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## On the underreporting of health-related quality of life and regulatory approval

Recently, Marandino et al. [1] published a systematic review highlighting the shortcomings with respect to reporting of health-related quality of life (HRQoL) in contemporary oncology trials. Notably, among the 446 randomized phase III clinical trials evaluated between 2012 and 2016, close to half (47.1%) did not assess HRQoL as an end point, which was true even for trials designed to treat advanced disease (40.1%). Surprisingly, there appeared to be no significant difference in reporting of HRQoL in the primary publication between trials with positive outcomes and negative outcomes. The omission of this important data from many trials unfortunately detracts from a thorough understanding of the risks and benefits of a given regimen.

To further investigate whether this deficit in oncology clinical trials exists even within the highest tier, we performed a systematic review of randomized phase III clinical trials published between 2009 and 2018 that resulted in an FDA approval. We believe that these trials directly impact treatment practice and patient care and therefore should be held to the highest standards. A search of Food and Drug Administration (FDA) database was performed for drugs and therapies approved for treatment of solid and hematologic malignancies. The phase III clinical trials that led to FDA approval of the given therapy were identified. In total, 140 phase III trials resulted in an FDA approval for 84 distinct drugs during this time period. Of the 140 trials, 78 (56%; 95% confidence interval: 47% to 64%) reported HRQoL with 50 (64%) reporting HRQoL outcomes in the primary publication and 28 (36%) reporting HRQoL outcomes in a separate publication.

This data support the findings of Marandino et al. demonstrating the low rate of HRQoL reporting even within pivotal practice changing phase III trials. About half of all these clinical trials do not report on HRQoL as an end point, undermining its value in clinical care. Interestingly, HRQoL was listed as an outcome measure on *ClinicalTrials*.gov in only 50% of trials, demonstrating that HRQoL reporting appears to reflect phase III trial construction rather than lack of reporting. It appears that a relatively low level of importance is placed on HRQoL measures and that lack of inclusion of HRQoL data does not appear to compromise the regulatory success of an investigational agent. It is important we continue to recognize the value of HRQoL measures, as survival outcomes do not necessarily match patients' experience while receiving treatment [2, 3]. These measures become increasingly important for advanced/metastatic disease where symptom improvement may outweigh marginal gains in length of life for patients. In a reflection of the importance of HRQoL, both the American Society of Clinical Oncology and European Society of Medical Oncology have integrated patient reported outcomes into their treatment evaluation tools [4, 5]. We believe the burden now falls on regulatory agencies to properly incentivize the inclusion and reporting of this valuable data.

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# Reply to the letter to the editor 'On the underreporting of health-related quality of life and regulatory approval' by Bhamidipati et al.

We are pleased that our publication [1] met the interest of Bhamidipati et al. [2] Data reported in their correspondence are based on the analysis of trials leading to Food and Drug Administration approval for solid or hematologic malignancies, between 2009 and 2018, which is a period of time entirely including the time-frame considered in our analysis. Their results are very similar to ours, showing sub-optimal adoption of quality of life (QoL) among end points and poor QoL reporting in publications.

We strongly believe that QoL assessment is crucial to evaluate the benefit–harm balance of new anticancer treatments. Especially when trial results show a questionable clinical relevance due to the adoption of surrogate endpoints, like progression-free survival (PFS), QoL results should be considered of paramount importance to prove the added value of a new treatment [3].

In the database, we used for our published analysis [1], 87 publications of trials conducted in the advanced/metastatic setting showed a positive result based on a primary endpoint different from overall survival (OS), mostly PFS [4]. Of these 87 publications, the majority (67) did not report positive OS results in the primary publication. Although this situation (a positive result in a surrogate end point, without evidence of benefit in OS) is exactly the situation requiring the availability of QoL data in order to judge the clinical relevance of the results, disappointingly 21 of those studies (31.3%) did not include QoL among study end points, and 40 publications (59.7%) did not present any QoL results.

In accordance with the analysis presented by Bhamidipati et al., these results highlight the lack of QoL information for several new treatments that, on the basis of positive results, are subject to evaluation for regulatory approval.

Bhamidipati et al. underline the recent position of most important scientific societies, which led to the inclusion of QoL within the evaluation tools of treatment value. As a matter of fact, the attention of scientific community to these issues is recently increasing. At 2018 ESMO meeting, a whole session of oral presentations about metastatic breast cancer was dedicated to QoL results of positive and potentially practice-changing randomized trials. Dr. Leslie Fallowfield, who acted as discussant of that session, recently commented our analysis [5] highlighting that unfortunately QoL is often still considered a 'Cinderella outcome'.

Also ASCO, at the end of 2018, dedicated a post to this specific topic, emphasising QoL as a key element for the assessment of new treatments, even more in those situations where the statistical significance of results conflicts with their clinical relevance [6].

As Bhamidipati et al. state, the burden now falls to regulatory agencies, which should make efforts to encourage the inclusion and timely reporting of QoL issues. On the other hand, we believe that also the scientific community should make efforts to pursue a more rigorous methodology in QoL assessment and reporting.

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