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Systematic Literature Review

Past and Current Practice of Patient-Reported Outcome Measurement in Randomized Cancer Clinical Trials: A Systematic Review

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ABSTRACT

Objectives: In our systematic review, we assessed past and current practice of patient-reported outcome (PRO) measurement in cancer randomized, controlled trials (RCTs).

Methods: We included RCTs with PRO endpoints evaluating conventional medical treatments, conducted in patients with the most prevalent solid tumor types (breast, lung, colorectal, prostate, bladder, and gynecological cancers) and either published in 2004 to 2018 or registered on clinicaltrials.gov and initiated in 2014 to 2019. Frequency of use of individual PRO measures was assessed overall, over time, and by cancer site.

Results: Screening of 42 095 database records and 3425 registered trials identified 480 published and 537 registered trials meeting inclusion criteria. Among published trials, the European Organisation for Research and Treatment of Cancer (EORTC) measures were used most often (54.8% of trials), followed by the Functional Assessment of Chronic Illness Therapy (FACIT) measures (35.8%), the EQ-5D (10.2%), the SF-36 (7.3%), and the MD Anderson Symptom Inventory (MDASI; 2.5%). Among registered trials, the EORTC measures were used in 66.1% of the trials, followed by the FACIT measures (25.9%), the EQ-5D (23.1%), the SF-36 (4.8%), the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE; 2.2%), the Patient-Reported Outcomes Measurement Information System (PROMIS) measures (1.7%), and the MDASI measures (1.1%).

Conclusion: The PRO measures most frequently used in RCTs identified in our review differ substantially in terms of content and domains, reflecting the ongoing debate among the scientific community, healthcare providers, and regulators on the type of PRO to be measured. Current findings may contribute to better informing the development of an internationally agreed core outcome set for future cancer trials.

Keywords: cancer, patient-reported outcome, questionnaire, randomized-controlled trial, systematic review.

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Introduction

Patient-reported outcomes (PROs), such as health-related quality of life (HRQOL), functional health, and symptom burden, are now frequently used in clinical trials to complement traditionally used cancer outcomes such as overall and progression-free survival. Patient-reported outcomes can provide valuable information from the patients' perspectives on the clinical benefits, safety, and tolerability of cancer treatments.[1,2]

Incorporation of rigorous assessment of PROs into cancer trials is also of critical importance for the international regulatory and health policy community. Indeed, the value of incorporating high-quality PRO data into regulatory decision-making process has also been recently well outlined.[3]

In 2014, a US National Cancer Institute (NCI)–driven initiative proposed that symptom endpoints should be used for evaluating new therapies from the patients' perspectives across cancer clinical trials.[4] The US Food and Drug Administration (FDA) subsequently published a suggested core set of concepts for cancer trials that recommended the addition of physical function[5-7] to provide context for the functional impact of symptomatic adverse events and disease-related symptoms. The FDA suggests this as an initial focus for defining patient-reported endpoints in cancer trials but states that "other aspects of the patient experience may also be important to measure, and all submitted PRO data will be taken into account during product review."[8] Taking a somewhat different approach, the European Medicines Agency more explicitly encourages taking a broader perspective, including dimensions of HRQOL.[9,10]

A number of measures are available and are widely used to assess PROs in cancer randomized, controlled trials (RCTs). Most have been developed after rigorous procedures[11-13] to ensure that they cover content that is relevant to clinicians and patients and meet standards set for measurement reliability and validity.[14]

Although measurement characteristics such as reliability and validity are often comparably high for the most commonly used PRO measures, they may differ substantially with regard to the type and number of health domains covered.

As discussed at a recent FDA–American Society of Clinical Oncology workshop: "the international community is also interested in identifying core clinical outcome sets that can be used to facilitate registries, pragmatic trials and other data sources that can be used to inform international regulatory, payer, provider and patient decision making."[15] To achieve this, it is important to understand the current practice of international PRO data collection, since it may reflect a certain degree of consensus on what health domains to assess in clinical trials.

Therefore, we investigated past and current practice of PRO measurement in cancer RCTs, conducting a systematic literature review covering studies published between 2004 and 2018 and an analysis of registered trials initiated during the years 2014 to 2019. We assessed in detail the frequency over time with which specific PRO measures have been used overall, as well as by funding source and by cancer site.

Methods

Identification of PRO Measures Captured in Completed Cancer RCTs Published Between 2004 and 2018

Data were gathered through the Patient-Reported Outcome Measurements Over Time In ONcology (PROMOTION) registry (promotion.gimema.it), which is a web-based password-protected database (REDCap[16]) that systematically collects several types of information on published cancer RCTs with a PRO component (either as primary or secondary/exploratory endpoint). This database currently contains information on 918 RCTs, conducted across several cancer malignancies, that were published from January 2004 to February 2019. Details on the standard methodology for the systematic identification of eligible studies, as well as data extracted from RCTs that populate the database, have been previously reported.[17,18] Briefly, RCTs comparing conventional medical treatment modalities and enrolling at least 50 patients (combined arms) are systematically identified, mainly through PubMed/Medline, and using ad hoc key searching strategies for each cancer disease site. Studies evaluating screening programs, complementary or alternative medicines, psychosocial interventions, or exercise and behavioral interventions are not considered for inclusion in the database. A double-blind data entry procedure is implemented to extract a set of predefined information (from each eligible RCT) by at least 2 independent reviewers, and a third one is consulted in case of disagreement. Information extracted includes RCT characteristics, PRO design and PRO questionnaires used, risk of bias, and accuracy of PRO reporting as defined by the International Society for Quality of Life Research criteria.[19] For the purpose of this analysis, we selected RCTs conducted in the following 6 most frequent cancer sites: breast, lung (ie, non-small-cell lung cancer), colorectal, bladder, prostate, and gynecological cancers, which were all published between January 2004 and December 2018.

Identification of PRO Measures Included in Cancer RCTs Registered as Starting Between 2014 and 2019

Trials registered on the clinicaltrials.gov trial registry were identified through use of a search strategy that was harmonized with the criteria for selecting trials for the PROMOTION registry, with the exceptions being the time period (registered trials starting between January 1, 2014, and June 30, 2019) and the inclusion criteria for PRO measures. Key searching strategies used for article identification in the PROMOTION Registry are available from the authors. We selected trials starting after January 2014 based on the assumption that trials starting earlier would most likely already be included in the PROMOTION registry.

Although the PROMOTION registry includes RCTs reporting results for any PRO measure, we limited the clinicaltrial.gov search to RCTs using the 5 PRO measures most frequently found in the PROMOTION registry: EORTC (European Organisation for Research and Treatment of Cancer)[20] measures, EQ-5D,[21] FACIT (Functional Assessment of Chronic Illness Therapy),[12] MDASI (MD Anderson Symptom Inventory),[22] and SF-36.[23] Also included were 2 measures developed more recently, which have been discussed at a recent American Society of Clinical Oncology–FDA workshop:[15] the PRO-CTCAE (Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events[24]) and the PROMIS (Patient-Reported Outcomes Measurement Information System[25]). For a short description of these PRO measures and the search terms used for their identification via the "Outcome" search field of clinicaltrials.gov, please see Table 1.

All selection criteria were evaluated independently by 2 reviewers, with consensus discussions in case of disagreements. In addition, the 2 reviewers checked the full registration information on the clinicaltrials.gov website to verify that the trials retrieved through our search strategy included the relevant PRO measures.

Data Analysis

The use of the PRO measures is described with absolute and relative frequencies (overall and by cancer site) for the 5 most commonly found measures in the PROMOTION registry, and for the 7 measures included in the analysis of registered trials. For both published and registered trials, the frequency with which the individual PRO measures were used was calculated using the total number of trials with any of the PRO measures under investigation (please see Table 1) as the denominator, and expressed as a percentage. We also report frequencies of trials that used the core questionnaires, the FACT-G and the EORTC QLQ-C30, with or without supplemental disease-specific modules (including symptom indices).

For evaluating time trends, we present the relative frequency (percentage) of use for each measure over time. Percentages were calculated relative to the number of trials in the respective periods. Industry involvement was investigated by comparing the frequency of use of the PRO measures between studies with or without industry funding.

Results

Analysis of Published RCTs (2004-2018)

We screened 42 095 PROMOTION registry records to identify 2654 full-text articles for review. In total, 646 cancer RCTs published between 2004 and 2018 were included in the PROMOTION registry and met the inclusion criteria (see Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.11.004).

Of these 646 trials, 480 trials (74.3%) used one of the PRO measures under investigation (see Table 1). In order of frequency, these 480 published trials were conducted in breast cancer (146 trials, 30.4%), lung cancer (111 trials, 23.1%), colorectal cancer (76 trials, 15.8%), prostate cancer (70 trials, 14.6%), gynecological cancers (69 trials, 14.4%), and bladder cancer (8 trials, 1.7%). In these 480 trials. The EORTC measures were used in 263 trials (54.8%), the FACIT measures in 172 trials (35.8%), the EQ-5D in 49

Table 1. Description of PRO measures and search terms used for identifying relevant cancer RCTs on www.clinicaltrials.gov.

PRO measure	Description	Search terms*
EORTC (European Organisation for Research and Treatment of Cancer) measures	The EORTC measures comprise the cancer-specific QLQ-C30 (Quality of Life Questionnaire Core 30[20];) a multidimensional HRQOL core measure that assesses 5 functional health domains, 9 symptom domains and global quality of life, and a number of questionnaire modules specific to certain cancer diagnoses or symptoms.	"eortc" OR "qlq" OR "c30" OR "qlqc30" OR "c-30" OR "core30" OR "core-30" OR "qlq30"
EQ-5D (Euroqol 5-Dimensions)	The generic EQ-5D[21] is a health utility measure covering 5 health domains and is frequently used in health economics to calculate quality-adjusted life-years.	"EQ-5D" OR "Euroqol" OR "EQ5D"
FACIT (Functional Assessment of Chronic Illness Therapy)	The FACIT system includes the cancer-specific FACT-G (Functional Assessment of Cancer Therapy – General) for the assessment of four HRQOL domains (physical, functional, emotional, and social well-being) and questionnaire modules for specific diagnoses and symptoms.[12]	FACIT OR "fact" OR "functional assessment" OR "function assessment" OR "cancer therapy-general" OR "FAACT"
MDASI (MD Anderson Symptom Inventory)	The MDASI core questionnaire[22] assesses the severity of 13 symptoms and their interference with different aspects of daily living. Next to the core questionnaire several modules are available.	"MDASI" OR "MDADI" OR "Anderson" OR "MD"
PRO-CTCAE (Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events)	The PRO-CTCAE is a self-report version of the cancer-specific Common Terminology Criteria for Adverse Events.[24]	"PRO-CTCAE" OR "PROCTCAE" OR "PRO CTCAE"
PROMIS (Patient-Reported Outcomes Measurement Information System)	PROMIS[25] provides item banks for the assessment of key health domains relevant across medical fields.	"promis" OR "Patient Reported Outcomes Measurement Information System"
SF-36 (Short-Form 36)	The SF-36 ([23]; and its SF-12 short-form) is a generic health questionnaire that is applied across medical fields to assess various HRQOL domains.	"SF-36" OR "SF36" OR "SF-12" OR "SF12" OR "SF-6D" OR "SF6D" OR "Short-form" OR "Shortform" OR "MOS"

PRO indicates patient-reported outcome.
*Please note that only nonredundant search terms are reported here (ie, search terms that increased the number of identified trials).

trials (10.2%), the SF-36 in 35 trials (7.3%), and the MDASI in 12 trials (2.5%).

The EORTC QLQ-C30 and FACT-G core questionnaires were supplemented with condition- or symptom-specific questionnaire modules in 55.5% and 94.8% of trials, respectively. The SF-36 was used in combination with the FACIT measures in 6 trials, with the EORTC measures in 3 trials, and with the MDASI in 2 trials.

Out of the 480 published trials, 284 (59.2%) trials were (at least in part) funded by industry, whereas 196 (40.8%) were not. The EORTC measures were used in 56.1% of the non-industry-funded

Table 2. Frequency of PRO measures used in randomized clinical trials by cancer site.

Cancer site	No. of trials	EORTC	FACIT	EQ-5D	SF-36	MDASI
Breast	146	47.9%	41.1%	5.5%	8.2%	7.5%
Lung	111	54.1%	34.2%	15.3%	1.8%	0.0%
Prostate	70	47.1%	47.1%	7.1%	11.4%	0.0%
Colorectal	76	68.4%	17.1%	15.8%	13.2%	1.3%
Gynecological	69	62.3%	36.2%	10.1%	4.3%	0.0%
Bladder	8	62.5%	37.5%	0.0%	0.0%	0.0%
Total	480	54.8%	35.8%	10.2%	7.3%	2.5%

Note. Percentages are given relative to the number of trials published between 2004 and 2018 that used one of the PRO measures under investigation (N = 480). EORTC indicates European Organisation for Research and Treatment of Cancer; FACIT, Functional Assessment of Chronic Illness Therapy; MDASI, MD Anderson Symptom Inventory; PRO, patient-reported outcome.

trials and 53.9% of the trials with industry funding. For the other PRO measures, these frequencies were as follows: FACIT measures 30.1% (non-industry) versus 39.8% (industry), SF-36 12.8% (non-industry) versus 3.5% (industry), EQ-5D 6.1% (non-industry) versus 13.0% (industry), and MDASI 4.1% (non-industry) versus 1.4% (industry). The EORTC QLQ-C30 core questionnaire was used in combination with modules in 54.9% of non-industry trials and 56.4% of industry-funded trials. For the FACT-G modules were used in 94.9% of non-industry trials and 94.7% of industry trials.

Across cancer sites, the EORTC measures were used most frequently in colorectal cancer trials (68.4% of trials) and least often in prostate cancer trials (47.1%). The FACIT measures were administered most often in prostate cancer trials (47.1%) and least often in colorectal cancer trials (17.1%). Further details are provided in Table 2.

Analyzing the time trend for the 3 most frequently used PRO measures, we found that the EORTC measures were used in 64.4% of the trials in the period 2004-2006, 50.0% of the trials in the period 2010-2012, and 51.9% in the most recent period (2016-2018). The EQ-5D showed a strong increase in use over time (frequency ≤4.0% for 2004-2009 and 21.0% for 2016-2018). Frequency of the FACIT measures use increased over time from 27.3% of trials in 2004-2006 to 41.8% in 2013-2015, and 35.8% most recently (2016-2018). Please see Figure 1 for further details.

Analysis of Registered RCTs (2014-2019)

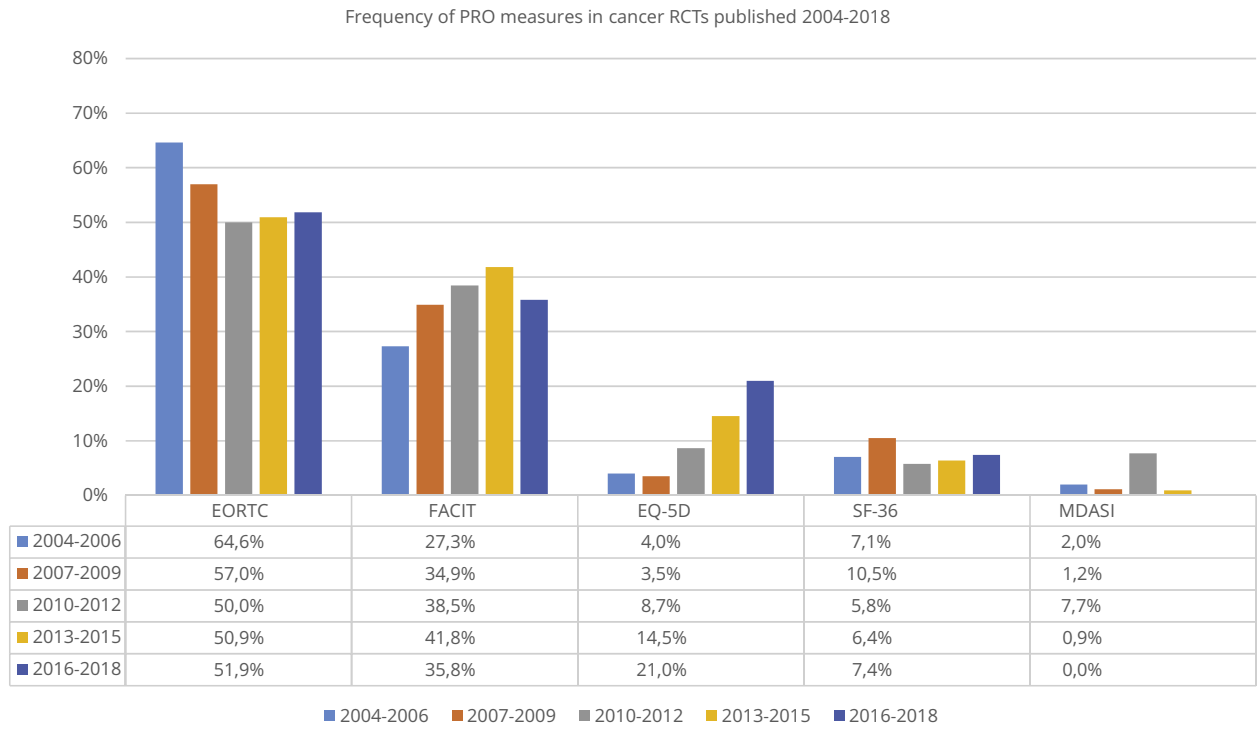
Our review of clinicaltrials.gov identified 3425 potentially eligible trials and after applying all exclusion criteria, 537 were included in the final analysis (see Appendix Figure 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.11.004).

Of 537 included trials, 137 (25.5%) were conducted in patients with lung cancer, 127 (23.6%) in patients with breast cancer, 86 (16.0%) in patients with colorectal cancer, 79 (14.7%) in patients with gynecological tumors, 71 (13.2%) in patients with prostate cancer, and 37 (6.9%) in patients with bladder cancer. The EORTC measures were used in 355 trials (66.1%), the FACIT measures in 139 trials (25.9%), the EQ-5D in 124 trials (23.1%), the SF-36 in 26 trials (4.8%), the PRO-CTCAE in 12 trials (2.2%), the PROMIS measures in 9 trials (1.7%), and the MDASI measures in 6 trials (1.1%).

The EORTC QLQ-C30 and FACT-G were supplemented with condition/symptom-specific questionnaires modules in 61.4% and 95.0% of trials, respectively. The SF-36 was used in combined with the FACIT measures in 3 trials, and with the EORTC measures in 2 trials.

Of the 537 registered trials, 278 (51.8%) trials were funded without industry involvement, and 259 (48.2%) were funded, at least in part, by industry. The EORTC measures were used in 59.7% of the non–industry-funded trials and 73.0% of the trials with industry funding. For the other PRO measures this ratio was as follows: FACIT measures 27.7% (non-industry) versus 23.9% (industry), SF-36 7.6% (non-industry) versus 1.9% (industry), EQ-5D 22.3% (non-industry) versus 23.9% (industry), PROMIS 2.9% (non-industry) versus 0.4% (industry), PRO-CTCAE 2.9% (non-industry) versus 1.5% (industry), and MDASI 0.4% (non-industry) versus 1.9% (industry). For the EORTC QLQ-C30 additional questionnaire modules were used in 63.3% of non-industry trials and 59.8% of industry-funded trials. The FACT-G was supplemented in 94.8% of non-industry trials and in 95% of industry-funded trials. For those trials with industry involvement, the type of sponsor and funding source were congruent for all but 5 trials, and thus no additional analysis was conducted by sponsor.

Figure 1. Time trend for the frequency of patient-reported outcome (PRO) measures used most frequently in cancer randomized controlled trials (RCTs) in the Patient-Reported Outcomes Measurements Over Time In ONcology (PROMOTION) registry. Percentages are given relative to the number of trials per period that used at least 1 PRO measure under investigation.



	EORTC	FACIT	EQ-5D	SF-36	MDASI
2004-2006	64,6%	27,3%	4,0%	7,1%	2,0%
2007-2009	57,0%	34,9%	3,5%	10,5%	1,2%
2010-2012	50,0%	38,5%	8,7%	5,8%	7,7%
2013-2015	50,9%	41,8%	14,5%	6,4%	0,9%
2016-2018	51,9%	35,8%	21,0%	7,4%	0,0%

Across cancer sites, the EORTC measures were used most frequently in colorectal cancer trials (75.6% of trials) and least often in prostate cancer trials (42.3%). The FACIT measures were administered most often in prostate cancer trials (46.5%) and least often in colorectal cancer trials (12.8%). Further details are given in Table 3.

An analysis of trends over time between January 2014 and June 2019 showed an increase in published trials using the EORTC measures (lowest frequency in 2015: 56.8%; highest frequency in 2018: 74.8%), a decrease for the FACIT (highest in 2015: 32.9%; lowest in 2019: 19.8%), and a fluctuating use of the EQ-5D (ranging from 19.3% in 2018 to 27.0% in 2015). For details, please see Figure 2. The percentage of trials supplementing the EORTC QLQ-C30 with a questionnaire module decreased from 70.8% in 2014 to 55.2% in 2019. For the FACT-G this proportion fluctuated between 90.9% in 2015 and 100% in 2014.

Discussion

Our review indicates that the EORTC measures were the most frequently used PRO tools in published and registered RCTs of most common solid cancers, followed by the FACIT measures and the EQ-5D. The analysis of published RCTs showed a clear increase in the use of the EQ-5D between 2004 and 2018 and a mostly stable frequency in the more recently registered trials.

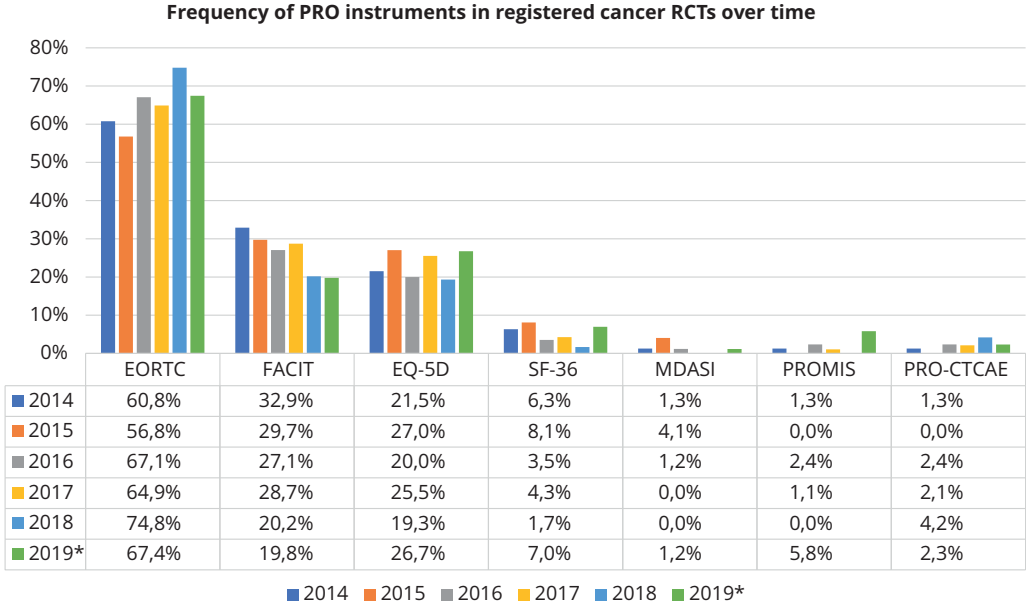
By analyzing 2 types of databases we were able to generate a detailed picture of past and current practice of PRO instrument selection in cancer RCTs. When interpreting our results on published trials, it should be taken into account that the decision to use a certain PRO measure usually has been made several years prior to publication of study results.[26] Therefore, we considered it important to extend our search to clinicaltrials.gov and also to assess registered trials starting before June 2019 to gain a more

Table 3. Frequency of PRO measures used in registered randomized clinical trials by cancer site.

Cancer site	No. of trials	EORTC	FACIT	EQ-5D	SF-36	PRO-CTCAE	PROMIS	MDASI
Lung	137	70.1%	20.4%	24.8%	2.2%	2.2%	0.7%	2.9%
Breast	127	66.1%	27.6%	21.3%	1.6%	3.1%	2.4%	0.8%
Colorectal	86	75.6%	12.8%	20.9%	14.0%	1.2%	1.2%	0.0%
Gynecological	79	67.1%	30.4%	20.3%	3.8%	2.5%	1.3%	1.3%
Prostate	71	42.3%	46.5%	26.8%	7.0%	1.4%	4.2%	0.0%
Bladder	37	73.0%	21.6%	27.0%	2.7%	2.7%	0.0%	0.0%
Total	537	66.1%	25.9%	23.1%	4.8%	2.2%	1.7%	1.1%

Note. Percentages are given relative to the number of trials starting between January 2014 and June 2019 and using any of the 7 PRO measures (N = 537).
EORTC indicates European Organisation for Research and Treatment of Cancer; FACIT, Functional Assessment of Chronic Illness Therapy; MDASI, MD Anderson Symptom Inventory; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PROMIS, Patient-Reported Outcomes Measurement Information System.

Figure 2. Time trend of the frequency of patient-reported outcome (PRO) measures registered on www.clinicaltrials.gov. Percentages are given relative to the number of trials per year that used any of the 7 PRO measures under investigation.



	EORTC	FACIT	EQ-5D	SF-36	MDASI	PROMIS	PRO-CTCAE
2014	60,8%	32,9%	21,5%	6,3%	1,3%	1,3%	1,3%
2015	56,8%	29,7%	27,0%	8,1%	4,1%	0,0%	0,0%
2016	67,1%	27,1%	20,0%	3,5%	1,2%	2,4%	2,4%
2017	64,9%	28,7%	25,5%	4,3%	0,0%	1,1%	2,1%
2018	74,8%	20,2%	19,3%	1,7%	0,0%	0,0%	4,2%
2019*	67,4%	19,8%	26,7%	7,0%	1,2%	5,8%	2,3%

*only January to June

contemporary perspective on planned use in registered studies. As a consequence of the time lag between writing of the trial protocol and publication of trial results, the related new PROMIS measures (published first in 2009[27]) and the PRO-CTCAE (published first in 2015[24]) were not used in any of the published trials, while a number of studies using these measures were identified in our search of www.clinicaltrials.gov. In addition, both databases differ regarding coverage. Whereas the PROMOTION registry only covers trials with published PRO results and is therefore prone to publication bias,[26] the analysis of clinicaltrials.gov does not include trial protocols that are registered in other registries or not registered at all.

Our study has several limitations that should be noted. We focused on only the most common cancer types and restricted the selection of studies to RCTs. In addition, we included only traditional medical treatments and did not consider behavioral or psychosocial interventions. Because the choice of a PRO measure also depends on the type of clinical benefit or harm expected from an intervention, frequencies of the use of PRO measures may differ across different types of interventions and study designs. However, our results are consistent with other studies on the frequency of the use of PRO measures in oncology that focused on specific measures,[28] or routine cancer clinical practice.[29] For trials submitted to regulatory authorities,[9,30] frequencies for the EORTC and FACIT measures are comparable to our findings, whereas the EQ-5D is used more frequently, in about half of such trials.

Our review also has notable strengths. To the best of our knowledge, this is the first and largest evidence-based review of the use of PRO measures stemming from a rigorous and systematic assessment of RCTs, both published and ongoing. This provides a broad picture of past and current practice with regard to PRO assessment in clinical trials in oncology.

In most cases, the decision to use a certain PRO measure in a cancer trial reflects conceptual considerations such as whether or not to conduct a multidimensional HRQOL assessment, to measure symptom burden only, or to focus on broader health domains. It is noteworthy that the majority of trials in our analysis used either the EORTC measures, the FACIT measures, the EQ-5D, or the SF-36, all of which are multidimensional questionnaires that are not limited to physical functioning or somatic symptoms, but also include broad HRQOL concepts and assess emotional, social, and (role) functional aspects of health. We found that the FACT-G core questionnaire was supplemented with a disease-specific FACIT module in about 95% of registered trials, whereas this was the case for only 61% of the registered trials using the EORTC QLQ-C30. This may reflect that the EORTC core questionnaire already includes key cancer symptoms in addition to the functional health domains, whereas the FACIT core questionnaire focuses more on functional health with symptoms being assessed within its subscales and the additional disease-specific modules and symptom indices. More recently, item libraries with supplementary items on specific health issues have been made available for both the EORTC and the FACIT measurement systems to allow for a more flexible assessment approach. The flexibility of these item libraries may be particularly beneficial when evaluating new treatment types with toxicity profiles that differ from traditional treatments.

In general, our results indicate that past and current practice of PRO assessment in clinical trials frequently includes health domains that go beyond those recommended by the NCI-initiative[4] and suggested as initial focus by FDA representatives.[8] The increasing use of the EQ-5D may reflect that health utility data are gaining importance in the context of health economics and for reimbursement of treatment costs.[31,32] PROMIS measures, targeting specific symptoms and functional domains, are seeing a significant rise in use, especially as multiple language versions are becoming available. Also, it is expected that newer measures such as the PRO-CTCAE will play an increasingly important role in the assessment of tolerability in future studies.[8] This may, in part, reflect an increasing popularity of item libraries and the impact of the views of regulatory authorities. Frequency of use, in and of itself, does not necessarily provide guidance about which PRO measures should be used in future RCTs. However, documentation of the frequency of use of PRO measures in this review may serve as a starting point for more detailed considerations on how best to match specific research questions with available PRO measures.

In conclusion, within the current evolving scenario of recently published PRO measurement guidelines and recommendations, our findings provide a historical and current perspective on PRO measures most frequently used in RCTs conducted across the most common solid tumor malignancies. Our research has identified the most commonly used PRO measures in (inter)national cancer trials and thus provides information on the scope and the type of health domains that have been assessed in cancer RCTs. We believe that this information can help inform the development of an internationally agreed core outcome set to be recommended for use in future cancer trials. In addition, newer emerging measures such as the PRO-CTCAE and the FACIT (https://wizard.facit.org/) and EORTC item library (https://www.eortc.be/itemlibrary/) should also be considered to provide an estimate of treatment tolerability. Similar analyses performed in cancer research settings other than RCTs will be important to further expand our knowledge of current practice of PRO measurement approaches in the wider cancer arena.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.11.004.

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Provision of study materials or patients: Efficace
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