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Health-related quality of life outcomes reporting associated with FDA approvals in haematology and oncology

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ABSTRACT

Objective Health-related quality of life (HRQoL) outcomes are important in making clinical and policy decisions. This study aimed to examine the HRQoL reporting in cancer drug trials leading to Food and Drug Administration (FDA) approvals.

Methods and analysis This retrospective cohort study analysed HRQoL data for trials leading to FDA approvals between July 2015 and May 2020. Proportion of included trials that reported HRQoL, latency between FDA approval and first report of HRQoL data, HRQoL outcomes, and their correlation with OS (overall survival) and PFS (progression-free survival) were analysed.

Results Of the 233 trials associated with 207 FDA approvals, HRQoL was reported in 50% of trials, of which only 42% had the data reported by the time of FDA approval. There were no changes in frequency of HRQoL reporting between 2015 and 2020. HRQoL data were first reported in the primary publication in only 30% trials. Of the 115 trials with HRQoL data available, HRQoL improved in 43%, remained stable in 53% and worsened in 4% of trials. Among the trials that led to FDA approvals based on surrogate endpoints (79%), HRQoL was reported in 45% and improved only in 18% trials. There was no association between OS and PFS benefit and HRQoL outcomes.

Conclusion Rates of HRQoL reporting were suboptimal in trials that led to FDA approvals with no improvements seen between 2015 and 2020. HRQoL reporting was often delayed and not presented in the primary publication. HRQoL reporting was further sparse in trials with approvals based on surrogate endpoints and HRQoL improved in only a minority of them.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Health-related quality of life (HRQoL) outcomes are crucial in delivery of patient-focused care. Earlier studies inquired HRQoL outcomes in either phase III or phase I/II clinical trials or in solid or haematological studies separately.

WHAT THIS STUDY ADDS

⇒ Our study comprehensively looked at the trials associated with Food and Drug Administration approvals in both solid tumours and haematological malignancies and included both early-phase and phase III trials over a duration of 5 years. We found that HRQoL outcomes were reported in 50% of trials, published with the primary publication in 30% of trials and improved in 43% of trials. Nearly 80% of trials were associated with approvals based on surrogate endpoints with HRQoL reported in 45% and improved in only 18% of these trials.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights that despite the known crucial importance of HRQoL outcomes, their reporting remains suboptimal. The majority of the trials reported HRQoL outcomes in an ancillary paper/abstract at a much later time. Lack of timely availability of HRQoL outcomes data deprives the opportunity of integrating patients' experiences into clinical and regulatory decision-making process.

INTRODUCTION

Over the last decade, treatment paradigms across oncology have been transformed by the approval of several new drugs by Food and Drug Administration (FDA). Increasingly, these approvals are based on surrogate endpoints (SEPs) such as radiologic or haematological response,[1 2] however, they may not be clinically meaningful without either health-related quality of life (HRQoL) or overall survival (OS) benefit.[3 4] HRQoL constitutes an important endpoint necessary for both regulatory and clinical decision-making.

Despite the crucial importance of HRQoL outcomes in the delivery of patient-focused care, their reporting remains poor.[5–7] HRQoL outcomes data are often not reported in the primary publication with the efficacy and safety data.[8] Information regarding HRQoL outcomes is infrequently included in FDA product labels, a commonly used source of information for drug benefits and safety.[9–12] Due to the lack of timely availability of HRQoL data, patient experiences are often not taken into consideration for decisions regarding regulatory approval, clinical decision-making, healthcare policy and reimbursement purposes.

We studied cancer drug FDA approvals over 5 years to estimate the percentage of approvals without any HRQoL data, the latency between approval and availability of HRQoL data and the association of HRQoL data with efficacy outcomes. We also evaluated chronological changes in HRQoL reporting to inform the oncology community of the current state of HRQoL reporting.

METHODS

Search strategy and selection criteria

We conducted a retrospective cohort study of trials associated with FDA approvals for oncology. Inclusion criteria for studies included (1) clinical trials associated with FDA approvals in oncology from July 2015 to May 2020 and (2) text available in English as publications or abstracts by February 2021 (data cut-off). Exclusion criterion included approvals for diagnostic tests, biosimilars, drugs for benign tumours and non-malignant haematological indications.

Initial study search was conducted using clinical trial information retrieved from the FDA approval notification page and FDA labels. A systemic literature search was then performed on PubMed, Google Scholar and ClinicalTrials.gov website using the terms: "NCT number" OR "trial name" OR "drug name" or within the FDA label. If HRQoL data were not reported in the primary publication, a search was conducted on PubMed and Google Scholar using the "NCT number", "trial name" or "drug name" and the following terms: "patient reported outcomes", "PROs", "health-related quality of life", "HRQoL", "quality of life" and "QoL".

Data extraction and endpoints

Collected variables included disease category, cancer subtype, localised or metastatic disease, phase of study, number of subjects, type of primary endpoint, and pharmacologic category. Trials in which the experimental arm involved more than one drug category, (eg, immunotherapy in combination with chemotherapy) were classified as combination therapy. OS and progression-free survival (PFS) data were collected at the time of FDA approval. Data from approvals with multiple trials were collected as separate entries. SEPs were defined as either PFS, disease-free survival (DFS), overall response rate (ORR), disease-control rate (DCR) or pharmacokinetics (PK).

Datapoints regarding HRQoL reporting included type of endpoint, timing of HRQoL assessment, type of assessment tool and latency defined as the time between the FDA approval and first reporting of HRQoL outcomes. The impact on HRQoL was stratified into three categories: improved, worsened or stable. For single-arm studies, impact on HRQoL was assessed by the differences between pretreatment and post-treatment assessments. For randomised studies, the pretreatment and post-treatment difference in the experimental group was compared with the pretreatment and post-treatment difference in the standard group to determine the net impact on HRQoL. This determination was based on statistical rather than clinical significance due to remarkable heterogeneity between studies. The overall impact on HRQoL was based on the impact on the global domain of the assessment tool where available and by the overall score and interpretation of other assessment tools for the rest.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical analysis

The objectives of the study were to assess (1) the percentage of trials with HRQoL as an endpoint, (2) the percentage of trials that reported HRQoL outcomes, (3) latency of HRQoL reporting and (4) impact on HRQoL and correlation with survival outcomes.

The study and reporting characteristics were summarised using frequencies and relative frequencies, with comparisons made using Fisher's exact test. HRQoL reporting was summarised by year of approval, with annual trends assessed using the Cochran-Armitage trend test. HRQoL reporting status and treatment impact on HRQoL were summarised by trial characteristics using frequencies and relative frequencies, with associations assessed using Fisher's exact test. OS and PFS benefit were summarised by impact on HRQoL using the median and IQR, and visually using boxplots. Comparisons were made using the Kruskal-Wallis test.

A multivariable logistic regression model was considered to identify a set of 'independent' factors associated with HRQoL reporting. A backwards selection approach was used (with an alpha exit of 0.2), where trial characteristics in table 1 (excluding comparator type) were considered candidate variables. ORs and corresponding 95% CIs were obtained from model estimates.

Latency was summarised using the median IQR and visually using a histogram. A categorised version of latency was developed using 6-month intervals. The OS and PFS benefit, HRQoL impact, and report type were summarised by categorised latency using frequencies and relative frequencies, with associations assessed using Fisher's exact test.

All analyses were conducted in RStudio V.4.0.2 using a two-sided significance level of 0.05.

RESULTS

Baseline characteristics of trials

There were 241 FDA approvals for haematology and oncology indications between July 2015 and May 2020. Of these, 34 approvals were excluded (non-malignant haematological, 23; biosimilars, 5; diagnostic tests, 3; benign tumour, 1; expanded indication based on previously reported trial, 1; OS update for a previously approved

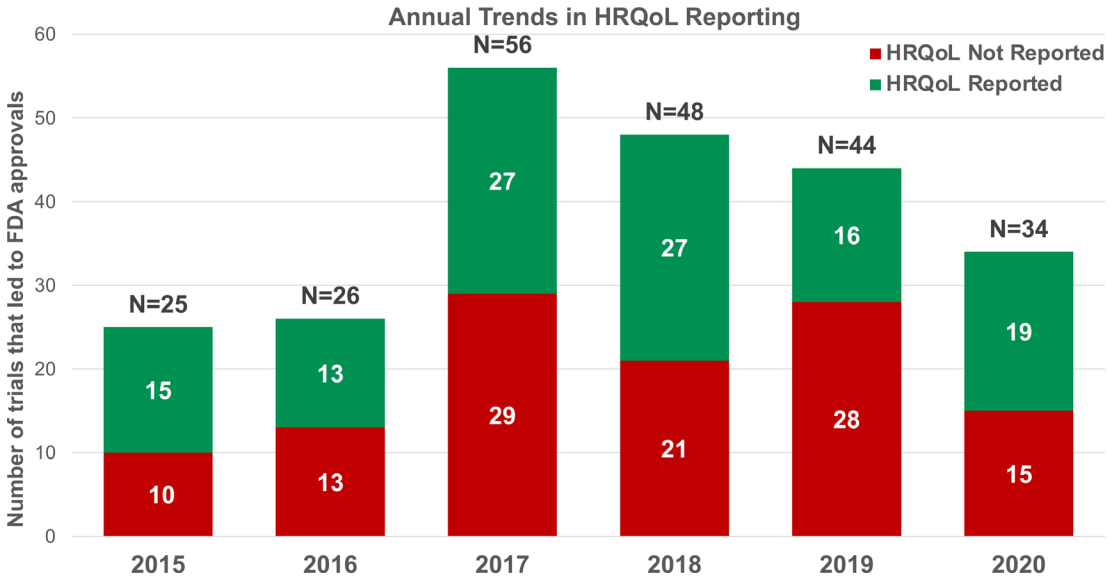

Figure 1 Annual trends in HRQoL reporting in clinical trials leading to Food and Drug Administration (FDA) approval of haematology/oncology drugs (N=233). HRQoL, health-related quality of life.

drug, 1). Our final cohort included 207 FDA approvals associated with 233 trials including 105 883 patients.

Key characteristics of these trials are highlighted in online supplemental table 1. The majority of trials involved solid tumours (68.2%), advanced/metastatic disease (90.6%), were phase 3 studies (57.9%), with a comparator arm in 63.1% studies of which 78.2% included standard of care active anticancer therapies. The most frequent pharmacological category was targeted therapies (39.5%). FDA approval was based on OS benefit in only 20.6% of trials. The remainder were approved based on SEP of PFS/DFS benefit (31.8%), ORR (34.3%), DCR (10.3%) and PK (3%).

Characteristics of HRQoL reporting

Overall, 55.8% trials had HRQoL assessment as a prespecified endpoint (online supplemental table 2). Of these, HRQoL was listed as a secondary endpoint in 67.7% and an exploratory endpoint in 32.3% trials. HRQoL was subsequently reported in 50.2% trials. The annual reporting rates were 60% in 2015, 50% in 2016, 48.2% in 2017, 56.3% in 2018, 36.4% in 2019 and 55.9% in 2020 (figure 1). There was no consistent trend in HRQoL reporting over time (p=0.474). HRQoLs were assessed during the treatment period in 98.3% of trials and after treatment completion in 47.9% of trials. European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-C30 was the most used general assessment tool (61.5%).

Associations of HRQoL reporting based on trial characteristics are summarised in table 1. HRQoLs were more likely to be reported in trials associated with solid tumours (59.1%) than haematological malignancies (31.1%, p<0.001), phase III trials (71.1%) than phase I/II trials (21.4%, p<0.001), trials with comparator arm (67.3%) than no comparator arm (20.9%, p<0.001) and trials where the comparator arm consisted of standard of care (whether placebo or active anticancer therapy, p=0.03). HRQoL reporting was higher in trials with approvals based on PFS/DFS benefit (74.3%) and OS benefit (70.8%) vs ORR (23.7%), DCR (33.3%) or PK benefit (14.3%) (p<0.001). There were no significant associations based on pharmacological category or disease stage. On multivariate analysis, phase I/II studies were less likely to report HRQoL versus phase III studies (OR 0.44, p<0.001) and trials for haematological malignancies were less likely to report HRQoL than solid tumours (OR 0.53, p<0.001) (online supplemental table 3). HRQoL reporting based on disease subtypes is summarised in online supplemental table 4.

Latency of HRQoL reporting

The median latency of HRQoL reporting was 1.1 months (IQR −3.0–11.5 months; figure 2). HRQoL data were first reported in the initial paper in only 29.9% trials (online supplemental table 2), with the remainder in either an ancillary paper (43.6%) or an abstract (26.5%).

Overall, among the 117 trials that reported HRQoL, HRQoL data were available by the time of approval in only 41.9% trials and by 6 months after approval in 62.4% trials (online supplemental table 5). HRQoL data were published >6 months and >12 months following approval in 37.6% and 25.6% trials, respectively. A higher percentage of solid tumour than haematological malignancies trials reported HRQoL data by 6 months of approval (65.9% vs 47.8%, p=0.05).

With increased latency of reporting from the time of approval, HRQoL data were increasingly reported in an ancillary paper/abstract (online supplemental figure 1).

Impact on HRQoL outcomes across clinical trials

Two studies were excluded from HRQoL impact analysis due to either a lack of data on the global domain or a lack of a total HRQoL score. Of the 115/117 studies included, 42.6% trials reported an improvement in HRQoL, 53% trials reported

Table 1 Baseline and disease characteristics of trials that led to drug approvals by HRQoL reporting

Baseline characteristics	Total N=233	No HRQoL reported N=116	HRQoL reported N=117	P value
Category of approval				
Chemotherapy	8 (100%)	4 (50.0%)	4 (50.0%)	0.94
Immunotherapy	45 (100%)	23 (51.1%)	22 (48.9%)	
Targeted therapy	92 (100%)	46 (50.0%)	46 (50.0%)	
Combination	50 (100%)	25 (50.0%)	25 (50.0%)	
Native monoclonal antibody	10 (100%)	5 (50.0%)	5 (50.0%)	
Cellular therapy/BITE	6 (100%)	2 (33.3%)	4 (66.7%)	
Antibody drug conjugates	13 (100%)	8 (61.5%)	5 (38.5%)	
Other	9 (100%)	3 (33.3%)	6 (66.7%)	
FDA approval				
OS/OS+PFS	48 (100%)	14 (29.2%)	34 (70.8%)	<0.001
PFS/DFS	74 (100%)	19 (25.7%)	55 (74.3%)	
ORR	80 (100%)	61 (76.3%)	19 (23.7%)	
Disease control	24 (100%)	16 (66.7%)	8 (33.3%)	
PK/PK+ORR	7 (100%)	6 (85.7%)	1 (14.3%)	
Clinical Trial Phase				
I/II	98 (100%)	77 (78.6%)	21 (21.4%)	<0.0001
III	135 (100%)	39 (28.9%)	96 (71.1%)	
Comparator				
No	86 (100%)	68 (79.1%)	18 (20.9%)	<0.0001
Yes	147 (100%)	48 (32.7%)	99 (67.3%)	
Comparator type				
Standard of care active anticancer therapy	115 (100%)	35 (30.4%)	80 (69.6%)	0.03
Best supportive care/placebo	28 (100%)	9 (32.1%)	19 (67.9%)	
Other	4 (100%)	4 (100.0%)	0 (0%)	
Disease characteristics	**Total**	**No HRQoL reported**	**HRQoL reported**	**P value**
Type of cancer				
Solid tumour	159 (100%)	65 (40.9%)	94 (59.1%)	<0.001
Haematological malignancies	74 (100%)	51 (68.9%)	23 (31.1%)	
Stage				
Early	15 (100%)	4 (26.7%)	11 (73.3%)	0.28
Advanced/metastatic	144 (100%)	61 (42.4%)	83 (57.6%)	

BITE, bispecific T-cell engager; DFS, disease-free survival; FDA, Food and Drug Administration; HRQoL, health-related quality of life; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics.

stable HRQoL and 4.3% reported a worsening in HRQoL (online supplemental figure 2). Impact on HRQoL based on trial characteristics is summarised in online supplemental table 6. Further, among trials with a latency of >6 months (n=44), HRQoL was improved in 43.2% trials (19/44), stable in 54.5% trials (24/44) and worsened in 2.3% trials (1/44) (online supplemental table 7).

HRQoL data were reported in 70.2% (33/47) of trials with approvals based on OS benefit vs 44.6% (82/184) of trials with approvals based on SEP (table 2). An improvement in HRQoL was seen in 34% of trials with OS benefit vs 17.9% of trials with approvals based on SEP. Importantly, all trials (n=5) with worsened HRQoL data led to approval based on PFS/DFS benefit.

Association between HRQoL and survival outcomes

Overall, by the time of FDA approval, OS and PFS data were reported in 64.4% and 72.1% trials, respectively. For trials reporting significant difference between experimental and control arms, the median OS and PFS benefit was 3.5 months (IQR 2.2–4.8 months) and 4.4 months (IQR 2.5–9.0 months), respectively. The distribution of median OS and PFS benefits across the trials is shown in figure 3A,C. To study whether there was an association between the latency

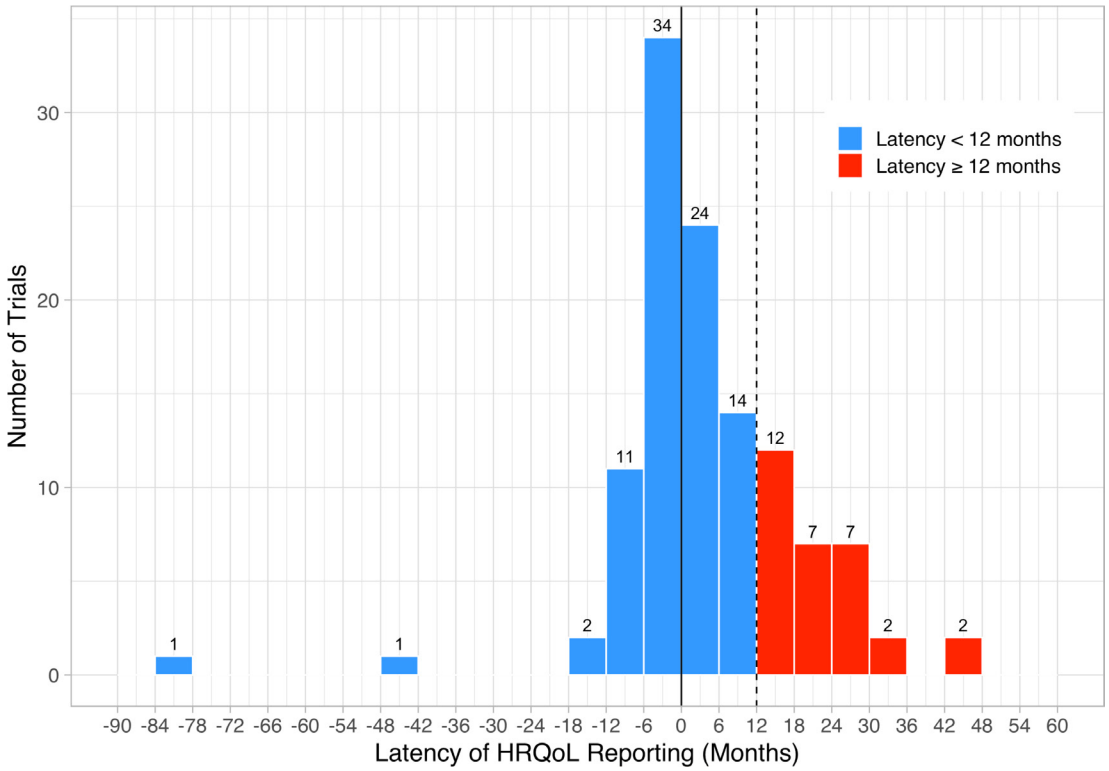

Figure 2 Latency of HRQoL reporting from time of FDA approval in months. Bars in red indicate a latency of ≥12 months. FDA, Food and Drug Administration; HRQoL, health-related quality of life.

of HRQoL reporting and survival benefit, we defined three survival benefit categories: <3 months, 3–6 months and >6 months. In trials with a latency of >6 months, an OS benefit of >6 months was seen in only 1/15 trials (figure 3B) and a PFS benefit of >6 months was seen in only 7/23 trials (figure 3D). Further, there was no association between median OS and PFS benefit and the impact on HRQoL (online supplemental figures 3 and 4).

DISCUSSION

In this study, we show that even among clinical trials associated with FDA approvals, HRQoL information was available for only half of the trials of which many reported HRQoL data more than 6 months after approval, sometimes only in an abstract form. Eighty percent of trials led to approvals based on SEPs of which only 45% reported HRQoL outcomes and only 18% were associated with an improvement in HRQoL. Our study demonstrates that despite calls for improving HRQoL reporting, the percentage of trials that provide any meaningful HRQoL information remains suboptimal, and physicians and patients need to wait several months and sometimes years for HRQoL information by which time the drug will already have been extensively used in practice.

Our data reinforce prior studies that demonstrated under-reporting of HRQoL in cancer trials.[13–16] An earlier

Table 2 Indication for approval, reporting and impact on HRQoL

	Approval indication					
Characteristic	**OS/OS+PFS**	**PFS/DFS**	**ORR**	**DCR**	**PK/PK+ORR**	**All surrogate endpoint studies**
HRQoL						
Not reported	14 (29.8%)	19 (25.7%)	61 (77.2%)	16 (66.7%)	6 (85.7%)	102 (55.4%)
Reported	33 (70.2%)	55 (74.3%)	18 (22.8%)	8 (33.3%)	1 (14.3%)	82 (44.6%)
Impact on HRQoL						
Improved	16 (34%)	21 (28.4%)	10 (12.7%)	1 (4.2%)	1 (14.3%)	33 (17.9%)
Worse	0 (0%)	5 (6.8%)	0 (0%)	0 (0%)	0 (0%)	5 (2.7%)
Stable	17 (36.2%)	29 (39.2%)	8 (10.1%)	7 (29.2%)	0 (0%)	43 (23.4%)
Total	47 (100%)	74 (100%)	79 (100%)	24 (100%)	7 (100%)	184 (100%)

DCR, disease control rate; DFS, disease-free survival; HRQoL, health-related quality of life; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics.

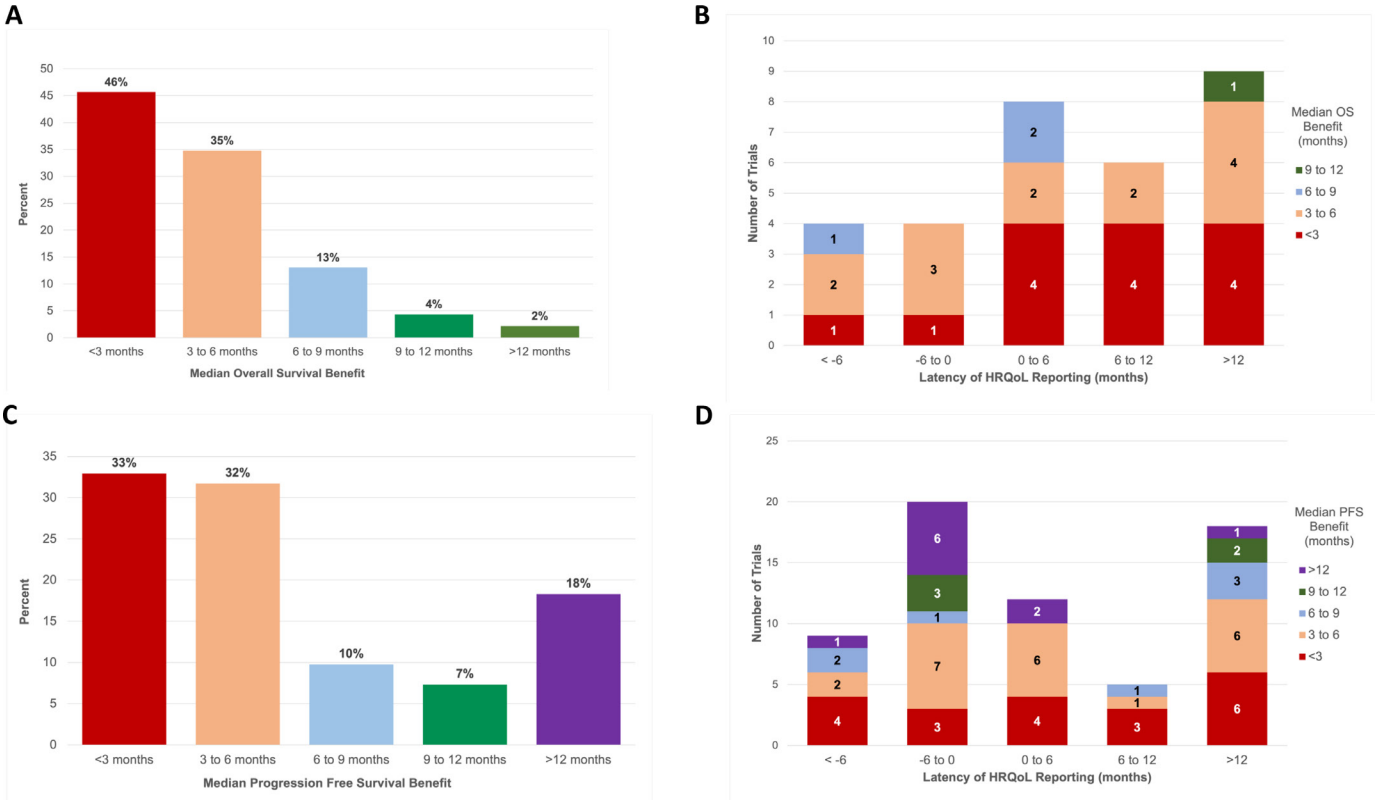

Figure 3 (A) Median OS benefit in clinical trials leading to FDA approval of haematology/oncology drugs (N=46). (B) Median OS benefit stratified by latency of HRQoL reporting in months (N=31). (C) Median PFS benefit in clinical trials leading to FDA approval of haematology/oncology drugs (N=82). (D) Median PFS benefit stratified by latency of HRQoL reporting in months (n=64). FDA, Food and Drug Administration; HRQoL, health-related quality of life, OS, overall survival; PFS, progression-free survival.

study from 2007 to 2013 showed that only 29% of registration trials in oncology used an HRQoL measure,[14] a number which increased to 50.2% in the current study suggesting that gains have been made over the past decade. However, disappointingly, there was no further improvement in HRQoL reporting rates between 2015 and 2020 in our study suggesting much work remains to be done, especially in malignant haematology and early-phase studies. In our study, 42% approvals were based on either phase I/II studies out of which 21% reported HRQoL data. Other studies looking at phase I trials showed that HRQoL reporting can be as low as 1%–2%.[17 18] This is not surprising since early-phase studies are primarily aimed at assessing safety and PK, have a small sample size and lack a comparator arm. Although assessing HRQoL in all phase I trials may not be feasible or cost-effective, if a phase I/II trial is being planned to seek approval, HRQoL data should be mandatorily collected to inform clinical decision-making. Importantly, there can be significant under-reporting of adverse events by clinicians versus patients in phase I trials, thereby missing the opportunity of taking patients' experience into consideration.[19] This can be mitigated by using patient-reported outcomes version of the common terminology criterion for adverse events (PRO-CTCAE) in studies.[20]

We found that more than one-third of trials have a latency of HRQoL data reporting of more than 6 months, and a quarter have a latency of HRQoL reporting of more than a year after the FDA approval. Moreover, two studies (NCT01968213, NCT01968213) published HRQoL data more than 3.5 years after the approval with unclear reasons behind the delay in HRQoL reporting.[21–24] Similarly, a study analysing malignant haematology trials showed that HRQoL data were reported in only 26% of primary publications.[16] A report in solid tumour trials showed that the average impact factor (IF) of the primary publication was[20] 26.5 vs IF of 6 for ancillary publication for HRQoL data.[13] The delay in availability and publication in low IF journals could lead to undermining of the importance of HRQoL data while making regulatory decisions. Since novel treatments are readily incorporated in clinical practice shortly after FDA approvals, publication of HRQoL data in a lower-impact paper/abstract months later is highly likely to be missed by the physicians.

We further looked at the association between HRQoL outcomes and efficacy outcomes. An improvement in HRQoL was seen in 42.4% of trials in solid tumours which is consistent with two other reports that showed an improvement in HRQoL in 56% and 42% of trials.[25 26] It was concerning to note that overall, only 18% of approvals based on SEP were associated with an HRQoL benefit. Further, all trials with a worse impact on HRQoL led to approvals based on PFS/DFS.[27–34] Given that HRQoL improvement is a major goal, especially in a palliative care

setting, these data are sobering. Our findings are also consistent with other studies that have shown that when PFS/DFS is used as a SEP, a benefit in HRQoL cannot be assumed and that drugs that improve only PFS can be associated with detrimental effects on HRQoL.[14 35–37] Several drugs are given accelerated approvals based on SEP in early-phase studies.[1 38] Few agents were withdrawn after confirmatory studies failed to show a survival benefit.[39–41] These data reinforce the importance of post-marketing studies for approvals based on SEP without an HRQoL benefit.

While the importance of examining the impact of new drugs on HRQoL is broadly acknowledged, there remain multiple potential challenges to integration of HRQoL data in clinical trials. PROs including HRQoL currently do not play a significant role in oncology drug marketing review, and how they can be used to support the approval of new oncology drugs is still in the exploratory stage.[42] As highlighted by the current study, the use of HRQoL data is limited by several issues related to study design and data collection. First, HRQoL data from single-arm or open-label trials can be difficult to contextualise in the absence of a comparator arm.[43] Even in trials with comparator arms, studies are often not statistically powered to determine the significance of longitudinal changes in HRQoL and caution is needed while interpreting HRQoL from a methodologically weak study. There is also considerable heterogeneity in the assessment tools used with inconsistent incorporation of disease-specific instruments. As we noted in our data collection, considerable variation also exists in the timing of HRQoL assessment across different trials. Potential solutions to these barriers include adequate funding for incorporation of HRQoL outcomes as a key endpoint (including in early-phase trials) with clinical studies powered to make meaningful interpretation of changes in HRQoL. The involvement of PRO experts and patient advocates at the time of trial inception and design would ostensibly help facilitate this. In addition, training research and clinical staff to collect HRQoL data and the use electronic PROs and PRO-CTCAE would help pivot the use of this data to the centre-stage of clinical decision-making.[20 44]

Our study has several limitations. Trials with approvals in the later study period have a shorter follow-up and may have unpublished HRQoL data. This limitation was partly mitigated by allowing a follow-up of at least 8 months after the FDA approval. We limited our sample to trials associated with FDA approvals and did not include studies that may have impacted treatment paradigms without new drug labelling. However, if the availability and delay in HRQoL data is so suboptimal even for registration trials, we would assume a worse scenario for trials that may influence practice but do not necessarily lead to registration of a drug. Additionally, unpublished HRQoL data from certain studies could have been submitted to FDA along with the new drug applications. Since our study did not include data from the FDA review documents, it is possible that proportion of approved treatments with available HRQoL results could be underestimated. Future studies should focus on comprehensive HRQoL data from published studies as well data from FDA review documents. Since HRQoL was not designated as the primary or key secondary endpoint in most trials, there was typically insufficient control over power or type one error in these studies. Hence, caution is warranted when interpreting the analysis of HRQoL changes, either in individual trials or in the current analysis which relies on data from these trials. During data collection, remarkable heterogeneity was noted among studies with use of multiple HRQoL assessment tools without prespecified definitions for improvement and analysis. To assess and interpret impact on HRQoL as uniformly as possible, we decided to use the global domain based on guidance from ESMO-MCBS.[45] There could be clinically relevant improvements in other scales/items even in the absence of global QoL results which were not captured in this study. Data regarding the impact of HRQoL in clinical trials should be interpreted with caution in clinical practice in any case, as patients enrolled in trials have a better performance status and undergo a more stringent clinical monitoring. In the real-world setting, the tolerability of drugs and associated impact on HRQoL could vary significantly from patients enrolled in clinical trials.[15]

CONCLUSIONS

Our study highlights that despite significant advances in oncology, HRQoL reporting in trials associated with FDA drug approvals remains suboptimal. The majority of registration trials reported HRQoL data either in an ancillary paper or an abstract and at a much later time. Cancer drugs approved based on SEP were rarely associated with an improvement in HRQoL. HRQoL measurement is crucial to integrate patients' experiences into drug development. An urgent collaboration is needed between stakeholders including investigators, industry, regulators, patients, clinicians and journal editorial boards to ensure timely availability of HRQoL information on cancer drugs for the delivery of the highest quality of care.

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Contributors MG: concept and design, acquisition, analysis, and interpretation of data, writing: draft, review, and editing, administrative, technical, or material support. OSA: concept and design, acquisition, analysis, and interpretation of data, writing: draft, review, and editing. BB: concept and design, acquisition, analysis, and interpretation of data, writing: review, and editing. AM-H: concept and design, acquisition, analysis, and interpretation of data, writing: review, and editing. KA: statistical analysis, writing: review and editing. KC: statistical analysis, writing: review and editing. BG: concept and design, analysis, and interpretation of data, writing: review, and editing. PT: concept and design, analysis, and interpretation of data, writing: review and editing, project supervision, guarantor of the study.

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Patient consent for publication Not applicable.

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