REVIEW ARTICLE

Patient-Reported Outcomes Are Changing the Landscape in Oncology Care: Challenges and Opportunities for Payers

Erin Zagadailov, PharmD, MS; Michael Fine, MD; Alan Shields, PhD

Background: A patient-reported outcome (PRO) is a subjective report that comes from a patient without interpretation by a clinician. Because of the increasingly significant role of PROs in the development and evaluation of new medicines, the US Food and Drug Administration (FDA) issued a formal guidance to describe how PRO instruments will be reviewed and evaluated with respect to claims in approved medical product labeling. Meanwhile, PROs continue to appear in oncology clinical trials more frequently; however, it is unclear how payers and policymakers can use PRO data in the context of decision-making for cancer treatments.

Objective: The objective of this article is to discuss the challenges and opportunities of incorporating oncology-related PRO data into payer decision-making.

Discussion: Payer concerns with PRO instruments are often related to issues regarding measurement, relevance, quality, and interpretability of PROs. Payers may dismiss PROs that do not independently predict improved outcomes. The FDA guidance released in 2009 demonstrates, as evidenced by the case of ruxolitinib, how PRO questionnaires can be generated in a relevant, trustworthy, and meaningful way, which provides an opportunity for payers and policy decision makers to focus on how to use PRO data in their decision-making. This is particularly relevant in oncology, where a recent and sizable number of clinical trials include PRO measures.

Conclusion: As an increasing number of oncology medications enter the market with product labeling claims that contain PRO data, payers will need to better familiarize themselves with the opportunities associated with PRO questionnaires when making coverage decisions. PRO measures will continue to provide valuable information regarding the risk–benefit profile of novel agents. As such, PRO measures may provide evidence that should be considered in payers' decisions and discussions; however, the formal role of PROs and the pertinence of PROs in decision-making has yet to be understood.

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A patient-reported outcome (PRO) is a subjective report that comes directly from a patient in regard to his or her health condition or treatment without interpretation by a clinician or anyone else.[1] PROs have long provided a unique insight into the effectiveness of novel medical treatments.[2] Indeed, PRO questionnaires have been developed to quantify a patient's self-reported health status in a variety of areas, including symptoms, functioning, quality of life (QOL), and health-related QOL. In addition, PRO questionnaires have been developed to assess other health-related outcomes, such as treatment adherence and satisfaction.

Because of its increasingly significant role in the development and evaluation of new medicines,[2-4] the US Food and Drug Administration (FDA), in conjunction with industry and academic experts, published a formal guidance, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," in 2009 to describe how the FDA will review and will evaluate the existing, modified, or newly created PRO instruments in support of the claims contained in FDA-approved drug labeling.[1] The guidance was in development since early 2000 when select members of the FDA, the International Society for Quality of Life Research, the International Society for Pharmacoeconomics and Outcomes Research, Pharmaceutical Research

Dr Zagadailov is Manager of Global Health Economics Outcomes Research, Xcenda, Chicago, IL; Dr Fine is Medical Director, HealthNet, Huntington Beach, CA; and Dr Shields is Director of Endpoint Development and Outcomes Assessment, Adelphi Values, Boston, MA.

and Manufacturers of America (PhRMA), and the European Regulatory Issues on Quality of Life Assessment Group began meeting to discuss how PRO data could be incorporated into drug labeling claims.[5] The FDA released its draft guidance document in 2006 and its subsequent final guidance in 2009 after receiving and responding to public commentary on the guidance.

By establishing a set of standards and parameters for the use and development of PROs, the FDA has clearly acknowledged and accepted PROs as important and trustworthy means for evaluating drugs, biologics, and medical devices. Furthermore, the FDA guidance may ultimately lead to the more efficient and more appropriate use of these tools; increased collaboration has been seen among measurement-focused researchers to offer suggestions for best practice with respect to the development, implementation, and evaluation of PROs across a variety of therapeutic areas.[5-10]

The impact of the FDA's PRO guidance has been felt in oncology, as evidenced by a rapidly growing body of literature regarding the development, interpretation, and incorporation of PROs into oncology. More specifically, several publications have focused on the use of PROs to support product claims labeling as a means of demonstrating further product differentiation in oncology.[5,11-15]

With the number of cancer survivors currently at 10 million and growing in the United States, it is clear that patients with cancer are living longer as a result of improvements in survival rates for several cancers thanks to new treatment options that have demonstrated control in tumor growth and reduced cancer-related morbidity and mortality.[12]

In addition, an increasing number of therapies offer equivalent survival benefits; however, there may be differences in the type and severity of adverse events or in the way the drug affects patient functioning. Often, these differences are material for patients, and they markedly influence the clinician's choice of therapy for corresponding malignancies from the perspective of the physician and payer. Furthermore, the difference in impact on patient-specific factors, in the absence of a substantial difference of survival benefits, has led to an emphasis on the totality of a patient's treatment experience and an enhanced understanding of how to balance the benefits of therapy with the risks associated with treatment.

Building on safety, efficacy, and health economics data, PROs further inform decision-making by contributing evidence that is reflective of the patient experience. PRO measures also add considerable value to treatment decisions made between providers and patients when they enable providers to address relevant decision-related questions (eg, does a new therapy deliver significant clinical benefit above and beyond the primary registration trial clinical end point, from the patient's perspective?).[15] PRO symptom measures can also be useful in predicting later-stage disease progression and survival.[12] The association between PRO symptom assessments and drug-related toxicity can be valuable when determining the risk–benefit profile of a treatment.[12]

KEY POINTS

- In 2009, the FDA published a formal guidance on the review and evaluation of patient-reported outcomes (PROs) related to claims included in FDA-approved medical product labeling.
- Payers are concerned with issues related to relevance, quality, and interpretability of PROs when evaluating data from these instruments.
- Cancer drugs currently in clinical trials are increasingly incorporating PRO measures and may soon be entering the market with product labeling claims containing PRO data.
- PRO measures can provide evidence that should be considered in payers' drug coverage decisions and providers' discussions with patients regarding drug choice.
- The case of ruxolitinib, to date the only cancer drug that has followed the FDA guidance for the development of a PRO instrument and received a PRO-based product labeling, is a good model for marketing applications of PRO-related measures.
- Payers need to become more familiar with the FDA PRO guidance and the various PRO measures for coverage decisions to determine how each measure fits in a drug's overall risk–benefit profile.

The use of PROs in clinical trials is increasingly necessary and accepted. Furthermore, as more oncology treatments that extend life or provide palliative care become available, PROs will continue to appear as end points in oncology trials. It is unclear, however, how payers and policymakers can use PRO data in the context of decision-making for cancer treatments,[15] and, to date, there is a paucity of literature from the perspective of the payer and policy decision maker.

To begin filling this gap, the objective of this article is to discuss the challenges and opportunities of incorporating oncology-related PRO data into payer decision-making. In turn, this will help third-party payers (public and private) understand the role and the potential added value that PRO data could have in determining a product's overall risk versus benefit. We use a case study to describe the value of PRO data from the payer's perspective for a novel oncology product (ie, ruxolitinib in patients with intermediate- or high-risk myelofibrosis) and

Table 1 Examples of Frequently Used PRO Instruments in Oncology

Type of tool	PRO instrument
Health-related quality of life	
Generic	• EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) • FACT-G (Functional Assessment of Cancer Therapy-General) • SF-36 (Short Form 36-Item) • PROMIS (Patient-Reported Outcomes Measurement Information System)
Cancer-specific	• FLIC (Functional Living Index-Cancer) • EORTC QLQ-BN20 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30 and Brain) • EORTC QLQ-BR23 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast) • EORTC QLQ-LC13 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung) • FACT-L (Functional Assessment of Cancer Therapy-Lung) • FACT-B (Functional Assessment of Cancer Therapy-Breast)
Symptoms and symptom burden	
Generic	• Visual analog scale • Symptom Distress Scale • Memorial Pain Assessment Card • Rotterdam Symptom Checklist
Cancer-specific	• LCSS (Lung Cancer Symptom Scale) • MDASI (Monroe Dunaway Anderson Symptom Assessment Inventory)

PRO indicates patient-reported outcome.

how PRO data were incorporated into its product labeling in accordance with US regulatory guidance.

Historical Context and Current Status of PROs in Oncology

PRO questionnaires collect information about the patient that can best, or only, be known by the patient (eg, pain) and cannot be evaluated through objective (eg, laboratory or marker) measurement. Many PROs are utilized in oncology: **Table 1** describes a sample of PRO measures such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy-General (FACT-G).

The number of oncology products and new technologies incorporating PRO measures into clinical trials and seeking PRO-related product labeling claims continue to increase. A 2010 analysis of all trials registered at ClinicalTrials.gov since 2004 showed that 12% of industry-sponsored trials and more than 15% of non–industry-sponsored trials incorporated some form of PRO assessment.[16] In an earlier, 2007 analysis of clinical trials between 2002 and 2006 registered at ClinicalTrials.gov focusing only on oncology trials, 12% of all industry-sponsored trials reported the inclusion of PRO measures.[12] To our knowledge, there have not been any more current estimates than these 2 analyses.

With this in mind, and considering the FDA guidance that was released in 2009, we used a similar search strategy to what Gondek and colleagues used in 2007[12] to determine the more current utilization of PRO measures in oncology clinical trials. Among a total of 636 oncology registered trials on ClinicalTrials.gov between September 2006 and June 2012, we found 545 oncology trials that incorporated PROs (**Table 2**). This reveals much higher utilization of PRO measures in recent oncology trials than what was reported by Gondek and colleagues in 2007[12] or by Doward and colleagues in 2010,[16] and translates to approximately 85% of recent oncology trials that incorporate some form of PROs that evaluate health-related QOL or symptom measures.

With respect to product labeling, several reviews have evaluated the frequency of PROs in FDA-approved product labeling.[2-4] In a review of end points that were included in product labeling for all new molecular entities from 1997 to 2002, 30% of product labels included a PRO.[2] In a separate systematic review from 2006 to 2010, 21% of FDA-approved drugs (93 of 432 total approvals) contained PROs.[3] Gnanasakthy and colleagues found similar results: 24% of product labels between

Table 2 Oncology Clinical Trials by Disease, with Quality of Life, Symptom Measures, or PROs as Study End Points

Cancer type	Total cancer trials, N	Trials with any PRO measures, N	HRQOL	Symptoms	Other PROs[a]
Multiple	6	5	4	2	1
Breast	69	55	46	11	6
Bone	6	5	5	4	–
Colorectal	37	36	28	6	4
Lymphoma	31	19	18	2	1
Leukemia	42	31	27	1	4
Lung	100	94	83	28	10
Pancreas	26	21	19	4	2
Prostate	45	41	36	12	2
Kidney	22	19	14	7	4
Liver	28	28	27	6	2
Brain	26	24	22	3	–
Head/neck	18	17	15	4	–
Melanoma	9	8	8	–	–
Ovarian	26	24	21	4	3
Hematologic[b]	42	37	35	11	2
Other[c]	103	81	71	26	4
Total	636	545	–	–	–

[a]Includes general PRO instruments that do not directly capture HRQOL or symptoms (eg, Cancer Therapy Satisfaction Questionnaire, patient preference) and trials that did not specify the PRO end point or a nonspecific term of PRO was used.
[b]Hematologic cancers include, but are not limited to, myelofibrosis, polycythemia vera, multiple myeloma, and myelodysplastic syndromes.
[c]Other cancers include, but are not limited to, uterine, gastrointestinal, thyroid, and bladder.
HRQOL indicates health-related quality of life; PRO, patient-reported outcome.

2006 and 2010 contained PRO claims, and the largest percentage of product claims was in oncology.[4]

Before the FDA guidance, selecting a PRO questionnaire for incorporation into a clinical trial was often based on the questionnaire's previous use. Because questionnaire selection should be based on the relevance of the content (ie, what the questionnaire measures) and the strength of its psychometric performance in the specific target patient population, the approach to selecting a questionnaire based on previous use is seen as inadequate.[16] The continued use of older generic instruments, such as the Short Form 36-Item (SF-36) health survey questionnaire, is often disputed. Older PRO instruments may also predate advances in measurement science; these advances have led to the development of PROs that measure meaningful changes in a specific disease following the new FDA guidance.[16]

Before the publication of the FDA's PRO guidance in 2009, the majority of oncology agents with PRO claims were based on generic- or symptom-related assessments, some of which might not have been published or evaluated for content validity or for psychometric performance (eg, reliability, construct-related validity, and sensitivity to change) within a given disease. This is the case for many of the oncology products with QOL or PRO claims before the development and release of the FDA guidance, as described in **Table 3**.

For example, topotecan was granted PRO-based product labeling claims for symptom improvement using a Symptom Distress Scale in patients with small-cell lung cancer. The 4-category symptom scale measures shortness of breath, interference with daily activity, fatigue, hoarseness, cough, insomnia, anorexia, chest pain, and hemoptysis.[17] Improvement was defined as a change in 1 category from baseline and sustained during 2 courses of treatment. Overall, patients receiving topotecan had

Table 3 FDA Oncology Drug Approvals with a PRO Claim in the Label

Generic (brand name)	Manufacturer	Therapeutic indications	PRO end points	PRO instruments	Approval date
Pre–FDA guidance					
Gemcitabine hydrochloride (Gemzar)	Eli Lilly	Carcinoma NSCLC Pancreatic neoplasms	HRQOL Clinical benefit response, a measure of clinical improvement based on analgesic consumption, pain intensity, performance status, and weight change	HRQOL was assessed using FACT-L, EORTC QLQ-C30, and EORTC QLQ-LC13 Pain intensity was assessed using Memorial Pain Assessment Card	May 1996
Imatinib mesylate (Gleevec)	Novartis	Chronic myeloid leukemia, acute lymphoblastic leukemia	Improvement in symptoms of interferon toxicity HRQOL	FACT-BRM questionnaire	May 2001
Irinotecan hydrochloride (Camptosar)	Pfizer	Colorectal neoplasms	HRQOL	EORTC QLQ-C30	June 1996
Leuprolide acetate (Eligard)	Atrix Laboratories	Prostatic neoplasms	Improvement in bone pain, urinary pain, and urinary signs and symptoms	Both bone pain and urinary pain were assessed by patients using a VAS ranging from 1 (no pain) to 10 (worst pain possible) Urination symptoms were assessed on a VAS ranging from 1 (no difficulty) to 10 (very difficult)	January 2002
Mitoxantrone (Novantrone)	Immunex Corporation	Prostatic neoplasms, acute nonlymphocytic leukemia	Improvement in pain and analgesic use	Pain intensity was measured using the Symptom Distress Scale pain item 2, a 5-point scale Analgesic use was measured using a 5-point scale where 0 = no analgesics, 1 = nonnarcotics taken occasionally, 2 = nonnarcotic analgesics taken regularly, 3 = narcotic analgesics taken occasionally, and 4 = narcotic analgesics taken regularly The pain scale was derived from the present pain intensity of the McGill Pain Questionnaire	December 1987
Paclitaxel (Taxol)	Mead Johnson, a Bristol-Myers Squibb Company	Carcinoma NSCLC	HRQOL	Quality of life was evaluated using the FACT-L questionnaire	December 1992

Table 3 FDA Oncology Drug Approvals with a PRO Claim in the Label (*Continued*)

Generic (brand name)	Manufacturer	Therapeutic indications	PRO end points	PRO instruments	Approval date
Pamidronate disodium (Aredia)	Novartis	Osteolytic bone metastases of breast cancer Osteolytic lesions of multiple myeloma	Pain narcotic use	Pain score was calculated as the product of pain severity times pain frequency Both were assessed on a 4-point scale, where 0 = none to 3 = severe for pain severity and from 0 = none to 3 = constant (most of the time) for pain frequency Narcotic score was also assessed using a 4-point scale, from 0 = none to 3 = strong narcotic	October 1991
Thyrotropin alfa (Thyrogen)	Genzyme	Thyroid neoplasm	HRQOL	HRQOL was measured using the SF-36 health survey	November 1998
Topotecan hydrochloride (Hycamtin)	GlaxoSmithKline	Small-cell lung cancer Metastatic ovarian carcinoma	Symptom improvement	Data were collected on patients' self-assessed scores for 9 symptoms of disease: shortness of breath, interference with daily activity, fatigue, hoarseness, cough, insomnia, anorexia, chest pain, and hemoptysis. Each symptom was rated on a 4-category scale	May 1996
Alitretinoin (Panretin)	Ligand Pharmaceuticals	Kaposi's sarcoma	Treatment satisfaction The subjective assessment of lesions	Patients were asked about their overall satisfaction with the treatment, which was 1 item of a 9-item QOL questionnaire The subjective assessment of all treated lesions was scored by patients using a 7-point ordinal scale	February 1999
Bicalutamide (Casodex)	AstraZeneca	Prostatic neoplasms	HRQOL	Self-administered patient questionnaires on pain, social functioning, emotional well-being, vitality, activity limitation, bed disability, overall health, physical capacity, general symptoms, and treatment-related symptoms No additional detail was provided	October 1995
Post–FDA guidance					
Ruxolitinib (Jakafi)	Incyte	Myelofibrosis	Reduction in total symptom score	Myelofibrosis Symptom Assessment Form	November 2011

EORTC QLQ-C30 indicates European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-LC13, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung; FACT-BRM, Functional Assessment of Cancer Therapy-Biologic Response Modifiers; FACT-L, Functional Assessment of Cancer Therapy-Lung; FDA, US Food and Drug Administration; HRQOL, health-related quality of life; NSCLC, non–small-cell lung cancer; PRO, patient-reported outcome; QOL, quality of life; SF-36, Short Form 36-Item; VAS, visual analog scale.

lower symptom scores in 8 of the 9 items.[17] No statistical comparisons with respect to differences in symptom improvement between topotecan and the trial comparator regimen, cyclophosphamide plus doxorubicin and vincristine were reported in the approved product labeling[17]; however, the results of a statistical comparison was previously reported by von Pawel and colleagues.[18]

The case of topotecan provides an example of an oncology agent with challenges regarding PRO labeling claims. First, the scale used to collect the PRO data has limited published evidence regarding the psychometric properties of the scores produced by this scale in patients with lung cancer, such as test–retest reliability and construct-related validity. Second, the prescribing information for topotecan states that the rating scale has limitations in interpretation and that responses precluded a formal statistical analysis.[17] In addition, the published results from the trial reporting these symptom outcomes also indicate that the questionnaire was not a validated QOL instrument.[18]

Case Study of Ruxolitinib

To date, only 1 oncology medication—ruxolitinib—has followed the FDA guidance for the development of a PRO instrument to obtain a PRO-based product labeling claim. Furthermore, the FDA indicated that the example of ruxolitinib provides a model for future marketing applications and may foster more frequent use of PRO instruments.[19]

Ruxolitinib is an oral Janus kinase (JAK)1 and JAK2 inhibitor approved by the FDA for the treatment of patients with intermediate- or high-risk myelofibrosis.[20] The results of 2 phase 3 trials (COMFORT-I and COMFORT-II) provided support for FDA approval.[19] COMFORT-I was a randomized, multinational, double-blind, placebo-controlled, phase 3 study, and COMFORT-II was an open-label, randomized, phase 3 study comparing ruxolitinib with best available therapy.[20]

The primary end point of both trials was a reduction in spleen volume (biologic end point), and COMFORT-I incorporated a key secondary end point based on a PRO instrument designed specifically for this population: ≥50% improvement from baseline to week 24 in total symptom score (TSS) based on the modified Myelofibrosis Symptom Assessment Form version 2.0 (MFSAF v2.0).[20]

The modified MFSAF v2.0 diary captures a patient's symptom severity (ie, night sweats, itching, abdominal discomfort, pain under ribs, early satiety, bone/muscle pain, and inactivity) on a scale of 0 (absent) to 10 (worst imaginable), with TSS as the sum of the individual symptom scores (with the exception of inactivity).[20] In the COMFORT-I trial, TSS continued to worsen over time for patients receiving placebo. After 24 weeks of treatment, 45.9% of patients treated with ruxolitinib and 5.3% of patients receiving placebo achieved ≥50% improvement from baseline in TSS.[20] In each individual symptom score, a greater proportion of patients taking ruxolitinib achieved ≥50% improvement compared with the patients receiving placebo.[20]

The presence of constitutional symptoms such as night sweats, fever, and weight loss have shown to be prognostic factors for reduced survival that are included in the International Prognostic Scoring System for myelofibrosis[21]; therefore, measuring a drug's ability to reduce symptom burden can be important in overall efficacy evaluations. Substantial symptom improvement was observed early in the first few patients treated with ruxolitinib in the phase 1/2 trial, and discussions with the FDA's Division of Drug Oncology Products (DDOP) indicated that one other clinically relevant benefit, such as symptom improvement, may support registration, along with objectively measured spleen size.[22] Therefore, a symptom assessment tool (an early version of the MFSAF) was incorporated into the phase 1/2 trial. This instrument was developed by a group of the study investigators[22] and was supported by symptom data from a cross-sectional survey of 458 patients with myelofibrosis.[23] Subsequent feedback from the FDA, cognitive testing, and patient interviews contributed to the further refinement of this symptom questionnaire to support the modified MFSAF v2.0 used in the COMFORT-I study.

In addition, to demonstrate whether the modified MFSAF v2.0 correlated with clinically meaningful improvements, the study sponsor grouped patients into TSS "responders" or "nonresponders" based on the key secondary end point in COMFORT-I, and these groups were categorized based on Patients' Global Impression of Change (PGIC) scores at week 24.[22] The PGIC asks patients, "Since the start of the treatment you've received in this study, your myelofibrosis symptoms are (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, or (7) very much worse?"[22] More than 90% of patients categorized as responders reported a PGIC score of "much improved" or "very much improved," supporting the ability of the modified MFSAF v2.0 to measure clinically meaningful changes in the symptoms of myelofibrosis.[22]

Challenges with PROs from the Payer Perspective

In the United States, payer concerns regarding the added value of PRO instruments are rooted in the meaning (ie, what is being measured?), relevance (ie, how important is what is being measured to the disease?), technical quality (ie, can I trust the scores produced by the questionnaire?), and interpretability (ie, at what

point does an observed change in scores begin to reflect a bona fide treatment gain?) of PROs.[15] Concern that PROs do not independently predict improved patient outcomes is also a barrier from the payer perspective.

Additional challenges germane to non-PRO and PRO data alike, such as unblinded trials, missing or incomplete data, the multiplicity of end points, and inconsistent findings, provide further barriers regarding the acceptance of PROs.[5,24] The potential dearth of appreciation for the clinical impact associated with aggregate symptom burden in rare disease states may also be a contributing factor.

Aside from these challenges, the use of poorly designed questionnaires that do not specifically assess the disease result in a missed opportunity to determine a patient-based treatment benefit that may be valuable in the context of payer decision-making. For example, the symptom scale used to evaluate topotecan lacks published information about the symptom scale, and the prescribing information reports limitations in the symptom scale; therefore, the PRO labeling claims may lack credibility and value from the payer perspective.

Payer Survey Results

Recent quantitative and qualitative payer market research conducted by Xcenda, LLC, in 2012,[25] has described payers' challenges with PRO data, such as the lack of familiarity with PRO measures, the perceived lack of value in using PRO data to support evidence regarding unmet needs, and the lack of impact that PRO data may have on decision-making; all of the above factors are accentuated in rare diseases. In the quantitative payer market research, a survey of 49 US payers, representing approximately 142 million covered lives, was used to determine payer perceptions of PRO data in oncology. This sample of payers represented 27 pharmacy directors, 16 medical directors (national or regional), and 6 other policy decision makers. The survey respondents represented national or regional health plans, including 3 integrated delivery systems, 6 pharmacy benefit managers, 27 managed care organizations, 4 preferred provider organizations, and 9 others.[25]

When asked about their familiarity with PRO data in oncology, the average response on a numeric rating scale (1, not familiar at all; 7, extremely familiar) was 3.6 (slightly below a neutral response of 4), indicating that many of the payers were not familiar with these types of data. Overall, most payers (N = 13) provided a value of 5, followed by values of 3 (N = 12), 4 (N = 8), 2 (N = 7), 6 (N = 4), and 1 (N = 5).[25]

The payers were also asked to what degree they believe PRO data can provide sufficient evidence that a drug is meeting an unmet need in oncology (1, do not believe evidence is sufficient; 7, strong belief that evidence is sufficient); the average response was also 3.6. Most payers (N = 13) provided a value of 4, followed by values of 5 (N = 12), 2 (N = 10), 3 (N = 9), 6 (N = 3), and 1 (N =2); no payers provided a value of 7.[25] This suggests that payers, although mostly neutral on the topic, may not believe that PRO data can provide sufficient evidence that a drug is meeting an unmet need.

More important, when asked if PRO data provide value in making formulary decisions for oncology drugs (1, no value; 7, extreme value), the average response was 2.8. Most payers (N = 18) provided a value of 2, followed by values of 4 (N = 17), 1 (N = 16), and 3 (N = 5). No payers responded with a value of 7 or 6. This indicates that payers place little value on PRO data in the context of coverage decision-making, which may be related to the challenges with PRO data noted earlier or with payers' lack of familiarity with PRO data in oncology.[25]

Feedback from a Payer Focus Group

Additional qualitative market research in the form of a double-blind focus group (ie, the study sponsor and the focus group participants do not know the identity of each other) included 13 payers, including pharmacy directors (N = 6), medical directors (N = 5), and other policymakers (N = 2) from national or regional plans. This sample of 13 payers represented approximately 114 million covered lives.

Although qualitative results with a small sample size are difficult to validate, several key insights were derived from this focus group. The first key insight was that payers often mistakenly consider PROs to be synonymous with QOL, but this is incorrect. Although QOL can be assessed by PRO methods, QOL's broad definition (an evaluation of the effect of all aspects of life on general well-being) typically precludes regulatory consideration for QOL-based medical claims.[1] However, the FDA will consider other PRO data for labeling, especially in cases where the concepts of measurement are well defined (eg, symptoms) or if they characterize the specific effect of treatment on disease-related symptoms and physical, psychological, and social aspects of life (eg, health-related QOL).

The second key finding from the payer focus group was that payers' internal committees and decision-making groups have not defined what PROs mean for their organizations or decision-making processes. Based on the recent FDA guidance, this is in contrast to the increasing importance of PROs to health authority regulatory scientists at the FDA,[1] the FDA's DDOP, healthcare providers, and patients. Subsequently, PRO data may be discarded or not considered as part of the evidence package for consideration when making key decisions in oncolo-

gy. Third, none of the payers were familiar with or had read the FDA guidance regarding the incorporation of PRO claims in product labeling.

Despite this, several payers were willing to evaluate PRO data in the context of understanding the comprehensive risks and benefits of a given oncology therapy. Therefore, an opportunity to increase awareness among payers will be a critical initiative. Ultimately, payers continue to manage members with larger populations in mind, which may explain why many payers do not perceive PRO data as valuable in the context of decision-making; however, PRO data also present several opportunities for payers to use in decision-making.

Opportunities Associated with PROs in Decision-Making

The FDA's guidance on the development, implementation, and interpretation of PRO measures directly supports PRO medical claims in product labeling, while also mitigating the challenges associated with PRO data.[1] In this way, payers and policy decision makers can have increasing confidence that the data generated by PRO questionnaires have been demonstrated to be relevant, trustworthy, and meaningful, which provides an opportunity to focus on how to use PRO data in decision-making. For example, during discussion in the focus group, some of the payers indicated that PRO data can be useful to differentiate treatments with similar efficacy or comparable toxicity profiles. Similarly, several publications have focused on this specific benefit of PROs, because growing cost pressure has created an increasing need for product differentiation.[5,14,16]

In the focus group, payers provided caution against shifting focus away from conventionally used end points, such as survival or surrogates of survival (eg, progression-free survival), and continuing to maintain PROs as a secondary measure. Consistent with this payer perception, PROs present an opportunity to incorporate patient-perceived effects as an adjunct to clinical efficacy measures in an era of oncology where there is an increasing number of therapies offering equivalent survival or other clinical end points.[12,16]

The payers in the focus group also viewed PROs as an opportunity to identify oncology products that may directly impact healthcare utilization. Rooted in the fact that several oncology treatments have high toxicity profiles (especially when compared with nonantineoplastic medicines), payers see PROs as an opportunity to identify potentially costly events reported by patients in the trials. Therefore, treatments with reduced toxicity that can demonstrate a positive impact on PROs may influence payer decision-making for the treatments with supporting PRO data. For example, PROs measuring bone pain and/or muscle pain may be more directly related to the utilization of pain medications; PROs measuring nausea may be related to the utilization of antiemetic treatments; and PROs capturing side effects, such as diarrhea, may correlate to substantive dehydration and subsequent hospitalization costs.

FDA-evaluated PRO questionnaires such as the MFSAF present an opportunity for payers to evaluate relevant, disease-specific treatment benefits in the context of important risk–benefit decisions that directly impact the livelihood of patients with cancer. In addition, instruments created in collaboration with and approved by the FDA may lead to increased confidence and less scrutiny than payers previously had. As more PRO label claims are approved, payers may see, and should be prepared to react to, symptom data in labels. Some health plans, such as WellPoint, have already issued formulary guidance regarding the effectiveness in improving patients' QOL.[16]

A recent review of PROs in labels discovered that between 2006 and 2010, 85.7% of PRO label claims were for symptoms.[4] Ultimately, payers will have to start evaluating and incorporating these data into the decision-making process despite the findings from the payer focus group that suggest that several payers may not be familiar with the volume of PRO evidence in development or with their subsequent inclusion into medical claims labeling. Therefore, in an attempt to further incorporate PRO data into product labeling claims and formulary decision-making processes, efforts to increase awareness of PROs among all stakeholders in oncology—specifically payers—will be necessary.

As evidenced by direct feedback in the focus group, payers anticipate that PROs could be incorporated into decision-making in several ways. First, payers specifically value PROs that could be used to direct treatment decisions in terms of continuation versus discontinuation of treatment. PROs that are related to or are incorporated into response criteria, prognostic scales, or other formal decision-making algorithms may be used to determine continued access to treatment.

Second, products with positive PRO data could be granted preferred status for agents within the same class (ie, in comparison with agents with similar mechanisms and indications but lacking PRO evidence).

Third, products that demonstrate a marked difference in adverse events may aid payers in managing these events at a population level.

Finally, payers should strongly anticipate that PROs will have the largest impact on drug selection between individual patients and their physicians or healthcare providers at the clinical care delivery level, which is consistent with an increasing emphasis on patient-centered medical homes and palliative care.

Call to Action: Incorporating PRO Data into Coverage Decision-Making

- Familiarize yourself and your committees with the FDA guidance on PROs
- Gather stakeholders within your organization to internally define PROs and to establish how PROs will impact your decision-making process
- For FDA-approved product labeling claims regarding PROs, determine how each PRO measure fits within the overall treatment risk–benefit profile
- Determine if the PRO measure will be related to changes in healthcare utilization
- Determine if PRO measures could be used to inform continuation or discontinuation of the therapy.

Conclusions

The 2009 FDA guidance and the subsequent example of incorporation of PRO labeling claims in the successful clinical development of ruxolitinib (leading to its approval for the treatment of intermediate- or high-risk myelofibrosis) have paved the way for drug manufacturers to develop and to disseminate PRO measures related to treatment benefit and/or risk in oncology. The growing body of literature regarding the incorporation of PRO claims into FDA labeling for oncology products has focused largely on the patient, regulatory, industry, and provider perspectives; however, the payer perspective and the impact of PRO labeling claims on decision-making has been of a lesser focus. More resources and tools regarding the use of PROs in oncology trials will be necessary for payers to further understand the value of PRO data in treatment decisions and of the identification of preferred pathways. Additional case studies need to be conducted to understand how payers and policymakers will use PRO measures and other secondary measures in coverage decisions and how PRO data will impact the future of cancer outcomes research.

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Author Disclosure Statement

Dr Zagadailov is an employee of Xcenda, which provides consulting services to pharmaceutical companies. Dr Fine has reported no conflicts of interest. Dr Shields is an employee of Adelphi Values, which provides consulting services to pharmaceutical companies, and was previously a consultant to Incyte, but was not compensated for this research.

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STAKEHOLDER PERSPECTIVE

Assessing the Value of Patient-Reported Outcomes

By Matthew Mitchell, PharmD, MBA
Manager, Pharmacy Services, SelectHealth, Salt Lake City, UT

The article by Zagadailov and colleagues addresses interesting points about the implications of patient-reported outcomes (PROs) for drug coverage and treatment decisions, as well as the associated challenges and opportunities.

PAYERS: When evaluating the coverage of drugs, particularly novel drugs, the 3 main factors considered by payers are efficacy, safety, and cost. In the assessment of efficacy outcomes, primary outcomes carry the most weight and, fittingly, secondary outcomes carry less weight. Historically, PROs have been included as secondary outcome measures within pivotal as well as non-pivotal studies that contribute to the literature that is evaluated by payers for coverage decisions.

There are many primary end points within each therapeutic class, and even more when considering all therapeutic classes. The large variety of objective, consistent primary outcomes makes consensus among payer evaluations difficult. Whereas one payer may define the true value of a pharmaceutical intervention by the reduction of a negative event, such as a myocardial infarction (MI), another payer may give credence to a drug with a more potent reduction of a surrogate marker, such as low-density lipoprotein lowering. Using both criteria, a number needed to treat and a relatively simple, cost-effective measure may be calculated. In this example of cardiovascular disease, symptoms of disease progression, as well as medication side effects, are relatively benign, and therefore PROs are not as relevant as in symptomatic conditions or in side-effect–heavy treatments. However, without consensus on the relative value of more traditional, objective measures, how are payers expected to agree on the relative value of subjective PROs? This question, of course, assumes that payers agree that PROs carry enough value to justify the time spent on their evaluation.

Zagadailov and colleagues focus on oncology care, an area where PROs are beginning to have an impact in drug development. But even within the evaluation of cancer therapies, several common primary outcome measures exist, including, but not limited to, overall survival (OS), progression-free survival, and overall response rate. Again, there is no consensus among payers on the most important measure or on the relative value of incremental differences within each measure. For instance, one payer may assign high value to a drug that demonstrates 6 months of OS improvement, whereas another payer may attribute similar value to a drug that adds only 4 months of OS for the treatment of the same cancer type. To reiterate, even with objective outcomes for cancer therapies, assigning an economic value for payers is more difficult than assessing the value of MI prevention. The enormity of different types of PROs further creates difficulties in understanding the measures and in assigning value to these measures in an arena as complicated as cancer care.

For many payers, the US Food and Drug Administration's pathway to drug approval is a moot point. State mandatory coverage regulations may leave payers little wiggle room to manage oncolytic therapies. The Centers for Medicare & Medicaid Services also has regulations that may prohibit a payer from designating coverage preference for one drug or another, even if the drug's PROs are seemingly superior to other drugs'.

Nevertheless, PROs are not going away any time soon, and payers need to spend time becoming familiar with their different types. Payers will also need to determine if more recent PROs bring significant value to formulary and coverage decisions. This may take some real-world validation of health resource utilization that is tied to the outcomes of PROs.

PROVIDERS: In oncology, many of the objective measures within clinical trials can be evaluated for individual patients, such as time to disease progression. Many providers will capture some type of PRO, which may be as simple as assessing activities of daily living or screening patients with the Patient Health Questionnaire-9 scale for depression.

In the case of ruxolitinib that is cited in the present article, the Myelofibrosis Symptom Assessment Form version 2.0 (MFSAF v2.0) was evaluated as a secondary end point. It is my assumption that few providers complete a routine analysis of the MFSAF v2.0 for every patient with myelofibrosis. Providers will also need to assess the real-world applicability of PROs in their practices and determine how PROs fit into their therapy selection decision. PROs could possibly contribute to the oncologist's selection process and could even contribute to the decision to place a drug on a pathway, which may affect payers.

PATIENTS: Overall, patients with cancer are most concerned with their quality of life and length of life. The assessment of quality of life may be better done through PROs, which can add an important perspective to treatment decisions. ■