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ORIGINAL ARTICLE

Methodological and reporting standards for quality-of-life data eligible for European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) credit

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Background: The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) has been developed to grade clinical benefit of cancer therapies. Improvement in quality of life (QoL) is considered relevant, especially in the non-curative setting. This is reflected by an upgrade of the preliminary ESMO-MCBS score if QoL is improved compared to the control arm or a downgrade if an improvement in progression-free survival is not paralleled by an improvement in QoL or overall survival. Given the importance of QoL for the final score, a need to ensure the robustness of QoL data was recognised.

Design: A checklist was created based on existing guidelines for QoL research. Field testing was carried out using clinical trials that either received an adjustment of the preliminary ESMO-MCBS score based on QoL or had QoL as the primary endpoint. Several rounds of revision and re-testing of the checklist were undertaken until a final consensus was reached.

Results: The final checklist consists of four items and can be applied if three prerequisites are met: (i) QoL is at least a secondary endpoint, (ii) evidence of reliability and validity of the instrument is provided, and (iii) a statistically and clinically significant improvement in QoL is observed. The four items on the checklist pertain to the (i) hypothesis, (ii) compliance and missing data, (iii) presentation of the results, and (iv) statistical and clinical relevance. Field testing revealed that a clear QoL hypothesis and correction for multiple testing were mostly lacking, while the main statistical method was always described.

Conclusions: Implementation of the ESMO-MCBS QoL checklist will facilitate objective and transparent decision making on QoL data within the ESMO-MCBS scoring process. Trials published until 1 January 2025 will have to meet the prerequisites and at least two items for crediting QoL benefit in the final ESMO-MCBS score. Trials published thereafter will have to meet all four items.

Key words: quality of life, checklist, guidelines, ESMO-MCBS

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INTRODUCTION

In 2015 the European Society for Medical Oncology (ESMO) introduced the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS), a validated tool to stratify the magnitude of clinical benefit derived from therapeutic approaches in a standardised way.[1] With the rapid increase of new treatment options and expanding cancer care costs, the ESMO-MCBS can assist as a tool for health-technology assessment. Every new anticancer medicine that receives approval from the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) is graded and assigned a score, which is publicly available on the ESMO website.[2] The highest grades of the ESMO-MCBS in the curative setting are A and B and in the non-curative setting are 5 and 4; these indicate medicines with a substantial clinical benefit. In 2017, ESMO-MCBS version 1.1 was published, incorporating several revisions and the ability to score single-arm studies.[3]

The ESMO-MCBS is based on the concept that potential benefits of a new treatment are not only to live longer, reflected by improved overall survival (OS), or surrogates such as disease-free survival (DFS) or progression-free survival (PFS) when validated, but also to live better, reflected by improved quality of life (QoL) or reduced toxicity compared to the previous standard of care. There are different settings in which QoL can determine the final ESMO-MCBS score. For new adjuvant or potentially curative therapies the combination of non-inferior OS or DFS with improved QoL results in a grade B (form 1). New treatment approaches not likely to be curative with OS or PFS as the primary endpoint receive a preliminary score based on OS or PFS benefit and are credited with an upgrade of 1 point if QoL is improved (forms 2a and 2b). Scores generated on PFS may also be downgraded in cases where there is no survival advantage with mature data and where QoL evaluation has not demonstrated any significant and clinically meaningful benefit. Furthermore, in non-inferiority studies with non-curative treatment approaches that have toxicity or QoL as the primary endpoint a treatment option can receive a grade 4 if QoL is improved and OS or PFS is at least non-inferior to the previous standard of care and a grade 3 if there is improvement in some pre-specified symptoms but not in overall QoL (form 2c). Finally, for single-arm studies for orphan diseases or situations with a high unmet need, the preliminary score that is based on PFS or overall response rate can be upgraded by 1 point if there is an improvement in QoL (form 3).

ESMO-MCBS version 1.1 instructions on scoring QoL benefit are limited to the requirements that QoL should be a primary endpoint (form 2c) or secondary endpoint (forms 2a, 2b, and 3), that a validated scale should be used, and that the gain must be statistically significant.

Given the importance of QoL for the final ESMO-MCBS score, a need to ensure the reliability and validity of the QoL data was recognised. This article describes the development of a checklist to guarantee that QoL data meet adequate methodological and reporting standards to justify an impact on ESMO-MCBS scoring.

Table 1. Guiding principles for QoL evaluation using the ESMO-MCBS

1	QoL data provide important information regarding patient benefit.
2	For an ESMO-MCBS credit, QoL must be either primary or secondary endpoint (not exploratory).
3	QoL must be assessed with a validated[a] health-related QoL instrument.
4	ESMO-MCBS assumes adequate validity, reliability, and responsiveness of the overall/global QoL scale.
5	Improvement in individual domains without significant overall/global QoL benefit is not sufficient for ESMO-MCBS credit, except when this is pre-specified in a study using QoL as the primary endpoint.
6	Benefit can be demonstrated by either improved QoL or delayed deterioration in overall/global QoL.
7	Benefit must be statistically and clinically[b] significant.
8	In studies with PFS as the primary endpoint, failure to demonstrate benefit in mature OS and QoL indicates weak surrogacy and scores are downgraded.

ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; OS, overall survival; PFS, progression-free survival; QoL, quality of life.
[a]A validated QoL instrument is a QoL tool with robust peer-reviewed data supporting its validity, reliability, and responsiveness.[7]
[b]A threshold for clinical significance must be defined upfront.

METHODOLOGY

In July 2019, the ESMO-MCBS Working Group established a collaboration with the Quality of Life Department of the European Organisation for Research and Treatment of Cancer (EORTC) to address this challenge.

Guidelines on the use of patient-reported outcomes (PROs) have previously been established and focus on inclusion in study protocols (SPIRIT-PRO),[4] reporting (CONSORT-PRO),[5] and analysis (SISAQOL).[6]

Items from CONSORT-PRO, SPIRIT-PRO, and SISAQOL and guiding principles agreed upon by the ESMO-MCBS team (Table 1) served as a basis to create the initial 17-item checklist (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.12.004). All clinical trials previously scored by the ESMO-MCBS Working Group that received an adjustment of the preliminary ESMO-MCBS score based on QoL as a secondary endpoint or had QoL as primary endpoint (up to August 2019, $n = 17$) were selected for field testing. If applicable, separate publications on QoL, identified on PubMed, and supplementary files and the study protocols available on the journals' websites were retrieved to extract information.[7-32] Each clinical trial was evaluated independently for compliance with the checklist criteria by three or four members of the project group (JB, BG, BK, FM, SFO, FR, and HV). Project group members were excluded from reviewing clinical trial articles which they co-authored.

Based on the feedback received from reviewers from the first round of field testing, checklist items were rephrased for clarity (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.12.004). For consistency, a second round of field testing was conducted using the revised

checklist. A reconciliation meeting took place between the reviewers and checklist items with a lack of agreement (≤50%) among the members were highlighted and re-discussed, with the goal of resolving discrepancies in the evaluation. If no agreement was found, another independent reviewer was involved. Subsequently, the clinical trials were ranked based on the number of checklist criteria that were met.

By combining the most important checklist items, determined by consensus, a condensed five-item checklist was created (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.12.004) with three prerequisites that have to be met before the checklist can be applied. With these prerequisites and the shortened checklist the evaluation process was repeated. For field testing purposes the checklist was completed also for trials that did not meet all three prerequisites. Finally, to optimise clarity and ease of use, the checklist was edited to a four-item checklist combining items 4 and 5 to indicate that the benefit must be both statistically significant and clinically meaningful, and the three prerequisites were re-worded to specify that compliance rates must be high and to emphasise that overall/global QoL needs to be improved (Supplementary Appendix 2, available at https://doi.org/10.1016/j.annonc.2022.12.004). Figure 1 summarises the methodology process.

RESULTS

The 17 clinical trials in which QoL data influenced the final ESMO-MCBS score, published between 2004 and 2018, were evaluated. Only 1 study included QoL as the primary endpoint,[21] 15 had received an upgrade of the preliminary ESMO-MCBS score based on QoL, and 1 was downgraded because an improvement in PFS did not translate into improvement in QoL or OS.[9] Eight clinical trials had a separate publication on QoL,[11,13,16,18,23,25,27,32] two of which were published in the same journal simultaneously with the primary study report.[15-18] Six QoL papers were published in a different journal with a lower impact factor at the time of the publication (mean difference = 34 points) and a mean time interval of 21 months since the primary publication. The details of the 17 clinical trials are shown in Table 2.

The first checklist version with 17 items took between 30 and 75 min per trial to complete, including the time needed to retrieve additional publications, supplementary files, and protocols, where relevant. Compliance of the evaluated studies with the 17-item checklist version 2 is presented in Table 3. Four clinical trials met at least 12 out of 17 criteria,[15,17,22,26] one of which met all 17.[15] Three clinical trials met five or fewer criteria.[8,28,29] The five-item checklist took on average 20 min to complete.

According to the final four-item checklist (Supplementary Appendix 2, available at https://doi.org/10.1016/j.annonc.2022.12.004, Table 4), 14 out of 17 clinical trials met all three prerequisites. For field testing, the checklist items were nevertheless scored for all trials. Compliance rates for QoL assessment of 14 clinical trials with adequate compliance data varied between 85% and 99% at baseline and between 64% and >95% during follow-up, which was deemed adequate. For the remaining three clinical trials, the compliance rates were not reported or could not be assessed because of limited information. Two trials satisfied all four items, another 2 trials satisfied three out of four items, 3 trials met two out of four, and 10 trials fulfilled one or zero items.

DISCUSSION

Endpoints used in cancer research require clear objective definitions and standard approaches for evaluation and reporting. These are well developed for event-based outcomes such as OS, DFS, PFS, and overall response rate which uses Response Evaluation Criteria In Solid Tumors (RECIST). Similarly, standards for toxicity reporting are established with the universal application of the Common Terminology Criteria for Adverse Events (CTCAE). In contrast, measuring QoL outcomes in clinical trials is complex and less well defined. There are many instruments and different ways to analyse the QoL data. Guidelines have been developed in the past decade, starting with recommendations for reporting,[5] followed by guidelines for incorporating QoL in study protocols,[4] and standards for statistical analysis.[6] However, there is no vigilance to ensure compliance to guidelines as a prerequisite to publication. Consequently, the methodological quality of QoL research is variable exposing QoL research to bias.

Since the results of QoL studies can substantially influence ESMO-MCBS scoring, the issue of methodological validity is important for the scale. For example, if a study receives a preliminary ESMO-MCBS grade 3, but a final grade 4 based on QoL, it crosses the threshold of having achieved substantial benefit for purposes of decisions on resource allocations, guidelines, and clinical decision making.

Starting with a comprehensive list and using a reductive approach, the ESMO-MCBS QoL team, together with EORTC team, have now developed a short four-item checklist to facilitate objective and transparent decision making on credentialing QoL studies for use in the ESMO-MCBS scoring. Applying this methodological screening tool, the ESMO-MCBS Working Group aims to ensure that QoL studies meet adequate methodological thresholds to justify the adjustment of the ESMO-MCBS score. An upgrade of the preliminary ESMO-MCBS score for QoL benefit requires that improvement in overall or global QoL is demonstrated when QoL is a secondary endpoint, either as improved QoL or delay in the deterioration of QoL. Overall or global QoL is derived from the summary score of a validated instrument in accordance with the specific guidelines for the application of the nominated scale. For example, using the EORTC 30-item Core Quality of Life Questionnaire (QLQ-C30), overall health-related QoL is derived from items 29 and 30.[33] The ESMO-MCBS QoL team recognises that improvement of disease-related symptoms is important for patients,

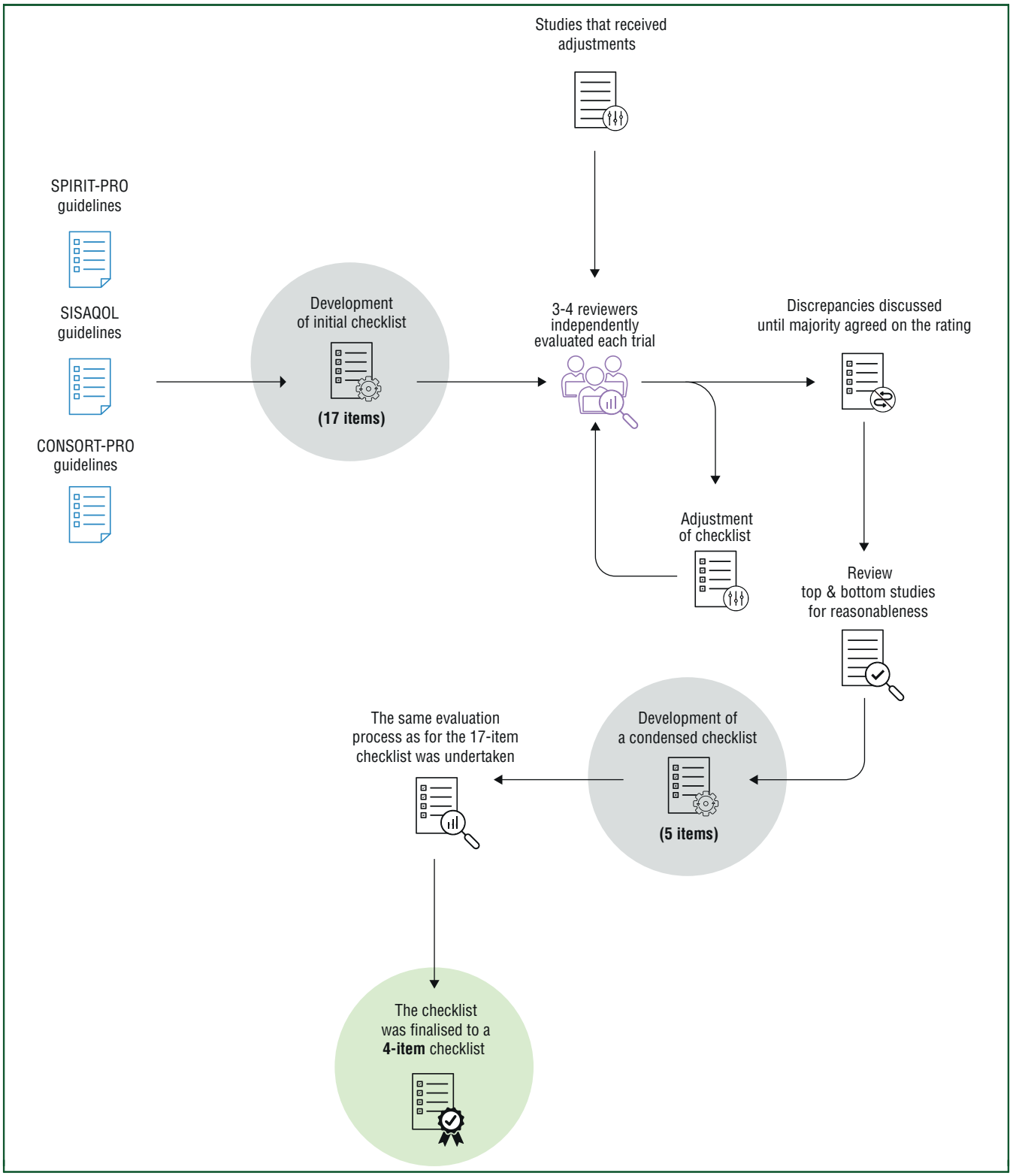

Figure 1. ESMO-MCBS QoL checklist methodology process. CONSORT-PRO, Consolidated Standards of Reporting Trials on Patient Reported Outcomes; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; QoL, quality of life; SISAQOL, Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data; SPIRIT-PRO, Standard Protocol Items Recommendations for Interventional Trials for Patient Reported Outcomes.

and that description of multiple QoL domains and other PRO measures is highly valuable to enhance understanding of the impact of new therapies. However, improving specific symptoms or one or more functional domains without a benefit in overall or global QoL is not considered sufficient for an upgrade of the ESMO-MCBS score. Only form 2c of the ESMO-MCBS v1.1 does credit symptom improvement with a grade 3, if this is the pre-specified primary endpoint of the trial, and a valid symptom evaluation scale is used.

Table 2. Trial characteristics of clinical trials used for field testing

Trial characteristics	Clinical trials *n* (%)
Disease	
Non-small-cell lung cancer	7 (41)
Prostate cancer	3 (18)
Breast cancer	2 (12)
Renal cell carcinoma	2 (12)
Ovarian cancer	1 (6)
Pancreatic cancer	1 (6)
Melanoma	1 (6)
Intervention	
Targeted therapy	9 (53)
Antiangiogenic therapy	3 (18)
Chemotherapy	2 (12)
Hormonal therapy	1 (6)
Early palliative care	1 (6)
Radio-isotope	1 (6)
Preliminary ESMO-MCBS score	
1	1 (6)
2	2 (12)
3	11 (65)
4	3 (18)
Separate publication on QoL	
Yes	8 (47)
No	9 (53)
QoL was a	
Primary endpoint	1 (6)
Secondary endpoint	16 (94)
Number of QoL instruments per trial	
One	6 (35)
Two	6 (35)
Three	3 (18)
More than three	2 (12)
Number of trials using QoL instrument	
EORTC QLQ-C30	10 (59)
EQ-5D-5L	6 (35)
EORTC QLQ-LC13	6 (35)
FACT-P	3 (18)
FACT-G	1 (6)
FACT-L	1 (6)
LCSS	1 (6)
EORTC QLQ-BR23	1 (6)
EORTC QLQ-OV28	1 (6)
FACT-B	1 (6)
FKSI-DRS	1 (6)
FKSI-15	1 (6)
FOSI	1 (6)
Main QoL analysis	
Proportion with improvement	7 (41)
Change from baseline over time	6 (35)
Time to deterioration	3 (18)
Between treatment differences in mean scores	1 (6)

EORTC, European Organisation for Research and Treatment of Cancer; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; EQ-5D-5L, EuroQol 5-dimensional descriptive system, 5-level version; FACT, Functional Assessment of Cancer Therapy scale (G, general; B, breast cancer; L, lung cancer; P, prostate cancer); FKSI-DRS, Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms; FKSI-15, 15-item Functional Assessment of Cancer Therapy-Kidney Symptom Index; FOSI, Functional Assessment of Cancer Therapy—Ovarian Symptoms Index; LCSS, Lung Cancer Symptom Scale; OS, overall survival; PFS, progression-free survival; QLQ-C30, 30-item Core Quality of Life Questionnaire (LC13, 13-item Lung Cancer module; BR23, 23-item BReast cancer module; OV28, 28-item OVarian cancer module); QoL, quality of life.

Table 3. Field testing results with the 17-item ESMO-MCBS QoL checklist[a]

	Checklist item	Clinical trials scoring positive *n* (%)
1	Were the background and rationale for PRO assessment stated?	9 (53)
2	Were the chosen PRO domains clearly stated?	10 (59)
3	Were the timepoints of the PRO assessment clearly stated?	16 (94)
4	Was the direction of the expected change (for example, we expect an increase—or decrease—in pain) clearly stated?	1 (6)
5	Was evidence of PRO instrument validity and reliability provided, or cited if available?	16 (94)
6	Was the statistical approach for dealing with missing data explicitly stated?	10 (59)
7	Were the baseline compliance rates for each treatment arm reported?	12 (71)
8	Were the follow-up compliance rates for each treatment arm and each time point reported?	8 (47)
9	Was the primary statistical method for PRO analysis described?	17 (100)
10	Were baseline PRO values reported, either in a table or in the text?	10 (59)
11	Were baseline scores reported for each treatment arm?	10 (59)
12	Were the primary analyses (as specified in the hypotheses) carried out by original assigned groups?	1 (6)
13	As specified in the hypotheses, were results from relevant domain(s) and time point(s) reported with the estimated effect size and its precision (such as 95% confidence interval)?	1 (6)
14	If more than one scale or domain and/or more than one follow-up assessment was included in the primary analysis, was statistical correction used?	2 (12)
15	Were PRO-specific limitations and implications for generalizability and clinical practice described?	8 (47)
16	Were PRO data not simply reported but also interpreted (i.e. trying to explain the relationship) in relation to clinical outcomes?	12 (71)
17	Was a measure of clinical relevance (for example, minimal important difference) taken into account when interpreting results?	13 (76)

ESMO-MCBS, European Society of Medical Oncology-Magnitude of Clinical Benefit Scale; PRO, patient-reported outcome; QoL, quality of life.
[a]Seventeen-item checklist version 2, provided in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.12.004.

The development process of the checklist revealed common methodological shortcomings in QoL studies in cancer. Most of the trials lacked a clear statement of the primary hypothesis for QoL, and for some studies it was not clear whether QoL was a secondary or exploratory endpoint. Two clinical trials were excluded from this evaluation because the type of endpoint for QoL was described differently in separate reports of the same study.[34-37] Frequently, more than one PRO instrument was used, and different types of analyses were reported, such as change from baseline and time to deterioration, and subdomains were analysed without a statistical correction for multiple comparisons. These findings are consistent with previous reports on the quality of PRO analysis and reporting in randomised controlled trials of cancer.[38,39] We also observed that there were long delays between the primary

Table 4. Field testing results with the final four-item ESMO-MCBS QoL checklist

Trial details					Prerequisites			Checklist items				Overall score	Ref
Medication	Treatment setting	Trial name	Reason to include	ESMO-MCBS score	(i) Primary or secondary endpoint	(ii) Valid and reliable instrument	(iii) Statistically and clinically significant improvement in overall/global QoL	(i) Clear hypothesis and methods	(ii) Compliance and missing data	(iii) Results	(iv) Statistical and clinical significance[a]	Number of positive items	
Bevacizumab	Recurrent platinum-resistant ovarian cancer	AURELIA	Upgrade based on QoL improvement	**4**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	4	15,16
T-DM1	HER2-positive, unresectable locally advanced, or metastatic breast cancer previously treated with trastuzumab and a taxane	EMILIA	Upgrade based on QoL improvement	**4**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	4	10,11
Palbociclib	Hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer previously treated with endocrine therapy	PALOMA-3	Upgrade based on QoL improvement	**4**	Yes	Yes	Yes	Yes	Yes	Yes	No	3	12
Palliative care	First-line stage IV NSCLC		QoL primary endpoint	**4**	Yes	Yes	Yes	Yes	Yes	Yes	No	3	21
Radium-223	Late-line castration-refractory prostate cancer	ALSYMPCA	Upgrade based on QoL improvement	**5**	Yes	Yes	Yes	No	Yes	NA	Yes	2	26
Enzalutamide	Second-line castration-refractory prostate cancer after docetaxel	AFFIRM	Upgrade based on QoL improvement	**4**	Yes	Yes	Yes	Yes	No	No	Yes	2	28
Docetaxel 3-weekly	Castration-refractory prostate cancer	TAX 327	Upgrade based on QoL improvement	**3**	Yes	Yes	Yes	Yes	No	Yes	No	2	29
FOLFIRINOX	First-line advanced or metastatic pancreatic cancer		Upgrade based on QoL improvement	**5**	Yes	Yes	Yes	Yes	No	NA	No	1	14
Afatinib	First-line EGFR TKI-naïve locally advanced or metastatic NSCLC with activating EGFR mutation	LUX-LUNG 3	Upgrade based on QoL improvement	**4**	Yes	Yes	Yes	No	Yes	NA	No	1	17,18
Ceritinib	First-line stage IIIB or IV ALK-rearranged non-squamous NSCLC	ASCEND-4	Upgrade based on QoL improvement	**4**	Yes	Yes	Yes	No	Yes	NA	No	1	7
Sunitinib	First-line metastatic RCC		Upgrade based on QoL improvement	**4**	Yes	Yes	Yes	No	Yes	NA	No	1	30,31
Afatinib	Squamous NSCLC progressing on or after platinum-based ChT	LUX-LUNG 8	Upgrade based on QoL improvement	**2**	Yes	Yes	Yes	No	Yes	NA	No	1	22
Crizotinib	First-line stage III or IV ALK-rearranged non-squamous NSCLC	PROFILE 1014	Upgrade based on QoL improvement	**4**	Yes	Yes	Yes	No	No	NA	No	0	20
Crizotinib	Second-line stage III or IV ALK-rearranged non-squamous NSCLC	PROFILE 1007	Upgrade based on QoL improvement	**4**	Yes	Yes	Yes	No	No	NA	No	0	19
Dabrafenib	First-line unresectable or metastatic melanoma with BRAF V600E mutation	BREAK-3	Upgrade based on QoL improvement	**4**	Yes	Yes	No	No	No	NA	No	0	24,25

Continued

Table 4. Continued

Trial details					Prerequisites			Checklist items				Overall score	Ref
					(i) Primary or secondary endpoint	(ii) Valid and reliable instrument	(iii) Statistically and clinically significant improvement in overall/global QoL	(i) Clear hypothesis and methods	(ii) Compliance and missing data	(iii) Results	(iv) Statistical and clinical significance[a]	Number of positive items	
Medication	Treatment setting	Trial name	Reason to include	ESMO-MCBS score									
Ceritinib	Stage IIIB or IV ALK-rearranged NSCLC previously treated with chemotherapy and crizotinib	ASCEND-5	Upgrade based on QoL improvement	**4**	Yes	No	Yes	No	No	NA	No	0	[8]
Tivozanib	First-line metastatic RCC or second line after progression on cytokine therapy	TIVO-1	Downgrade for lack of QoL improvement	**1**	Yes	Yes	No	No	No	NA	No	0	[9]

ChT, chemotherapy; ECOG score, Eastern Cooperative Oncology Group score; EGFR, epidermal growth factor receptor; ESMO-MCBS, European Society of Medical Oncology-Magnitude of Clinical Benefit Scale; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NSCLC, non-small-cell lung cancer; QoL, quality of life; RCC, renal cell carcinoma; T-DM1, trastuzumab emtansine.

[a]The difference in the results for prerequisite 3 and checklist item 4 is caused by the fact that for a positive score on item 4, a positive answer on three questions is required: a clear description of primary statistical method, correction for multiplicity, and the use of a pre-defined threshold for clinical relevance.

publications and separate publications on QoL data. If QoL was a secondary endpoint but has not been published, this will be annotated on the ESMO-MCBS Scorecard.

The ESMO-MCBS Working Group appreciates that it takes time to adopt the SPIRIT-PRO, CONSORT-PRO, and SISAQOL guidelines, published between 2013 and 2020, in study protocols and reports. It acknowledges that clinical trials incorporating QoL endpoints until now were not designed to meet these criteria which are the basis of the ESMO-MCBS QoL checklist. Consequently, the ESMO-MCBS Working Group plans for a stepwise implementation plan for its checklist criteria with a transition period during which not all items of the ESMO-MCBS QoL checklist will have to be met. Clinical trials published until January 2025 that meet the prerequisites and score at least two out of four items on the QoL checklist will be eligible for ESMO-MCBS grading. Clinical trials published thereafter will have to meet the prerequisites and score positive on all four items. If QoL analysis and reporting does not meet the standards defined by the prerequisites or the checklist items, this will be annotated on the ESMO-MCBS Scorecard. The results of QoL studies not showing benefit will be documented as 'no QoL benefit observed'. However, the checklist will not be applied retroactively to studies that already have received a final score.

A limitation of the four-item checklist is that it does not cover all aspects of the design, analysis, and reporting of QoL research. This was done with the intention to create a pragmatic, user-friendly tool for use in the context of ESMO-MCBS. Furthermore, QoL research is rapidly evolving and we anticipate that the QoL checklist will be revised as standards for QoL research develop. Much anticipated in this regard are the recommendations that will be generated for PRO analysis in clinical cancer trials by the international multidisciplinary consortium SISAQOL-IMI. Once available, these recommendations will be used to inform future refinements of the checklist. For example, the checklist item on compliance rates now relies on the expert opinion of the reviewer on what should be considered a 'high rate', because there is no general agreed acceptance threshold for missing data. This is related to the finding that the effect of missing data on bias and power is dependent on several factors, including sample size, disease stage, and missing data mechanism.[6]

Similarly, there is currently no international established standard for a minimal clinically important difference for QoL improvement or deterioration. Several initiatives to define minimum important differences for specific instruments have been published, but thresholds differ by the method that was used, by the direction of change, by domain, and by tumour type.[40-42] Therefore, checklist item 4 regarding clinical relevance asks whether a threshold for clinical relevance was pre-specified and taken into account rather than asking for a minimum percentage improvement. 'Clinically Meaningful Change' is one of the work packages of SISAQOL-IMI, and if a consensus is reached on a definition, this will be incorporated into the next version of the checklist.

Finally, the QoL checklist has not been validated in single-arm studies. Currently, there is no consensus on whether QoL data from single-arm studies can be used to make conclusions on clinical benefit from medicines, because an improvement in QoL may not necessarily be attributable to the treatment. However, also 'Single-Arm Studies' is a topic that will be addressed by SISAQOL-IMI and will be part of future refinement of the checklist.

In summary, implementing this QoL checklist will facilitate objective and transparent decision making on credentialing QoL research within the ESMO-MCBS scoring process. To facilitate accurate QoL scoring, the ESMO-MCBS Working Group encourages timely reporting of all QoL results, including negative studies, according to existing guidelines for QoL research.[4-6] This can be either in a separate publication within a reasonable time, or in an extensive data supplement. We hope and anticipate that this initiative will promote greater methodological rigour in designing, implementing, and reporting studies that include QoL as an endpoint.

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DISCLOSURE

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