Reporting of clinical trial uncertainties with new cancer drugs in journal publications and clinical guidelines

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More than 75% of cancer drugs are approved by the US Food and Drug Administration (FDA) through expedited regulatory programs,[1] the use of which often leaves clinical uncertainties that may arise from issues related to trial design, conduct, analysis, or reporting – such as unvalidated endpoints, limited long-term data, or approval based on a single trial – about drug efficacy and safety.[2] Communicating these uncertainties is important, as clinicians may otherwise be unaware and overestimate a drug's benefits and underestimate its risks.[3]

Although FDA describes these uncertainties in detail in its benefit-risk assessments,[2] these documents are not widely read by clinicians. Instead, clinicians often rely on journal publications and guidelines. It is unclear whether clinical trial uncertainties about newly approved cancer drugs are reported in these sources.

Methods

We used Drugs@FDA to identify cancer drugs approved by FDA from 2019 to 2022. We searched FDA review documents for uncertainties identified by FDA reviewers related to the primary outcomes of pivotal trials (**eMethods**; **eTable**). We focused on uncertainties included in the FDA's Benefit-Risk Framework, as these are considered by FDA as important to its decisions.[4]

In April 2025, we searched for publications of trials cited in FDA reviews and identified National Comprehensive Cancer Network (NCCN) guidelines that referenced each drug's approved indication. We also recorded the level of evidence for these recommendations. Our primary outcome was the proportion of uncertainties reported in publications and guidelines. We also assessed whether drugs with more uncertainties had lower evidence ratings and consensus recommendations in guidelines. We used descriptive statistics to summarize our findings. This study was exempt from ethics review as no data were collected from human participants. We followed the STROBE reporting guidelines.

Results

From 2019 to 2022, FDA approved 52 cancer drugs based on evidence from 56 pivotal trials. By April 2025, 51 trials (for 48 drugs) had been both published in journals and referenced in NCCN guidelines.

Of these 48 cancer drugs, 38 (79.2%) had clinical trial uncertainties highlighted in the FDA's Benefit-Risk Framework. FDA reviewers identified 94 uncertainties associated with these 38 drugs. Journal publications reported 22% (21/94) of the uncertainties identified by FDA reviewers and NCCN guidelines reported 23% (22/94) (**Table**). More than half of publications (20/38, 53%) and 47% (18/38) of guidelines did not report any of the identified uncertainties. O

Thirty-seven percent (14/38) of cancer drugs were recommended in NCCN guidelines with category 1, high levels of evidence , 58% (22/38) with category 2A evidence, and 5% (2/38) were not recommended. Drugs that were not recommended had the highest number of uncertainties (**Figure**).

Discussion

Among cancer drugs approved by FDA from 2019 to 2022, nearly 80% had clinical trial uncertainties highlighted in the FDA's Benefit-Risk Framework. However, journal publications and clinical guidelines rarely reported the uncertainties identified by FDA reviewers. While some divergence is expected, the extent of this discrepancy suggests that clinicians may be unaware of important clinical trial limitations identified by the FDA when making prescribing decisions.

One reason for this discrepancy may be that research reporting guidelines do not consistently require disclosure of key clinical trial uncertainties. For example, CONSORT-Surrogate only recently began requiring authors to justify the use of surrogate endpoints and consider their limitations.[5] Additionally, journal editors, peer reviewers, and guideline developers lack access to individual participant-level data available to FDA reviewers.

This study has limitations. First, some clinical trials were published before FDA approval and may not have reported uncertainties later identified by FDA reviewers. Second, NCCN guidelines may have incorporated more mature evidence published after approval that may have addressed some of the concerns raised in the initial FDA assessments, which has been found to take place in prior research.[6]

Nevertheless, to improve transparency and clinical decision-making, FDA should make its benefit-risk assessments more accessible and user-friendly. Reporting guidelines should consistently require disclosure of key clinical trial uncertainties, and guideline developers should systematically incorporate FDA assessments into their recommendations.

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Data Sharing Statement.

Data available: No additional data are available.

Explanation: All data used in the study are publicly available from the Drugs@FDA database, clinical trial publications in medical journals, and NCCN clinical practice guidelines.

Table: Reporting of clinical trial uncertainties in publications and NCCN guidelines identified by FDA reviewers in Benefit-Risk Frameworks for cancer drugs approved by FDA from 2019 to 2022.

	Clinical trial publications	**NCCN guidelines**
Uncertainties identified in the FDA's Benefit-Risk Framework	21/94 (22%)	22/94 (23%)
Uncertainty type		
Long-term benefits and harms	5/23 (22%)	7/23 (30%)
Single-arm trial design	4/22 (18%)	3/22 (14%)
Benefit-risk balance	4/16 (25%)	1/16 (6%)
Generalizability	1/8 (13%)	1/8 (13%)
Selection of the reported result	2/7 (29%)	5/7 (71%)
Magnitude of therapeutic benefit	1/5 (20%)	2/5 (40%)
Data integrity	0/3 (0%)	2/3 (67%)
Statistical analysis	1/3 (33%)	1/3 (33%)
Missing outcome data	2/2 (100%)	0/2 (0%)
Unvalidated endpoint	0/2 (0%)	0/2 (0%)
Deviation from the intended intervention	1/1 (100%)	0/1 (0%)
Randomization	0/1 (0%)	0/1 (0%)
Outcome measurement	0/1 (0%)	0/1 (0%)

FDA indicates US Food and Drug Administration; NCCN; National Comprehensive Cancer Network.