


Patient-reported outcome measures in studies of myelodysplastic syndromes and acute myeloid leukemia: Literature review and landscape analysis

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Abstract

Objectives: This study aims to describe the use of patient-reported outcome measures (PROMs) in myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) studies and the PROMs landscape.

Methods: A comprehensive literature review was performed in Medline/Embase (since 2000) and ClinicalTrials.gov (since 2013) to identify PROMs used in MDS and AML clinical studies. Additionally, PROMs included in approved drug labels since 2000 were reviewed.

Results: Overall, 112 different PROMs were used in 168 published MDS studies and 152 PROMs were used in 172 AML studies. From ClinicalTrials.gov, 16 different PROMs were used in 22 ongoing registered studies in MDS, and 24 were reported in 41 AML studies. The most frequently used PROMs were cancer-specific (eg, EORTC QLQ-C30, FACT-An) or generic (SF-36, EQ-5D) instruments, whereas MDS- and AML-specific instruments (eg, QUALMS and QOL-E in MDS; FACT-Leu and EORTC QLQ-Leu in AML) were used in a minority of studies. Two EMA-approved drugs for MDS included PROMs in their label. EORTC QLQ-C30 is by far the most frequently used cancer-specific PROM in both MDS and AML studies.

Conclusions: This research indicated an underuse of AML/MDS-specific PROMs for these two indications in clinical studies and labeling claims. However, AML/MDS-specific instruments in development might be considered in future studies.

KEYWORDS

acute myeloid leukemia, myelodysplastic syndromes, quality of life

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1 | INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematological malignancies, characterized by cytopenias and the risk of transformation to acute myeloid leukemia (AML).^{1,2} The age-adjusted incidence of MDS is 4.8 per 100 000 annually in the United States (US) with significantly higher incidence rates among adults over 70 years of age.³ Patients with MDS often present with symptoms related to low blood counts such as fatigue, paler skin, frequent infections, bleeding, and bruising.^{4,5} However, fatigue and impaired health-related quality of life (HRQOL) can only be partially explained by anemia and may also be caused by molecular aberrations, hyperinflammation, and dyspnea.⁶⁻⁹

AML is a heterogeneous blood cancer, most commonly associated with bone marrow dysfunction and the production of high numbers of immature myeloid cells.^{1,10} AML is the most frequent acute leukemia in adults¹¹ having an annual incidence of 4.3 per 100 000 in the US,¹² with more than 60% of newly diagnosed patients being over 60 years of age.¹³ Patients living with AML also experience a wide range of symptoms essentially linked to pancytopenia and blast proliferation and can include bleeding, bruising, and infections,¹⁴ which further significantly impact their HRQOL.¹⁵ Therapeutic options in MDS and AML include watchful waiting, supportive therapy (including red blood cell transfusions), application of growth factors, hypomethylating agents, immunomodulatory drugs, low-dose and high-dose chemotherapy, and stem cell transplantation.^{5,11}

Patient-reported outcome (PRO) is a collective name for any information about a patient's health condition that comes directly from the patient without any interference or interpretation from clinical experts.¹⁶ Patient-reported outcome measures (PROMs) are designed to measure the patient experience that cannot be obtained from an observer, but from the patient only, for example, fatigue, symptom severity, impact on daily activities,¹⁷ and HRQOL.¹⁸ The importance of PROMs, which can form the basis for individualized treatment decisions and evaluate the benefits of treatment, is rapidly growing in healthcare systems and in clinical studies.^{19,20} In clinical trials, PROMs are commonly used to assess the effectiveness of an intervention or to address a concept or group of concepts that are best measured from the patient perspective. Furthermore, PROMs can help to interpret clinical changes, and they can be used to collect other crucial information in both real-world and clinical studies, such as determining the eligibility of patients, assessing patient compliance or reasons for non-compliance, as well as obtaining patient preference for different treatments. However, it might be challenging to identify the correct PROMs to use in a study, to administer them at the right time, and to minimize and deal with missing data.^{7,21}

Many PROMs are tailored to measure the patient perspective in particular areas, for example, symptom-specific (eg, pain, fatigue, and anxiety) and disease-specific instruments that are most relevant to a patient population. In contrast, there are generic instruments that do not focus on a particular disease or symptom but aim to assess HRQOL in general, allowing comparisons between different conditions, and providing valuable data for economic evaluation

Plain language summary

What is the new aspect of your work?

Understanding the patients' perception of their disease is becoming increasingly important. In order to capture patients' experiences of their disease symptoms, treatment, and the impact on their day-to-day life, a number of questionnaires have been developed. Some of these are general and applicable to patients' suffering from a number of different diseases, while others are disease-specific. However, information on how widely these questionnaires are used in clinical trials and drug approvals for myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) is lacking. Therefore, we carried out a search of the published literature, current clinical trials, and recent drug approvals to determine which questionnaires are used, and how frequently they are used.

What is the central finding of your work?

We found that a large number of different questionnaires were used in the published studies, current clinical trials, and recent drug approvals for MDS and AML. The majority of questionnaires used were general instruments, designed for use in a broad range of illnesses. Only a small proportion of studies and clinical trials used MDS- or AML-specific questionnaires, meaning that the most relevant aspects of the patients' experiences of MDS and AML may not have been captured. Information on the patients' experience of their disease was also rarely included in drug approvals.

What is (or could be) the specific clinical relevance of your work?

Our research suggests that patients' experiences of their disease are not always captured during studies of MDS and AML and that this information is rarely used to support approval of drugs for these diseases. It also seems that disease-specific questionnaires are underused, and therefore, specific information on how patients with MDS and AML feel is lacking. Our findings could be used to encourage more hematologists and scientists involved in clinical studies to gather information on the patient experience. Increased use of questionnaires to capture the patient's perspective, and of disease-specific questionnaires in particular, would give doctors and nurses a greater understanding of how their patients are coping with their disease and help to improve their quality of life.



studies. With a wide variety of PROMs available, it is crucial when designing clinical studies to select the instrument or instruments most appropriate for the study aims and target population.²²

Both MDS and AML patients experience a significant symptom burden and restrictions in their HRQOL, which can negatively influence their clinical outcomes.^{5,15} Furthermore, their self-reported experience could even provide a reliable prediction for overall survival.²³ Therefore, it is crucial to find the most suitable PROMs that have been validated for use in these patient populations. At the instrument selection stage, several factors should be considered, including disease stage, treatment type, concerns about respondent burden, and the PROMs proven ability to measure HRQOL in the context of these hematological malignancies.²⁴

The aim of this study was to describe the PROMs landscape in MDS and AML studies, including a comprehensive literature review of all PROMs used to assess different symptoms and domains of HRQOL. This work should guide and support the future design of clinical studies that aim to include the perspective of patients with MDS and AML.

2 | METHODS

A comprehensive literature review was performed using the PRISMA guidelines²⁵ for literature reviews to identify the PROMs used to assess symptoms and HRQOL in MDS and AML. The review included various sources and was conducted in four steps: Step 1: A search was conducted to identify published clinical studies in MDS and AML; Step 2: Ongoing clinical studies in MDS and AML were reviewed; Step 3: PRO claims in MDS and AML labels of European Medicines Agency (EMA)- and US Food and Drug Administration (FDA)-approved drugs were analyzed; Step 4: Guidelines issued by regulatory agencies in MDS and AML were reviewed. Figure 1 details the steps and their processes. SD-A performed the searches, screened the data, and extracted the information. ISa quality checked the findings and, when needed, JL intervened to discuss specific questions or to solve non-conclusive situations.

2.1 | Search strategies

To find studies published since 2000 (Step 1), searches in Medline and Embase (via OVID platform) were performed, and retrieved references were reviewed in three phases: (a) abstract review, (b) full-text review, and (c) data extraction from relevant publications. The titles and abstracts were screened using preset inclusion criteria that included clinical trials of patients with AML or MDS, interventional and non-interventional studies, all types of comparators, and PRO evaluations assessing symptoms and HRQOL. Studies with a mix of MDS and AML populations were counted separately, and different versions of the same instrument were counted as different PROMs.

To identify all ongoing studies in MDS and AML registered since 2013 (Step 2), a search was conducted in the US National Institutes of Health clinical trial register database, ClinicalTrials.gov. Results were screened for keywords related to PRO questionnaires, symptoms, and HRQOL. Preset selection criteria were applied to include studies of patients with AML or MDS, using any type of drug products, with all types of comparators, and any PRO evaluations assessing symptoms and/or HRQOL.

To gain insight into EMA/US FDA-approved drug labels that might have included PRO claims (Step 3), a search was performed in the PROLABELS™ database (through the ePROVIDE platform). The search focused on treatments for MDS and AML approved by the EMA and/or US FDA since 2000. PRO instruments used in the studies but not approved in the label were retrieved by reviewing the US FDA Medical Review documents and the EMA Scientific Discussion/Assessment report documents.

To identify guidance documents published by the US FDA, the EMA, National Institute of Health and Clinical Excellence (NICE), Health Canada, or Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (iQWiG) with AML or MDS as a topic (Step 4), a search was completed in the PROINSIGHT™ database (through the ePROVIDE platform).

The PRO instruments identified in Steps 1 and 2 were classified by frequency of occurrence in Medline/Embase and ClinicalTrials.gov. Relevant data from PRO claims search and review of guidance documents (Steps 3 and 4) were summarized to establish which PRO evaluations (domains or specific concepts within a domain) and instruments should be recommended in future studies in MDS and AML.

3 | RESULTS

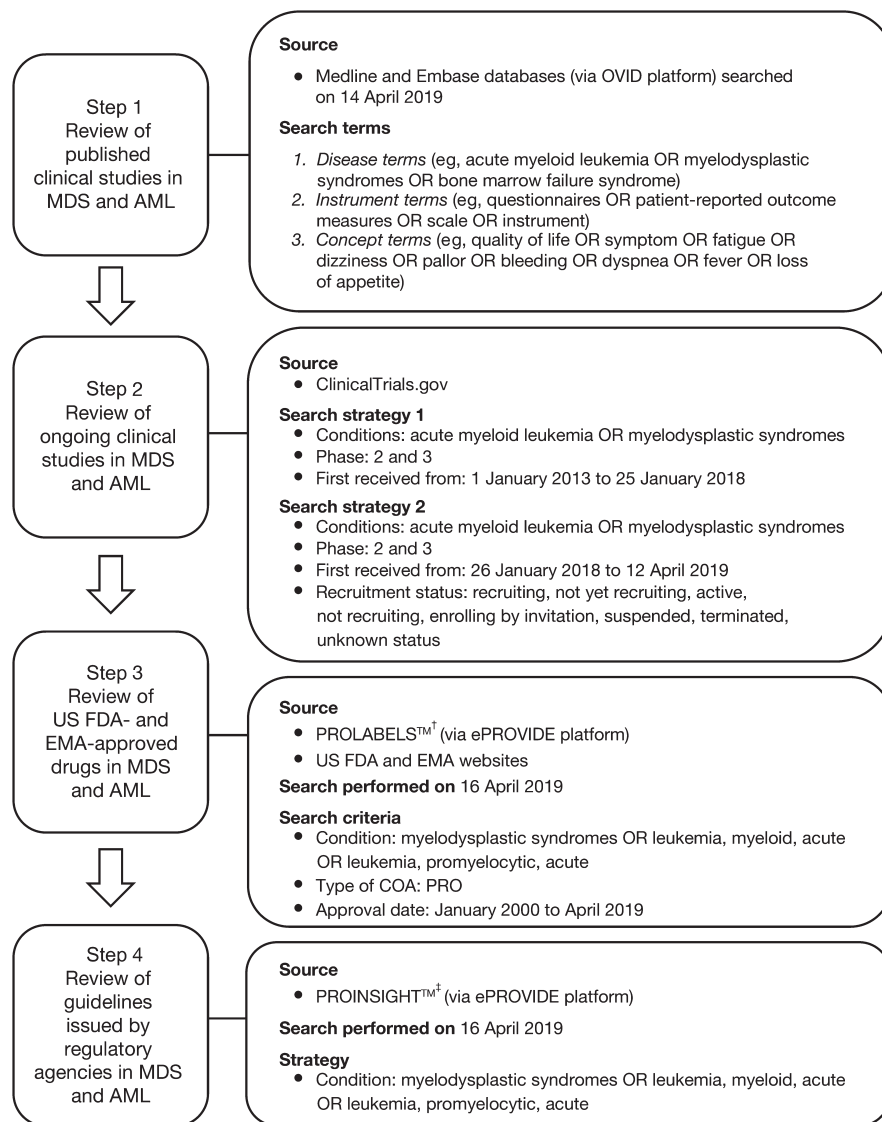
3.1 | PROMs used in published MDS and AML studies

Searches in Medline and Embase were performed in April 2019 and retrieved 782 abstracts. These included 669 results through a search from January 1, 2000, to January 28, 2018, and 113 results through a search from January 1, 2018, to April 14, 2019. After removing duplicates and reviewing the abstracts according to the preset inclusion criteria, 275 articles were selected for full-text review (Figure 2). The identified studies reported on the use of PROMs to assess symptoms, HRQOL, or HRQOL-associated domains in MDS and AML. Out of the 275 articles, 168 articles described MDS studies with the use of 112 different PROMs, five of which were MDS-specific, and 172 reported on AML studies with the use of 152 different PROMs, nine of which were AML-specific. In light of the large number of PROMs identified, only generic PROMs identified in five or more MDS or AML studies and disease-specific PROMs identified in four or more studies are shown in Table 1.

In the included MDS studies, PROMs were essentially used to assess symptoms, overall HRQOL, or specific HRQOL domains (eg,

**FIGURE 1** Overview of searches.

Abbreviations: AML, acute myeloid leukemia; COA, clinical outcome assessment; EMA, European Medicines Agency; FDA, Food and Drug Administration; MDS, myelodysplastic syndromes; PRO, patient-reported outcome. [†]Database of all US FDA-/EMA-approved drug products with COA cited in their labels. [‡]Centralizes and summarizes published regulatory recommendations concerning the use of COA to determine treatment benefit and inform on drug approval



psychological, physical, or social functioning). Other domains such as burden, coping, resilience, locus of control, self-efficacy, intrusiveness, and sexuality were each measured in <1% of the reviewed studies.

Regarding instruments measuring HRQOL, the EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30)²⁶ appeared most frequently, being used in more than a third of the included studies (n = 63 of 168 included studies), followed by the Functional Assessment of Cancer Therapy-Anemia (FACT-An)²⁷ (n = 34), and the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation (FACT-BMT)²⁸ (n = 21).

The most frequently found symptom-specific measure was the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue and FACIT-F)²⁷ (n = 10).

In terms of PROMs evaluating psychological functioning, the Hospital Anxiety and Depression Scale (HADS) was the most frequently used (n = 11), followed by the Profile of Mood State-Short Form (POMS-SF) (n = 4).

Similar to the findings in MDS, several different domains were measured in the published AML studies. Nearly all PROMs identified

aimed at capturing and assessing HRQOL or specific domains of HRQOL and/or symptoms. Further domains such as burden, hope, optimism, resilience, coping, sexuality, self-esteem, intrusiveness, body image, and self-efficacy were each assessed in < 1% of the reviewed studies.

The most frequently used PROM was the EORTC QLQ-C30, appearing in nearly one third (n = 54) of the 172 included studies followed by the HADS (n = 24) and the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)²⁹ (n = 23).

Similar to the findings in MDS, FACIT-Fatigue and FACIT-F were the most frequently used fatigue-specific instruments in the AML population (n = 14), and the HADS was the most frequently used PROM evaluating psychological functioning (n = 24).

3.2 | PROMs used in ongoing MDS and AML trials

The search for ongoing trials on ClinicalTrials.gov identified 695 results. After applying the preset selection criteria, 50 individual trials

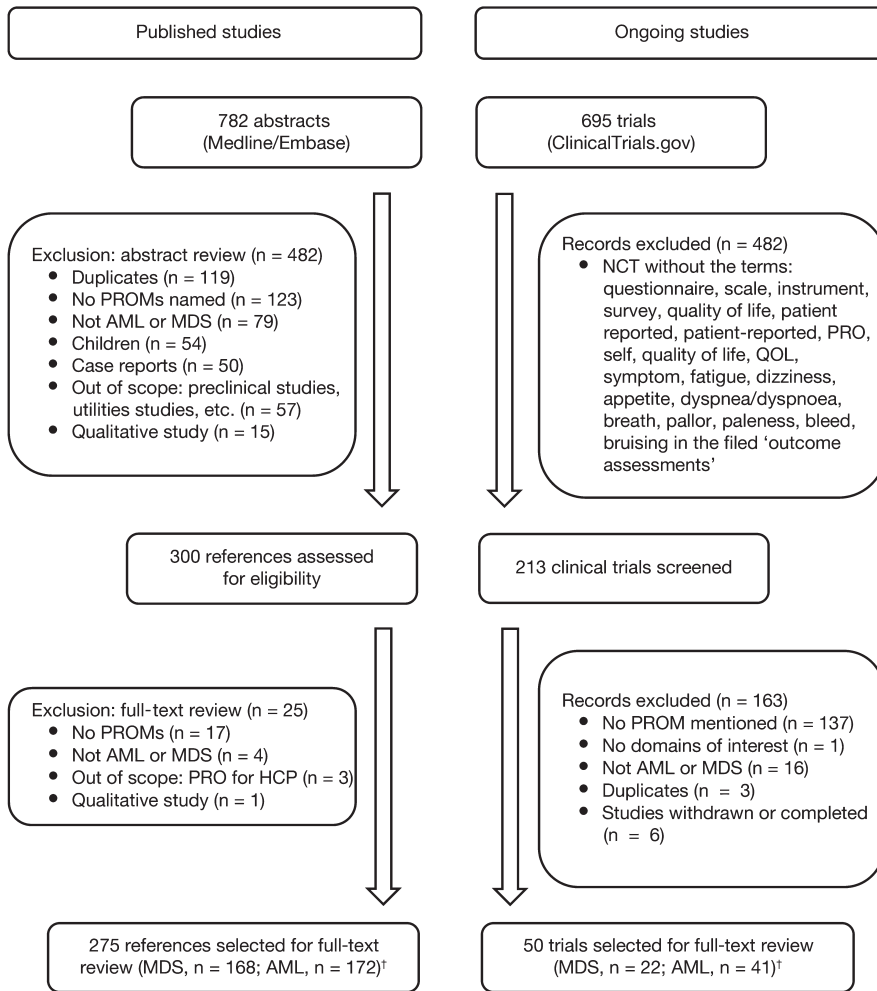


FIGURE 2 Selection process of published and ongoing studies. Abbreviations: AML, acute myeloid leukemia; HCP, healthcare professional; MDS, myelodysplastic syndromes; NCT, national clinical trial; PRO, patient-reported outcome; QOL, quality of life. [†]Some studies included both MDS and AML patient populations

were identified for full-text review: 22 studies in MDS with 16 different PROMs and 41 studies in AML with 24 different PRO instruments (Figure 2). The list of generic PROMs used three or more times and disease-specific PROMs used one or more times in ongoing MDS and AML trials, including frequency of usage, are shown in Table 2.

Bold numbers denote most frequently used instrument. Regarding the clinical phase distribution of the ongoing MDS studies, half of the trials were phase 3 (50%), about a quarter were phase 2 (27%), and the remaining trials were marked as phase 1/phase 2 (14%) or phase 2/phase 3 (9%). The majority of studies used PROs as a secondary endpoint (97%), and in the remaining 3%, PROs were defined as a primary endpoint. In terms of the measured PRO concepts, the majority of studies assessed HRQOL (77%). Other concepts including symptoms (11%), symptoms and functioning (6%), and psychological functioning (3%) were also assessed by PROMs. The EORTC QLQ-C30 was the most frequently used instrument, administered in half of all trials (n = 11), followed by the FACT-An (n = 5), and the EuroQol five dimensions (EQ-5D) instrument (n = 4) (Table 2).

Nearly half of the ongoing AML trials were phase 3 (46%), 34% were phase 2, and the remaining trials were marked as phase 1/phase 2 (17%) or phase 2/phase 3 (3%). Regarding endpoint hierarchy, most of the studies used PROMs as a secondary endpoint (87%), 6% used

PROMs as a primary endpoint, and the remaining 7% provided no information on the endpoint hierarchy. Of the 24 identified PROMs, 65% measured HRQOL, over a quarter evaluated symptoms (28%). Similar to the MDS trials, the EORTC QLQ-C30 was the most frequently used instrument in the AML studies, administered in half of all trials (n = 22), followed by the EQ-5D (n = 7) and the FACT-Leu (n = 4) (Table 2).

3.3 | PROMs included in labels of approved drugs for the treatment of MDS/AML

The PROLABELS™ database was searched to identify EMA-/US FDA-approved drug labels that included PRO claims. In total, 13 unique drugs were reviewed that gained approval by either one or both agencies for the treatment of MDS and/or AML between 2000 and 2019 as shown in Table 3. Of these 13 drugs, two were approved by the EMA with PRO evaluation mentioned in their label for the treatment of MDS: azacitidine and lenalidomide. In these studies, PROs were used as secondary endpoints to assess HRQOL and the identified PROMs included EORTC QLQ-C30, Functional Assessment of Cancer Therapy-General (FACT-G),³⁰ FACT-An, and EQ-5D. No PRO claims were granted by the US FDA for drugs approved for the

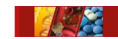


TABLE 1 Use of PROMs in published studies in AML and MDS (listed ≥ 4 [disease-specific] or ≥ 5 times [generic] in the literature)

PROMs	AML		MDS	
	(N = 172 studies)	%	(N = 168 studies)	%
Generic instruments (listed ≥ 5 times)				
EORTC Quality of Life Questionnaire-Core Questionnaire (EORTC QLQ-C30)	54	31	63	38
Hospital Anxiety and Depression Scale (HADS)	24	14	11	7
FACT-Bone Marrow Transplantation (FACT-BMT)	21	12	21	13
SF-36 Health Survey (SF-36)	20	12	19	11
FACT-General (FACT-G)	16	9	14	8
FACT-Fatigue (FACIT-F/ FACIT-Fatigue)	14	8	10	6
NCCN Distress Thermometer (DT)	11	6	2	1
EuroQol five dimensions-three levels/visual analog scale (EQ-5D-3L/VAS)	13	8	17	10
Center for Epidemiologic Studies Depression Scale (CES-D)	10	6	3	2
MD Anderson Symptom Inventory (MDASI)	9	5	4	2
Memorial Symptom Assessment Scale (MSAS)	9	5	1	1
Profile of Mood State-Short Form (POMS-SF)	8	5	4	2
FACT-Anemia (FACT-An)	7	4	34	20
Patient Care Monitor v2.0 (PCM)	6	3	1	1
Brief Fatigue Inventory (BFI)	6	3	4	2
Medical Outcomes Study (MOS) Social Support Survey	6	3	1	1
Edmonton Symptom Assessment Scale (ESAS)	5	3	3	2
Disease-specific instruments (≥ 4 times)				
FACT-Leukemia (FACT-Leu)	23	13	3	2
EORTC Quality of Life Questionnaire-Leukemia module (EORTC QLQ-Leu)	4	2	0	0
Hematological Malignancies-Patient-Reported Outcome (HM-PRO)	4	2	3	2
MD Anderson Symptom Inventory (MDASI)—AML/MDS	4	2	3	2
Quality of Life E (QOL-E)	3	2	16	10
Quality of Life in Myelodysplasia Scale (QUALMS)	0	0	4	2

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; PROM, patient-reported outcome measure.

Bold numbers denote most frequently used instrument.

treatment of MDS; however, the EORTC QLQ-C30 instrument was used to assess HRQOL as a secondary endpoint for two drugs as per the medical review, but no information was ultimately reported in the label. Of all the drugs approved for the treatment of AML, none had PRO data reported in their label, regardless of whether the drug was approved by the US FDA or by the EMA.

3.4 | PRO guidelines issued by regulatory agencies

Although a targeted search was completed in the PROINSIGHT™ database for guidance documents related to the therapeutic indications, no specific guidelines for PRO use in trials of MDS and AML treatments were identified. However, a PROM-related suggestion was found in

Appendix 4 of the EMA's condition-specific guidance on the evaluation of anticancer medicinal products in man (published in 2015). While the agency states that the recommended primary endpoints were overall survival and progression-free survival, it also suggested considering the use of PROMs in future guidelines and trials, due to the impact of MDS on HRQOL, without specifying any generic or disease-specific PROM.³¹

3.5 | Description of frequently used PROMs in MDS and AML

A description of a selection of generic and disease-specific instruments most frequently used in MDS or AML, including information about their content, available translations, development, and



PROMs	AML		MDS	
	(N = 41 studies)	%	(N = 22 studies)	%
Generic instruments (≥3 times)				
EORTC Quality of Life Questionnaire-Core Questionnaire (EORTC QLQ-C30)	22	54	11	50
EuroQol five dimensions-three levels (EQ-5D-3L)	7	17	4	18
Brief Fatigue Inventory (BFI)	3	7	0	0
MD Anderson Symptom Inventory (MDASI)	3	7	2	9
FACT-Fatigue (FACIT-F/ FACIT-Fatigue)	3	7	2	9
SF-36 Health Survey (SF-36)	2	5	1	5
FACT-Anemia (FACT-An)	1	2	5	23
Disease-specific instruments (≥1 time)				
FACT-Leukemia (FACT-Leu)	4	10	1	5
Quality of Life in Myelodysplasia Scale (QUALMS)	0	0	1	5

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; PROM, patient-reported outcome measure.

Bold numbers denote most frequently used instrument.

psychometric validation, is provided in Table 4.^{32,33} All instruments were developed following the US FDA-recommended approach to include a review of the literature and interviews with patients. Most instruments have been psychometrically validated to ensure they are valid and reliable instruments; only the Hematological Malignancies-Patient-Reported Outcome (HM-PRO)³⁴ and the AML Quality of Life (AML-QOL) are currently missing information on their validation, which is ongoing.

4 | DISCUSSION

This study aimed to identify the PROMs used in published and ongoing clinical studies to assess patients' perception of their symptoms and HRQOL in relation to their MDS or AML. This study further aimed to describe the PROMs landscape; in particular, the recognition of PROs in labels of MDS and AML drugs approved by the US FDA and the EMA.

A total of 190 published or ongoing studies including patients with MDS and 213 published and ongoing studies including patients with AML have been identified in the literature with 112 and 152 different PROMs or different versions of PROMs mentioned, respectively. With these numbers of PROMs, our study clearly shows the current absence of a systematic approach to capture the patient experience of AML and MDS patients. About one third of the studies used EORTC QLQ-30C, the remainder used other PROMs. FACT-An, FACT-BMT, 36-Item Short Form (SF-36), Quality of Life E (QOL-E),³³ EQ-5D, and FACT-G were frequently mentioned (≥10 of the identified studies) to measure symptoms and HRQOL in patients with MDS; similarly, SF-36, FACT-Leu, FACT-BMT, EQ-5D, and FACT-G were frequently mentioned to assess symptoms and

TABLE 2 Use of PROMs in ongoing trials (listed ≥ 1 [disease-specific] or ≥ 3 times [generic] in the literature)

HRQOL in patients with AML. The EORTC QLQ-C30 cancer-specific HRQOL instrument is a well-developed and validated tool to capture symptoms, treatment-related adverse events, and HRQOL, including physical, social, and emotional functioning. In our search, several FACT questionnaires were also found to be frequently used in both MDS and AML. Both the EORTC and FACT groups have created a series of standard instruments in oncology indications proposing a core module to which a symptom or cancer-specific module can be added. Our study showed that AML/MDS-specific PROMs were rarely used in both the published and ongoing studies in favor of broader, cancer-specific instruments, like the EORTC QLQ-C30. Our finding echoes what is found in other oncology indications, with the EORTC family of questionnaires and the FACIT family of questionnaires being the most frequently used PROMs despite the existence of disease-specific instruments in those indications. Depending on the indications and the availability of the modules of interest, the most frequently used PROMs are from one or the other family.³⁵⁻³⁷

Our study found that PRO claims were included in the EMA-approved labels for the two drugs which received marketing authorization in 2007 and 2008 in Europe for the treatment of MDS. No PRO claims were identified in the labels of US FDA-approved MDS drugs or in the labels of any EMA- or US FDA-approved AML drugs. These PRO claims were granted by the EMA for the only two available drugs for MDS, thus anticipating the EMA guidelines on the evaluation of anticancer medicinal treatments³¹ which recommended the consideration of PROMs in future trials due to the impact of MDS on HRQOL. Collecting PROs is slowly becoming a standard approach in oncology clinical studies, and such data are expected and valued by European Health Technology Assessment bodies.³⁸ PRO data are also highly promoted by both the EMA and the US FDA. The US FDA is particularly interested

**TABLE 3** US FDA/EMA-approved products for the treatment of MDS and AML since 2000

INN	Brand name	Agency	Agency product number	Marketing authorization date	PROM used to support a PRO claim in the drug label	PROM used in submitted studies but not supporting a PRO claim in the drug label
Approved drugs in MDS with PRO claims						
Azacitidine	Vidaza	EMA	EMA/H/C/000978	2008	EORTC QLQ-C30	-
Lenalidomide	Revlimid	EMA	EMA/H/C/000717	2007	FACT-G FACT-An EuroQoL EQ-5D	-
Approved drugs in MDS without PRO claims						
Decitabine	Dacogen	FDA	NDA 021790	2006	-	EORTC QLQ-C30
Decitabine	Decitabine	FDA	NDA 205582	2014	-	EORTC QLQ-C30
Azacitidine	Azacitidine	FDA	NDA 208216	2016	-	-
Lenalidomide	Revlimid	FDA	NDA 021880	2005	-	-
Approved drugs in AML without PRO claims						
Decitabine	Dacogen	EMA	EMA/H/C/002221	2012	-	EORTC QLQ-C30
Histamine dihydrochloride	Ceplene	EMA	EMA/H/C/000796	2008	-	EORTC QLQ-C30
Daunorubicin, cytarabine	Vyxeos	FDA	NDA 209401	2017	-	-
		EMA	EMA/H/C/004282	2018	-	-
Enasidenib	Idhifa	FDA	NDA 209606	2017	-	-
Gemtuzumab ozogamicin	Mylotarg	FDA	BLA 761060	2017	-	-
		FDA	NDA 021174	2000	-	-
		EMA	EMA/H/C/004204	2018	-	-
Gilteritinib	Xospata	FDA	NDA 211349	2018	-	-
Glasdegib	Daurismo	FDA	NDA 210656	2018	-	-
Ivosidenib	Tibsovo	FDA	NDA 211192	2018	-	-
Mitoxantrone	Novantrone	FDA	NDA 021120	2000	-	-
Midostaurin	Rydapt	FDA	NDA 207997	2017	-	-
Venetoclax	Venclexta	FDA	NDA 208573	2016	-	Use of PROMs mentioned in the medical review but no names or domains specified

Abbreviations: AML, acute myeloid leukemia; EMEA, Europe, the Middle East, and Africa; EMA, European Medicines Agency; EORTC QLQ-C30, EORTC Quality of Life Questionnaire-C30; EQ-5D, EuroQol five dimensions; FACT-An, Functional Assessment of Cancer Therapy-Anemia; FACT-G, Functional Assessment of Cancer Therapy-General; FDA, Food and Drug Administration; INN, international non-proprietary name; MDS, myelodysplastic syndromes; NDA, new drug application; PROM, patient-reported outcome measure.

in separately capturing treatment-related adverse effects, disease-related symptoms, and physical functioning.³⁹ While both EMA- and US FDA-issued guidance to incorporate the patient voice in drug development to support treatment benefit, there has been a concomitant increase in the documentation of the patient's perspective in oncology trials. Between 2006 and 2012, approximately 85% of clinical oncology trial sponsors disclosed the inclusion of a PRO to address an endpoint evaluating HRQOL and/or symptoms on ClinicalTrials.gov. Between 2002 and 2006, this was only 12%.⁴⁰ Nevertheless, as supported by our findings, the number of drug labels in oncology that has a PRO claim is limited, in particular with regard to US FDA-approved labels,⁴¹ probably due to a lack of evidence supporting the appropriateness of

the selected instruments.⁴² In parallel, the US FDA confirmed its interest in using PROMs, in particular the PROM version of the National Cancer Institute's Common Terminology Criteria for Adverse Events (PRO-CTCAE) in oncology trials to document safety profiles of newly developed cancer drugs.⁴³

In light of the poor clinical prognosis, and in the absence of a cure for AML, high-risk MDS, and other hematological malignancies, it is important to consider assessing HRQOL to fully understand treatment benefits and disease burden.²⁵

At the time, the EORTC and FACT questionnaires were developed; around two decades ago, chemotherapy was standard of care; therefore, they may not fully capture the experience of MDS and AML patients receiving less intensive therapies such as

**TABLE 4** Evidence table with description of the selection of PROMs

Name	Purpose	No. items	Domain	Translations	Development and psychometric validation
Quality of life-Cancer specific					
EORTC Quality of Life Questionnaire-Core Questionnaire (EORTC QLQ-C30)	To assess quality of life in a wide range of cancer patient populations	30	Global health status/quality of life (2 items) Functional scales <ul style="list-style-type: none"> • Physical functioning (5 items) • Role functioning (2 items) • Emotional functioning (4 items) • Cognitive functioning (2 items) • Social functioning (2 items) • Symptom scales • Fatigue (3 items) • Nausea and vomiting (2 items) • Pain (2 items) • Dyspnea; Insomnia; Appetite loss; Constipation; Diarrhea; Financial impact (1 item each) 	Original: US English >105 translations	Developed based on a literature review and interviews with patients with cancer Validated in patients with cancer ²⁶
FACT-General (FACT-G)	To measure the quality of life in individuals with cancer	27	Physical Well-being (7 items) Social/Family Well-being (7 items) Emotional Well-being (6 items) Functional Well-being (7 items)	Original: US English >65 translations	Developed based on a literature review and interviews with patients with cancer Validated in patients with cancer ³⁰
Quality of life-Leukemia specific					
FACT-Leukemia (FACT-Leu)	To measure the HRQOL of patients with acute and chronic leukemia	44	FACT-G (see above) + FACT-Leu subscale: Additional concerns (17 items)	Original: US English >45 translations	Developed based on a literature review and interviews with patients with acute and chronic leukemia and healthcare professionals Validated in patients with acute or chronic leukemia ²⁹
Quality of life-Anemia specific					
FACT-Anemia (FACT-An)	To assess specific quality of life concerns related to anemia and fatigue in patients with cancer	47	FACT-G (see above): + Additional concerns: 20 items (including the Fatigue Subscale [13 items] and 7 miscellaneous non-fatigue items)	Original: US English >50 translations	Developed based on a literature review and interviews with patients with cancer Validated in patients with cancer ²⁷
Quality of life-AML or MDS specific					
Acute Myeloid Leukemia-Quality of Life (AML-QOL)	To measure HRQOL in patients with AML and MDS	27	Physical (6 items) Social (2 items) Cognitive (2 items) Anxiety (6 items) Mood (4 items) Disease/Treatment effects (6 items) Quality of life (1 item)	Original: US English Translations: no information	Developed based on interviews with AML and high-risk MDS patients and healthcare professionals ¹⁵ The instrument is currently under validation

(Continues)



TABLE 4 (Continued)

Name	Purpose	No. items	Domain	Translations	Development and psychometric validation
Quality of Life in Myelodysplasia Scale (QUALIMS)	To measure disease-specific HRQOL in MDS	33	Physical burden (14 items) Benefit finding, disease information, and uncertainty) (3 items) Emotional burden (16 items)	Original: US English 17 translations	Developed based on interviews with MDS patients and healthcare professionals Validated in MDS patients ⁴²
Quality of Life E (QOL-E)	To measure the health- and treatment-related HRQOL in MDS	29	General Health status (2 introduction items not belonging to any domain) Physical (4 items) Functional (3 items) Social (4 items) Sexual (2 items) Fatigue (7 items) MDS-related specific (7 items)	Original: Italian 18 translations	Developed based on a literature review and interviews with MDS patients and hematologists Validated in MDS patients ³³
Quality of life-Hematological malignancy specific					
Hematological Malignancy-Patient-Reported Outcome (HM-PRO)	To measure quality of life of people with hematological malignancy (including AML and MDS)	57	Impact (34 items) Symptoms (23 items)	Original: US English Translations: no information	Developed based on a literature review and interviews with physicians and patients with hematological malignancies ³² The instrument is currently under validation
Symptoms/Symptoms burden-Cancer specific					
FACIT-Fatigue (FACIT-F)/ FACIT-Fatigue	The FACIT-Fatigue was originally developed to assess the fatigue associated with anemia	40	FACT-G (see above) + FACIT-Fatigue: 13-item Fatigue Scale (FACIT-Fatigue Scale)	Original: US English >55 translations	Developed based on a literature review and interviews with patients with cancer Validated in patients with cancer ²⁷
MD Anderson Symptom Inventory (MDASI)-Generic instrument	To assess the severity of multiple symptoms and the impact of symptoms on daily functioning	19	Symptom severity (13 items pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, trouble remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness and tingling) Symptom interference (6 items: general activities, mood, work, relations with others, walking, and enjoyment of life)	Original: US English >40 translations	Developed based on a literature review and interviews with patients with cancer and oncologists Validated in patients with cancer ³²
Symptoms/Symptoms burden-AML and MDS specific					
MD Anderson Symptom Inventory (MDASI)-AML/MDS	To measure symptoms burden for patients with AML and MDS	23	MDASI core module (see above) + AML/MDS symptoms (4 items: muscle weakness, malaise, diarrhea, skin problems)	Original: US English Translations: no information	Developed based on a literature review and input from MDS and AML patients Validated in MDS and AML patients ³³

Abbreviations: AML, acute myeloid leukemia; HRQOL, health-related quality of life; MDS, myelodysplastic syndromes; PROM, patient-reported outcomes measure.



targeted therapy or immunotherapy. A number of new disease-specific instruments such as the Quality of Life in Myelodysplasia Scale (QUALMS),⁴⁴ QOL-E,⁴⁵ and the AML-QOL¹⁵ are in the development and validation stages and could fit into today's management landscape.

Our study does have some limitations. The search strategy was aimed at covering studies published and indexed in Medline or Embase. We considered Medline as a major source of information and added Embase to further cover conference proceedings. Despite this, the selection of screened databases, along with the search terms and time frame used, may have led to us missing some other relevant studies. In addition, all studies screened were written in the English language, so any report in a different language and not published in English would have been missed. Another limitation with regard to ongoing trials retrieved from ClinicalTrials.gov is that the information reported by sponsors on this platform may not be comprehensive, as sponsors do not have the obligation to list and detail all endpoints. It is therefore likely that we did not identify PROMs used in all trials as the information had not been reported in ClinicalTrials.gov by the study sponsor. Lastly, we did not merge the numbers from Steps 1 and 2 as there could be some overlap between publications. For example, ongoing studies may also publish preliminary results, which could have been retrieved in both Steps 1 and 2. Our results should be considered step-by-step.

Our study provides an initial overview of the PROM landscape in AML and MDS, which was missing in the current literature. Additional work should be done to explore how systematic the assessment of patient perspective is, not only in the context of a clinical trial but in the context of real-world clinical practice to support the discussion with patients and inform treatment decision-making. Future work should also investigate whether the same PROMs could be used in a clinical trial and in clinical practice, bearing in mind the difference in time constraints, resources, and access to the PROMs.

In conclusion, as for many other oncology indications, this research showed that the EORTC QLQ-C30 is the most frequently used PROM in patient populations with MDS or AML. In addition, this research unveiled the underuse of disease-specific PROMs for these two indications; however, once their reliability, validity, and responsiveness have been demonstrated in the target population, these specific tools might be worth considering for future studies. Overall, in the absence of a clear recommendation by health authorities for a specific PROM,³¹ our work should inform and guide those planning future clinical studies including PROs as endpoints and could be a starting point for physicians willing to capture patient perspective in their clinical practice.

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CONFLICTS OF INTEREST

RS has no conflict of interest related to this work; however, for COI general disclosure, he has received honoraria and served as a member on a board of directors or advisory committee for Celgene Corporation, a wholly owned subsidiary of Bristol-Myers Squibb, and Novartis; and has received research funding from Teva. JL is an employee of ICON plc and a paid consultant to Celgene Corporation, a wholly owned subsidiary of Bristol-Myers Squibb. SD-A and ISa are employees of Mapi Research Trust and paid consultants to Celgene Corporation, a wholly owned subsidiary of Bristol-Myers Squibb. ISt and US have no conflicts of interest to disclose. LG and HC-S are employees of Celgene Corporation, a Bristol-Myers Squibb Company.

AUTHOR CONTRIBUTIONS

SD-A and ISa completed the research and analyzed the results. JL and HC-S wrote the manuscript draft. RS, JL, SD-A, ISa, LG, ISt, US, and HC-S contributed to the interpretation of the results, reviewed and edited the manuscript, and approved the final manuscript for publication.

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