup>38</sup>	Persson 199 <sup>44</sup>	List 2009 <sup>37</sup>
Type of Study	RCT	Prospective observational cohort study	Interview study	On-line survey
<b>Selection bias</b>	<b>Low Risk</b>  <i>Adequate sequence generation</i> Computer-generated minimisation algorithm that equalised groups on gender and type of treatment.  <i>Allocation concealment</i> Tablet computer was programmed so that the randomization algorithm could only be accessed after completion of baseline assessment	<b>Unclear Risk</b>  <i>Appropriate source population</i> 100 of 148 eligible patients approached agreed to participate but did not describe how it was decided which patients should be approached.	<b>Unclear Risk</b>  <i>Appropriate source population</i> “A consecutive sample of five patients” with a cute leukaemia or a high grade lymphoma. Did not describe whether they were consecutive admissions, or in what way they were consecutive.	<b>High Risk</b>  <i>Appropriate source population</i> Selected group of patients. Invited into study on attendance at MDS Foundation forum, or via internet
<b>Performance bias</b>	<b>High Risk</b>  <i>Blinding of clinician and patient</i> Due to nature of study the patient’s group assignment could not be concealed after baseline data were obtained as it was to	<b>Unclear Risk</b>  <i>Appropriate methods to deal with any design-specific issues</i> Self-report by patient, however research nurses had provided education. Not enough	<b>Unclear Risk</b>  <i>Appropriate methods to deal with any design-specific issues</i> No information on: who conducted interview; whether a relationship was	<b>High Risk</b>  <i>Appropriate methods to deal with any design-specific issues</i> Self-report by patient

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	provide nurses and physicians with assessment summaries of patient symptoms, problems, and concerns	detail provided on education regarding completion of forms.	established between the interviewer and patient prior to study commencement; whether the setting for the interview was appropriate; whether interviewer may be biased.	
<b>Detection bias</b>	<b>Low Risk</b>  <i>Blinding of outcome assessor</i> To compare groups, two trained raters who were blinded to patients' study group assignment conducted independent chart audits for inpatient and outpatient visits and abstracted both physicians' and nurses' inpatient and outpatient notes for symptoms, problems and concerns equivalent to those contained in the Choice ITPA.	<b>High Risk</b>  <i>Blinding of outcome assessor</i> Only ECOG PS (Eastern Co-operative Oncology Group Performance Status) was used to assess the health care provider's estimate of patient's functional status at each time point. Laboratory variables that might affect patient's symptoms were also recorded. No independent blind assessment of outcome reported.	<b>High Risk</b>  Patients minimised their physical problems. Weight loss evident in all patients, but only one saw it as a problem. Severe oral complications noted by interviewer, but patients did not talk about them much. No independent report by nurse or family member.	<b>High Risk</b>  Self-report by patient.
<b>Incomplete outcome data (attrition bias)</b>	<b>High Risk</b>  Authors mentioned attrition rates, only 51 patients were followed up for 1 year. The planned duration of the study.	<b>High Risk</b>  3 patients lost to follow up before blood count nadir. 9 patients lost by the time of last assessment at 30 days (Missing data	<b>Unclear Risk</b>  No discussion of possibility of saturation of data	<b>High Risk</b>  200 patients participated in on-line study. Only 137 completed section on bleeding and platelet count*

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		replaced by last observation carried forward)		
<b>Selective reporting (reporting bias)</b>	<b>High Risk</b>  Bleeding and infection assessed under single sub-group of symptom distress	<b>High Risk</b>  FACT-BMT P-values only reported in study for baseline against symptoms of fatigue, sleep disturbance, lack of appetite and pain	<b>Low Risk</b>  Tape-recorded interview transcribed verbatim and 'analysed from a hermeneutic phenomenological perspective'. Independently assessed by 2 authors. Quotations provided and organised into themes: 'physical problems; psychosocial problems; patients' coping strategies...; patients' opinions of the care provided'. 'Methodological triangulation was applied'.	<b>Low Risk</b>  Unpublished data from MDS foundation provided*
<b>Other bias (including funding)</b>	<b>Low Risk</b>  No other sources of bias identified	<b>Low Risk</b>  No other sources of bias identified	<b>Low Risk</b>  No other sources of bias identified	<b>Low Risk</b>  No other sources of bias identified
<b>Protocol deviation</b>	<b>Unclear Risk</b>	<b>Unclear Risk</b>	<b>Unclear Risk</b>	<b>Unclear Risk</b>

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	No protocol available	No protocol available	No protocol available	No protocol available
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\* = unpublished data

NA = type of bias not applicable to study design

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**Table 3: Primary and secondary outcomes of the review**

Study	Primary Outcome	Secondary Outcomes		Comment
	Quality of life/illness perception and its relation to bleeding	Number and severity of bleeding episodes	All-cause mortality and mortality secondary to bleeding	
Ruland 2010 <sup>39</sup>	NR	NR	19 died during first 100 days. 11 intervention group 8 control group Mortality due to bleeding not reported	Bleeding and infection assessed under single sub-group of symptom distress
Anderson 2007 <sup>38</sup>	NR	Percentage of patients with moderate or severe bleeding 0% baseline 3% count nadir 1% day 30	NR	MDASI-BMT mean symptom score bleeding 0.14 (0.62 SD) baseline 0.31 (1.20 SD) count nadir 0.15 (0.89 SD) day 30
Persson 1995 <sup>44</sup>	2 patients who had epistaxis during interview did not consider it important	2 patients experienced epistaxis during interview. Interviewer noted bruising. Severity of bleeding was not reported	NA	
List 2009 <sup>37</sup>	NR	Self-reported bleeding in week prior to survey. (Table 4)	NA	Significant differences in platelet count groups were obtained on worry about serious bleeding, pinpoint bleeding and vaginal

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				bleeding, 30-49 platelet count group (9 patients) reporting most problems*
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\* = unpublished data

NR = not reported; NA = not applicable

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**Table 4: Bleeding present during preceding week within List 2009<sup>37</sup> [unpublished data]**

	Platelet count < 30	Platelet count 30 to 49	Platelet count 50 to 99	Platelet count > 100	Total
<b>Presence or absence of bleeding reported</b>	18/19 (94.7%)	7/9 (77.8%)	9/23 (39.1%)	42/86 (48.8%)	137
<b>Spontaneous bleeding</b>	4/18 (22.2%)	3/7 (42.9%)	0/9 (0%)	2/42 (4.8%)	76
<b>Bruises</b>	11/18 (61.1%)	6/7 (85.7%)	3/9 (33.3%)	14/42 (33.3%)	76
<b>Blood blisters in mouth</b>	1/18 (5.6%)	1/7 (14.3%)	0/9 (0%)	4/42 (9.5%)	76
<b>Blood in urine</b>	0/18 (0%)	0/7 (0%)	0/9 (0%)	0/42 (0%)	76
<b>Blood in stool</b>	3/18 (16.7%)	1/7 (14.3%)	2/9 (22.2%)	2/42 (4.8%)	76

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## Appendix I- Search Strategy

### THE COCHRANE LIBRARY

1. BLOOD PLATELETS single term (MeSH)
2. platelet\* or thrombocyte\*
3. 1 or 2
4. BLOOD TRANSFUSION explode all trees (MeSH)
5. transfus\*:ti
6. 4 or 5
7. 3 and 6
8. PLATELET TRANSFUSION single term (MeSH)
9. ((platelet\* or thrombocyte\*) NEAR/5 (transfus\* or infus\* or administ\* or requir\*))
10. 7 or 8 or 9
11. THROMBOCYTOPENIA explode all trees (MeSH)
12. thrombocytopeni\*
13. PLATELET COUNT single term (MeSH)
14. (platelet\* Near/5 (count\* or low or lower\* or below or level\* or reduc\*))
15. 11 or 12 or 13 or 14
16. ATTITUDE TO HEALTH explode all trees (MeSH)
17. PATIENT COMPLIANCE single term (MeSH)
18. PATIENT SATISFACTION explode all trees (MeSH)
19. ADAPTATION, PSYCHOLOGICAL single term (MeSH)
20. MODELS, PSYCHOLOGICAL explode all trees (MeSH)
21. PSYCHOLOGICAL THEORY single term (MeSH)
22. STRESS, PSYCHOLOGICAL single term (MeSH)
23. PATIENT-CENTERED CARE single term (MeSH)
24. PSYCHOLOGY, MEDICAL single term (MeSH)
25. "common sense model"
26. (coping NEAR/5 (strateg\* or behav\*))

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27. (illness NEAR/5 cogniti\*)
28. ((patient\* or illness\* or risk\*) NEAR/5 (perception\* or perceiv\* or perspective\* or belie\*))
29. (psycholog\* NEAR/5 (research\* or theor\*))
30. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. QUALITY-OF-LIFE single term (MeSH)
32. QUESTIONNAIRES explode all trees (MeSH)
33. HEALTH-STATUS explode all trees (MeSH)
34. HEALTH-STATUS-INDICATORS explode all trees (MeSH)
35. HEALTH-SURVEYS explode all trees (MeSH)
36. INTERVIEWS AS TOPIC explode all trees (MeSH)
37. HEALTH CARE SURVEYS single term (MeSH)
38. ACTIVITIES-OF-DAILY-LIVING single term (MeSH)
39. SELF-CARE single term (MeSH)
40. QUALITY-ADJUSTED-LIFE-YEARS single term (MeSH)
41. PSYCHOMETRICS single term (MeSH)
42. COST-OF-ILLNESS single term (MeSH)
43. LIFE-STYLE explode all trees (MeSH)
44. (QOL or HQOL or HRQOL or HRQL or PedQL\* or Ped-QL\* or PedsQL\* or Peds-QL\*)
45. (quality NEAR/2 life)
46. (quality adjusted life year\* or QALY\*)
47. (health NEAR/2 (state or status))
48. (well being or wellbeing)
49. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. 30 or 49
51. LEUKEMIA explode all trees (MeSH)
52. LYMPHOMA explode all trees (MeSH)
53. NEOPLASMS, PLASMA CELL explode all trees (MeSH)
54. MYELOYDYSPLASTIC-MYELOPROLIFERATIVE DISEASES explode all trees (MeSH)
55. MYELOYDYSPLASTIC SYNDROMES explode all trees (MeSH)

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56. MYELOPROLIFERATIVE DISORDERS explode all trees (MeSH)
57. HEMATOLOGIC NEOPLASMS explode all trees (MeSH)
58. (leukemia\* or leukaemia\* or lymphoma\* or hodgkin\* or burkitt\* or myeloma\* or waldenstr\* or plasmacytoma\*)
59. (plasma cell NEAR/3 (tumor\* or tumour\*))
60. (myelodysplas\* or myelofibrosis)
61. ((anaemia or anemia) NEAR/2 (refractory or sideroblastic or myelophthisic))
62. ((haematologic\* or hematologic\*) NEAR/3 (malignan\* or neoplasm\* or cancer\* or tumor\* or tumour\*))
63. 51 or 52 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62
64. HEMORRHAGE explode all trees (MeSH)
65. (bleed\* or rebleed\* or hemorrhag\* or haemorrhag\* or bloodloss\* or (blood NEXT loss\*))
66. (petechia\* or purpura\*)
67. 64 or 65 or 66
68. 15 or 63
69. 10 or 67
70. 50 and 68 and 69

#### **MEDLINE & ERIC (Ovid)**

1. BLOOD PLATELETS/
2. (platelet\* or thrombocyte\*).tw.
3. 1 or 2
4. exp BLOOD TRANSFUSION/
5. transfus\*.ti.
6. 4 or 5
7. 3 and 6
8. PLATELET TRANSFUSION/
9. ((platelet\* or thrombocyte\*) adj5 (transfus\* or infus\* or administ\* or requir\*)).tw.
10. or/7-9
11. exp THROMBOCYTOPENIA/
12. thrombocytopeni\*.tw.

Quality of life and bleeding

13. PLATELET COUNT/
14. (platelet\* adj5 (count\* or low or lower\* or below or level\* or reduc\*)).tw.
15. or/11-14
16. exp ATTITUDE TO HEALTH/
17. PATIENT COMPLIANCE/
18. exp PATIENT SATISFACTION/
19. ADAPTATION, PSYCHOLOGICAL/
20. exp MODELS, PSYCHOLOGICAL/
21. PSYCHOLOGICAL THEORY/
22. STRESS, PSYCHOLOGICAL/
23. PATIENT-CENTERED CARE/
24. PSYCHOLOGY, MEDICAL/
25. common sense model\*.tw.
26. (coping adj5 (strateg\* or behav\*)).tw.
27. (illness adj5 cogniti\*).tw.
28. ((patient\* or illness\* or risk\*) adj5 (perception\* or perceiv\* or perspective\* or belie\*)).tw.
29. (psycholog\* adj5 (research\* or theor\*)).tw.
30. or/16-29
31. QUALITY-OF-LIFE/
32. PSYCHOLOGY.fs.
33. exp QUESTIONNAIRES/
34. exp HEALTH-STATUS/
35. exp HEALTH-STATUS-INDICATORS/
36. exp HEALTH-SURVEYS/
37. exp INTERVIEWS AS TOPIC/
38. HEALTH CARE SURVEYS/
39. ACTIVITIES-OF-DAILY-LIVING/
40. SELF-CARE/
41. QUALITY-ADJUSTED-LIFE-YEARS/

Quality of life and bleeding

42. PSYCHOMETRICS/
43. COST-OF-ILLNESS/
44. exp LIFE-STYLE/
45. (QOL or HQOL or HRQOL or HRQL or PedQL\* or Ped-QL\* or PedsQL\* or Peds-QL\*).tw.
46. (qualityadj2 life).tw.
47. (qualityadjusted life year\* or QALY\*).tw.
48. (health adj2 (state or status)).tw.
49. (well being or wellbeing).tw.
50. or/31-49
51. 30 or 50
52. exp LEUKEMIA/
53. exp LYMPHOMA/
54. exp NEOPLASMS, PLASMA CELL/
55. exp MYELOYDYSPLASTIC-MYELOPROLIFERATIVE DISEASES/
56. exp MYELOYDYSPLASTIC SYNDROMES/
57. exp MYELOPROLIFERATIVE DISORDERS/
58. exp HEMATOLOGIC NEOPLASMS/
59. (leukemia\* or leukaemia\* or lymphoma\* or hodgkin\* or burkitt\* or myeloma\* or waldenstr\* or plasmacytoma\*).tw.
60. (plasma cell adj3 (tumor\* or tumour\*)).tw.
61. (myelodysplas\* or myelofibrosis).tw.
62. ((anaemia or anemia) adj2 (refractory or sideroblastic or myelophthisic)).tw.
63. ((haematologic\* or hematologic\*) adj3 (malignan\* or neoplasm\* or cancer\* or tumor\* or tumour\*)).tw.
64. or/52-63
65. exp Hemorrhage/
66. (bleed\* or rebleed\* or hemorrhag\* or haemorrhag\* or bloodloss\* or (blood adj loss\*)).tw.
67. (petechia\* or purpura\*).tw.
68. or/65-67
69. 15 or 64
70. 10 or 68

Quality of life and bleeding

71. 69 and 70
72. 71 and 51
73. exp \*LEUKEMIA/
74. exp \*LYMPHOMA/
75. exp \*NEOPLASMS, PLASMA CELL/
76. exp \*MYELOYDYSPLASTIC-MYELOPROLIFERATIVE DISEASES/
77. exp \*MYELOYDYSPLASTIC SYNDROMES/
78. exp \*MYELOPROLIFERATIVE DISORDERS/
79. exp \*HEMATOLOGIC NEOPLASMS/
80. (leukemia\* or leukaemia\* or lymphoma\* or hodgkin\* or burkitt\* or myeloma\* or waldenstr\* or plasmacytoma\*).ti.
81. (plasma cell adj3 (tumor\* or tumour\*)).ti.
82. (myelodysplas\* or myelofibrosis).ti.
83. ((anaemia or anemia) adj2 (refractory or sideroblastic or myelophthisic)).ti.
84. ((haematologic\* or hematologic\*) adj3 (malignan\* or neoplasm\* or cancer\* or tumor\* or tumour\*)).ti.
85. or/73-84
86. 30 and 50 and 85
87. 72 or 86

#### **EMBASE (Ovid)**

1. THROMBOCYTE/
2. (platelet\* or thrombocyte\*).tw.
3. 1 or 2
4. exp BLOOD TRANSFUSION/
5. transfus\*.ti.
6. 4 or 5
7. 3 and 6
8. THROMBOCYTE TRANSFUSION/
9. ((platelet\* or thrombocyte\*) adj5 (transfus\* or infus\* or administ\* or requir\*)).tw.
10. or/7-9

Quality of life and bleeding

11. exp THROMBOCYTOPENIA/
12. thrombocytopeni\*.tw.
13. THROMBOCYTE COUNT/
14. (platelet\* adj5 (count\* or low or lower\* or below or level\* or reduc\*)).tw.
15. or/11-14
16. exp MYELOPROLIFERATIVE DISORDER/
17. exp LYMPHOMA/
18. exp MALIGNANT PLASMACYTOMA/
19. exp MYELOYDYSPLASTIC SYNDROME/
20. exp HEMATOLOGIC MALIGNANCY/
21. (leukemia\* or leukaemia\* or lymphoma\* or hodgkin\* or burkitt\* or myeloma\* or waldenstr\* or plasmacytoma\*).tw.
22. (plasma cell adj3 (tumor\* or tumour\*)).tw.
23. (myelodysplas\* or myelofibrosis).tw.
24. ((anaemia or anemia) adj2 (refractory or sideroblastic or myelophthisic)).tw.
25. ((haematologic\* or hematologic\*) adj3 (malignan\* or neoplasm\* or cancer\* or tumor\* or tumour\*)).tw.
26. or/16-25
27. 15 or 26
28. exp BLEEDING/
29. (bleed\* or rebleed\* or hemorrhag\* or haemorrhag\* or bloodloss\* or (blood adj loss\*)).tw.
30. (petechia\* or purpura\*).tw.
31. or/28-30
32. 10 or 31
33. 27 and 32
34. exp \*MYELOPROLIFERATIVE DISORDER/
35. exp \*LYMPHOMA/
36. exp \*MALIGNANT PLASMACYTOMA/
37. exp \*MYELOYDYSPLASTIC SYNDROME/
38. exp \*HEMATOLOGIC MALIGNANCY/
39. (leukemia\* or leukaemia\* or lymphoma\* or hodgkin\* or burkitt\* or myeloma\* or waldenstr\* or plasmacytoma\*).ti.

Quality of life and bleeding

40. (plasma cell adj3 (tumor\* or tumour\*)).ti.
41. (myelodysplas\* or myelofibrosis).ti.
42. ((anaemia or anemia) adj2 (refractory or sideroblastic or myelophthisic)).ti.
43. ((haematologic\* or hematologic\*) adj3 (malignan\* or neoplasm\* or cancer\* or tumor\* or tumour\*)).ti.
44. or/34-43
45. exp QUALITY-OF-LIFE/
46. HEALTH SURVEY/
47. QUESTIONNAIRE/
48. exp HEALTH-STATUS/
49. exp NAMED-INVENTORIES-QUESTIONNAIRES-AND-RATING-SCALES/
50. OUTCOMES RESEARCH/
51. SCORING SYSTEM/
52. RATING-SCALE/
53. FUNCTIONAL-ASSESSMENT/
54. SELF-REPORT/
55. (QOL or HQOL or HRQOL or HRQL or PedQL\* or Ped-QL\* or PedsQL\* or Peds-QL\*).tw.
56. (quality adj2 life).tw.
57. (quality adjusted life year\* or QALY\*).tw.
58. (health adj2 (state or status)).tw.
59. (well being or wellbeing).tw.
60. or/45-59
61. ATTITUDE TO HEALTH/
62. exp PATIENT ATTITUDE/
63. ADAPTIVE BEHAVIOR/
64. PSYCHOLOGICAL MODEL/
65. PSYCHOLOGICAL THEORY/
66. MENTAL STRESS/
67. MEDICAL PSYCHOLOGY/
68. common sense model\*.tw.

Quality of life and bleeding

69. (coping adj5 (strateg\* or behav\*)).tw.

70. (illness adj5 cogniti\*).tw.

71. ((patient\* or illness\* or risk\*) adj5 (perception\* or perceiv\* or perspective\* or belie\*)).tw.

72. (psycholog\* a dj5 (research\* or theor\*)).tw.

73. or/61-72

74. 60 or 73

75. 33 and 74

76. 44 and 60 and 73

77. 75 or 76

#### **CINAHL & PSYCINFO (NLH)**

1. BLOOD PLATELETS/

2. (platelet\* or thrombocyte\*).tw.

3. 1 or 2

4. exp BLOOD TRANSFUSION/

5. transfus\*.ti.

6. 4 or 5

7. 3 and 6

8. PLATELET TRANSFUSION/

9. ((platelet\* adj5 transfus\*) or (platelet adj5 infus\*) or (platelet\* a dj5 administ\*) or (platelet\* adj5 requir\*)).tw.

10. ((thrombocyte\* a dj5 transfus\*) or (thrombocvte\* a dj5 infus\*) or (thromocyte\* adj5 administ\*) or (thrombocyte\* a dj5 requir\*)).tw.

11. 7 or 8 or 9 or 10

12. exp THROMBOCYTOPENIA/

13. thrombocytopeni\*.tw.

14. PLATELET COUNT/

15. ((platelet\* adj5 count\*) OR (platelet\* adj5 low) OR (platelet\* adj5 lower\*) OR (platelet\* adj5 below) OR (platelet\* adj5 level\*) OR (platelet\* adj5 reduc\*)).ti,ab

16. 12 OR 13 OR 14 OR 15

#### **Quality of life and bleeding**

17. exp ATTITUDE TO HEALTH/
18. HEALTH BELIEFS/
19. ATTITUDE TO ILLNESS/
20. exp PATIENT COMPLIANCE/
21. ADAPTATION, PSYCHOLOGICAL/
22. exp MODELS, PSYCHOLOGICAL/
23. PSYCHOLOGICAL THEORY/
24. STRESS, PSYCHOLOGICAL/
25. exp PATIENT CENTRED CARE/
26. "common sense model\*".ti,ab
27. ((coping adj5 strateg\*) or (coping adj5 behav\*)).ti,ab
28. (illness adj5 cogniti\*).ti,ab
29. ((patient\* adj5 perception\*) or (patient\* adj5 perceiv\*) or (patient\* adj5 perspective\*) or (patient\* adj5 belie\*)).ti,ab
30. ((illness\* adj5 perception\*) or (illness\* adj5 perceiv\*) or (illness\* adj5 perspective\*) or (illness\* adj5 belie\*)).ti,ab
31. ((risk\* adj5 perception\*) or (risk\* adj5 perceiv\*) or (risk\* adj5 perspective\*) or (risk\* adj5 belie\*)).ti,ab
32. ((psycholog\* adj5 research\*) or (psycho\* adj5 theor\*)).ti,ab
33. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. QUALITY OF LIFE/
35. exp INSTRUMENT BY NAME/
36. exp QUESTIONNAIRES/
37. exp HEALTH STATUS/
38. HEALTH STATUS INDICATORS/
39. exp SURVEYS/
40. exp SABA CLINICAL CARE NURSING INTERVENTIONS/
41. QUALITY ADJUSTED LIFE YEARS/
42. PSYCHOMETRICS/
43. exp LIFE STYLE/
44. (QOL or HQOL or HRQOL or HRQL or PedQL\* or Ped-QL\* or PedsQL\* or Peds-QL\*).ti,ab
45. (quality adj2 life).ti,ab

Quality of life and bleeding

46. (qualityadjusted life year\* or QALY\*).ti,ab
47. ((healthadj2 state) or (healthadj2 status)).ti,ab
48. (well being or wellbeing).ti,ab
49. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. 33 or 49
51. exp LEUKEMIA/
52. exp LYMPHOMA/
53. exp MYELOYDYSPLASTICSYNDROMES/
54. exp MYELOPROLIFERATIVE DISORDERS/
55. exp HEMATOLOGIC NEOPLASMS/
56. (leukemia\* or leukaemia\* or lymphoma\* or hodgkin\* or burkitt\* or myeloma\* or waldenstr\* or plasmacytoma\*).ti,ab
57. ("plasma cell" adj3 tumor\*) or ("plasma cell" adj3 tumour\*).ti,ab
58. (myelodysplas\* or myelofibrosis).ti,ab
59. ((anaemiaadj2 refractory) or (anaemiaadj2 sideroblastic) or (anaemiaadj2 myelophthisic)).ti,ab
60. ((anemiaadj2 refractory) or (anemiaadj2 sideroblastic) or (anemiaadj2 myelophthisic)).ti,ab
61. ((haematologic\* adj3 malignan\*) or (haematologic\* adj3 neoplasm\*) or (haematologic\* adj3 cancer\*) or (haematologic\* adj3 tumor\*) or (haematologic\* adj3 tumour\*)).ti,ab
62. ((hematologic\* adj3 malignan\*) or (hematologic\* adj3 neoplasm\*) or (hematologic\* adj3 cancer\*) or (hematologic\* adj3 tumor\*) or (hematologic\* adj3 tumour\*)).ti,ab
63. 51 or 52 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62
64. exp HEMORRHAGE/
65. (bleed\* or rebleed\* or hemorrhag\* or haemorrhag\* or bloodloss\* or (bloodadj loss\*)).ti,ab
66. (petechia\* or purpura\*).ti,ab
67. 64 or 65 or 66
68. 11 or 67
69. 16 or 63
70. 68 and 69 and 50

## ISI PROCEEDINGS

Quality of life and bleeding

"quality of life" OR QOL OR HQOL OR HRQOL OR HRQL OR PedQL\* OR Ped-QL\* OR PedsQL\* OR Peds-QL\* OR questionnaire\* OR survey\*

AND

leukemia\* OR leukaemia\* OR lymphoma\* OR hodgkin\* OR burkitt\* OR myeloma\* OR waldenstr\* OR plasmacytoma\*

AND

bleed\* OR rebleed\* OR hemorrhag\* OR haemorrhag\* OR bloodloss\* OR petechia\* OR purpura OR "platelet transfusion\*"

#### **CLINICALTRIALS.GOV**

Search Terms: "Quality of Life" OR QALY OR QOL OR HQOL OR HRQOL OR HRQL OR PedQL OR Ped-QL OR PedsQL or Peds-QL OR questionnaire OR questionnaires OR survey OR surveys

Conditions: leukemia OR leukaemia OR lymphoma OR hodgkin OR myeloma OR plasmacytoma OR myelodysplasia OR myelodysplastic OR myeloproliferative OR thrombocytopenia

#### **ISRCTN**

("Quality of Life" OR QALY OR QOL OR HQOL OR HRQOL OR HRQL OR PedQL OR Ped-QL OR PedsQL or Peds-QL or questionnaire OR questionnaires OR survey OR surveys) AND (leukemia OR leukaemia OR lymphoma OR hodgkin OR myeloma OR plasmacytoma OR myelodysplasia OR myelodysplastic OR myeloproliferative OR thrombocytopenia OR thrombocytopenic) AND (haemorrhage OR hemorrhage OR haemorrhaging OR hemorrhaging OR bleeding OR platelet OR platelets OR petechiae OR purpura)

#### **WHO ICTRP**

Condition: leukemia OR leukaemia OR lymphoma OR hodgkin OR myeloma OR plasmacytoma OR myelodysplasia OR myelodysplastic OR myeloproliferative OR thrombocytopenia OR thrombocytopenic

Intervention: "Quality of Life" OR QALY OR QOL OR HQOL OR HRQOL OR HRQL OR PedQL OR Ped-QL OR PedsQL or Peds-QL or questionnaire OR questionnaires OR survey OR surveys

#### **PUBMED (e-publications) & TRANSFUSION EVIDENCE LIBRARY ([www.transfusionevidencelibrary.com](http://www.transfusionevidencelibrary.com))**

#1 "Quality of Life" OR QALY OR QOL OR HQOL OR HRQOL OR HRQL OR PedQL OR Ped-QL OR PedsQL or Peds-QL or questionnaire OR questionnaires OR survey OR surveys

Quality of life and bleeding

#2 leukemia\* OR leukaemia\* OR lymphoma OR Hodgkin\* OR myeloma OR plasmacytoma OR myelodysplasia\* OR  
myeloproliferative OR thrombocytopenia\*

#3 haemorrhage\* OR hemorrhage\* OR bleed\* OR platelet OR platelets OR petechia\* OR purpura

#4 #1 AND #2 AND #3

#5 publisher[sb]NOT pubstatusnihms

#6 #4 AND #5

Quality of life and bleeding

## **Appendix 2:**

### *Data recorded on data extraction form*

1. *General information* (e.g. study ID, citation of paper, objectives of the trial).
2. *Study details* (e.g. trial design, location, treatment allocation, randomisation, blinding, inclusion and exclusion criteria, reasons for exclusion, comparability of groups if applicable, length of follow up)
3. *Characteristics of participants at baseline* (e.g. age, gender, total number recruited, total number randomised (if appropriate), total number analysed, types of haematological disease, lost to follow-up numbers, drop outs (percentage in each arm))
4. *Quality of Life Tool* (Conceptual (A priori hypothesis, rationale for instrument used), Measurement (psychometric properties, cultural validity, adequacy of domains), Methodology (instrument administration, baseline compliance, timing of assessments, missing data) Interpretation (clinical significance)).
5. *Interventions* (if performed)
6. *Outcomes measured* (e.g. quality of life in bleeding and non-bleeding patients, number and severity of bleeding episodes, mortality).

### *Risk of bias assessment Non-randomised studies*

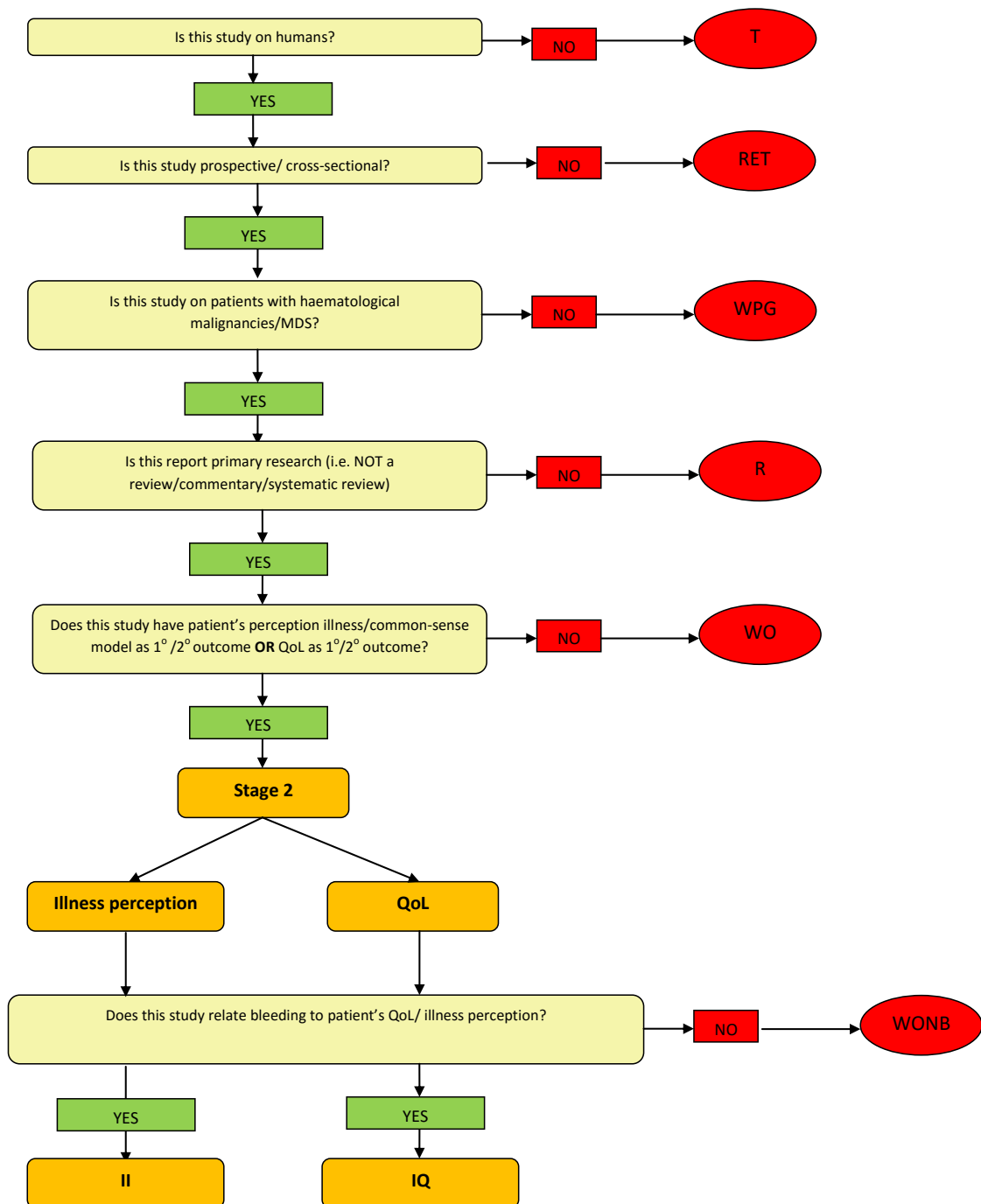
- Appropriate source population (selection bias)
- Appropriate measurement methods for both exposure(s) and or outcome(s) (detection bias)
- Appropriate methods to deal with any design-specific issues such as recall bias, interviewer bias, biased loss to follow-up or blinding (performance bias & attrition bias)
- Appropriate design and/or analytical methods (confounding)
- Appropriate use of statistics for primary analysis of effect (reporting bias)

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- Declaration of conflict of interest or identification of funding sources (other bias).

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### Appendix 3: Screening of full text for systematic review QoL/Illness perceptions



II = Include illness perception; IQ = Include QoL; R = Review; T = Theoretical; WO = Wrong outcome; WONB = Wrong outcome not bleeding WPG = wrong patient group

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## Appendix 4 – Excluded Studies

- Retrospective (n=15)[1-15]
  - Wrong patient group (n=5)[16-20]
  - Review (n=29)[21-49]
  - No patient related outcome reported (n=42)[50-91]
  - No bleeding reported (n=204)[92-295]
- 
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## Appendix 5:

**Table S1: On-going studies**

Study & country	Study design	No. of participants	Main aim of study	Study Intervention	Assessment of patient-related outcomes	Type of patient
OPTIMAL Study <sup>43</sup> (Outpatient platelet transfusions in myelodysplastic syndromes and leukemia) (NCT01615146) Canada	Multi-centre Open-label RCT Feasibility study	60	Feasibility study  Overall enrollment Off protocol transfusions/arm Total number of plt transfusions/arm Patient compliance with daily self-assessment of bleeding	Intervention: Therapeutic plt transfusions only. Patients allocated to this group will not receive routine prophylactic plt transfusions. Plt transfusions will be given to treat clinically relevant bleeding (WHO bleeding of grade 2 or greater). Control: Prophylactic plt transfusions. Patients allocated to this group will receive a plt transfusion when the measured plt count is $< 10 \times 10^9/L$ .	EuroQoL-5D	Adults ( $\geq 18$ years)  MDS (including CMML) or AML (WHO criteria)  Severe thrombocytopenia (2 plt counts $\leq 10 \times 10^9/L$ $\geq 7$ days apart).  Receiving outpatient supportive or palliative care  ECOG performance status of 0 - 2.
McKenna 2011 <sup>40</sup> UK	In-depth, one-to-one qualitative interviews	30	Assess how MDS impacts affects patients' lives.  Thematic analysis using three key outcomes: Impairments (symptoms); Activity limitations and QoL.	None	In-depth, one-to-one qualitative interviews.  Analysis of QoL issues to be guided by the needs-based model of QoL.	MDS  Participants recruited through the MDS UK Patient Support Group and Leukaemia CARE.

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AML = acute myeloid leukaemia; CMML = chronic myelomonocytic leukaemia; ECOG = Eastern Cooperative Oncology Group; plt = platelet; QOL = quality of life; RCT = randomised controlled trial;  
WHO = World Health Organization

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**Online Table S2: Patient-related Outcome Measures used in included studies**

Tool/Scale	Original design and specification	Target group	Content	Administration and scoring	Validity and reliability	Comments and concerns with bleeding /thrombocytopenia
EQ-5D-3L	Designed 1990 <sup>53</sup>  Survey to describe HRQoL in Europe for use in evaluative studies, policy research and economic evaluation  Multidimensional	Generic	5 dimensions relating to deficits in i) Mobility ii) Self-care iii) Usual activity iv) Anxiety and depression v) Pain and discomfort in addition to: Rating of own health today	Self-administered  Relates to health state today  Range of item responses on 3 point VDS according to severity. From 'no problems' to 'extreme problems' or 'inability to perform tasks'.  VAS to rate own health today from 'worst imaginable health state' (0) to 'best imaginable health state' (100).	Published data demonstrating reliability and validity <sup>54</sup>	Scale does not assess: 1) presence of bleeding/thrombocytopenia 2) impact of bleeding / thrombocytopenia 3) impact of treatment/management of bleeding/thrombocytopenia 4) psychological impact  Although widely used in many disease groups it remains a generic instrument  Recall period may be too short to demonstrate the impact of bleeding and any intervention/treatment
LGC  Lund Geronotological Centre global quality of life questionnaire	Designed 1992 <sup>44</sup>  Designed to measure global QoL in older people <sup>55</sup>	Generic	49 items including: Current quality of life Mental stability Life-span quality Satisfaction with residential environment Psychosomatic health Relationships with neighbours Satisfaction with economic situation Importance of social activities Close relationships View of daily life	Unclear how it is administered  Scores calculated as a mean value for all areas or total mean for all areas. From 0 (worst possible) to 1 best possible <sup>55</sup>	Not extensively validated. Used in Sweden in studies of older people <sup>55</sup>	Unable to establish if the scale assesses: 5) presence of bleeding/thrombocytopenia 6) impact of bleeding / thrombocytopenia 7) impact of treatment/management of bleeding/thrombocytopenia 8) psychological impact
POMS Profile of Mood States	Designed 1971 <sup>56</sup>  Measure of subjective well-being  Originally designed to assess mood in psychiatric out-patient attenders <sup>56</sup>	Generic	65 items measuring 6 mood states: i) Tension - Anxiety ii) Depression - Dejection iii) Anger - Hostility iv) Vigour - Activity v) Fatigue - Inertia vi) Confusion - Bewilderment	Self-administered  Relates to feelings during last week including 'today' <sup>57</sup>  Items rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely)  Total mood disturbance calculated by subtracting the Vigour subscale score from the sum of the Tension,	Published data demonstrating reliability and validity <sup>58</sup>	Scale does not assess: 1) presence of bleeding/thrombocytopenia 2) impact of bleeding / thrombocytopenia 3) impact of treatment/management of bleeding/thrombocytopenia 4) psychological impact

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				Depression, Anger, Fatigue, and Confusion subscale scores.		
SF-36 Medical Outcomes Study, Short Form 36	Designed 1993 <sup>18</sup>  For population surveys and detecting changes in health status that might be expected to occur from health service use within a short time frame.  Discriminates between people with chronic disease and general populations  Multidimensional	Generic	36 items with 8 dimensions i) Physical functioning (10) ii) Social functioning (2) iii) Role limitations due to physical problems (4) iv) Role limitations due to emotional problems (3) v) Mental health (5) vi) Energy/vitality (4) vii) Pain (2) viii) General health perception (5) In addition to perception of health changes over the past year	Self-administered  Relates to experiences during the past 4 weeks; in general; and compared to 1 year ago  Range of item responses from 3 to 7 points  Item scores of each dimension are added together and calculated using an algorithm to a scale of poor health (0%) or good health (100%)	Published data demonstrating reliability and validity <sup>59</sup>	Scale does not assess: 5) presence of bleeding/thrombocytopenia 6) impact of bleeding / thrombocytopenia 7) impact of treatment/management of bleeding/thrombocytopenia 8) psychological impact  Recall period of 1 month and 1 year could be too long for elderly and/or unwell patients
SOC Sense of Coherence Scale	Designed 1987 <sup>60</sup>  Generic scale to assess coherence as an indicator of coping with stressful life situations <sup>61</sup>	Generic	29 items assessing 3 elements i) Comprehensibility (cognitive) (11) ii) Manageability (instrumental/behavioural) (10) iii) Meaning (motivation) (8)	Self-administered  Relates to experiences “in past ten years”, “until now” or no time-scale specified  Range of item responses on a 7 point NRS. Items are summed from 29 to 203. A higher score relates to a higher sense of coherence <sup>61,62</sup>	Published data demonstrating reliability and validity <sup>60</sup>	Scale does not assess: 1) presence of bleeding/thrombocytopenia 2) impact of bleeding / thrombocytopenia 3) impact of treatment/management of bleeding/thrombocytopenia 4) psychological impact
EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30	Designed 1993 <sup>63</sup>  QoL measure for international cancer trials. Current version 3.0.  Multidimensional  Supplementary scales developed for specific cancers with unique problems  Shown to detect changes over time	Disease: Cancer	30 items with A) 5 functional scales: i) Physical ii) Role iii) Cognitive iv) Emotional v) Social B) Global health and QoL C) 6 single items assess common cancer symptoms - Dyspnoea - Appetite loss - Sleep disturbance - Diarrhoea - Constipation - Perceived financial impact	Self-administered  Relates to experiences during the past week  Overall QoL and physical health condition during the past week uses a NRS from ‘very poor’ (1) to excellent (7)  Other items 4 point response from ‘not at all’ (1) to ‘very much’ (4)  Scales summed up to	Published data demonstrating reliability and validity <sup>64,65</sup>	Scale does not assess: 1) presence of bleeding/thrombocytopenia 2) impact of bleeding / thrombocytopenia 3) impact of treatment/management of bleeding/thrombocytopenia 4) psychological impact of bleeding

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			disease/treatment D) 3 symptom scales <ul style="list-style-type: none"> <li>- Fatigue</li> <li>- Nausea/vomiting</li> <li>- Pain</li> </ul>	produce sub-scale scores		
FACT – Functional Assessment of Cancer Therapy	Designed in 1990 <sup>66</sup>  Assess HRQoL in cancer, also include chronic illness (FACIT).  Modular system of generic core with specific disease /symptom ‘add-on’  Multidimensional	Disease: Cancer  Chronic illness	Core generic (FACT-G) 27 items with 4 dimensions i) Physical well-being (7) ii) Social/Family well-being (7) iii) Emotional well-being (6) iv) Functional well-being (7)  FACT-Th11- 38 items with 5 dimensions <sup>19</sup> FACT-G (27) plus v) Additional concerns (11)  FACT-Th18 - 45 items with 5 dimensions <sup>19</sup> FACT-G (27) plus v) Additional concerns (18)  FACT-BMT- 50 items with 5 dimensions <sup>19</sup> FACT-G (27) plus v) Additional concerns (23)	Self-administered  Relates to experiences during the past week  5 point VDS according to severity. From ‘not at all’ (0) to ‘very much’ (4).	Published data demonstrating reliability and validity in cancer and wide range of chronic diseases for FACT-G <sup>66,67</sup> and FACT-BMT.  FACT-Th18 only tested for validity in 108 patients within urban USA <sup>68</sup>  FACT-Th11 not tested <sup>68</sup> .	Only the FACT-Th Scales assess: <ol style="list-style-type: none"> <li>1) presence of bleeding/thrombocytopenia</li> <li>2) impact of bleeding / thrombocytopenia upon the patient</li> <li>3) impact of potential treatment delay due to bleeding/thrombocytopenia</li> </ol> 1) psychological impact  FACT G and FACT-BMT make no assessment of bleeding or thrombocytopenia
MDASI MD Anderson Symptom Inventory	Designed 2000 <sup>69</sup>  To measure symptom severity, burden and interference in cancer  Modular system of generic core with specific disease /symptom ‘add-on’  Multidimensional	Disease: Cancer	Core generic MDASI 19 items with 2 dimensions  Symptom severity items (13): pain, fatigue, nausea, disturbed sleep, being distressed, shortness of breath, problems remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, numbness/tingling  Symptom interference items (6): general activity, mood, work; walking, relations with other people, enjoyment of life  MDASI-BMT 24 items. Core MDASI (19) plus additional symptom severity items (5): feeling physically sick; feeling physically weak; diarrhoea; mouth sores,	Self-administered  Relates to symptoms experienced during last 24 hours  0 to 10 point NRS to assess severity of symptoms and interference. From ‘not present/did not interfere’ (0) to ‘as bad you can imagine/completely interfered’ (10)	Published data demonstrating reliability and validity in cancer for core MDASI <sup>69,70</sup> .  MDASI-BMT not validated.	The MDASI-BMT asks one question relating to the presence of bleeding at its worst only  Scale does not assess: <ol style="list-style-type: none"> <li>1) impact of bleeding/ thrombocytopenia</li> <li>2) impact of treatment/management of bleeding/thrombocytopenia</li> <li>3) psychological impact</li> </ol> Recall period may be too short to demonstrate the impact of bleeding and any intervention/treatment

Quality of life and bleeding

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EORTC = European Organization for Research and Treatment of Cancer; FACT-BMT = Functional assessment of Cancer Therapy – Bone Marrow Transplantation; FACT-G = Functional assessment of Cancer Therapy – General; FACT- Th = Functional assessment of Cancer Therapy – Thrombocytopenia; MDASI-BMT = MD Anderson Symptom Inventory- Bone Marrow Transplant; NRS = numerical rating scale; POMS = Profile of Mood States; QoL = Quality of Life; SF-36 = Short Form 36; VAS = Visual Analogue Scale; VDS = Verbal Descriptor Scale

Quality of life and bleeding