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Trustworthiness of Patient-Reported Outcomes in Unblinded Cancer Clinical Trials

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There is substantial and growing interest in measuring patient-reported outcomes in drug development trials,[1] for example, to understand the effects of treatment on tumor-associated pain. Although there is enthusiasm at the US Food and Drug Administration (FDA) for such a patient-centered approach, evidenced by guidance for industry published on this topic in 2009,[2] most oncology trials and FDA-approved medication labels still do not include information on patient-reported outcomes.[3]

Several reasons for the limited inclusion of patient-reported outcomes in cancer trials and drug labels have been cited, including cost and logistics, but the barrier that has most prevented progress in this area is the FDA's concern that patients cannot provide unbiased reports of their own symptoms if a trial is unblinded to study treatment allocation.[3] For example, the FDA asserts that patients with pain associated with metastatic prostate cancer might be inclined to report improvements in their pain based simply on the knowledge that they have been assigned to receive a novel therapeutic agent, regardless of the actual properties of that drug or of their actual pain responses.[2,3] The FDA extends this concept to encompass single-arm trials, open-label trials, and blinded trials in which they believe study arm allocation has likely been unmasked owing to imbalances in readily apparent toxic effects between arms. Indeed, in oncology, this scenario now represents most pivotal registration trials.

However, there is no empirical evidence that this type of bias exists, or, if it does, that it is sufficient to meaningfully affect results of clinical trials. Findings from published

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psychobehavioral literature suggest that cognitively, respondents are not prone to altering the content of their self-reports of symptoms associated with treatments that they are receiving.[4]

How might one empirically evaluate whether this type of bias exists, or at least whether it is sufficient to meaningfully affect results of analyses of patient-reported outcomes in clinical trials? One approach is to identify published double-blind controlled trials with negative efficacy results for primary clinical end points that had substantial imbalances of readily apparent toxic effects on patients between arms that might inadvertently unblind participants to their study arm allocations, which also included patient-reported outcomes as secondary end points. In such cases, we would expect the patient-reported outcome end points to yield negative results (unless they pertained directly to the imbalanced toxic effects). If the patient-reported outcomes differed between arms, it would suggest that bias may indeed meaningfully affect the results. Conversely, if patient-reported outcomes did not differ between arms, it would suggest that inadvertent unblinding is not a meaningful source of bias.

Indeed, a structured literature review identified 5 randomized, double-blind negative trials with imbalances by 10% or more in at least 3 symptomatic toxic effects between arms (as measured by the National Cancer Institute's Common Terminology Criteria for Adverse Events), and at least 1 secondary patient-reported outcome end point that included pain (Table).[5–9] In these trials, despite imbalances in multiple toxic effects, no significant differences in patient-reported outcomes were detected between study arms. This result suggests that, in cases of inadvertent unblinding associated with readily apparent toxic effects, there is not a sufficient bias to affect patient-reported outcomes between arms. Moreover, these findings also support the notion that this type of bias is not sufficiently present to meaningfully affect patient-reported outcomes in open-label studies.

To further explore this question in the future, prospective or retrospective analyses could be conducted of drug development programs that include both an open-label trial and a blinded controlled trial with inclusion of the same patient-reported outcome measure in both trials, to evaluate whether differences are comparable between arms. Regardless, in the interim, based on the information described above, we believe that inadvertent unblinding should not be considered a meaningful source of bias, and patient-reported outcomes should be included in cancer drug development trials and FDA drug labels regardless of blinding status. Patient-reported outcomes provide essential information that cannot be reliably captured any other way about the patient experience with products, and are necessary for complete evaluations of risks and benefits and the value of cancer therapeutics.[10] In light of the value of this information, in the absence of compelling evidence that a bias associated with knowledge of treatment allocation exists, there is little justification for withholding patient-reported outcomes from drug development trials or FDA drug labeling.

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Table

Results of Patient-Reported Outcome Comparisons in Randomized Clinical Trials[a]

Source/NCT (if applicable)	Comparison	Absolute Between-Arm Differences in Patients With Toxic Effects, %	Patient-Reported Outcome Measures	Results of Patient-Reported Outcome Comparisons
Eckhardt et al,[6] 2009	Tipifarnib + gemcitabine vs placebo + gemcitabine	Anorexia, 31 Diarrhea, 10 Rash, 14	MPAC pain intensity; VAS	Daily diaries of pain intensity showed no differences between arms
Kindler et al,[7] 2011 NCT00471146	Axitnib + gemcitibine vs placebo + gemcitabine	Anorexia, 10 Diarrhea, 11 Dysphonia, 18 Hypertension, 19 Mucositis, 13 Nausea, 10	EORTC QLQ-C30; EORTC QLQ-PAN26	Patients in both arms reported ≥5-point mean improvement from baseline pain on the EORTC QLQ-C30 and pancreatic pain on the EORTC QLQ-PAN26
Michaelson et al,[8] 2014 NCT00676650	Sunitinib + prednisone vs placebo + prednisone	Anorexia, 23 Diarrhea, 31 Dysgeusia, 20 Fatigue, 26 Hand-foot syndrome, 26 Hypertension, 17 Mucositis, 24 Nausea, 22	mBPI-SF worst pain score	No difference in percentage of patient-reported pain between arms at 2 mo (17.3% vs 12.5%; $P = .25$), 4 mo (20.9% vs 16.3%; $P = .32$), or 6 mo (21.4% vs 17.3%; $P = .39$)
Natale et al,[9] 2011 NCT00364351	Vandetanib vs erlotinib	Diarrhea, 12 Hypertension, 14 Rash, 10	EORTC QLQ-C30	No significant differences between study arms in time to deterioration of disease-associated symptoms for patient-reported pain (HR, 0.96; 95% CI, 0.83–1.11; $P = .58$), cough (HR, 0.94; 95% CI, 0.80–1.09; $P = .40$), or dyspnea (HR, 1.08; 95% CI, 0.93–1.25; $P = .33$)
Sonpavde et al,[10] 2012 NCT00286793	AT-101 + docetaxel + prednisone vs placebo + docetaxel + prednisone	Dehydration, 10 Nausea, 15 Peripheral neuropathy, 12	PPI	Patient-reported pain response rates did not differ significantly between study arms across all postcycle assessments (29% vs 28%)

Abbreviations: AT-101, *R*-(–)-gossypol acetic acid; EORTC QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-PAN26, European Organisation for the Research and Treatment of Cancer Pancreatic Cancer Module; HR, hazard ratio; mBPI-SF, Modified Brief Pain Inventory-Short Form; MPAC, Memorial Pain Assessment Card; NCT, clinicaltrials.gov registration number; PPI, Present Pain Index; VAS, visual analog scale.

[a]Trials had negative efficacy results but imbalances in toxic effects between arms by ≥10% for at least 3 toxic effects.