# A systematic review of patient reported outcomes in phase II or III clinical trials of myelodysplastic syndromes and acute myeloid leukemia

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## ABSTRACT

The purpose of this systematic literature review was to identify clinical trials of MDS and AML that included patient-reported outcome (PRO) instruments, and to summarize the symptom and other health related quality of life (HRQOL) concepts most frequently assessed and the PRO instruments that were used. Sixteen manuscripts describing 14 distinct trials met all criteria (i.e., phase 2 or 3 clinical trial for MDS or AML which included PRO assessment) and were published between 1996-2017. In trials evaluating anemia, PRO scores showed significant improvement in relevant domains (e.g. fatigue, function) among patients identified as responders. In trials evaluating the impact of anti-cancer therapies, improvements the baseline to end of treatment were observed in physical functioning and HRQOL, however the rates of missing data in many of the trials was high or unreported. PRO instruments have the ability to capture changes over time in patients' function and well-being, and PRO instruments and guidance documents are available to support the assessment of HRQOL in AML/MDS clinical trials.

## 1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematological diseases of ineffective hematopoiesis with a risk for progression to acute myeloid leukemia (AML) [1,2]. More than 80% of individuals with MDS are 65 years old or older at the time of diagnosis [3]; the average age at diagnosis is 67 years old [4]. Anemia and fatigue are common in MDS, and are often managed through red blood cell transfusions. In addition, MDS can transform into AML requiring intensive chemotherapy and prolonged hospital stays of approximately 30 days [5], which can lead to severe toxicities and functional impairments [5–8]. To date, the primary foci of MDS and AML clinical trial research have been disease free survival and overall survival, with little attention on patient-reported symptoms, health related quality of life (HRQOL), and treatment satisfaction [9].

Patient-reported outcome (PRO) instruments are used in oncology research to evaluate new therapies, supportive care interventions, and quality of care. PRO instruments are designed to capture patient's experiences and perspectives on a broad array of concepts including symptoms (e.g., pain, nausea, and fatigue), function (e.g., physical function, social function, and activities of daily living), quality of life, and treatment experience (e.g., quality of communication, decisional regret, and satisfaction). The FDA accepts PRO data in support of labeling claims, which provides information about the benefits of treatment. The FDA defines patient-reported outcomes as "*A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response*" [10]. The characteristics of well performing PRO instruments include content validity, measurement reliability and responsiveness to change [11]. Content validity refers to whether an instrument measures what it is intended to measure and whether it includes relevant domains. Reliability is the degree to which the instrument produces the same result on repeated administrations. Responsiveness to change is the ability of the instrument to detect change over time. An introduction to measurement theory, methods for the development and validation of PRO instruments, and statistical methods for analyzing PRO data are described in a number of clearly written texts [12,13].

The purpose of this systematic literature review was: (1) to identify MDS and AML drug trials that included PRO instruments, (2) to summarize the symptom and other HRQOL concepts most frequently assessed, including the use of specific PRO instruments, and (3) to

**Table 1**
Query used in PubMed search.

| Search | Query |
|---|---|
| #1 | (((("Leukemia, Myeloid, Acute"[MeSH] OR "Acute Myeloid Leukemia" OR "Acute Myeloid Leukemias" OR ANLL OR "Acute Myeloblastic Leukemia" OR "Acute Myeloblastic Leukemias" OR "Acute Myelocytic Leukemia" OR "Acute Myelocytic Leukemias" OR "Acute Nonlymphoblastic Leukemia" OR "Acute Nonlymphoblastic Leukemias" OR "Acute Nonlymphocytic Leukemia" OR "Acute Nonlymphocytic Leukemias" OR "Acute Myelogenous Leukemia" OR "Acute Myelogenous Leukemias") AND ("drug therapy"[MeSH] OR "drug therapy"[sh] OR "drug therapy"[tw]) AND ("Clinical Trial" [Publication Type:NoExp] OR "clinical trial, phase i"[publication type] OR "clinical trial, phase ii"[publication type] OR "clinical trial, phase iii"[publication type] OR "clinical trial, phase iv"[publication type] OR "controlled clinical trial"[publication type] OR "multicenter study"[publication type] OR "randomized controlled trial"[publication type] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled [TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB]))) AND ("phase 2" OR "phase ii" OR "phase 3" OR "phase iii")) NOT (Review[ptyp] OR Clinical Trial, Phase I[ptyp] OR "animals"[MeSH Terms:noexp] OR ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms])) AND English[lang]) |
| #2 | ((((("Leukemia, Myeloid, Acute"[MeSH] OR "Acute Myeloid Leukemia" OR "Acute Myeloid Leukemias" OR ANLL OR "Acute Myeloblastic Leukemia" OR "Acute Myeloblastic Leukemias" OR "Acute Myelocytic Leukemia" OR "Acute Myelocytic Leukemias" OR "Acute Nonlymphoblastic Leukemia" OR "Acute Nonlymphoblastic Leukemias" OR "Acute Nonlymphocytic Leukemia" OR "Acute Nonlymphocytic Leukemias" OR "Acute Myelogenous Leukemia" OR "Acute Myelogenous Leukemias") AND ("Cladribine"[tw] OR Leustatin[tw] OR fludarabine[tw] OR fludara[tw] OR beneflur[tw] OR "Topotecan"[tw] OR Hycamtamine[tw] OR Hycamtin[tw] OR "Etoposide"[tw] OR "Eposide"[tw] OR "Etopos"[tw] OR "Exitop"[tw] OR "Lastet"[tw] OR "Riboposid"[tw] OR "Toposar"[tw] OR "Vepesid"[tw] OR "Vépéside-Sandoz"[tw] OR "Vépéside Sandoz"[tw] OR "Celltop"[tw] OR "Eposin"[tw] OR "Etomedac"[tw] OR "Eto-GRY"[tw] OR "Eto GRY"[tw] OR Tioguanine[tw] OR "Thioguanin GSK"[tw] OR Tioguanina[tw] OR Lanvis[tw] OR "Hydroxyurea"[tw] OR Hydroxycarbamid[tw] OR Oncocarbide[tw] OR Hydrea[tw] OR prednisone[tw] OR dexamethasone[tw] OR decadron[tw] OR spersadex[tw] OR spersadox[tw] OR methotrexate[tw] OR amethopterin[tw] OR mexate[tw] OR Mercaptopurine[tw] OR leupurin[tw] OR purimethol[tw] OR purinethol[tw] OR "puri nethol"[tw] OR azacitidine[tw] OR azacytidine[tw] OR vidaza[tw] OR decitabine[tw] OR dacogen[tw] OR "2-cda"[tw] OR "vp-16"[tw] OR "6-tg"[tw] OR mtx[tw] OR "6 mp"[tw]) AND ("Clinical Trial" [Publication Type:NoExp] OR "clinical trial, phase i"[publication type] OR "clinical trial, phase ii"[publication type] OR "clinical trial, phase iii"[publication type] OR "clinical trial, phase iv"[publication type] OR "controlled clinical trial"[publication type] OR "multicenter study"[publication type] OR "randomized controlled trial"[publication type] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled [TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])))) NOT (Review[ptyp] OR Clinical Trial, Phase I[ptyp] OR "animals"[MeSH Terms:noexp] OR ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms])) AND English[lang]) NOT ((Review[ptyp] OR systematic[sb] OR Case Reports[ptyp] OR Comment[sb] OR Editorial[ptyp] OR Guideline[ptyp] OR Letter[ptyp] OR Meta-Analysis[ptyp] OR News[ptyp] OR Observational Study[ptyp] OR Validation Studies[ptyp]))) |
| #3 | #1 OR #2 |

describe the PRO results of the trials.

## 2. Materials and Methods

### 2.1. Search Strategy

A systematic literature review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines was conducted by the authors. Eligible manuscripts described phase 2 and phase 3 clinical trials of drug therapies for MDS or AML which included PRO instruments for assessing symptoms, function or quality of life. In March 2017, the electronic databases of PubMed and EMBASE were searched using search strategy developed in conjunction with a UNC Health Sciences Library research librarian; the PubMed search terms are listed in Table 1. Additional articles were identified through clinicaltrials.gov, World Health Organization International Clinical Trials Registry Platform, and manual search. Case reviews, summary reports, clinical reviews, literature and systematic reviews, and dissertations were excluded. Abstracts retrieved via the database searches were reviewed to identify those that were phase 2 or 3 clinical trials of drug therapies for MDS or AML. Of these, the full text of the article was reviewed to identify the clinical trials which had included PRO assessment.

## 3. Results

A total of 1798 articles were identified through PubMed, EMBASE, other sources and manual searches. One hundred and fifty-eight were duplicate articles. After removal of duplicate articles, 1640 were assessed for eligibility and 1623 were excluded. (Fig. 1)

Sixteen manuscripts describing 14 distinct trials met all criteria (i.e., phase 2 or 3 clinical trials of drug therapy for MDS or AML, which included PRO assessment). A summary of these trials can be found in

Table 2. All 16 manuscripts were published between 1996-2017, and eight manuscripts [14–21] were published in the past 5 years. Treatments included: lenalidomide, darbepoetin, erythropoietin, mitoxantrone, cytarabine, amscarine, lintuzumab, etoposide, decitabine, all trans-retinoic acid (ATRA), daunorubicin, idarubicin, arsenic trioxide, and azacitidine. Eight distinct phase 3 clinical trials were identified. The foci of the trials were drug efficacy and symptom improvement, and were conducted primarily in older adults (> 65 years). Total sample size ranged from 67-481 for the phase 2 trials [17,19,20,22–25], and 110-488 for phase 3 trials [2,14,15,18,21,26–28].

### 3.1. Commonly used patient-reported outcome instruments

The Functional Assessment of Cancer Therapy-Anemia (FACT-An) was used in 2 trials [14,19], one of darbapoeitin alpha and one of lenalidomide. The FACT-Leu, an HRQOL measure specific to leukemia, was included in 1 trial [17]. The most commonly used HRQOL measure was the EORTC QLQ-C30, which was used in 9 trials [2,15,18,20,21,23–27,29], and the EORTC QLQ-Leu subscale was used in 2 trials [23–25]

The FACT-An includes the domains of the FACT-General, which are physical well-being, social well-being, emotional well-being, and functional well-being, and 20 additional questions specific to anemia (e.g. fatigue, weakness, lightheadedness, headaches, difficulty doing usual activities). The FACT-Leu includes the domains of the FACT-General (as listed above) and 17 additional questions specific to leukemia (e.g. fever, chills, lumps/swelling, bruise easily, pain, weakness, appetite loss, worry, social isolation). The EORTC QLQ-C30 assesses the HRQOL issues common to most types of cancer, which are the symptoms of fatigue, nausea, pain, dyspnea, sleep disturbance, appetite loss, constipation, and diarrhea, as well as physical function, role function, social function, emotional function, cognitive function, financial stress, and global QOL. The MRC/EORTC QLQ-Leu, also referred to as the
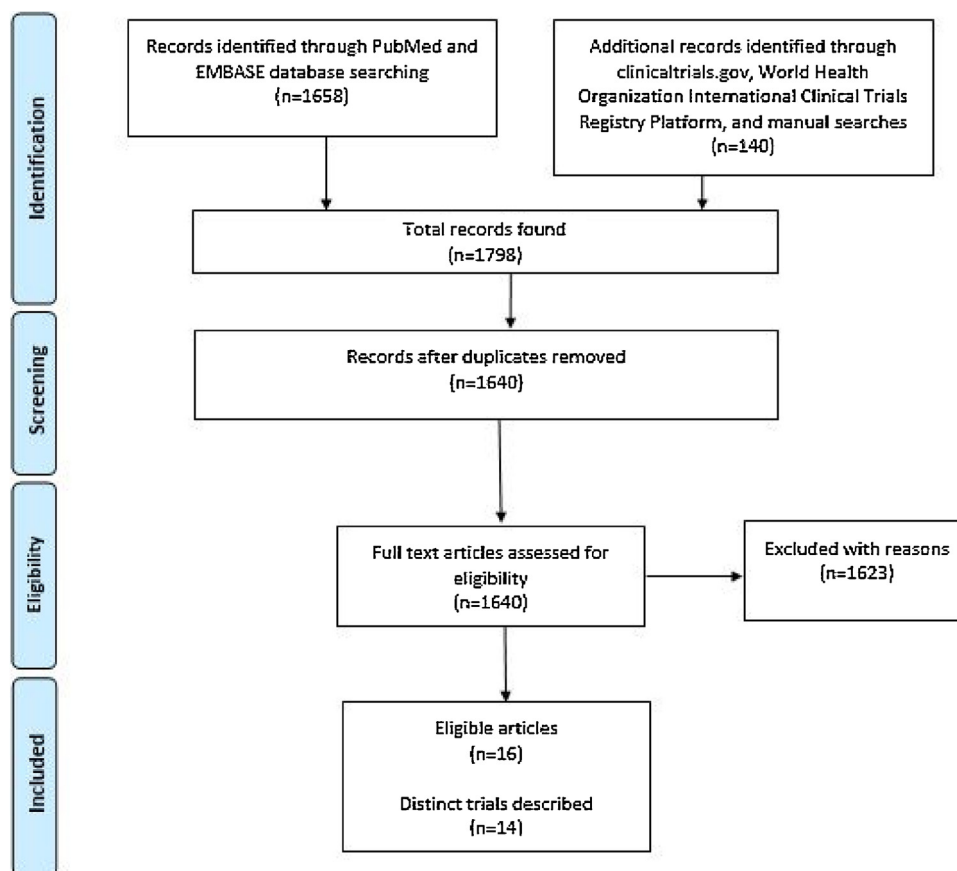
**Fig. 1.** PRISMA Diagram.

QLQ-LEU-BMT, was developed by Watson, Zittoun, et al (1996) [30] to capture known late side-effects of BMT in adult patients treated for leukemia, including the symptoms of graft versus host disease; it contains 32 items, most of which form two subscales corresponding to graft versus host disease and infection.

### 3.2. Focus on fatigue: Lenalidomide, darbepoetin and erythropoietin

Fatigue is the most distressing symptom in adults with acute leukemia [5]. Anemia is a common disease and treatment-related sign of both MDS and AML. In Fenaux et al [14], anemia was assessed using the FACT-An at baseline and at weeks 12, 24, 36, and 48, and it was found that treatment with lenalidomide improved HRQOL (FACT-An) at week 12. Baseline and week 12 data were available for 71% of randomized patients. Kelaidi et al [19], also used the FACT-An to assess the efficacy of treating anemia with darbepoetin and found a steady improvement over 24 weeks in those who received darbepoetin with filgrastim. The mean difference in HRQOL (FACT-An) over 6 months in the responders vs non-responders was significant (p = 0.007). Rates of missing PRO data were not reported [19]. Greenberg et al [28] found no differences in FACT-General and FACT-Fatigue scores between treatment arms (EPO with BSC vs BSC alone), however there were significant improvements from baseline in physical (p = .007), emotional (p = .02), and functional well-being (p = .005), fatigue (p = .02), and overall QOL (p = .02) in those with an erythroid response at 4 months. PRO assessments were completed by 102 patients at baseline and 84 patients at month 4 [28].

### 3.3. Cytarabine and lintuzumab

Bow et al [22] found Global QOL scores as measured by the Functional Living Index-Cancer (FLI-C) improved from baseline to 60 days in older adults (60-80 years) untreated with AML after receiving a non-cytarabine containing remission-induction regimen (mitoxantrone and etoposide) followed by intermediate-dose cytarabine postremission. Rates of missing PRO data were not reported. Sekeres et al [17] found the median change from baseline in FACT-Leu scores was similar for both treatment arms (LD-C and lintuzumab vs LD-C and placebo).

### 3.4. Decitabine

Kantarjian et al [27] found improvements in fatigue (p < .05), dyspnea (p < .05), and global health status (p < 0.05) as measured by the EORTC QLQ-C30 for patients receiving decitabine versus BSC. Rates of missing PRO data were not reported. Lubbert et al [15] found significant improvement of fatigue and physical functioning as measured by the EORTC QLQ-C30 in those given low dose decitabine. The rates of missing data were substantial, and authors note: "Missing data were an issue (baseline compliance was only 60%, decreasing from 50% to 30% during the first year), and the observed treatment differences could not be confirmed consistently when imputing the missing data."

### 3.5. All-trans-retinoic acid (ATRA)

Efficace et al [18] found the severity of fatigue differed for those receiving ATRA and chemotherapy compared to ATRA and arsenic trioxide (p = .022). The survey completion rates were very high in both treatment arms. Out of 156 patients who received at least one dose, 150 completed the first PRO assessment and 142 completed the second. Burnett et al. [20] found no long term differences in QOL in regimens of ATRA and ADE (daunorubicin, cytarabine and etoposide) compared to ATRA and idarubicin. Burnett et al. [21] reported separately no differences in QOL, except for "role functioning", or in anxiety and depression between patients treated with ATRA, idarubicin and

**Table 2**

Summary of included manuscripts in systematic review (N = 16), describing 14 distinct trials.

| Author/Year Trial Design | Objective | Drug | Sample (N and age in years, by group) | Survival Outcomes (median, in months) |
|---|---|---|---|---|
| Bow et al., [22] Phase II Single Arm Longitudinal | Examine safety, efficacy and impact on QOL of a non-cytarabine containing remission-induction regimen followed by intermediate-dose cytarabine postremission therapy for untreated AML patients 60-80 years | mitoxantrone (10 mg/m$^2$) and etoposide (100 mg/m$^2$) Complete remitters received single course of cytarabine 0.5 g/m$^2$ for 6 days | All patients N = 67 Median age = NR No Remission N = 30 Median age = 67 Remission N = 37 Median age = 68 | Disease-free survival = 8.4 OS = 9.2 |

**QOL Outcomes**
Instruments: FLIC
Global QOL scores improved from baseline to 60 days; Complete remitters and partial responders achieved similar global QOL scores
**Missing Data**
No additional information on the number of patients who completed QOL measure at each time point.
The mean scores at baseline compared with those observed at approximately day 30 (the time of marrow recovery from induction) and at approximately day 60 (the time complete remitters would be expected to start post-remission consolidation). (Fig. 2)

| Author/Year Trial Design | Objective | Drug | Sample (N and age in years, by group) | Survival Outcomes (median, in months) |
|---|---|---|---|---|
| Zittoun et al., [25] Phase II Multi-arm (Allo-BMT Vs. Auto-BMT vs. 2$^{nd}$ course CCT) Cross-sectional | To examine disease-free survival and OS in 3 post-remission treatments of AML (Allo-BMT, Auto-BMT, and CCT) | Arm 1 (Allo-BMT): 1$^{st}$ CCT course [cytarabine, amsacrine], HLA sibling donor-matched Allo-BMT Arm 2 (Auto-BMT): 1$^{st}$ CCT Course; Auto-BMT Arm 3 (2$^{nd}$ course CCT): 1$^{st}$ course CCT; 2$^{nd}$ course CCT [high-dose cytarabine & daunorubicin] | All patients N = 623 (QOL N = 98) Median age = NR Allo-BMT N = 168 (QOL N = 35) Median age = 39 Auto-BMT N = 128 (QOL N = 29) Median age = 29 CCT N = 126 (QOL N = 34) Median age = 44 | No significant differences in OS between the three arms 4-year OS was 59% Allo-BMT, 56% Auto-BMT, and 46% 2$^{nd}$ course CCT [45] |

**QOL Outcomes**
Instruments: EORTC QLQ-C30; EORTC QLQ-Leu; Sexual Functioning Scale; Disease-Related Modifications module
QOL was assessed once at a median of 53 months after CR (range 12-89 months). Statistically significant differences by treatment arm were observed for EORTC QLQ-C30 subscales of overall physical condition, overall QOL, and global health status.
The prevalence of 10 of the 32 items in the EORTC QLQ-Leu scale were significantly different amongst the 3 arms (generally following the trend of Allo-BMT greater than Auto-BMT greater than CCT): fever, mouth sores, dental problems, cough, hair loss, headache, pain during sexual intercourse, acute disease within the last month, seeing a doctor, and taking pills/medicine.
Sexual functioning was significantly more impaired for Allo-BMT compared to Auto-BMT or CCT.
**Missing data**
Out of 155 patients from the participating centers (18 centers that agreed to participate in the QOL study) who were alive and in first CR for 1 year or more, 98 agreed to enter the QOL study (AlloBMT N = 35, AutoBMT N = 29, CCT N = 34). QOL data for all 98 patients are available.

| Author/Year Trial Design | Objective | Drug | Sample (N and age in years, by group) | Survival Outcomes (median, in months) |
|---|---|---|---|---|
| Watson et al.,* [23] Watson et al.,* [24] Phase II Multi-arm (CCT alone vs. CCT and Allo-BMT vs. CCT and Auto-BMT] *Two QOL studies using data from same trial (MRC AML 10) Cross- sectional | To determine the adverse effects of BMT in comparison to intensive CCT in AML patients | Arm 1: Four courses of CCT alone Arm 2: Four courses of CCT and Allo-BMT Arm 3: Four courses of CCT and Auto-BMT | All patients N = 481 Median age = 39 Range:15-58 CCT alone N = 310 Median age = 43 Allo-BMT N = 97 Median age = 32 Auto-BMT N = 74 Median age = 37 | 81 % of patients achieved complete remission [46] 7-year OS was 40% for all patients. The difference in 7-year OS between Auto-BMT and CCT was not significant (57% vs. 45%, respectively; p = 0.2). 7-year OS for Allo-BMT was not reported. |

**Table 2** (*continued*)

| Author/Year<br>Trial Design | Objective | Drug | Sample<br>(N and age in<br>years, by group) | Survival Outcomes (median, in months) |
|---|---|---|---|---|
| | **QOL Outcomes**<br>Instruments: EORTC QLQ-C30; EORTC QLQ-Leu; Sexual Functioning Scale [25]; Disease-related modification scale<br>EORTC QLQ-C30: Overall QOL was significantly poorer in those treated with Allo-BMT than either Auto-BMT or CCT alone (p < 0.001). A majority of patients reported fatigue (79%), and some degree of problem with emotional (75%), social (56%), and cognitive functioning (53%). Allo-BMT patients reported significantly more problems with physical functioning and role and social functioning than either CCT alone or Auto-BMT patients (p < 0.001 in each case).<br>EORTC QLQ-Leu: The majority of patients (86%) reported symptoms related to GVHD, such as itching, dry skin, stiff joints, and chills, and older patients reported worse symptoms than younger (p = 0.07) and females had worse symptoms than males (p < 0.001). Allo-BMT patients showed worse leukemia-specific problems (eye dryness, difficulty swallowing, and coughing) than either CCT alone (p < 0.001, p = 0.02, p = 0.04, respectively) or Auto-BMT (p = 0.03, p = 0.03, p = 0.003, respectively) patients.<br>Sexual Functioning Scale [25]: Significantly more BMT patients than CCT patients reported a decrease in interest in sex (48% vs. 24%), sexual activity (53% vs. 35%), pleasure from sex (36% vs. 18%), and ability to have sex (38% vs. 18%) (p < 0.001 in each case).<br>Disease-related Modification Scale: Results showed that post-treatment overall QOL was worse than pre-treatment.<br>**Missing Data**<br>Out of 716 patients who were considered eligible (138 Allo-BMT, 116 Auto-BMT, 462 CCT),<br>- 109 have developed recurrent disease or died<br>- 19 were not considered suitable by the clinicians<br>- For 50 cases, the clinician did not reply<br>- 55 patients did not return the questionnaire<br>- 4 did not answer sexual functioning questions<br>479 patients completed questionnaires, yielding a 89% patient compliance rate (95 Allo-BMT, 73 Auto-BMT, 311 CCT) | | | |
| Silverman et al., [26]<br>Kornblith et al., [29]<br>Phase III<br>Multi-Arm (Aza C vs. BSC)<br>Longitudinal | Compare the clinical efficacy and QOL of SQ Aza C treatment and BSC in patients with MDS | <u>Arm 1:</u><br>Aza C, 75 mg/m²/d<br><u>Arm 2:</u><br>BSC | All patients<br>N = 191<br>Median age = 68<br>Range: 31-92<br>Aza C<br>N = 99<br>Median age = 69<br>BSC<br>N = 92<br>Median age = 67 | Aza C<br>OS = 20<br>BSC<br>OS = 14<br>No significant difference (p = 0.1) |
| | **QOL Outcomes**<br>Instruments: EORTC QLQ-C30; MHI<br>Aza C arm had statistically significant improvements over time in fatigue, dyspnea, psychosocial distress, and positive affect. Clinically significance improvement (i.e., EORTC QLQ-C30 score improved by at least 10 points from baseline to follow-up) was seen in physical functioning, 3 physical symptom subscales and overall QOL. Aza C group had 10% greater likelihood that psychological distress would be reduced by end of treatment.<br>**Missing Data**<br>191 patients completed baseline QOL assessment.<br>Of the 99 patients on Aza C treatment, "56% (n = 56) remained on active treatment by day 182; 16% (n = 16) had died; 22% (n = 22) had terminated protocol treatment due to treatment failure, toxicity, or transformation to AML; and 5% (n = 5) refused to complete the QOL questionnaires."<br>Of the 92 patients on supportive care, "47% (n = 43) remained on study with QOL data collected through day 182, including 13% (n = 12) who remained on supportive care, 34% (n = 31) who remained on Aza C after cross-over, 23% (n = 21) who had died, 26% (n = 24) who had terminated protocol treatment, and 4% (n = 4) who refused to continue in the QOL study. There were 80.4% (n = 74) and 61.9% (n = 57) of supportive care patients still on supportive care, completing quality-of-life assessments, at days 50 and 106, respectively." | | | |
| Kantarjian et al., [27]<br>Phase III<br>Multi-Arm<br>(decitabine and BSC vs. BSC alone)<br>Longitudinal | Compare efficacy of decitabine 15 mg/m² and BSC vs. BSC alone in patients with AML | <u>Arm 1:</u><br>Decitabine, 15 mg/m², and BSC, as needed<br><u>Arm 2:</u><br>BSC alone | All patients<br>N = 170<br>Median age = 70<br>Range: 62-76<br>Decitabine and BSC<br>N = 89<br>Median age = 70<br>BSC alone<br>N = 81<br>Median age = 70 | Decitabine and BSC<br>OS = 14<br>BSC alone<br>OS = 14.9<br>No significant difference |
| | **QOL Outcomes**<br>Instrument: EORTC QLQ-C30<br>Decitabine arm had statistically significant improvements in global health status (p < .05 at the end of Cycles 2 and 4), fatigue (p < .05 at the end of Cycles 2, 4, 5, and 6), and dyspnea (p < .05 at the end of all 6 cycles)<br>**Missing Data**<br>6 patients randomized to Decitabine arm withdrew before treatment initiation – 164 patients (Decitabine and BSC 83 vs. BSC alone 81) included in the safety analysis.<br>"According to the evaluations that were completed at the end of each treatment cycle, decitabine resulted in a statistically superior QOL compared with best supportive care in several QOL parameters." (p.7) | | | |
| Greenberg et al., [28]<br>Phase III<br>Multi-Arm<br>(EPO and BSC vs. BSC alone)<br>Longitudinal | Evaluate efficacy and long-term safety of EPO with or without G-CSF plus BSC vs BSC alone for treatment of anemic and lower risk MDS patients | <u>Arm 1:</u><br>EPO, 150U/kg, and BSC for 4 months<br><u>Arm 2:</u><br>BSC alone | | EPO + BSC<br>OS = 37.2<br>BSC alone<br>OS = 31.2<br>No significant difference |

**Table 2** (*continued*)

| Author/Year<br>Trial Design | Objective | Drug | Sample<br>(N and age in<br>years, by group) | Survival Outcomes (median, in months) |
|---|---|---|---|---|
| | | | All patients<br>N = 110<br>Median age = 73<br>85% were over the<br>age of 65<br>EPO and BSC<br>N = 53<br>BSC alone<br>N = 57 | |

**QOL Outcomes**
Instruments: FACT-G; FACT-Fatigue
No differences in FACT-G and FACT-F scores between groups
Significant improvement from baseline in physical, emotional, and functional well-being, fatigue, QOL in those with an erythroid response at 4 months
**Missing Data**
"QOL assessments were completed by 102 patients (53 SC, 49 EPO) at baseline and by 84 patients at 4 months (42 SC, 42 EPO)" (p. 2398, QOL analyses) – *no information on 18 missing patients other than following:*
"7 patients, on step 1 (4 on arm A, 3 on arm B) either withdrew or died before the initial 4-month response evaluation time point and were determined to be ineligible. One patient on step 1 (arm A) never started treatment." (p. 2394, Demographics)

| Author/Year<br>Trial Design | Objective | Drug | Sample | Survival Outcomes |
|---|---|---|---|---|
| Fenaux et al., [14]<br>Phase III<br>Multi-Arm (LEN-5 mg vs. LEN-10 mg vs. placebo)<br>Longitudinal | Test efficacy and safety of LEN in red blood cell transfusion-dependent patients with IPSS Low/ Intermediate-1-risk MDS with del5q | <u>Arm 1:</u><br>LEN, 5 mg<br><u>Arm 2:</u><br>LEN, 10 mg<br><u>Arm 3:</u><br>Placebo | All patients<br>N = 205<br>Median age = 69<br>LEN 5 mg<br>N = 69<br>Median age = 66<br>LEN 10 mg<br>N = 69<br>Median age = 68<br>Placebo<br>N = 67<br>Median age = 70 | LEN 5 mg<br>OS ≥ 35.5<br>LEN 10 mg<br>OS = 44.5<br>Placebo<br>OS = 42.4<br>3-year OS for combined LEN groups = 56.5%<br>Significance not reported |

**QOL Outcomes**
Instrument: FACT-An
Mean change in FACT-An score from baseline to week 12 was significantly higher for LEN 10 mg and LEN 5 mg vs placebo
**Missing Data**
"Baseline and week 12 (ie, before crossover) FACT-An scores were available for 71% (n = 145) of randomized patients (lenalidomide 10 mg, n = 48; 5 mg, n = 45; placebo, n = 52)."
*Note:* Only 139 patients included in the mITT population for 16-week responder assessment (lenalidomide 10 mg, n = 41; lenalidomide 5 mg, n = 47; and placebo, n = 51). Reasons for exclusion (n = 66): Inadequate BM sample (n = 40); IPSS Int-2/High Risk (n = 11); Insufficient IPSS information (n = 4); No del5Q31 by central review (n = 9); TI prior to randomization (n = 2)

| Author/Year<br>Trial Design | Objective | Drug | Sample | Survival Outcomes |
|---|---|---|---|---|
| Lubbert et al., [15]<br>Phase III<br>Multi- Arm (low-dose decitabine vs. BSC)<br>Longitudinal | Compare low-dose decitabine to BSC in higher risk patients with MDS | <u>Arm 1:</u><br>Decitabine, 15 mg/m²<br><u>Arm 2:</u><br>BSC | All patients<br>N = 233<br>Median age = NR<br>Decitabine<br>N = 119<br>Median age = 69<br>BSC<br>N = 114<br>Median age = 70 | Decitabine<br>OS = 10.1<br>BSC<br>OS = 8.5<br>No significant difference (p = 0.38) |

**QOL Outcomes**
Instrument: EORTC QLQ-C30
Significant improvement in fatigue and physical functioning for low-dose decitabine
**Missing Data**
"Missing data were an issue (baseline compliance was only 60%, decreasing from 50% to 30% during the first year), and the observed treatment differences could not be confirmed consistently when imputing the missing data." (p.1992-1993)
No. of patients evaluated for QOL (see Fig 4)
(From baseline to week 48 (every 6 weeks)
**Fatigue:**
BSC 72-62-42-41-21-22-22-13-11
Decitabine 68-44-36-32-28-25-20-15-17
**Physical Functioning:**
BSC 71-62-42-40-21-22-22-12-11
Decitabine 66-43-35-32-28-25-20-15-17

| | | | | |
|---|---|---|---|---|
| To compare the combination of standard chemotherapy combined with ATRA (MRC Treatment regimen) with the Spanish anthracycline and ATRA combination (Spanish Treatment regimen) in patients with APL | | | | 5-year OS was not statistically significant for MRC treatment vs. Spanish treatment (83% vs. 84%, respectively; p = 0.11) |

**Table 2** (*continued*)

| Author/Year<br>Trial Design | Objective | Drug | Sample<br>(N and age in<br>years, by group) | Survival Outcomes (median, in months) |
|---|---|---|---|---|
| Burnett et al., [20]<br>Phase II<br>Multi-arm (MRC Treatment regimen vs. Spanish Treatment regimen)<br>*For full schema of treatment schedule and randomization, please refer to Fig. 1 in Burnett 2013.<br>Longitudinal | | <u>Arm 1 (MRC Treatment):</u><br>ADE 10 + 3+5 (daunorubicin, cytarabine, etoposide) and ATRA, followed by<br>ADE 8 + 3 + 5 (daunorubicin, cytarabine, etoposide) and ATRA<br><u>Arm 2 (Spanish Treatment):</u><br>idarubicin, 12 mg/m$^2$, and ATRA, followed by idarubicin, 7 mg/m$^2$, and ATRA | All patients<br>N = 291<br>Median age = 42<br>Range: 16-69<br>MRC<br>N = 145<br>Median age = 42<br>Spanish<br>N = 146<br>Median age = 43 | |

**QOL Outcomes**
Instruments: EORTC QLQ-C30; HADS
EORTC QLQ-C30: Overall QOL was no worse in the patients receiving Spanish treatment (p = 0.05), and there was a significant benefit for the Spanish treatment arm during the treatment period. The largest differences were observed at 3 months, and there was little to no difference between treatment arms beyond 12 months.
HADS: Results not reported
**Missing data**
Of 291 patients, 145 patients were allocated to MRC treatment arm and 146 patients to Spanish treatment arm. After excluding 3 patients from each arm who were not PML-PARA positive, 142 patients from MRC treatment arm and 143 from Spanish treatment arm were included in the analysis.
No. of patients evaluated (at baseline, 3, 6, 12 and 24 months) for each function are presented in Fig. 4 (p.849)
e.g. For Global Health - MRC 88-63-57-63-59 ; Spanish 92-65-68-66-65
"QOL data is analysed using repeated measures analysis to give an overall difference under a symptomatic relief (that is, a difference in values as opposed to a disease-modifying assumption of increasing difference over time) assumption **with missing data treated as being missing at random**" (p.844, Statistical Considerations)

| | | | | |
|---|---|---|---|---|
| Kelaidi et al., [19]<br>Phase II<br>Single Arm<br>Longitudinal | Test efficacy of darbepoetin alfa of 500 units every 2 weeks in MDS patients, with G-CSF added for non-responders | darbepoetin alfa for 12 weeks<br>At 12 weeks, non-responders added G-CSF | All patients<br>N = 95<br>Median age = 72<br>Range: 66-77 | 3-year OS was 70%<br>Median OS not reached |

**QOL Outcomes**
Instruments: FACT-An; SF-36
FACT-An: QOL and anemia steadily improved in responders compared to non-responders (p = 0.007)
SF-36: Physical component summary score was improved over time in responders, but not the mental component summary score
**Missing Data**
No information on missing data or decrease of N over time in QOL measurement. Fig. 3 Flow chart (p. 627) shows survival outcomes (From 95 to 64)
QOL measured at baseline, 12 and 24 weeks (SF-36: N = 68, Fact-An: N = 70) (Table 3S)

| | | | | |
|---|---|---|---|---|
| Sekeres et al., [17]<br>Phase II-B<br>Multi-Arm (LD-C + lintuzumab vs. LD-C + placebo)<br>Longitudinal | Determine whether addition of lintuzumab to LD-C would increase overall survival in adults aged 60 years and over with untreated AML | <u>Arm 1:</u><br>LD-C and lintuzumab<br><u>Arm 2:</u><br>LD-C and placebo | All patients<br>N = 211<br>Median age = 71<br>Range: 60-90<br>LD-C and lintuzumab<br>N = 107<br>Median age = 70<br>LD-C and Placebo<br>N = 104<br>Median age = 71 | LD-C and lintuzumab<br>OS = 4.7<br>LD-C and Placebo<br>OS = 5.1<br>No significant difference (p = 0.76) |

**QOL Outcomes**
Instrument: FACT-Leu
No consistent pattern of change in FACT-Leu scores over time. Median change from baseline was similar for both arms.
**Missing Data**
Number of patients who completed 12 cycles of treatment: 21 (Lintuzumab) and 20 (Placebo) (Fig. 1). Time points of QOL measurement are not clearly described in the paper.

| | | | | |
|---|---|---|---|---|
| Efficace et al., [18]<br>Phase III<br>Multi-Arm (ATRA and chemotherapy vs. ATRA and arsenic trioxide)<br>Longitudinal | Determine if combination of ATRA plus arsenic trioxide was inferior to ATRA plus chemotherapy on 2-year event-free survival, and impact of arsenic trioxide on patient symptoms and well-being for patients with APL | <u>Arm 1:</u><br>ATRA and arsenic trioxide<br><u>Arm 2:</u><br>ATRA and chemotherapy | All patients<br>N = 156<br>Range:18-70<br>ATRA and arsenic trioxide<br>N = 77<br>Median age = 44.6<br>ATRA and chemotherapy<br>N = 79<br>Median age = 46.6 | 2-year OS was statistically better for ATRA plus arsenic trioxide (99%) than ATRA plus chemotherapy (91%) (p = 0.02) [47]<br>2-year event-free survival years was 97% for ATRA plus arsenic trioxide and 85% for ATRA plus chemotherapy |

**Table 2** (*continued*)

| Author/Year<br>Trial Design | Objective | Drug | Sample<br>(N and age in<br>years, by group) | Survival Outcomes (median, in months) |
|---|---|---|---|---|
| | **QOL Outcomes**<br>Instrument: EORTC QLQ-C30<br>An overall difference between arms in fatigue was observed (p = .022). After induction therapy, fatigue severity was significantly lower in the ATRA and arsenic trioxide arm (p = 0.34). Small clinically relevant differences were also observed in severity of nausea/vomiting, appetite loss, and constipation, and in physical and cognitive functioning that favored patients treated with ATRA and arsenic trioxide<br>**Missing Data**<br>"We compared mean observed HRQOL scores after induction between patients who returned the questionnaire after consolidation therapy and those who did not, and no statistically significant differences were found between groups." (p. 3409) (Detailed missing data analysis methods are described in the statistical analysis section – p. 3408)<br>"For each scale with a missing score, the value predicted by the linear regression model was imputed (single imputation). (p.3410)"<br>In ATRA and arsenic trioxide arm:<br>- Out of 77 patients who received at least one dose, 75 were available for 1st HRQOL analysis (after induction therapy) and 72 were available for 2nd HRQOL assessment (after 3rd consolidation course). Reasons for discontinuation: major protocol violation (2), medical decision (1), toxic effect (1), death (1). (Fig. 1. p.3407)<br>In ATRA and chemotherapy arm:<br>- Out of 79 patients who received at least one dose, 75 were available for 1st HRQOL analysis and 70 for 2nd HRQOL assessment. Reasons for discontinuation: death (7), toxic effect (1), lost to follow-up (1). | | | |
| Burnett et al., [21]<br>Phase III<br>Multi-arm<br>(SOC vs. ATRA and arsenic trioxide) | To investigate potential improvements in QOL for APL patients being treated with SOC vs. ATRA and arsenic trioxide | Arm 1 (SOC):<br>ATRA,<br>idarubicin, 12 mg/m², and mitoxantrone<br>Arm 2:<br>ATRA and arsenic trioxide | All patients<br>N = 235<br>Median age = 47<br>Range: 16-77<br>SOC<br>N = 119<br>ATRA and arsenic trioxide<br>N = 116<br>Median age = 47 | 4-year OS was 89% for SOC and 93% for ATRA and arsenic trioxide (p = 0.25; no significant difference)<br>4-year event free survival was 70% for SOC and 91% ATRA and arsenic trioxide (p = 0.002) |
| | **QOL Outcomes**<br>Instruments: EORTC QLQ-C30; HADS<br>EORTC QLQ-C30: No statistically significant difference was found between the two treatment arms in global functioning, or any other subscale, except role functioning.<br>HADS : No statistically significant difference found in anxiety and depression between groups<br>**Missing Data**<br>QOL forms were received from 156 patients at baseline, 137 at 3 months, 139 at 6 months, 136 at 12 months, and 103 at 24 months. The numbers of completed QOL forms in each treatment were: ATRA and idarubicin 76 vs. ATRA and arsenic trioxide 80 at baseline; 64 vs. 73 at 3 months; 70 vs. 69 at 6 months; 64 vs. 72 at 12 months; and 49 vs. 54 at 24 months. | | | |
| Dombret et al., [2]<br>Phase III<br>Multi-Arm (Aza C vs. CCR)<br>Longitudinal | Evaluate efficacy and safety of Aza C vs CCR in AML patients | Arm 1:<br>Aza C 75 mg/m²<br>Arm 2:<br>CCR (BSC, and LD-C or IC) | All patients<br>N = 488<br>Median age = 75<br>Aza C<br>N = 241<br>Median age = 75<br>CCR<br>N = 247<br>Median age = 75 | Differences in OS (Aza C = 10.4 and CCR = 6.5) and in relapse free survival (Aza C = 9.3 and CCR = 10.5) were not statistically significant |
| | **QOL Outcomes**<br>Instrument: EORTC QLQ-C30<br>No QOL detriment was found in those treated with Aza C or CCR at the group level during treatment. Both treatment arms showed improvement in QOL domains over 9 treatment cycles. Patients in the CCR group met the minimally important threshold for the fatigue (cycles 7 & 9) and global health status/QOL (cycle 9) domains.<br>**Missing Data**<br>"The population that was evaluable for HRQoL initially comprised 291 patients (azacitidine, 157; CCR, 134). This patient sub-set decreased over time in both groups, but at a faster rate in the CCR arm after cycle 3, and there was large variation in QLQ-C30 responses within each treatment group". (p.297)<br>- Information available in 'Supplementary Table 1 - Mean (SD) Changes from Baseline QLQ-C30 Domain Scores' showing N at each measurement cycle | | | |

Note: AML = Acute Myeloid Leukemia; APL = Acute Promyelocytic Leukemia; MDS = myelodysplastic syndrome; QOL = quality of life; FLIC = Functional Living Index- Cancer; BSC = best supportive care; SQ = subcutaneous; Aza C = Azacitidine; MDS = Myelodysplastic Syndrome; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30; MHI = Mental Health Inventory; EPO = Erythropoietin; FACT-G = Functional Assessment of Cancer Therapy- General; FACT-Fatigue = Functional Assessment of Cancer Therapy-Fatigue; IPSS = International Prognostic Scoring System; del5q = deletion 5q; LEN = Lenalidomide ; FACT-An = Functional Assessment of Cancer Therapy- Anemia; G-CSF = granulocyte-colony stimulating factor; SF-36 = Short Form Survey- 36; LD-C = Low-dose Cytarabine; FACT-Leu = Functional Assessment of Cancer Therapy-Leukemia; ATRA = all-trans-retinoic acid; HRQOL = health-related quality of life; APL = acute promyelocytic leukemia; CCR = conventional care regimen; BMT = bone marrow transplant; Allo-BMT = allogenic bone marrow transplant; Auto-BMT = autologous bone marrow transplant; CCT = consolidation chemotherapy; MRC = Medical Research Council; SOC = standard of care; EORTC QLQ-Leu = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Leukemia; HADS = Hospital Anxiety & Depression Scale

mitoxantone compared to ATRA and arsenic trioxide. The rates of missing data were high – across both arms 156/235 patients completed the baseline assessment and 136 completed the month 12 assessment.

### 3.6. Azacitidine (Aza C)

Dombret et al [2] reported no HRQOL detriment was found in those treated with Aza C or conventional care regimens at the group level during treatment, as measured by the EORTC QLQ-C30. Rates of missing data were not reported. Silverman et al. [26] found patients receiving Aza C had significantly greater improvement over time in a variety of domains, including fatigue (p < 0.001), physical function (p < 0.002), and dyspnea (p < .0014) as measured by the EORTC QLQ-C30 and psychological distress (p < 0.015) as measured by the Mental Health Index (see also Kornblith. [29] for detailed reporting of HRQOL study results). The rates of study drop out and the rates of missing PRO data for patients remained on study were substantial.

### 3.7. Bone marrow transplant

Zittoun et al [25] found cross-sectional differences following complete remission between Allo-BMT, Auto-BMT, and CCT alone in symptom burden, sexual function, overall physical condition, overall QOL, and global health status. 98/155 of patients on study participated in the PRO assessment. In a subsequent trial, Watson et al. [23,24] found Allo-BMT patients had greater symptom burden and significantly more problems with physical, role, and social functioning than patients treated with either CCT alone or Auto-BMT. In this cross-sectional evaluation, 479/719 completed the PRO assessment.

### 3.8. Missing PRO data

Substantial missing data was a prevalent issue among the PRO endpoints of these trials. The rates of missing data for each trial are described in Table 1 and reported in the description of each trial (above). The information about missing data reported in Table 1 is based on what was reported in the study manuscript. Eleven of the trials reported the rates of missing data [2,14,15,18,20–29]and three did not [17,19,22]. Only one trial reported missing data analysis methods in the statistical analysis section of the manuscript [18].

## 4. Discussion

This review identified only 14 MDS and AML drug trials in the past 20 years with published results that included PRO data. In trials evaluating anemia, PRO scores showed significant improvement in relevant domains (e.g. fatigue, function) among those patients identified as responders. The most commonly used HRQOL measure in these trials was the EORTC QLQ- C30, which assesses both symptoms and other domains of HRQOL. While the EORTC QLQ-C30 detected change over time and/or differences between treatment arms in general domains such as physical function, overall health and quality of life, the leukemia specific scales which assess symptoms specifically relevant to leukemia and its treatment were able to evaluate the more the proximal effects of treatment and more directly capture issues such as graft versus host disease and infection.

This review focused on drug trials conducted primarily in adults. The search process excluded trials conducted in adolescents, and trials evaluating non-drug interventions. The review was also limited to published manuscripts, which would exclude trial results that were only reported as conference abstracts or not yet reported. This under-represents trials which were not published at all or for which the PRO assessment was not reported in the manuscript because of null results or substantial missing data.

Studies which reported low rates of missing PRO data were in the minority; the rates of missing data were frequently not reported or were

quite high. Therefore, the PRO findings reported by many of the trials may be impacted by comparisons that were underpowered and/or by missing data that was more common among the more impaired patients which could bias results. Trials in which participants make scheduled visits to clinic for receiving protocol based treatment or evaluation are one of the study designs most amenable to PRO assessment. When site principal investigators are aware of the value of the data to the trial, and when site clinical research staff have clear guidance regarding the procedures for PRO assessment, high response rates can be achieved. In the authors experience it is not the disease severity of the patients, but the study team's attention to the PRO data collection, which determines the rates of missing data in treatment trials.

In diseases such as high-risk MDS and AML where survival among non-responders is low, clinical trials typically focus on survival but may also include HRQOL endpoints. PRO data collection and therefore HRQOL endpoints are limited to those who survive to a particular timepoint. In this case, HRQOL data provide information about the disease burden of survivors and/or treatment responders. In economic evaluation of treatments, in particular cost-utility analysis, quality-adjusted life years is a unit of analysis that combines survival time and HRQOL information. HRQOL data are converted to health utilities which range from 0 (death) to 1 (perfect health) [31]. This latter approach can provide a single comprehensive assessment of treatment benefit.

Newly emerging targeted therapies and biologics for AML have toxicity profiles which are not well studied; inclusion of PROs in phase II and phase III trials will provide information about the impact of treatment on patients. The Leukemia and Lymphoma Society has recently launched a master clinical trial of multiple novel targeted therapies for AML (clinicaltrial.gov NCT03013998), and it was requested by Food and Drug Administration reviewers that PRO assessment be included in order to document the patient experience of these new therapies, in particular the impact of disease and treatment on symptoms and HRQOL.

A systematic instrument review conducted by Bryant et al [32] in 2015 found limited availability of symptom and HRQOL instruments for adults with acute leukemia, and the most commonly used instruments were the EORTC QLQ-C30 and the FACT-Fatigue. To the best of our knowledge, there are two leukemia specific measures available – the FACT-Leu and the MRC/EORTC QLQ-LEU-BMT (each described above), and an increasing number of measures for subtypes of leukemia. It should be noted the QLQ-LEU-BMT is not an official EORTC measure. An AML/MDS specific instrument for the MD Anderson Symptom Inventory (MDASI) is under development and available for use [33,34]. It includes the MDASI Core symptom items and additional items identified as relevant to AML/MDS. The Quality of Life in Myelodysplasia Scale (QUALMS) was recently developed and tested [35,36], and is currently being used in trials. It contains 38 items, which compose three subscales: physical burden, emotional burden, and benefit finding. A review by Cannella et al [37] in 2015 highlights drug and behavioral intervention studies for AML/MDS with scientifically rigorous HRQOL assessment.

We note that instruments are available for other leukemia sub-types as well. For chronic myeloid leukemia (CML), the MDASI-CML [38,39] is composed of the MDASI Core symptom items and additional symptoms specific to CML (e.g., diarrhea, swelling, rash/skin change, muscle soreness/cramping, bruising/bleeding easily, malaise, and headache). Lastly, the EORTC has two instruments in development and available for use for chronic myeloid leukemia (QLQ-CML24) and chronic lymphocytic leukemia (QLQ-CLL17) [40,41].

The field of PRO assessment in cancer research is well developed; standard methods for implementing PROs into clinical trials and for the analysis and interpretation of PRO data are documented in a variety of contexts. These include FDA guidance on the use of PROs to support labeling claims [10], published recommendations for incorporating PROs into comparative effectiveness research in adult oncology [42], a

textbook for researchers describing measurement, implementation and interpretation of PRO data in clinical trials [12], the SPIRIT guideline extension for specifying PRO data collection in clinical trial study protocols [43], and the CONSORT guideline extension for describing PRO findings in clinical trial manuscripts [44]. The ability of PRO instruments to capture important changes in symptoms and HRQOL and the availability of PRO instruments appropriate for AML and MDS strongly support the use of PRO assessment in AML and MDS therapeutic trials.

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