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REVIEW ARTICLE

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Toward a more patient-centered drug development process in clinical trials for patients with myelodysplastic syndromes/neoplasms (MDS): Practical considerations from the International Consortium for MDS (icMDS)

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Abstract

Notable treatment advances have been made in recent years for patients with myelodysplastic syndromes/neoplasms (MDS), and several new drugs are under development. For example, the emerging availability of oral MDS therapies holds the promise of improving patients' health-related quality of life (HRQoL). Within this rapidly evolving landscape, the inclusion of HRQoL and other patient-reported outcomes (PROs) is critical to inform the benefit/risk assessment of new therapies or to assess whether patients live longer and better, for what will likely remain a largely incurable disease. We provide practical considerations to support investigators in generating high-quality PRO data in future MDS trials. We first describe several challenges that are to be thoughtfully considered when designing an MDS-focused clinical trial with a PRO endpoint. We then discuss aspects related to the design of the study, including PRO assessment strategies. We also discuss statistical approaches illustrating the potential value of time-to-event analyses and their implications within the estimand framework. Finally, based on a literature review of MDS randomized controlled trials with a PRO endpoint, we note the PRO items that deserve special attention when reporting future MDS trial results. We hope these practical considerations will facilitate the generation of rigorous PRO data that can robustly inform MDS patient care and support treatment decision-making for this patient population.

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BACKGROUND

Myelodysplastic syndromes/neoplasms (MDS)[1] are heterogeneous hematopoietic stem cell disorders characterized by cytopenias, ineffective hematopoiesis, related symptoms such as fatigue, and a variable tendency to progress to acute myeloid leukemia (AML) depending on initial disease risk.[2] At diagnosis, patients are typically classified according to the International Prognostic Scoring System (IPSS)[3] or its revised version (IPSS-R)[4] and can be broadly grouped into lower and higher risk disease categories. More recently, a new prognostic model that combines genomic profiling with hematologic and cytogenetic parameters, the IPSS-Molecular (IPSS-M), has been developed and validated.[5] Risk classification is critical during the diagnostic work-up to better inform treatment decisions and provide an accurate prognosis. As MDS are only curable with stem cell transplantation, which may be precluded by advanced age and/or comorbidity at diagnosis, improving health-related quality of life (HRQoL) is a key goal of therapy for both lower and higher risk patients.[6]

Even at diagnosis, the HRQoL of patients with MDS is substantially impaired in many respects.[7–9] For example, a considerable proportion of newly diagnosed patients with lower risk disease report clinically important problems in terms of physical functioning (male, 54% and female, 65%), fatigue (male, 29% and female, 37%), and dyspnea (male, 53% and female, 55%).[10] It was also recently observed that over one-third of patients with MDS at diagnosis can be considered "vulnerable" (at risk for health deterioration), most often reporting difficulty with prolonged physical activity as reported by patients themselves.[11]

The importance of measuring overall HRQoL and other types of patient-reported outcomes (PROs), such as specific symptoms or functional limitations,[12] has been widely acknowledged by both patients with MDS and hematologists and efforts to establish a core set of PROs have also been made.[13] Additionally, there is also evidence that PROs can provide independent prognostic information for survival and HRQoL outcomes.[14–18] The prognostic value of PROs in MDS is consistent with similar observations across several other cancer populations, including solid and hematologic malignancies,[19–23] underscoring the richness of information that can be obtained from validated PRO measures. As an example, the inclusion of patient-reported fatigue into the original IPSS was found to enhance the accuracy of survival prediction in higher risk patients with MDS,[15] and such evidence has been replicated in subsequent analyses.[24] Several clinical trials and observational studies have addressed the impact of MDS treatments on patients' HRQoL,[25–29] and many have specifically focused on the relationships between fatigue, anemia, and HRQoL outcomes.[30,31] For example, a recent systematic review by Mo and colleagues[30] examined the impact of treatments for anemia on HRQoL and physical function among patients with MDS, finding many methodologic limitations in 26 studies enrolling more than 2000 patients, and making it difficult to understand the true value of these treatments in improving patients' well-being. Their comprehensive analysis underscores the need for future MDS trials to elucidate whether anemia treatments are indeed associated with better PROs.

The importance of PRO assessment in the evolving MDS treatment landscape

The past 5 years have yielded notable advances in MDS research that have led to changes in clinical practice. For example, based on results from the MEDALIST randomized controlled trial (RCT),[32] luspatercept was approved for the treatment of anemia in patients with lower risk MDS previously exposed to an erythropoiesis-stimulating agent, and this drug has more recently received an extended indication to the first line setting based on interim results from the COMMANDS RCT.[33]

Another example is the IMerge RCT, whose data supported the clinical value of imetelstat, compared to placebo, in lower risk transfusion-dependent patients.[34,35]

Another important advance in MDS therapy is the emerging availability of oral MDS therapies, holding the promise of improving HRQoL, given the decreased need for clinic visits and infusions.[36] Indeed, decitabine cedazuridine is already in wide use in the United States, and a number of other oral drugs are being developed for patients with both lower and higher risk diseases.[37,38]

This rapidly evolving treatment landscape necessitates the collection and publication of high-quality PRO data to help inform the benefit/risk assessment of each new therapy when applied to an individual patient and assess whether patients live longer and live better. The need to incorporate PROs in the assessment of adverse events (AEs), to enhance the understanding of toxicity in clinical trials in hematologic malignancies has been highlighted in previous reports,[39] and the importance of including PROs in future MDS trials has been noted in international consensus-based recent recommendations.[40] There are several illustrative examples of how PROs contribute to our understanding of the total value of novel drugs in hematology trials.[41] Most notably, the use of PROs in myelofibrosis research was critical to the development of ruxolitinib and its approval by the US Food and Drug Administration (FDA).[42] Years later, the recent FDA approval of momelotinib was also based on pivotal RCTs using PROs as primary endpoints.[43]

From a regulatory standpoint, the FDA includes PROs in its list of clinical outcome assessments (COAs) that can be used to determine whether or not a drug has demonstrated a clinical benefit.[44] In a four-

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part guidance series, the FDA has published its perspective on how to include data from COAs in medical product development and regulatory decision making, covering aspects such as sampling methods, identification of outcomes relevant to patients, selection and adaptation of measures, and interpretation of PRO data.[45–48] The European Medicines Agency (EMA) has previously provided similar (albeit less detailed) guidance to support the inclusion of PROs in clinical trials.[49,50] Moreover, PROs are also considered by health technology assessment bodies (in the United Kingdom and Germany) for their review of benefit assessments of medical interventions.[51,52]

On the other hand, for PRO data to fulfill their potential and help patients and clinicians to make more informed treatment decisions, investigators must be mindful of several dimensions of their collection, from the initial trial setup to publication of study results, as nonrigorous PRO assessments are unlikely to generate meaningful information that can robustly inform patient care.[53–57] International guidelines now exist to assist investigators in designing a clinical trial protocol with a PRO endpoint[56] and reporting study results.[57] Figure 1 outlines broad steps that could facilitate investigators to maximize the uptake of trial results by the MDS scientific community, payers, and regulators. For descriptive purposes, the flow of the discussion below reflects the broad aspects depicted therein. Importantly, we do not endorse individual PRO measures or analytic methods to be used but provide practical information to support investigators when including PROs in future MDS trials.

KEY SELECTED ASPECTS TO CONSIDER DURING PROTOCOL DEVELOPMENT AND PRO DATA COLLECTION IN MDS TRIALS

The initial study setup

Evaluating PROs in clinical trials requires thoughtful consideration of several aspects, some of which are to be addressed at the time of protocol writing, while others deserve special attention during the enrollment period. These latter issues are mainly related to the logistics of the protocol, which must ensure high-quality PRO data collection during the study. As most patients with MDS are of advanced age, an added issue to consider is minimizing respondent burden in deference to the ability of older patients to reliably start and complete PRO questionnaires.

In 2018, the international SPIRIT-PRO guidelines provided recommendations for key items to be addressed and included in clinical trial protocols with PRO endpoints.[56] To facilitate the uptake of these recommendations, detailed implementation instructions were published thereafter.[58] MDS trial protocols that include PROs should be written in line with these recommendations[56] (Supporting Information S1: Table 1). The stakes are high. Indeed, it may be possible that a difference between treatment arms for a given PRO domain may not become evident simply because of not having appropriately addressed its methodological aspects. Examples include selecting a PRO measure that is not sufficiently sensitive to capture the underlying PRO endpoint, selecting PRO

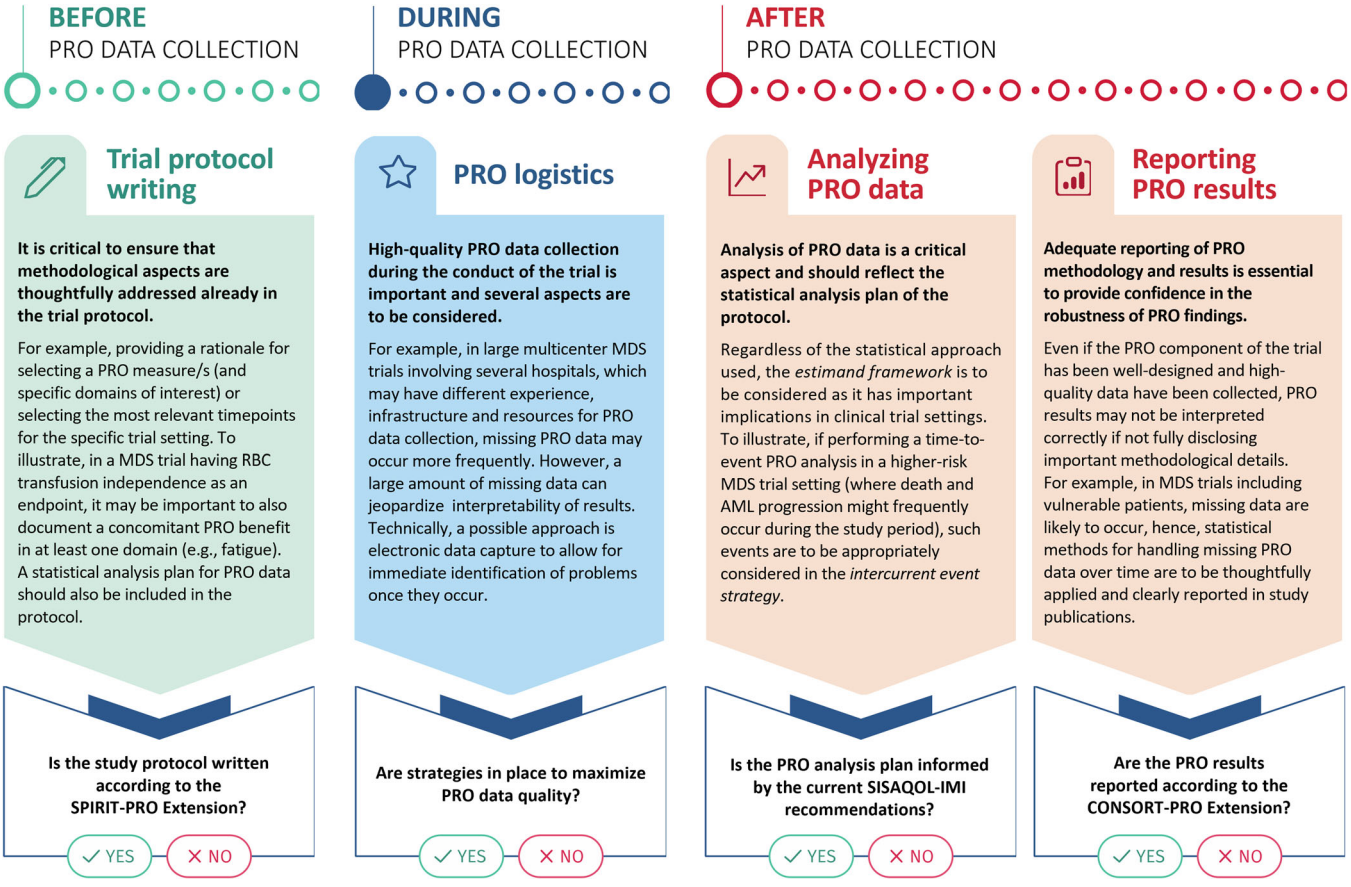

FIGURE 1 Illustrative example of key patient-reported outcome (PRO) aspects and selected guidelines to consider in the conduct of a myelodysplastic syndromes/neoplasms clinical trial. AML, acute myeloid leukemia; CONSORT, Consolidated Standards Of Reporting Trials; RBC, red blood cell; SISAQOL-IMI, Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

assessment time points that are unlikely to capture potential HRQoL differences between treatment arms, or studies underpowered to detect significant differences in PRO endpoints.

Selecting specific PRO research objectives

There is substantial variability in the definition of PRO research objectives in cancer clinical trials, which reflects the wide range of research questions answered by such data. While this variability requires detailed specification of specific PRO research objectives, cancer trial protocols often lack such detail and only report vaguely defined objectives,[55] a limitation also observed in MDS trials.[28]

Clearly defining the primary and secondary objectives in a trial protocol is needed to inform decisions about other methodological aspects. This decision should be based on a specific research hypothesis and will guide the selection of PRO measures that can robustly capture the concept of interest. PRO measures may be general (such as the 36-Item Short-Form Health Survey[59] or EQ-5D[60]) or cancer-specific. These latter may be either generic multidimensional, such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (EORTC QLQ-C30)[61] and the Functional Assessment of Cancer Therapy - General,[62] or MDS-specific multidimensional, such as the QOL-E[63] and the Quality of Life in Myelodysplasia Scale (QUALMS).[64,65] However, there are also measures, such as the PROMIS Fatigue,[66] which assesses a specific health domain (i.e., fatigue) highly relevant for MDS patients.

It is common to see a combination of questionnaire types in MDS trials and, as long as the question item burden is not too high, we advocate for including at least one MDS-specific measure. While using more than one PRO measure is acceptable, it is still critical to identify specific health domains/concepts to be used as primary and secondary/exploratory objectives.

For example, the recently developed QUALMS has three subscales assessing physical burden (QUALMS-P), emotional burden (QUALMS-E), and benefit finding (QUALMS-BF), plus a total QUALMS score.[64,65] Therefore, a hypothetical trial using only this questionnaire should clearly identify which specific scale will be used as the primary endpoint of the PRO analysis. If a new drug is felt to ameliorate anemia and hopefully reduce the physical burden of fatigue, then the QUALMS-P is appropriate; if a new oral form of an older drug is felt to reduce the stress of disease management by decreasing clinic visit burden, then the QUALMS-E or total QUALMS is likely more appropriate.

In a draft guidance document by the FDA published in 2021,[67] the following core set of PROs were recommended to be used in cancer trials: (1) disease-related symptoms; (2) symptomatic AEs; (3) overall side effect impact summary measure; (4) physical function; and (5) role function. This is an important document as it guides the key PRO concepts that should be highly considered in anticancer therapy registration trials.

Although several symptoms are impaired in patients with MDS (albeit to a different degree) and can be considered as valuable PRO endpoints, fatigue is almost universal,[8,9,14,24,31] and we advocate it should be considered in every MDS trial with the appropriate component of a well-validated multidimensional measure or with a unidimensional fatigue measure.

On the other hand, we note that in higher risk MDS trials where the primary objective may be most focused on improved overall or leukemia-free survival in the experimental arm, a demonstration that this does not come at the cost of worse symptoms or functional aspects may suffice. In lower risk disease trials where the therapy is typically not disease-modifying and the goals focus on the amelioration of symptomatic cytopenias, it is important that the PROs are powered to demonstrate a clinically significant improvement in selected symptoms and/or functional aspects in the experimental arm.

Practical considerations when selecting and administering PRO measures

In addition to the specific study objective(s) for PRO endpoints, there are logistical aspects to consider. For example, the intended schedule of the PRO assessments and the respondent burden. This latter aspect needs to be considered as it may negatively impact rates of missing PRO data[68] and, in this respect, we note that recommendations to address respondent burden have been recently published.[69] This issue is relevant in the context of MDS trials, which often involve older patients and/or patients with fatigue who may have trouble with electronic interfaces and frequent requests to fill out questionnaires.

The EORTC QLQ-C30 has so far been the most frequently used PRO measure in MDS research[70] and reflects the trend of published results from this most commonly deployed questionnaire in solid cancer RCTs.[71] While useful, this is a cancer-generic measure that, if used alone, may not capture important MDS-specific disease/treatment-specific aspects (e.g., bruising or worry about progression to AML). In this respect, we note that two MDS-specific PRO measures are currently available, the QOL-E[63] and the QUALMS,[64,65] which have been used both in the context of MDS RCTs[72] and real-world studies.[11]

A relatively novel approach to increase the sensitivity of PRO measurement is the use of *PRO item libraries*, which allow researchers to select ad hoc PRO items most relevant to the given research settings. Table 1 reports some of the available *PRO item libraries* that could be considered in future MDS trials, and recommendations on how to use them are available.[73] We suggest they may be used to complement already-existing validated PRO questionnaires (but not instead of validated PROs), except for perhaps in phase I or II MDS trials when they may be used on their own to establish a potential PRO signal and to generate data that can better inform the PRO design of phase III RCTs. While PRO measures used in MDS studies may not include specific symptomatic AEs of a novel MDS drug, these AE items can still be sourced via these libraries to best capture important aspects that would have been otherwise missed. An example of additional uses of item libraries in MDS research has been recently published.[74]

Another important consideration is the way these PRO measures are administered. Traditionally PRO measures have been administered to patients during hospital or clinical visits in paper format; however, advances in digital health technology now allow the implementation of electronic PRO (ePRO) measures that patients can complete remotely at home or just before the clinical visits via web platforms. Such ePROs data collection systems might be more consistently used in future MDS trials, providing special attention to those groups who may be digitally excluded, such as older people, people with low incomes, and other marginalized groups.[75] For this purpose, different modes of PRO completion (e.g., electronic or paper) may be considered and offered, as well as language, cultural needs, and literacy requirements should be addressed to promote inclusivity and produce results as generalizable as possible.[75,76] Remote monitoring systems may also consider collecting biometric data using wearable technology. A recent study conducted in a small sample of vulnerable patients with hematologic malignancies suggested that longitudinal data collection systems combining ePRO and wearable technology are feasible.[77] However, future research is needed to examine the potential benefits, barriers, and disadvantages of this approach in the MDS setting, which may often include older patients.

TABLE 1 Selected PRO item libraries that can be used in MDS trials.

PRO item libraries	
EORTC item library	*FACIT item library*
>900 items from >60 EORTC questionnaires representing 208 symptomatic toxicities	>700 items from >100 questionnaires
It enables more flexible usage of the EORTC questionnaires by facilitating flexible and timely measurement of symptoms and problems, and by allowing users to integrate aspects related, for example, to novel treatments that were not common when a questionnaire was initially being developed.	Is a collection of health-related PRO questions that appear in the FACIT Measurement System, which assesses a wide variety of disease- and treatment-related symptoms, functional abilities, general perceptions of health and well-being, and other aspects of health-related quality of life.
https://itemlibrary.eortc.org/	https://www.facit.org/facit-searchable-library
PRO-CTCAE	*MDASI symptom library*
124 items representing 78 symptomatic toxicities	92 items
Developed to evaluate patients' symptomatic toxicity in cancer clinical trials and to be used as a companion to the CTCAE. PRO-CTCAE items evaluate the symptom attributes of frequency, severity, interference, amount, and presence/absence.	Includes a set of symptoms to be added to the MDASI core or an MDASI module to create an experimental MDASI tailored to clinical research or practice
https://healthcaredelivery.cancer.gov/pro-ctcae/	https://www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/MDASI%20symptom%20library.pdf

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organization for Research and Treatment of Cancer; FACIT, Functional Assessment of Chronic Illness Therapy; MDASI, MD Anderson Symptom Inventory; MDS, myelodysplastic syndromes; PRO, patient-reported outcomes.

The importance of timing of assessment and minimizing missing PRO data

Defining the most appropriate PRO time points and time windows for each scheduled assessment is critical to capturing unbiased treatment effects on patients' HRQoL. Strategies used to define a PRO assessment schedule may vary depending on several aspects, including the disease trajectory and type of treatment, but should carefully consider the potential burden on patients. Ideally, the first assessment should be before treatment starts and, in any case, it should be described if therapy starts immediately after initial diagnosis or at a later time point in the disease trajectory. The schedule of assessments may be driven by different factors, such as treatment events or conditions (e.g., at every visit; at the start of each course of chemotherapy), or time (e.g., every month).[78]

For example, the importance of this aspect for MDS patients receiving transfusions has been shown in a recent study, which suggested that a peri-transfusion PRO assessment (i.e., the day before and 7 days after the transfusion) may offer a strategy to inform shared decision making regarding transfusions, as it is able to discriminate between those patients who perceive a clinically meaningful HRQoL benefit or not.[79] Since red blood cell transfusions may improve symptoms of fatigue and physical functioning, it may be sometimes difficult to demonstrate improvements in selected symptom and functional domains in the experimental arm of RCTs, even when the agents are active. In these instances, the timing of PRO completion at hemoglobin nadirs rather than immediately following transfusions, and the use of PROs that address the burden of red blood cell transfusions, may better help clarify evidence of potential benefit.

Missing PRO data (i.e., missing PRO questionnaires at specific time points) can be expected in any prospective study due to several reasons, and this problem has also been observed in MDS drug trials.[26] In the MDS setting, this may be due to the older population who often have associated comorbidities and/or debilitating health conditions that contribute to hospitalizations, missed clinic visits, forgetfulness, and early death. In trials involving heavily transfused patients or those with higher-risk diseases, the risk of missing data may be higher. Additionally, given the relatively rare nature of the disease, MDS RCTs often include many centers and countries, each with variable resources and infrastructures, thereby possibly further increasing this risk of missing PRO data.

Although a certain amount of missing data is expected, it should be minimized as much as possible for two reasons: (1) too much missing data over time may diminish the power to detect PRO differences between groups; (2) missing data may bias the validity of model-based estimates of PRO longitudinal analyses (especially if the dropout pattern differs between the treatment arms). Primary prevention strategies are needed to reduce the amount of missing data as much as possible.[80] Frequently, lapses in staff oversight and other types of logistical/administrative issues are the main causes.[81,82] Actions to prevent and/or minimize missing data should be integrated into the protocol development phase. Finally, as missing data may also depend on factors unrelated to administrative and/or logistic issues, it is important to document during the course of the study the actual reasons to better inform the statistical analysis. Table 2

TABLE 2 Selected strategies to minimize missing PRO data.

Recommendations
Maximize PRO compliance through study design (e.g., specify PRO assessment schedule and time windows, specify clear eligibility criteria)
Minimize the burden for patients and trial staff associated with PRO assessment
Identify personnel responsible for PRO assessment and distribution of questionnaires (e.g., nurse, data manager)
Educate and train all the trial staff of participating institutions
Develop guidelines for PRO administration for trial staff
Engage patients and give them detailed information on the value of PROs (e.g., sheets explaining reasons for collecting PROs, and how PRO data will be used)
Develop quality assurance procedures to monitor compliance and intervene if issues raise
Ensure that the trial staff remains committed to the PRO study (e.g., by sending updates or newsletters)

Note: Based on: (1) Fayers and Machin[8]; (2) Mercieca-Bebber et al.[85,86]
Abbreviation: PRO, patient-reported outcomes.

provides a list of selected strategies to minimize missing PRO data. Indeed, encouraging recent evidence from MDS RCTs indicates that good compliance rates can be obtained even in the context of debilitated transfusion-dependent patients.[34,83,84]

Implications of open-label versus blinded study designs on PRO results

Blinding is considered a crucial method in RCTs to minimize the potential influence of clinicians' and patients' expectations with respect to possible benefits and harms associated with the interventions compared in the trial.[87] For example, nonblinded patients may report a level of symptoms according to what they believe the researchers would be pleased to observe.[87] Given that many cancer RCTs now include PROs and the number of open-label studies is increasing,[88] interest in investigating the relationship between study design (i.e., open-label vs. blinded trials) and PRO results is growing. The potential impact of a patient knowing their treatment arm is also relevant to contemporary MDS research. The IMerge[35] and MEDALIST[32,72] trials were both double-blind, placebo-controlled trials but the recently published COMMANDS RCT was open-label.[33]

Whether overall trial design impacts PRO results is a legitimate question. For example, it has been suggested that PRO *distal outcomes* (e.g., social or emotional functioning, or HRQoL) could be more susceptible to open-label bias than the so-called *proximal outcomes* (i.e., symptoms), as they are more subject to nondrug influences.[89] Moreover, some concerns about potential bias in PRO results from open-label RCTs have also been raised by the FDA and EMA.[12,48,50]

While an open-label bias has been suggested by previous studies,[90–92] other recent studies have found no significant effects of treatment concealment on trial results or even PRO completion rates.[93–98] For example, in a large analysis of possible open-label bias in more than 500 RCTs in patients with solid tumors, no association between treatment concealment and the chance of favorable PRO results was found.[94] Another systematic review found that open-label designs had no impact on PRO compliance, observing similar completion rates between experimental and control arms, irrespective of trial design.[96] In the hematology setting, an analysis of two registration trials in multiple myeloma found that the knowledge of treatment assignment had no effect on symptoms, function, and health status reported by the patients.[98] For clinical trials of MDS, while a blinded design may be preferred, these findings suggest that an open-label design would not have a detrimental effect on missingness and PRO conclusions.

Interpretation of PROs in studies with a placebo arm

The interpretation of PROs in RCTs comparing a potentially active drug versus a placebo for MDS should be approached with nuance. Some trials have not shown a change in HRQoL despite significantly better responses in the treatment arm, which may be due to a number of factors including, for example, selection of assessed PRO domains, timing of assessments, missing data, or the statistical approach.

An example is the lack of HRQoL difference that has been seen in some RCTs that have demonstrated efficacy in decreasing transfusion needs. Given a response rate of at best 50% in those trials (active drug vs. placebo), it is possible that a potential benefit of the drug on PROs in patients with a response may not become evident. To further inform potential PRO benefits, trialists may also prespecify plans to analyze PROs of patients who respond in the treated arm (e.g., become transfusion independent and will continue but may have counterbalancing side effects) and PROs of patients in the placebo arm (who continue to be regularly transfused). Such an approach aligns with the principal stratum strategy described in the estimand framework,[99] described in the next paragraph.

To illustrate, in a post hoc analysis, Santini et al.[83] compared HRQoL changes from baseline between lenalidomide responders, lenalidomide nonresponders, and placebo. This analysis suggested that patients who responded to lenalidomide not only benefitted in terms of transfusion independence but also experienced a significant alleviation of patient-reported symptoms compared to patients who did not respond or those in the placebo arm.[83] At the same time, a comparison between patients who did not respond to lenalidomide and those in the placebo arm suggested that even in the absence of a response, no statistically significant difference was found.[83]

KEY SELECTED CONSIDERATIONS AFTER DATA COLLECTION AND WHEN REPORTING PRO RESULTS FROM MDS TRIALS

Statistical analyses of PRO data

Although some statistical considerations are discussed in this section to reflect the timeline of Figure 1, we note that a well-detailed statistical analysis plan should be integrated into the trial protocol.

The choice of the most appropriate type of analysis of PRO data mainly depends on the specific PRO research question for the trial and the corresponding endpoints. A taxonomy of common PRO trial objectives and corresponding statistical methods has been established.[100] This clearly distinguishes PRO research objectives focusing on the *mean change of PRO scores over time* from those assessing *time to deterioration/improvement of individual PRO scores*, and those evaluating the *proportion of responders according to a PRO-based criterion*. Frequently used statistical methods in this taxonomy are linear mixed models for comparing mean change over time between treatment arms; Cox regression models for analysis of time to deterioration/improvement; and descriptive statistics or logistic models for analyzing proportions of responders.

A thorough discussion of statistical approaches is beyond the scope of this paper. However, we herein report some considerations on time-to-event analyses of PRO data as they may be relevant in some MDS trials; for example, those aimed at demonstrating a sustained improvement in a given PRO domain. An example of a time-to-event approach has been recently provided in the IMerge trial, which included heavily transfused lower risk patients with MDS.[34,35]

Time-to-event analyses focus on the time until a PRO domain (e.g., fatigue or physical functioning) improves (or deteriorates) to a clinically relevant extent (e.g., time until a patient experiences the first increase of at least 10 points on a fatigue scale). The cornerstone of such an analysis is the exact definition of the event of interest (e.g., deterioration), which needs to specify: (a) the threshold for a clinically meaningful change (e.g., 10 points) and (b) whether it considers the first clinically meaningful improvement/deterioration, or only the first clinically meaningful improvement/deterioration that is not reversed at a later time point.[101]

While useful to interpret clinically, this type of analysis for PRO data presents challenges that are to be considered.[102] For example, longitudinal PRO measurements need to be repeated with sufficient

frequency to capture the event of interest close to when it occurs,[103] and the interpretation of results may be affected by the loss of detailed information on score changes over time. On the other hand, interpreting PRO trial results analyzed this way is greatly facilitated by having similarities with the widely used survival analyses.

The estimand framework and time-to-event analyses of PRO data

In 2019, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) released the ICH E9 (R1) addendum on statistical principles for clinical trials.[99] This document introduced the estimand framework, a conceptual model to ensure consistency among trial objectives, design, conduct, analysis, and interpretation of results. This document was officially implemented by the EMA in 2020[104] and by the FDA in 2021.[105] In addition, complementing the estimand framework, the international, multi-stakeholder consortium[106] *Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative (SISAQOL-IMI)* is developing detailed recommendations for design, analysis, presentation, and interpretation for PRO data from cancer clinical trials, as well as harmonized terminology for clinically meaningful difference (CMD) thresholds and related concepts.

The estimand framework provides a strategy for clearly defining research objectives based on five attributes: treatment, population, variable, population-level summary, and intercurrent event (ICE) strategy. The "treatment" attribute provides a detailed description of the treatments under investigation, while the "population" is defined by inclusion/exclusion criteria. The "variable" attribute represents the outcome and time point/period under investigation (e.g., change in a fatigue scale between baseline and 3-month follow-up) and aligns with previous recommendations[56] to explicitly define a priori which PRO scales are primary, secondary, or exploratory endpoints. The variable is complemented by the "population-level summary," which is the statistical parameter to be investigated (e.g., the mean difference between treatment arms in change since baseline). The most important and innovative part of the estimand framework, however, is the introduction of the ICEs and strategies to deal with them when defining study endpoints. ICEs are defined as "events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the research question of interest,"[105] for example, death, treatment switch, treatment discontinuation (either temporary or definitive), treatment restart, and concomitant medications. The ICE strategies help in defining how various types of ICEs could be considered in alignment with the overall research question. Details on ICE strategies with hypothetical examples for MDS trials are provided in Table 3.

The definition of ICEs and the corresponding strategies have an impact on the choice of the appropriate statistical methodologies and the interpretation of results. This may be crucial, for example, in the setting of higher risk MDS trials, where different types of ICEs may occur with high frequency (e.g., death, progression to AML, treatment discontinuation).

A detailed explanation on how to use the estimand framework and handle ICEs specifically for PRO research objectives has been provided by Lawrance et al.[107] Furthermore, Cottone et al.[108] have published an analysis on how different ICE strategies and

TABLE 3 Intercurrent event strategies according to the estimand framework and hypothetical examples for MDS trials.

Intercurrent event strategy	Description	Hypothetical examples for MDS trials
While on treatment strategy	The treatment effect is investigated before the occurrence of the intercurrent event	A patient's fatigue scores until treatment discontinuation are included in the analysis (requiring repeated PRO assessments that provide sufficient time resolution throughout the treatment period)
Treatment policy strategy	The treatment effect is investigated regardless of the occurrence of the intercurrent event (similar to an intention-to-treat analysis)	Change in fatigue score between baseline and 3-month follow-up is analyzed regardless of the treatment discontinuation (requiring PRO data collection after treatment discontinuation)
Hypothetical strategy	The treatment effect is investigated under the assumption that the intercurrent event has not occurred	Change in fatigue score between baseline and 3-month follow-up is analyzed under the assumption that treatment has not been discontinued (this requires data prediction, using imputation methods)
Composite variable strategy	The intercurrent event is included in the definition of the endpoint variable	The analysis focuses on the time to deterioration (i.e., clinically meaningful increase) of pain defined as either a deterioration of 5 score points for a pain scale, or the use of concomitant pain medication (i.e., the intercurrent event)
Principal stratum strategy	Treatment effect in a group (stratum) of patients in which the intercurrent event does (not) occur	Change in fatigue score between baseline and 3-month follow-up is analyzed in those patients who have received concomitant treatment for fatigue

Abbreviations: MDS, myelodysplastic syndromes/neoplasms; PRO, patient-reported outcomes.

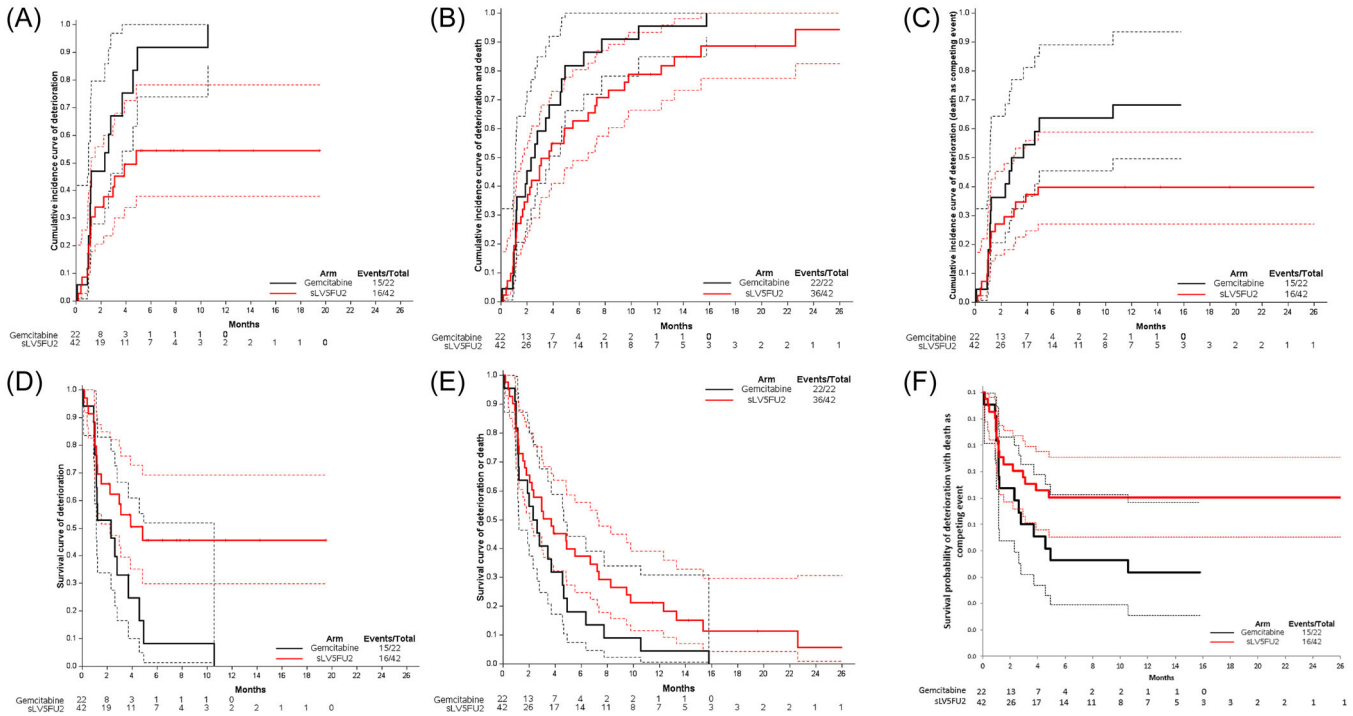

FIGURE 2 Cumulative incidence curves and survival probability curves of the time to deterioration in physical functioning according to different approaches to assess death in time to deterioration analysis. Reprinted with permission: Copyright 2023, Elsevier.[108] (A) Cumulative incidence curves (CIFs) of deterioration considering death as censored; (B) CIFs of deterioration considering death as deterioration; (C) CIFs considering death as a competing event; (D) survival probability curve of deterioration considering death as censored; (E) Survival probability curve of deterioration considering death as deterioration; (F) survival probability curve of deterioration considering death as a competing event; Kaplan–Meier estimation method was used for approach 1 (panels A and D) and 2 (panels B and E) while competing risk approach was used for approach 3 (panels C and F). Probability of survival was obtained by reversing cumulative incidence curves, and vice versa. 95% Confidence intervals are provided as dashed lines.

corresponding statistical models impact trial results and showed substantial variation in the rate of deterioration of patient-reported physical function depending on if and how death (the ICE) was included in the time to PRO deterioration analysis as an ICE (Figure 2). In addition, the impact of ICEs has been also described in the context of the time to PRO improvement analysis.[109] This statistical approach can be of special relevance in the context of anticancer drugs, which are expected to improve HRQoL outcomes and, therefore, "measure" the time to HRQoL improvement and the time to sustained HRQoL improvement.[109]

It is important to note that when designing an MDS trial, the planned statistical analysis should also include a strategy for handling missing data.[80] Missing data may be frequently associated with ICEs or other clinically important events (e.g., deterioration of health status that prohibits questionnaire completion by a patient). Thus, along with a carefully selected ICE strategy, elaborate data imputation methods and sensitivity analyses are needed to avoid or quantify bias and investigate the robustness of PRO trial results[80] (Table 4).

TABLE 4 Key aspects of statistical analysis of PRO trial data.

When writing the trial protocol (or statistical analysis plan) and the trial publication
Define primary, secondary, and exploratory endpoints in line with the estimand framework
Distinguish clearly between the main analysis (defined a priori), sensitivity analyses, and supplementary analyses
Plan sensitivity analyses to investigate the robustness of the results (e.g., evaluating how the choice of different patient-level CMD thresholds impacts results in a responder analysis, or analysis of time to deterioration/improvement)
Include a strategy for handling missing data
When reporting the results provide an overview of the amount of PRO data available for analysis at each time point in each treatment group

Abbreviations: CMD, clinically meaningful differences; PRO, patient-reported outcomes.

Interpretation of clinical meaningfulness of PRO trial results

Well-defined research objectives and adequate use of statistical methods facilitate interpretation of PRO results, but nonetheless evaluating the clinical meaningfulness of group differences between treatment arms or improvement or deterioration of scores from individual patients is another key challenge for PRO trial endpoints. The concept of CMDs has been introduced to support the interpretation of PRO results and the definition of informative endpoints, but CMDs have also created some challenges of their own, due to a lack of harmonized terminology and the variety of methods used to establish such thresholds. CMD thresholds used to interpret differences between groups or changes over time (of individuals or groups) have

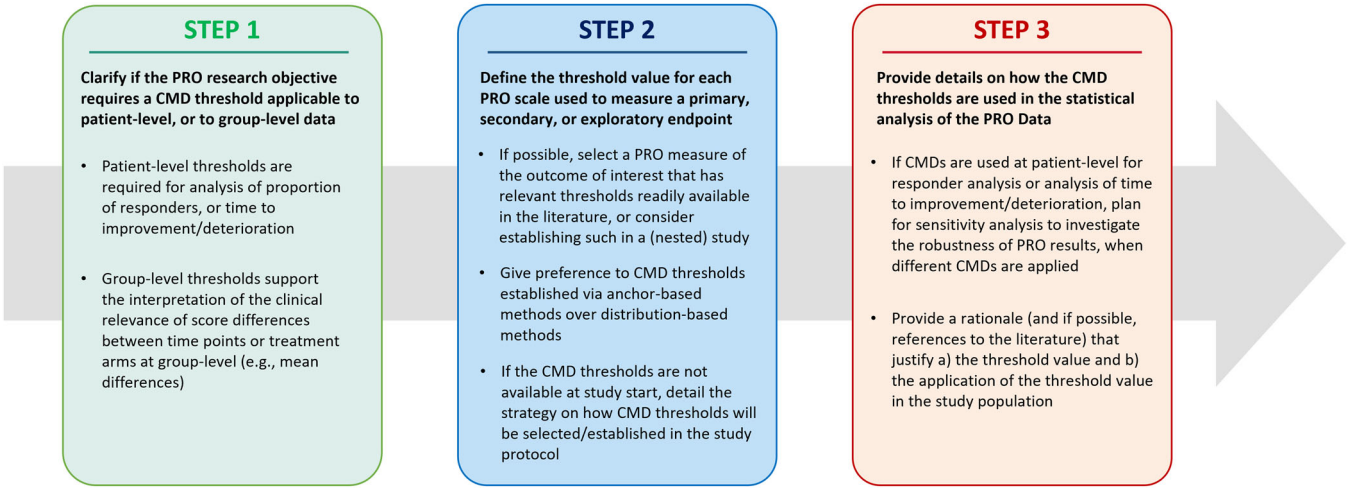

FIGURE 3 Key aspects to consider when using thresholds for clinically meaningful differences in a clinical trial. CMD, clinically meaningful differences; PRO, patient-reported outcomes.

been labeled with different terms, such as "CMD," "minimal important difference," or "minimum clinically important difference" even when referring to the same concept.

A key aspect to consider and pre-emptively establish when designing statistical methods is whether the trial is distinguishing the application of such thresholds at the patient level (to interpret the change over time of an individual patient) or at the group level (differences between groups, changes within a group over time, or between-group differences in change over time). Additionally, the correct choice of thresholds is another important factor for the interpretation of results, as statistical methods will not directly provide the clinical meaning of the PRO results. In an effort to facilitate the planning of future MDS trials, we provide a graphical overview of key steps to consider when applying appropriate thresholds for a PRO measure (Figure 3).

The impact of frailty and comorbidity on PROs

With a median age of diagnosis of 76 years,[110] the majority of patients with MDS have one or more comorbidities of potential clinical relevance,[111] and 25%–33% will qualify as vulnerable or frail using conventional frailty screening tools, such as the Rockwood frailty scale,[112] the Vulnerable Elders Survey-13 (VES-13),[113] or the Geriatric 8 (G8).[114] In addition to adding independent prognostic value for overall survival,[17,115–117] these patient-related factors may independently impact on and confound the magnitude of a given intervention (e.g., the achievement of transfusion independence) on PRO results.[7,11,118–123] For example, a patient with MDS who is vulnerable or frail, or suffering from an ongoing comorbidity (such as congestive heart failure or severe back osteoarthritis), may not experience an improvement in dyspnea, fatigue, and or physical functioning despite achieving hematologic improvement on a clinical trial. Moreover, recent data have revealed that populations of patients with MDS who are vulnerable per the VES-13 do not show the same PRO changes seen with known groups, such as increasing disease risk, that are found among the nonvulnerable.[11] Consequently, frailty and comorbidity should be considered and even adjusted for in analyses of prospectively gathered PRO results in clinical trials, especially when they are not used as an eligibility criterion.

The importance of accurate and timely reporting of PRO results

While a number of PRO methodological issues are to be addressed at the stage of protocol writing to ensure the appropriate execution of PRO assessments, it is equally important to provide adequate details of PRO methodology in trial publications to facilitate a critical appraisal of the robustness of PRO findings. Unfortunately, a substantial proportion of published RCTs (both for solid tumors and hematologic malignancies) have failed to report adequate information about PRO methodology, thereby precluding the uptake of PRO results by the scientific community and the impact of these data on real-world practice.[27,53,124–127]

As PROs are often secondary endpoints, it is not uncommon to see this data being disclosed in a separate manuscript (other than the primary trial publication reporting efficacy and safety results). Although this strategy may be acceptable and may have the advantage of allowing sufficient space to provide all necessary methodological reporting, including appropriateness of analyses and interpretation of data, a timely PRO report is essential to allow readers to understand the overall value of a new drug being tested in an RCT.[55] Indeed, it has been observed that PRO data from RCTs are frequently published much later than the main clinical efficacy report.[125,128,129] Additionally, there is evidence that many RCTs with clearly prespecified PRO endpoints fail to disseminate PRO findings in the scientific literature,[129,130] raising important ethical concerns.[76] The Consolidated Standards of Reporting Trials-PRO (CONSORT-PRO) extension reporting guidelines were published in 2013 to help improve the transparent and complete reporting of PRO results from RCTs[57,131] (Supporting Information S1: Table 2), and should be considered in all future MDS reports.

Specific PRO items requiring special consideration in future MDS trial reports

To inform the identification of specific areas for improvements when publishing PRO findings, we performed a systematic literature search in PubMed to identify RCTs with a PRO endpoint in patients with MDS that were published between January 2010 and August 2023 (key searching strategy provided in the Appendix). Additional

publications were identified by hand searching the reference lists of these articles. We considered RCTs comparing conventional medical treatments and including patients with MDS only. Editorials and conference abstracts were excluded. If a selected study had multiple publications (from the original trial), relevant PRO information was extracted from all published papers. For each of the identified RCTs, information about the general characteristics of the trial and the quality of PRO reporting by the CONSORT-PRO extension[57] were independently extracted by two reviewers.

We identified a total of 11 MDS-related RCTs including a PRO endpoint (secondary endpoint in all studies), enrolling 1828 patients. The most frequently used PRO measure was the EORTC QLQ-C30 ($n = 6$), followed by the Functional Assessment of Chronic Illness Therapy (FACIT) measures (FACT-An or FACIT-Fatigue) ($n = 5$), EQ-5D measures (EQ-5D-5L, EQ-5D-3L, or EQ-VAS) (n = 3), and the QOL-E ($n = 2$). For three RCTs, a secondary paper that focused exclusively on PRO results was published (between 17 and 23 months after the publication of the main clinical efficacy manuscript). A summary of clinical findings from these trials is provided in Supporting Information S1: Table 3.

We note that after our search, two RCTs with a PRO endpoint were also published, that is, the IMerge[34,35] and the COMMANDS[33] trials. PRO data from the IMerge trial suggested a sustained clinically meaningful improvement in fatigue for imetelstat-treated patients compared to placebo.[34,35] Preliminary PRO analyses (published as an abstract) from the COMMANDS trial indicated that luspatercept significantly increases the probability of sustained improvement in several domains.[132]

With respect to the quality of PRO reporting, we observed that overall, the adherence to the CONSORT-PRO recommendations[57,131] was suboptimal, but was higher in the three RCTs which published stand-alone papers about PRO findings.[72,83,133] This evidence is consistent with the wider literature on this topic showing that the quality of PRO reporting is generally higher in trials that publish a separate paper on PRO findings.[124,127] We found that slightly more than half (56%) of the CONSORT-PRO recommendations were addressed in more than 50% of the RCT publications (Supporting Information S1: Table 4). Among the items less frequently addressed were reporting statistical approaches for dealing with missing data, and reporting the number of questionnaires submitted/available for analysis at follow-up time points (both available in 46%). An example of how compliance rates for PRO questionnaires should be reported, to help interpret PRO data collected and assess potential bias, can be found in Santini et al.[83]

Evidence from this systematic literature search bolsters the specific aspects in need of special consideration by MDS investigators when reporting study results. Although we note that all CONSORT-PRO items[57,131] should be carefully addressed when disseminating PRO results from future MDS RCTs, in Figure 4 we highlight those deserving more attention as they concern aspects often overlooked in the current MDS literature (being addressed in less than half of published studies) but key to making a critical appraisal of PRO results. While speculating on PRO results from the RCTs identified in our review lies beyond the scope of our work, it is important to consider that high-quality PRO components in the initial trial protocols could help collect robust PRO data and improve the completeness of PRO reporting in publications.[55]

CONCLUSIONS

The inclusion of PROs in MDS clinical trials has the potential to generate critical information that is needed to understand the overall value of a new therapy. These measures must be chosen, incorporated, collected, and analyzed with rigor, paying attention to a number of methodological aspects throughout the course of the study (i.e., from the initial protocol writing to publication of results). There are precedents for other malignancies in hematology where PROs have advanced standards of care for many patients, and we hope similar advances can be made in the MDS arena. The time is ripe for international initiatives that can facilitate

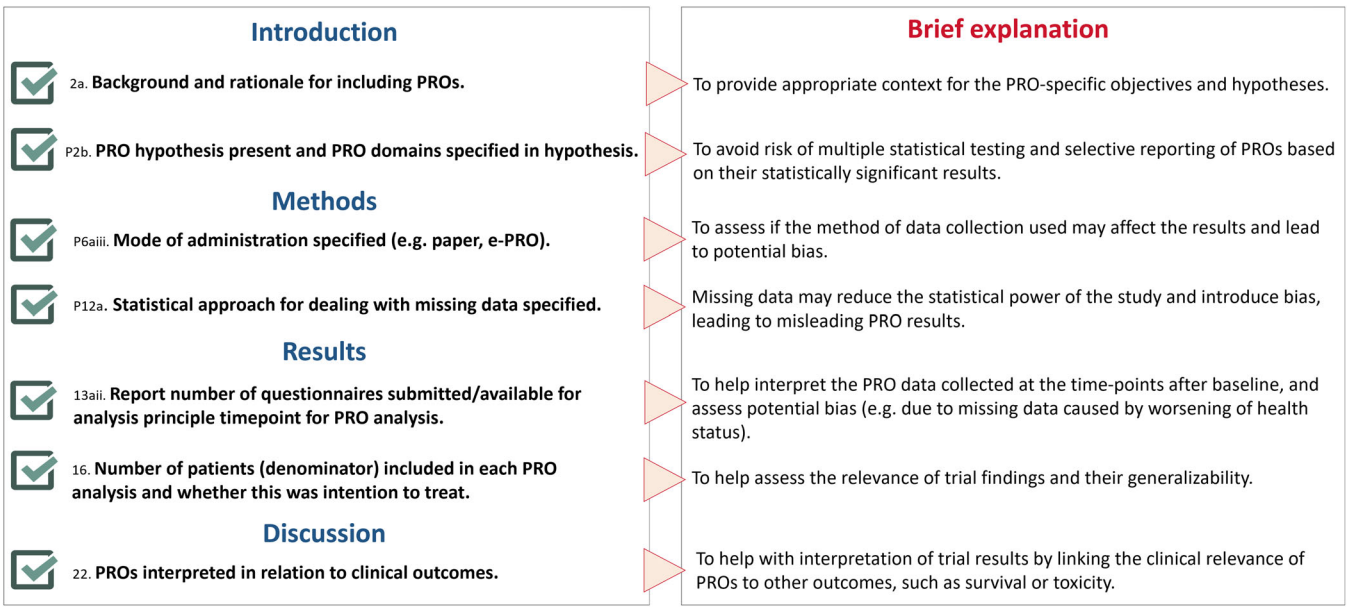

FIGURE 4 Selected Consolidated Standards of Reporting Trials-patient-reported outcome (CONSORT-PRO) items requiring more attention in future myelodysplastic syndrome randomized controlled trial (RCT) reports. To provide high-quality evidence from RCTs with a PRO endpoint, all CONSORT-PRO items[57,129] should be documented when reporting study results. However, special attention should be paid in future RCTs to the above-reported items as these have been less frequently addressed in the literature.

TABLE 5 Next steps to maximize the value of PROs in MDS clinical trials.

- Develop international consensus-based guidelines involving key stakeholders using e.g., a Delphi process, about PRO elements which are to be harmonized in future MDS trials.
- Include PROs in all phase III RCTs of patients with MDS (at least as secondary or exploratory endpoints), and possibly also consider the inclusion of PROs in early-stage trials to assess treatment tolerability.
- Make major efforts to publish PRO results of a trial in a timely manner and with full methodological details to allow a critical appraisal of the robustness of PRO findings.
- Consider available international recommendations, for example, on the use of PROs in trials when designing protocols (the SPIRIT-PRO Extension), analyzing data (SISAQOL-IMI), and reporting results (the CONSORT-PRO Extension).
- Promote educational initiatives around the importance of PROs in the MDS drug development process.

Abbreviations: CONSORT, consolidated standards of reporting trials; MDS, myelodysplastic syndromes; PRO, patient-reported outcome; RCT, randomized controlled trial; SISAQOL-IMI, setting international standards in analyzing patient-reported outcomes and quality of life endpoints in cancer clinical trials-innovative medicines initiative; SPIRIT, standard protocol items: recommendations for interventional trials.

a shift toward a more patient-centered MDS drug development process (Table 5), and this initial step by the icMDS will hopefully facilitate this sorely needed transition.

AUTHOR CONTRIBUTIONS

Conception and design: All authors. *Collection and assembly of data*: Fabio Efficace, Johannes M. Giesinger, and Francesco Sparano. *Data analysis and interpretation*: All authors. *Manuscript writing*: All authors. Final approval of manuscript: All authors. *Accountable for all aspects of the work*: All authors.

CONFLICT OF INTEREST STATEMENT

Fabio Efficace had consultancy or advisory role for AbbVie, Incyte, Syros, Novartis, and JAZZ Pharmaceuticals outside the submitted work. Rena Buckstein: Research funding and honoraria for advisory boards and speaking engagements from BMS, TAIHO, and Abbvie. Gregory A. Abel has consulted for Novartis and Geron outside the submitted work. Pierre Fenaux received research funding from BMS, Abbvie, Jazz Pharmaceuticals, Novartis, and Janssen; and had a consultancy with and received honoraria from BMS, Abbvie, Jazz Pharmaceuticals, and Novartis. Andrew M. Brunner received consulting or advisory board honoraria from Novartis, Acceleron, Agios, Abbvie, Takeda, Celgene/BMS, Keros Therapeutics, Taiho, Gilead; and has research support from the NIH SPORE in Myeloid Malignancies, and from the Edward P. Evans Foundation. Rafael Bejar owns equity in and is employed by Aptose Biosciences; he has served as an advisor to BMS, Servier, Gilead, and Ipsen; he is on the SAB for NeoGenomics. Amy E DeZern participated in advisory boards, and/or had a consultancy with and received honoraria from Celgene/BMS, Agios, Regenergon, Sobi, Novartis, Astellas, and Gilead. Amy E. DeZern served on clinical trial committees for Novartis, Abbvie, Kura, Geron, and Celgene/BMS. Gail J. Roboz: Consultancy: Abbvie, Amgen, Astra Zeneca, Bristol-Myers Squibb, Caribou Biosciences, Celgene, Daiichi Sankyo, Ellipses Pharma, Genoptix, Geron, GlaxoSmithKline, Janssen, Jasper Pharmaceuticals, Jazz Pharmaceuticals, Molecular Partners, Novartis, Pfizer, Oncoverity, OncoPrecision, Rigel, Roche, Syndax, Takeda (IRC Chair), Telix Pharma; and research support: Janssen. Michael R. Savona: Membership on a board or advisory committee: Bristol Myers Squibb, CTI, Forma, Geron, GSK, Karyopharm, Rigel Ryvu, Taiho, Takeda, Treadwell; patents and royalties: Boehringer Ingelheim, Empath Biosciences; research funding: ALX Oncology, Astex, Incyte, Takeda, TG Therapeutics; equity ownership: Empath Biosciences, Karyopharm, Ryvu; consultancy: Forma, Geron, Karyopharm, Ryvu. Rami Komrokji: Abbvie: Speaker Bureau, Advisory board; BMS: Research grant, Advisory board; DSI: Advisory board; Geron: Consultancy; Janssen: Consultancy; Jazz: Speaker Bureau, Advisory board; Pharma Essentia: Speaker Bureau, Advisory board; Rigel: Speaker Bureau, Advisory board; Servio: Speaker Bureau, Advisory board; Sobi: Speaker Bureau, Advisory board; Sumitomo Pharma: consultancy, Advisory board. David A. Sallman served on the advisory board or panel for Agios, Avencell, BlueBird Bio, BMS, Dark Blue, Jasper Therapeutics, Kite, Magenta Therapeutics, NKARTA, Novartis, Rigel Shattuck Labs, Servier, Syndax, Syros; and had a consultancy with AbbBie, Gilead, Molecular Partners AG, Takeda. Guillermo Sanz received honoraria, advisory board membership, or consultation fees from AbbVie, BMS, ExCellThera, Novartis, Roche, and Takeda and participated in sponsored speaker's bureau for BMS, Novartis, and Takeda. Hetty E. Carraway: Consultancy: Abbvie, Amgen, Bristol-Myers Squibb, Celgene, Daiichi Sankyo, Jazz Pharmaceuticals, Novartis, Rigel, Syndax, Servier; and research support: Celgene. Maximilian Stahl consulted for Curis Oncology and Boston Consulting; served on the advisory board for Novartis and Kymera, GSK, Rigel, and Sierra Oncology; and participated in GME activity for Novartis, Curis Oncology, Haymarket Media, and Clinical care options (CCO). Mikkael A. Sekeres has served on advisory boards for BMS, Novartis, Kurome, and Gilead. Amer M. Zeidan received research funding (institutional) from Celgene/BMS, Abbvie, Astex, Pfizer, Medimmune/Astra Zeneca, Boehringer-Ingelheim, Cardiff oncology, Incyte, Takeda, Novartis, Aprea, and ADC Therapeutics. He participated in advisory boards, and/or had a consultancy with and received honoraria from AbbVie, Otsuka, Pfizer, Celgene/BMS, Jazz, Incyte, Agios, Boehringer-Ingelheim, Novartis, Acceleron, Astellas, Daiichi Sankyo, Cardinal Health, Taiho, Seattle Genetics, BeyondSpring, Cardiff Oncology, Takeda, Ionis, Amgen, Janssen, Epizyme, Syndax, Gilead, Kura, Chiesi, ALX Oncology, BioCryst, Notable, Orum, and Tyme. He served on clinical trial committees for Novartis, Abbvie, Gilead, BioCryst, Abbvie, ALX Oncology, Geron, and Celgene/BMS. Fabio Efficace, Rena Buckstein, and Gregory A. Abel report being involved in the development and validation of the QUALMS, one of the PROs discussed in this paper. The QUALMS is copyrighted by Dana-Farber Cancer Institute (DFCI) and the Children's Hospital of Eastern Ontario (CHEO). The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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