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How are patient-reported outcomes and symptoms being measured in adults with relapsed/refractory multiple myeloma? A systematic review

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Abstract

Purpose—Patients with relapsed and/or refractory multiple myeloma (RRMM) are living longer due in part to changing treatment patterns. It is important to understand how changing treatment patterns affect patients' lives beyond extending survival. Research suggests that direct patient report is the best way to capture information on how patients feel and function in response to their disease and its treatment. Therefore, the purpose of this review is to summarize evidence of patients' experience collected through patient-reported outcomes (PRO) in RRMM patients, and to explore PRO reporting quality.

Methods—We conducted a systematic search to identify manuscripts reporting PROs in RRMM and summarized available evidence. We assessed PRO reporting quality using the Consolidated Standards of Reporting Trials (CONSORT) PRO Extension checklist.

Results—Our search resulted in 30 manuscripts. Thirteen unique PRO measures were used to assess 18 distinct PRO domains. Pain, fatigue, and emotional function were commonly assessed domains though reporting formats limited our ability to understand prevalence and severity of PRO challenges in RRMM. Evaluation of PRO reporting quality revealed significant reporting deficiencies. Several reporting criteria were included in less than 25% of manuscripts.

Conclusions—Existing evidence provides a limited window for understanding the patient experience of RRMM and is further limited by suboptimal reporting quality. Observational studies are needed to describe prevalence, severity and patterns of PROs in RRMM overtime. Future studies that incorporate PROs would benefit from following existing guidelines to ensure that study evidence and conclusions can be fully assessed by readers, clinicians and policy makers.

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Conflict of interest Matthew R. LeBlanc, Rachel Hirschey, and Sophia K. Smith declare that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Keywords

Patient-reported outcomes; Relapsed/refractory multiple myeloma; Multiple myeloma; CONSORT PRO; Quality of life; Systematic review

Background

In 2019 there will be an estimated 32,110 new multiple myeloma (i.e., myeloma) cases, 12,960 myeloma deaths, and 131,392 people living with myeloma in the United States [1, 2]. Median age at diagnosis is 69 and more than 75% of new diagnoses happen between the ages of 55 and 84 [2]. New cases have increased 54% over the past decade and are forecasted to continue increasing due to an aging population [3–6]. Incidence is slightly higher in men than women, and two times higher in African Americans compared to other racial/ethnic groups [2].

While still incurable, this once acutely terminal illness has become chronic for many [5, 7, 8]. Overall median survival for myeloma was about 2 years before the year 2000 [9]. Today, overall median survival is more than 5 years, and is greater than 10 years for younger patients or those with less aggressive disease [7, 10, 11]. Improvements in survival have been made possible by the rapid introduction of new therapies beginning in 2003, and resulting changes in treatment patterns [9, 12].

It is important to understand how changing treatment patterns may affect patient's lives beyond extending survival. Research suggests that symptom burden and health-related quality of life (HRQoL) for those with myeloma are quite poor [13–16]. Effects of myeloma and its treatment may impact HRQoL domains such as physical and emotional well-being, social functioning, and financial burden. These issues are particularly important in relapsed and/or refractory multiple myeloma (RRMM).[1] RRMM represents a new stage of disease and treatment for patients, in which they move from treatment to treatment in hopes of maintaining control of their disease, until all treatments ultimately fail. The exposure to many lines of therapy that RRMM patients face increases risk of cumulative toxicities and burdensome side effects [18–20]. In light of the detrimental effects of RRMM and its treatment it is important to better understand the RRMM patient's experience so interventions can be designed to reduce suffering. Previous reviews have explored the experiences of all myeloma patients and we feel the unique circumstances of patients with RRMM deserve to be explored separately [15, 21].

Research suggests that direct patient report is the best way to capture information on how patients feel and function in response to disease and treatment [22–24]. Historically these data were assessed and reported by clinicians. We now know that collecting this information through direct patient report improves detection, is more sensitive to change and more highly correlated to overall health status than clinicians' assessments [22, 25, 26]. Additionally, these patient-reported outcomes (PROs) capture important data that lie outside

[1]Multiple myeloma relapse is defined as progressive disease following a response to treatment, and refractory disease is defined as failure to respond to treatment, or progressive disease while on treatment or within 60 days of treatment [17].

of the traditional clinical outcomes of efficacy and safety and can help us to more completely understand how a myeloma diagnosis affects a patient's life [27, 28].

PROs have become increasingly important in evaluating new therapies, and are also being used to inform clinical and health policy decision making [28–31]. To be useful, PRO evidence must be clearly and comprehensively reported [32]. In response, the CONSORT PRO Group proposed guidelines to improve reporting of PROs in randomized clinical trials [32]. The purpose of this review is to summarize what is known about PROs in people living with RRMM, and to evaluate PRO reporting quality using the CONSORT PRO Extension guidelines.

Methods

This review was conducted following PRISMA guidelines. Review protocol was registered with PROSPERO (https://www.crd.york.ac.uk/prospero/); Registration ID: CRD42019114886.

Search strategy

We conducted a systematic search of the following databases: PubMed, Comprehensive Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, SCOPUS and EMBASE in November 2018. Search terms, outlined in Table 1, were grouped into three major domains; (1) Multiple myeloma, (2) Relapsed/refractory, and (3) Symptoms and quality of life, and searched as both keywords and subject headings, where applicable. In addition, reference lists from eligible articles and previous systematic reviews were searched to identify additional relevant manuscripts. Our full search strategy can be found in the online supplemental material Table S1.

Study selection

Clinical trials, and observational studies assessing patient outcomes through direct report were eligible for inclusion. Criteria for inclusion were: (1) Study population was either exclusively adults (≥ 18 years old) with RRMM or separate results were reported for adults with RRMM; (2) Results included HRQoL domains, functional status, or symptoms assessed through direct patient report; (3) Written or published in English; and, (4) Published in or after 2003, when the proteasome inhibitor bortezomib was FDA approved for use in myeloma marking the beginning of significant changes in myeloma treatment and outcomes [33, 34]. Qualitative studies, editorials, commentaries, letters, reviews, published abstracts, conference proceedings, and unpublished studies were excluded.

Identified articles were downloaded into reference management software (EndNote X8.2, Clarivate Analytics, Philadelphia PA) to identify and remove duplicates and uploaded into a systematic review management platform (Covidence, Melbourne Australia) for screening and full text review by two independent reviewers, MRL and RH. Discrepancies were resolved through discussion. If consensus could not be reached, a third reviewer, ALB, made the final decision.

Data extraction

Data were extracted by author MRL into a standardized matrix developed and refined by MRL, RH, and ALB, and then applied across all included studies using an electronic spreadsheet (Excel 16.22, Microsoft, Seattle WA) [35]. The matrix captured information on study and sample characteristics, PRO measurement strategies, and study instruments and results. Online supplemental material, primary study reports and clinicaltrials.gov records were referenced when available for additional study information.

Assessing PRO reporting quality

Clear and comprehensive reporting of study results help ensure that results can be understood, assessed and useful to guide care and policy. To this end, the Consolidated Standards of Reporting Trials (CONSORT) statement was developed to improve the quality of randomized clinical trial reporting [36]. In February 2013 an extension was published providing guidance for reporting PROs in randomized clinical trials in which PROs were primary or secondary endpoints [32]. Regardless of study design, all study reports benefit from clear and comprehensive reporting in ways that allow readers to fully assess the evidence presented. In the absence of guidelines specific to non-RCT study designs (e.g., single arm clinical trials, observational studies) we applied the CONSORT PRO guidelines across study designs. We believe the CONSORT PRO Extension criteria provide a useful way to assess PRO reporting in a variety of study designs, though it exceeds its intended purpose.

We developed a standardized rubric based on the CONSORT PRO guidelines to evaluate PRO reporting quality (online supplementary material Table S2). The rubric contains 15 criteria each scored ‘1’ if met and ‘0’ if not met. Possible scores ranged from 0 to 15. Two CONSORT PRO criteria require assessment across multiple timepoints and are less applicable to cross-sectional studies; ‘Assessment timepoints specified’ and ‘Number of PRO participants at each timepoint reported’. Several scoring strategies were considered for cross-sectional studies, including omitting these two criteria when scoring or scoring them ½ point each if met for a study’s one timepoint. Either of these strategies would lower the potential scores cross-sectional studies could achieve. We decided instead to award a full point for these criteria if met for a cross-sectional study’s one timepoint, in order to avoid reducing potential scores by default. Two of our authors, MRL and RH used this rubric to independently score PRO reporting quality. Scoring discrepancies were resolved through discussion.

Please note PRO CONSORT extension guidelines are meant to evaluate reporting quality of PRO results and not the psychometric soundness of the PRO measures (PROMs) used. Also note suboptimal reporting quality does not indicate that reported results are invalid or that studies were not conducted rigorously. Suboptimal reporting quality does however make it difficult for readers to assess a study’s evidence and conclusions.

Results

Our literature search identified 5426 manuscripts, of which 2655 duplicates were removed; 2771 manuscripts were screened for eligibility. Screening and full text review resulted in 30 manuscripts representing 23 separate studies. Results of the search strategy and screening process are documented in Fig. 1 according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [37].

In some cases, two or more manuscripts reporting PRO results, originated from a single clinical trial, often a primary report focused on efficacy and safety results and a secondary report focused on patient-reported outcomes. For example, 25 manuscripts included in this review were the result of 18 clinical trials. Fifteen manuscripts report primary efficacy/safety results from clinical trials and ten manuscripts represent secondary reports focused on PRO results. Additionally, five manuscripts reported results of observational studies. Eight studies were conducted in Europe, nine internationally, five in the United States of America, and one in the Middle East. Sixteen (53.3%) manuscripts were published after the CONSORT PRO guidelines were published in February, 2013 [32]. Selected study characteristics are presented in Table 2.

Study participant characteristics

A total of 5635 RRMM patients were included in the studies reported here. Sample size ranged from 3 to 792 with an overall mean sample size of 235. Mean sample size for clinical trials was 270 and for observational studies 101. Median age was 63.5 years, and ages ranged from 27 to 93. Overall, samples contained more males (57.0%) mirroring the higher incidence of myeloma among men in the United States (56.0%) and globally (54.4%) [38, 39]. Of the twelve studies that reported race/ethnicity data, the combined sample was 82.2% white, 6.1% black, and 10.0% other.

Summarizing patient-reported outcomes in RRMM

Nine individual symptoms and nine PRO domains were reported across studies using 13 unique PROMs (Table 3). *Individual symptoms* refer to specific physical or emotional effects of RRMM or its treatment. *PRO domains* refers to more integrated concepts, which include collections of symptoms measured and reported together (i.e., symptom indexes), or concepts that involve symptoms, effects on function, and/or changes in behaviors together (e.g., physical well-being). Many PROs were assessed with a variety of PROMs. For example, the outcome ‘Global Health Status/QoL’ was assessed using three unique PROMs.

Individual symptoms—Pain was the most commonly assessed symptom, followed by fatigue, dyspnea, nausea/vomiting, and constipation (Table 3). PRO results for symptoms were most often reported as change from baseline scores (e.g., improved, maintained, or worsened from baseline), as group differences in change, or as between group differences, without reporting baseline prevalence or severity (Table 2). Six studies reported baseline PROM scores though with limited information on how to interpret scores. Four studies reported individual symptom results grouped by treatment response [40–44]. In each case, better treatment response was associated with better symptom outcomes.

Pro domains—‘Emotional Function’ was the most commonly assessed PRO domain, followed by ‘Global Health status/QoL’, ‘Physical Function’, and ‘Social Function’. Results for PRO domains were also most often reported as change from baseline, group differences in change or between group differences. Five studies compared PRO domains between patients grouped by disease response. As with individual symptoms, patients who experienced a complete or partial response had better outcomes than those with minimal responses or disease progression [40–42, 45–47].

Characteristics of PRO reporting in RRMM

Our analysis of PRO reporting quality occurred at the manuscript level using a grading rubric based on the CONSORT PRO Extension checklist. Scores indicate the number of CONSORT PRO Extension criteria met. Possible scores ranged from 0 to 15. Higher scores indicate more met criteria and higher reporting quality. Individual PRO reporting quality scores across 25 clinical trial and five observational study manuscripts along with selected study characteristics are presented in Table 2.

Table 4 presents reporting quality scores evaluated across several study design characteristics. Overall mean reporting quality score was 8.0 out of a possible 15, indicating that on average, manuscripts did not meet 7 CONSORT PRO criteria. Scores ranged from 2 to 15. Reporting quality scores were higher in observational studies (9.4, $n = 5$) than in clinical trials (7.7, $n = 25$). Within clinical trials, the highest scores were achieved by manuscripts for which a PRO was identified as a primary endpoint (10.5, $n = 10$) and for manuscripts that were secondary reports of study results focused on PROs (10.2, $n = 10$). The mean scores for cross-sectional studies was 11.0 ($n = 2$) and for longitudinal studies (clinical trials, or longitudinal observational studies) was 7.8 ($n = 28$). Mean scores for manuscripts published before the introduction of the CONSORT PRO guidelines were 7.9 ($n = 14$) and for manuscripts published after, 8.1 ($n = 16$).

The most commonly adhered to items from the CONSORT PRO criteria checklist included ‘PRO data is interpreted in relation to clinical outcomes’ (93%) ‘Assessment timepoints specified’ (90%), ‘PRO identified in abstract as primary or secondary outcome’ (73%) and ‘PRO results for each domain presented’ (73%), (see Table 5). The least commonly adhered to items from the checklist included ‘PRO hypothesis stated’ (10%), ‘Method of questionnaire administration specified’ (17%), ‘Statistical approaches for missing data specified’ (23%) and ‘PRO specific limitations and implications for generalizability and clinical practice’

Discussion

Our systematic review aimed to summarize evidence of patients’ experience collected through patient-reported outcomes (PRO) in RRMM patients and assess PRO reporting quality. We identified thirteen unique PROMs used to assess 18 PROs. We found it difficult to summarize patient experience given the contours of the available evidence and the format in which it is reported. Additionally, we identified suboptimal PRO reporting quality across studies as measured by the CONSORT PRO Extension checklist.

PRO results were often reported in a format that precluded readers from understanding the severity of symptoms or PRO domain problems. The majority of manuscripts report change in PRO scores without reporting baseline values and/or prevalence data. This reflects the current mix of study designs in RRMM PRO research, which is predominated by clinical trials. The practice of reporting change scores, or group differences aligns well with the purposes of clinical trials, however it limits our ability to summarize evidence or make conclusions about the burden (prevalence, severity) of symptoms and HRQoL issues in RRMM patients. Key questions about the prevalence, severity and patterns of symptoms and other patient challenges remain unanswered. Clinical trial designs have other limitations that must be considered, for example highly selected trial populations may not reflect the general population of patients [48]. A diverse mixture of study designs is needed to comprehensively capture the experiences of patients with RRMM. Observational cohort studies that focus on describing PROs (prevalence, severity, patterns over time) across the trajectory of myeloma treatment could further inform the relationship between treatment patterns and patient outcomes such as symptom burden and HRQoL issues. There is also an opportunity assess PROs not explored in studies reported here such as patient clinician communication, self-efficacy in managing chronic illness, and fear of recurrence. Additionally, non-cancer specific PROs deserve attention, especially given patients with myeloma are likely older and experiencing multiple comorbid conditions affecting their quality of life [49]. Further, in light of the limited racial/ethnic diversity in existing studies, future work should prioritize recruiting racially representative samples and begin to explore relationships between race/ethnicity and PROs.

Our review concluded that overall PRO reporting quality in RRMM studies is suboptimal, with wide variability. As may be expected, manuscripts that included PRO as the primary outcome tended to score higher, although even in this group serious deficiencies remained. Some of the common reporting deficits undermine the reader's ability to fully assess the evidence and conclusions drawn from PRO data. For example, many manuscripts failed to report the amount of missing data in their analyses, or a statistical analysis plan to account for the potential bias missing data introduces. In addition to evaluating PRO reporting quality we identified frequently missed reporting criteria which provides a roadmap for improving the quality of PRO reporting in future RRMM research.

These findings are similar to what was found in reviews of PRO evidence across a variety of cancer diagnoses. Reviews in head and neck, ovarian, colorectal and prostate cancer similarly found suboptimal reporting quality [50–53]. In an overview of PRO reporting quality in randomized clinical trials evaluating systemic cancer therapy Bylicki et al. found 'PRO hypothesis stated' (26%), 'Method of questionnaire administration specified' (38%), 'Statistical approaches for missing data specified' (37%) and 'PRO specific limitations and implications for generalizability and clinical practice' (35%) were the least adhered to CONSORT PRO Extension criteria, matching our findings closely [54].

These common reporting deficiencies may be due to a lack of awareness of recommended guidelines, or a perceived lack of importance of PROs in relation to other outcomes like survival. Authors may also struggle to thoroughly report on all outcomes within the limited space available in journals. Somewhat paradoxically the existence of guidelines such as

CONSORT PRO, may contribute to the perception that PRO measurement lacks rigor as it highlights reporting deficiencies that are sometimes unavoidable due to space limitations. Higher scores for secondary PRO focused manuscripts would support the theory that with dedicated space PRO reporting quality improves. It is important to note however, that even amongst these PRO focused secondary manuscripts, on average 1/3 of the CONSORT PRO criteria were not met. Score comparisons for manuscripts published before and after the introduction of the CONSORT PRO guidelines revealed no appreciable difference (7.9 and 8.1 respectively), suggesting that the CONSORT PRO guidelines have not had much impact on PRO reporting quality in the RRMM literature. Together this suggests that RRMM researchers have room for improvement in the reporting of PROs and that increased adherence to reporting guidelines like the CONSORT PRO will be important to improve the quality of PRO reporting and increase the usefulness of evidence generated in guiding clinical practice and policy decisions.

This systematic review has some important limitations. The CONSORT PRO guidelines were introduced in 2013 and designed to evaluate the reporting of PROs that were primary or secondary endpoints in randomized controlled trials. We developed a rubric, that was applied to manuscripts written before 2013 and applied it to study designs beyond the intended scope. Our scoring rubric had limitations and there are some important caveats to consider. Each item was given equal weight in the total score, though some items may be more important than others. Scoring posed a particular problem for cross-sectional studies (n = 2) as some criteria assumed multiple timepoints. Several possible scoring modifications were considered to address this. We decided to award a full point to cross-sectional studies if these criteria were met for their one timepoint, though it could be argued that meeting reporting criteria for one time point is easier than for multiple time points. Despite these scoring complications we believe The CONSORT PRO guidelines and our scoring rubric are useful tools for broadly understanding the quality of PRO reporting in the RRMM literature, particularly by highlighting aspects of PRO reporting that are frequently missing.

Conclusions

Our systematic review summarized available PRO evidence in RRMM and evaluated PRO reporting quality using the CONSORT PRO guidelines. We found the available PRO evidence base was predominately from clinical trials and that the format results were reported in made it difficult to describe prevalence, severity or patterns of symptoms and HRQOL issues. Observational studies are needed to describe the RRMM patient experience and should include a variety PROs including those not usually assessed in clinical trials. We also found that PRO reporting quality was suboptimal and future studies which incorporate PROs would benefit from following existing guidelines to ensure that study evidence and conclusions can be fully assessed by readers, clinicians and policy makers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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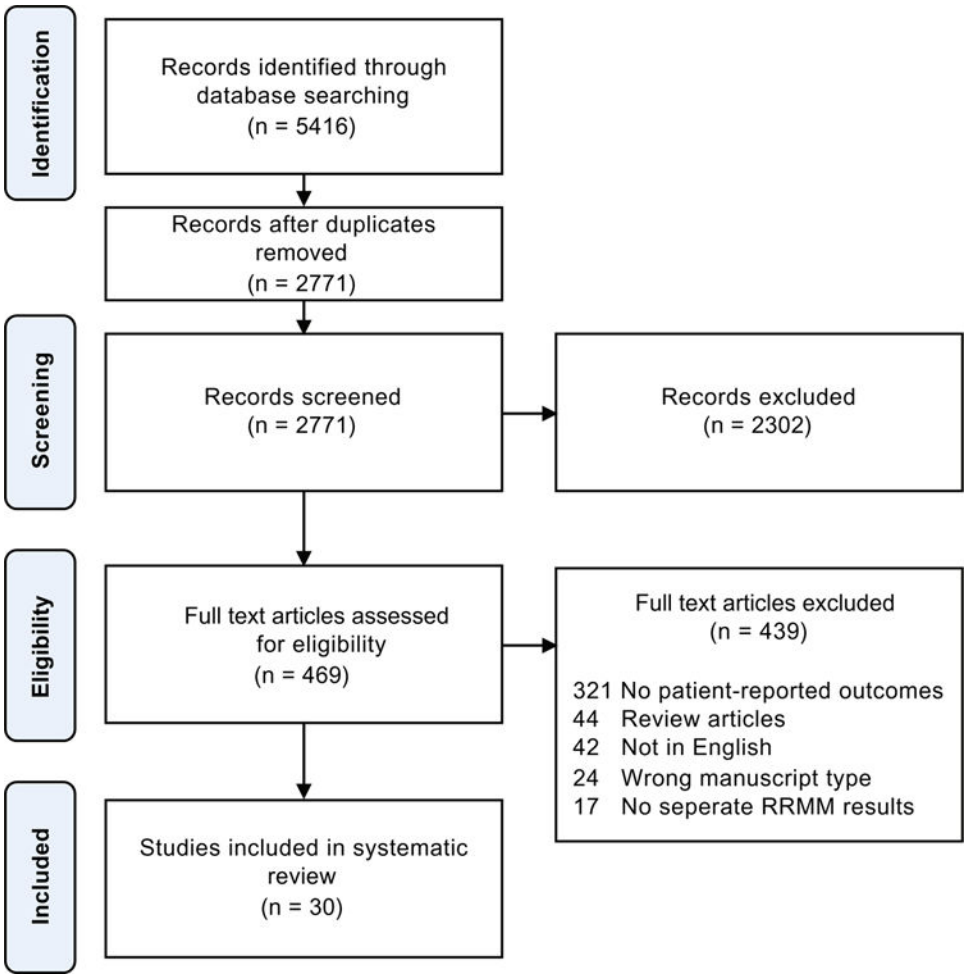

Fig. 1.
PRISMA diagram

Table 1

Search strategy

Concepts	Search terms
Multiple myeloma	Multiple myeloma, myeloma, myelomas, myelomatosis, myelomatoses, Kahler's disease
AND	
Relapsed/ refractory	Recurrence, neoplasm recurrence local, retreatment, relapse, relapses, relapsed, refractory, RRMM, recurrence, recurrences
AND	
Symptoms and quality of life	Quality of life, life quality, well being, well-being, health related quality of life, health-related quality of life, health status, function, functional, surveys and questionnaires, survey, questionnaire, measure, signs and symptoms, symptoms, nausea, nauseous, vomiting, constipation, diarrhea, diarrhea, shortness of breath, dyspnea, peripheral neuropathy, peripheral neuropathies, cognition, memory, pain, insomnia, sleep disturbance, fatigue, anxiety, anxieties, anxious, nervousness, depression, depressions, depressive, depressed, distress, burden, stress psychological, stress, stresses, suffering

Table 2

Selected study characteristics

Clinical trials					PRO reporting quality[a]
Citation sample size	**Study design**	**PRO endpoint**	**PRO measures**	**Reporting format**	
Richardson et al. 2003 [40] *n* = 202	Phase 2 open label single arm clinical trial	Secondary	EORTC QLQ-C30[b] EORTC QLQ-MY24[c]	Change over time	2
Dubois et al. 2006 [41] *n* = 202		Primary	FACT/GOG-NTX[d] FACIT Fatigue[e]		8
Jagannath et al. 2004 [55] *n* = 54	Phase 2 open label randomized clinical trial	Secondary	FACT/GOG-NTX	Change over time	6
Richardson et al. 2006 [56] *n* = 256		Primary			10
Waage et al. 2004 [57] *n* = 65	Phase 2 open label single arm clinical trial	Primary	EORTC QLQ-C30	Mean PROM scores	9
Lee et al. 2008 [58] *n* = 598	Phase 3 open label randomized clinical trial	Primary	EORTC QLQ-C30 FACT/GOG-NTX	Between group differences in change over time	12
Richardson 2009 [59] *n* = 296		Primary			10
Vij et al. 2009 [60] *n* = 96	Phase 2 open label single arm clinical trial	Exploratory	BPI-SF[f] FACT-G[g] EuroQol 5D[h]	Change over time	6
Alegre et al. 2012 [42] *n* = 63	Open label single arm clinical trial	Secondary	EORTC QLQ-C30 EORTC QLQ-MY20[i]	Change over time	8
Hjorth et al. 2012 [61] *n* = 131	Phase 3 open label randomized clinical trial	Secondary	EORTC QLQ-C30	Change over time, group differences	10
Safaee et al. 2012 [62] *n* = 30	Historical control trial	Secondary	VAS Pain[j]	Mean PROM scores	9
Vij et al. 2012 [63] *n* = 35	Phase 2 open label single arm clinical trial	Secondary	FACT/GOG-NTX	Change over time	8
Vij et al. 2012 [64] *n* = 129					3
Richardson et al. 2013 [65] *n* = 55	Phase 2 open label single arm clinical trial	Secondary	FACT/GOG-NTX subscale	Change over time	4
Callander et al. 2015 [66]	Unspecified two arm clinical trial	Primary	FACT/GOG-NTX FACIT Fatigue	Mean PROM Scores, Change over time	40

Clinical trials					PRO reporting quality[a]
Citation sample size	**Study design**	**PRO endpoint**	**PRO measures**	**Reporting format**	
n = 32					
Lonial et al. 2015 [67] *n* = 646	Phase 3 open label randomized controlled trial	Exploratory	BPI-SF EORTC QLQ-C30 EORTC QLQ-MY20	Between group differences in change over time	3
Cella et al. 2018 [44] *n* = 646		Primary			9
Stewart et al. 2015 [68] *n* = 792	Phase 3 open label randomized controlled trial	Secondary	EORTC QLQ-C30 EORTC-MY20	Group differences	6
Stewart et al. 2016 [45] *n* = 792		Primary			15
Weisel et al. 2015 [69] *n* = 433	Phase 3 open label randomized controlled trial	Primary	EORTC QLQ-C30 EORTC-MY20	Between group differences in change over time	12
Moreau et al. 2016 [70] *n* = 722	Phase 3 double blind randomized placebo-controlled trial	Secondary	EORTC QLQ-C30 EORTC-MY20	Between group differences in change over time	3
Leleu et al. 2018 [47] *n* = 722		Secondary			13
Baljevic et al. 2017 [43] *n* = 16	Phase 2 open label single arm clinical trial	Exploratory	EORTC QLQ-C30 EORTC-MY20 MDASI-MM[k]	Change overtime	3
Richardson et al. 2017 [46] *n* = 768	Phase 3 double blind randomized placebo-controlled trial	Secondary	EORTC QLQ-C30 GHS/QOL subscale[l]	Change overtime	3
Robinson et al. 2017 [71] *n* = 263	Phase 2 double blind randomized placebo-controlled clinical trial	Primary	Economic Questionnaire EORTC QLQ-C30 FACIT Fatigue	Mean PROM scores	10
Observational studies					PRO reporting quality
Citation sample size	**Study design**		**Measures**	**Results reporting format**	
Basile et al. 2010 [72] *n* = 3	Retrospective review	Longitudinal	VAS Pain	Mean PROM scores	9
Briani et al. 2013 [73] *n* = 30	Prospective longitudinal cohort	Longitudinal	NRS Pain[m]	Change overtime	5
Ramsenthaler et al. 2016 [16] *n* = 182	multi-site cross-sectional cohort	Cross-sectional	EORTC QLQ-C30 EORTC QLQ-MY20 EuroQol 5D MyPOS[n]	Mean PROM scores	15
Samuelson et al. 2016 [74] *n* = 32	cross-sectional cohort	Cross-sectional	EORTC QLQ-C30	Correlations with BNP	7

Clinical trials					PRO reporting quality[a]
Citation sample size	**Study design**	**PRO endpoint**	**PRO measures**	**Reporting format**	
Leleu et al. 2017 [75] *n* = 258	Prospective longitudinal cohort	Longitudinal	EORTC QLQ-C30 EORTC QLQ-MY20 EORTC QLQ-CIPN20[o]	Mean PROM score, change overtime	11

[a] *PRO Reporting Quality* Possible scores range from 0 to 15. Higher scores indicate higher quality.

[b] *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

[c] *EORTC QLQ-MY24* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Myeloma 24.

[d] *FACIT Fatigue* Functional Assessment of Chronic Illness Therapy Fatigue.

[e] *FACT/GOG-NTX* Functional Assessment of Cancer Therapy Gynecologic Oncology Group Neurotoxicity.

[f] *BPI-SF* Brief pain inventory short form.

[g] *FACT-G* Functional Assessment of Cancer Therapy General.

[h] *EuroQOL 5d* European Quality of Life Five Dimension.

[i] *EORTC QLQ-MY20* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Myeloma 20.

[j] *VAS Pain* Visual Analog Scale Pain.

[k] *MDASI-MM* MD Anderson Symptom Index Multiple Myeloma.

[l] *EORTC QLQ-C30 GHS/QOL* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Global Health Status/Quality of Life subscale.

[m] *NRS Pain* Numeric Rating Scale Pain.

[n] *MyPOS* Myeloma Palliative care Outcome Scale.

[o] *EORTC QLQ-CIPN20* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy Induced Peripheral Neuropathy 20

Table 3

Patient-reported outcomes (PROs)

	PROs assessed	PROs reported	PRO measures
PRO Domains			
Emotional function	26	11	EORTC QLQ-C30[a] EORTC QLQ-MY20[b] FACT-G[c] MyPOS[d]
Global health satus/QoL	19	16	EORTC QLQ-C30 FACT-G EuroQol 5D[e]
Physical function	16	14	EORTC QLQ-C30 FACT-G
Social function	16	10	EORTC QLQ-C30 FACT-G
Financial burden	16	6	EORTC QLQ-C30 Financial burden
Role function	15	8	EORTC QLQ-C30
Cognitive function	15	8	EORTC QLQ-C30
Symptom index	12	8	EORTC QLQ-MY20 FACT-G MyPOS MDASI-MM[f]
Healthcare factors	2	2	Financial burden MyPOS
Individual symptoms			
Pain	20	15	BPI-SF[g] EORTC QLQ-C30 NRS pain[h] VAS pain[i]
Fatigue	18	11	EORTC QLQ-C30 FACIT fatigue[j]
Dyspnea	15	8	EORTC QLQ-C30
Constipation	15	7	EORTC QLQ-C30
Nausea/vomiting	15	7	EORTC QLQ-C30

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	PROs assessed	PROs reported	PRO measures
Diarrhea	15	6	EORTC QLQ-C30
Appetite loss	15	6	EORTC QLQ-C30
Sleep disturbance	15	6	EORTC QLQ-C30
Peripheral neuropathy	8	8	EORTC QLQ-CIPN20[k] FACT/GOG-NTX[l]

[a] *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

[b] *EORTC QLQ-MY20* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Myeloma 20.

[c] *FACT-G* Functional Assessment of Cancer Therapy General.

[d] *MyPOS* Myeloma Palliative care Outcome Scale.

[e] *EuroQOL 5d* European Quality of Life Five Dimension.

[f] *MDASI-MM* MD Anderson Symptom Index Multiple Myeloma.

[g] *BPI-SF* Brief pain inventory short form.

[h] *NRS Pain* Numeric Rating Scale Pain.

[i] *VAS Pain* Visual Analog Scale Pain.

[j] *FACIT Fatigue* Functional Assessment of Chronic Illness Therapy Fatigue.

[k] *EORTC QLQ-CIPN20* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy Induced Peripheral Neuropathy 20.

[l] *FACT/GOG-NTX* Functional Assessment of Cancer Therapy Gynecologic Oncology Group Neurotoxicity

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Table 4

PRO reporting quality score

Study design	*n*	CONSORT PRO score	
		m	**Range**
All manuscripts	30	8.0	2–15
Pre 2013	14	7.9	2–12
Post 2013	16	8.1	3–15
Clinical trials	25	7.7	2–15
Phase			
II	11	6.3	2–10
III	11	8.7	3–15
Unspecified	3	9.0	8–10
Design			
Randomized trial	14	8.7	3–13
Single arm	9	5.7	2–9
Historical control	1	9.0	~
Unspecified	1	10.0	~
PRO endpoint			
Primary	10	10.5	8–15
Secondary	12	6.3	2–13
Exploratory	3	4.0	3–6
Manuscript type			
Primary efficacy/safety report	15	6.0	2–10
PRO focused secondary report	10	10.2	3–15
Observational	5	9.4	5–15
Longitudinal	3	8.3	5–11
Cross-sectional	2	11.0	7–15

PRO patient-reported outcome. Possible scores range from 0 to 15. Higher scores indicate higher quality

Table 5

CONSORT PRO extension criteria

Criteria	Manuscripts meeting criteria *n* = 30 (%)
1. PRO identified in abstract as primary or secondary outcome	22 (73.3)
2. Background and rationale for PRO assessment	18 (60.0)
3. PRO hypothesis stated	3 (10.0)
4. Relevant domains identified	21 (70.0)
5. Present evidence and/or reference of reliability and validity for PRO instruments	15 (50.0)
6. Person completing PRO specified	17 (56.7)
7. Method of administration specified	5 (16.7)
8. Assessment timepoints specified	27 (90.0)
9. Statistical methods for analyzing PRO data specified	18 (60.0)
10. Statistical approaches for missing data specified	7 (23.3)
11. Number of PRO participants at each timepoint reported	12 (40.0)
12. Baseline PRO data reported	16 (53.3)
13. PRO results for all domains reported	22 (73.3)
14. PRO specific limitations and implications for generalizability and clinical practice	8 (26.7)
15. Patient-reported outcome data are interpreted in relation to clinical outcomes including survival data	28 (93.3)

CONSORT PRO consolidated standards of reporting trials patient-reported outcomes. patient-reported outcome,