


Stakeholder Perspectives on Addressing Adverse Events From Adjuvant Cancer Therapy: A Qualitative Study

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BACKGROUND: With increasing survival rates, a growing population of patients with cancer have received or will receive adjuvant therapy to prevent cancer recurrences. Patients and caregivers will confront the complexities of balancing the preventative benefits of adjuvant therapy with possible near-term or long-term adverse events (AEs). Adjuvant treatment-related AEs (from minimal to severe) can impact therapeutic adherence, quality of life, emotional and physical health, and survival. However, to the authors' knowledge, limited information is available regarding how stakeholders use or desire to use adjuvant-related AE information to inform the care of patients with cancer. **METHODS:** A qualitative, purposeful sampling approach was used to elicit stakeholder feedback via semistructured interviews (24 interviews). Drug development, drug regulatory, clinical, payer, and patient/patient advocacy stakeholders were questioned about the generation, dissemination, and use of adjuvant treatment-related AE information to inform the care of patients with cancer. Transcripts were coded independently by 2 senior health care researchers and reconciled to identify key themes. **RESULTS:** All stakeholder groups in the current study identified needed improvements in each of the following 4 areas: 1) improving the accessibility and relevance of AE-related information; 2) better integrating and implementing available information regarding AEs for decisions; 3) connecting contemporary cultural and economic value systems to the generation and use of information regarding adjuvant treatment-related AEs; and 4) addressing a lack of alignment and ownership of stakeholder efforts to improve the use of AE information in the adjuvant setting. **CONCLUSIONS:** Despite commonalities in the overall needs identified by the diverse stakeholders in the current study, broad systemic change has been stymied. The current study identified the lack of alignment and the absence of a central "owner" of these diffuse efforts as a previously unrecognized hurdle to realizing the desired systemic improvements. Future initiatives aimed at improving quality of life and outcomes for patients receiving adjuvant therapy through the improved use of AE information must address this challenge through innovative collectives and novel leadership strategies. **Cancer 2019;125:4471-4480.** © 2019 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: adjuvant, adverse effects, adverse events (AEs), quality of life, survivorship.

INTRODUCTION

Earlier detection and improved therapeutic efficacy for many cancer types have increased cancer survival rates in the United States by a factor of 5 over the past 40 years.^{1,2} Survival rates for many of the most common cancers in the United States (eg, breast cancer, prostate cancer, and lung cancer) often are improved further by adjuvant therapy. Adjuvant therapy is administered to patients after primary treatment, when the patient is "cancer free," to lower the risk of disease recurrence.³ Unfortunately, in addition to their potentially life-prolonging efficacy, adjuvant therapies also may cause adverse events (AEs) that can affect a patient's adherence to drug therapy, as well as their immediate and long-term physical, emotional, and financial health and quality of life.^{4,5} AEs vary by treatment, dosing, duration, and patient and can range from mild fatigue, to severe chronic pain, to potentially fatal organ failure. As this potential for extended survival increases, so too does the focus on patient quality of life, both during and after treatment.^{6,7} However, despite their importance, to our knowledge treatment-related AEs and their effect on quality of life, care, and outcomes are understudied. Furthermore, the effect of potential acute or treatment-related AEs and an uncertain potential for tumor recurrence are important challenges in balancing the risks and benefits of adjuvant therapy.

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TABLE 1. Stakeholders Interviewed for Their Perceptions of Studying and Treating Adverse Events Related to Adjuvant Cancer Therapy

Stakeholders	Description
Patient advocates (4 stakeholders)	<ul style="list-style-type: none"> • Cancer survivors/patient perspective • Organizational leaders • Work with patients concerning adjuvant therapy
Clinicians (5 stakeholders)	<ul style="list-style-type: none"> • Oncologists, cardiologists, and rheumatologists • Physician input
Drug regulators (5 stakeholders)	<ul style="list-style-type: none"> • US and European drug regulators • Safety and efficacy evaluators
Drug developers (5 stakeholders)	<ul style="list-style-type: none"> • Pharmaceutical industry • Researcher and physician input • Most with >25 y of industry experience
Health care payers (5 stakeholders)	<ul style="list-style-type: none"> • Public and private payers in the United States • Senior leaders responsible for designing and implementing insurance coverage

The growing body of literature regarding the mechanisms, detection, tracking, and management of adjuvant treatment–related AEs typically focuses on the needs of one or a small subset of stakeholders, such as data collected in clinical trials for regulators and information provided by clinicians to their patients.^{8–11} This limited perspective does not adequately reflect the complexities of generating, disseminating, and using information concerning AEs.

To address this issue, we interviewed a range of stakeholders—drug developers, regulators, clinicians, patients/patient advocates, and payers—and explored their perspectives as individuals whose decisions directly affect adjuvant treatment decision making.

MATERIALS AND METHODS

The current study was approved by the institutional review board of the University of North Carolina (IRB-17-2590). Consent to participate was confirmed by verbal agreement at the start of the interview. All data were deidentified and stored in a password-protected network.

Stakeholder Interviews

Qualitative interview questions were used to elicit information regarding the respondent's roles in developing, disseminating, or using AE information related to adjuvant therapy decision making for cancer care (as well as their perceptions of the roles of others). Interviews lasted between 30 and 60 minutes.

Stakeholder Selection

A purposeful sampling technique was used to achieve a breadth of representation.¹² Stakeholder groups engaged in the current study were selected because they represented different points along the continuum of adjuvant therapy development and use, including patient/patient advocate, clinical, pharmaceutical regulatory, drug development,

and health care payer perspectives. Sampling blended an informant sample emphasis (those selected for their specific expertise) with a maximum variation sample emphasis (those selected to represent diverse experience).¹³ A total of 4 to 5 stakeholders per category (24 stakeholders) were engaged in the current study. This approach to breadth over depth has been used previously to characterize complex multistakeholder systems in qualitative research (Table 1).¹⁴

Data Collection

One-to-one, semistructured, qualitative interviews with stakeholders were conducted by the principal investigator to elicit information regarding several aspects of AEs, as well as their perceptions of the roles of other stakeholders. Interviews were conducted via telephone and lasted between 30 and 60 minutes (interview questions are shown in Supporting Information A). Interviews were digitally recorded and transcribed.

Data Analysis and Coding

Text transcripts of all interviews were housed and coded in Dedoose (version 8.0.42). All interviews were coded independently by 2 senior researchers with expertise in health care systems. Iterative meetings then were held to reconcile code application and reach unanimity on coding for all transcripts. Code book development and dual-coding process details are available as Supporting Information B and Supporting Information C.

Analytic Approach

Coded excerpts were reviewed to identify similarities and differences within and across stakeholder groups for a given code (eg, how did “barriers to information use” vary across stakeholders?). Based on this review, 4 emergent themes were identified and used to frame the results and discussion below. Emergent theme identification is

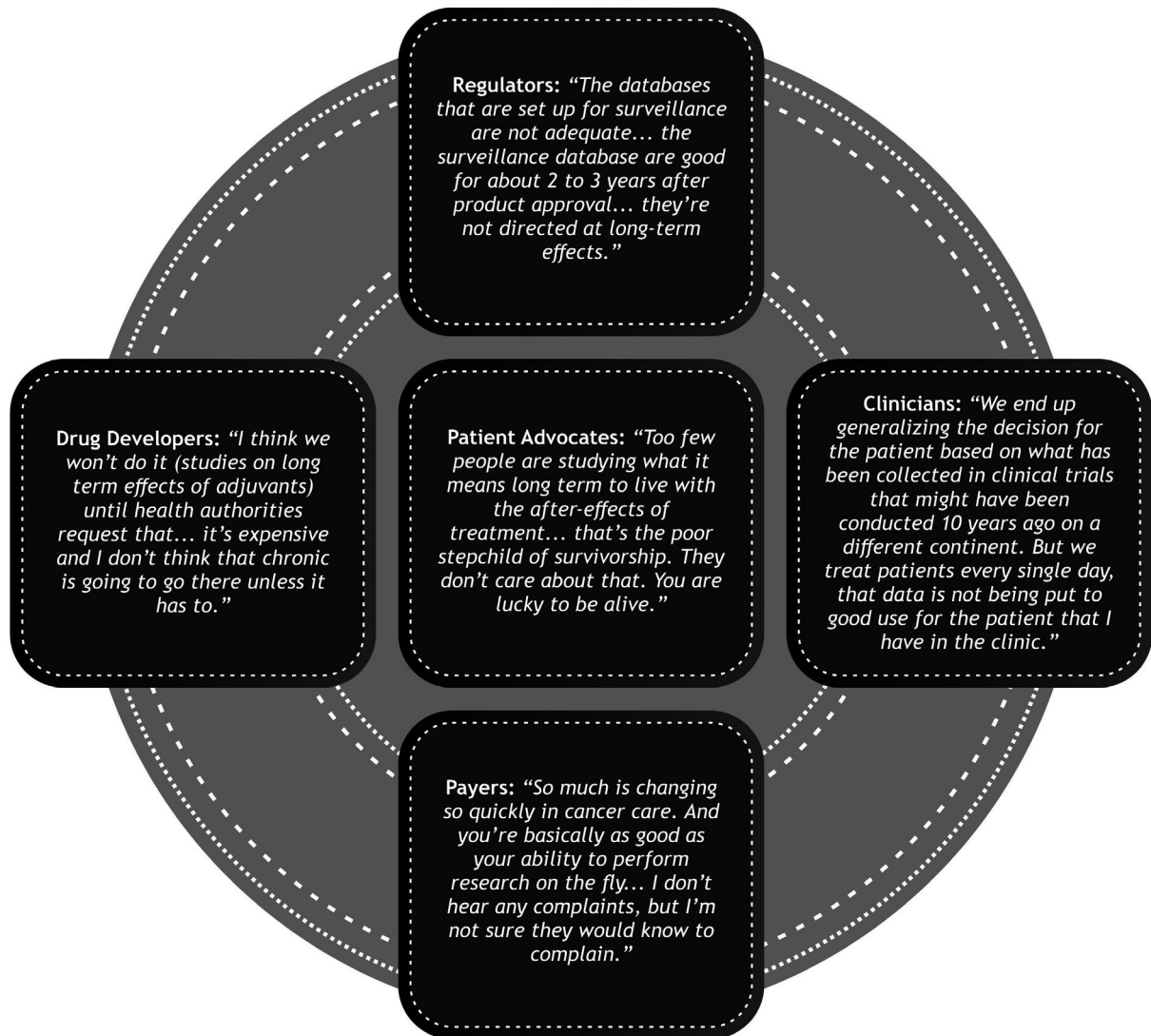


Figure 1. Exemplary quotes regarding the quality and accessibility of information concerning adverse events.

an accepted method for organizing and evaluating qualitative data on health systems.^{15,16}

Qualitative Study Design

This study's fulfillment of the COnsolidated criteria for REporting Qualitative research (COREQ) is reported as Supporting Information D.¹⁷

RESULTS

The current study provided initial evidence of cross-stakeholder calls for changes in the generation, dissemination, and use of AE information to improve the care of patients with cancer in the adjuvant setting. We identified 4 major thematic areas: 1) the quality, accessibility, and relevance

of AE-related information resources; 2) the practice of integrating and implementing available information regarding AEs into decision making; 3) the impact of cultural and economic value systems on the generation and use of adjuvant-related AE information; and 4) the alignment and ownership of interstakeholder and intrastakeholder efforts to improve the development and use of AE information in the adjuvant setting. A detailed discussion of stakeholder views and exemplary quotes for each theme follows below.

AE-Related Information Resources

The limited availability of demographically relevant and timely AE data was reported consistently as a problem by all stakeholder groups. However, stakeholders varied considerably with regard to the perceived reasons for

these described limitations (Fig. 1). For example, drug developers and regulators focused heavily on the technical and experimental challenges in generating translationally relevant adjuvant safety data. They noted the lack of robust experimental animal or in vitro models for many of the AEs associated with adjuvant treatments, such as chronic pain, fatigue, and memory impairment. Challenges in sustaining patient participation in longer-term clinical studies (or maintaining animals for longer nonclinical studies) were cited. A lack of standardization in reporting and interpreting patient-reported outcomes also was mentioned. Both groups also noted that adjuvant therapies often are variations of primary therapies and that current regulatory guidelines do not require long-term safety data for the majority of oncology treatments, including adjuvant treatments. The current lack of a regulatory mandate to collect long-term safety data was cited as a disincentive to data collection.

The clinicians, both oncologists and nononcologists, focused extensively on the issue of data relevance, more so than any other group. Many expressed frustrations that AE data were not collected routinely in standard-of-care settings and therefore were difficult to apply in those settings. Furthermore, the data that were collected were not readily applicable to many treatment decisions regarding adjuvant care (eg, available data concerning AEs often are derived from clinical trials for the treatment of metastatic cancer and thus are of limited relevance to standard care in the adjuvant setting). Payers did not reference these same concerns but did note a lack of robust, reproducible data regarding the effect of nontraditional (eg, psychosocial) or “wrap-around” (eg, transportation) services that might justify coverage. Clinicians and payers reported challenges in maintaining current information given evolving treatment guidelines, best practices, or research publications. In this regard, staff bandwidth and capacity, and not access to or the content of data, were the primary limitations observed.

Patient advocates echoed all of these frustrations through broad concerns that neither data regarding post-treatment AEs nor data concerning patient experience after therapy were receiving enough attention.

Integrating and Implementing Information Regarding AEs

Although the specified implementation challenges varied, all stakeholder groups cited barriers to integrating adjuvant treatment-related AE information into decisions or practices to benefit patients (Fig. 2). Drug developers, clinicians, regulators, and patients/patient advocates called for better ways to address the “burden of treatment” or

to integrate the “patient perspective” into drug design and clinical treatment standards. Stakeholders were particularly focused on enhancing the inclusion of data regarding less severe effects (eg, grade 1 or 2 effects using the Common Terminology Criteria for Adverse Events), patient-reported symptoms, functional effects, and effects that are more difficult to measure (eg, fatigue, pain, etc). Some stakeholders described specific needs such as risk calculators or other data integration tools that can produce graphical representations of the risk:benefit trade-off and enhance the integration of patient preferences into treatment plans and called for systematic methods to integrate patient experiences and quality-of-life impacts into future drug design. However, most stakeholders struggled to specify what these integrative methods or resources should look like or how to usher them into use.

The need to better integrate AE-related information across and within different stakeholder groups also was identified broadly as a barrier to developing the data and methods required to enhance adjuvant care decision making. For example, drug developers called for more collaboration between clinical and nonclinical research teams to enhance the translational usefulness of data regarding adverse and beneficial effects of adjuvant therapies. Many of the clinicians also called for better coordination and information sharing among oncologists and other clinicians who treat adverse therapy-related symptoms. Patient advocates and payers highlighted the critical need for, and the shortage of, “patient navigators” (ie, a professional who aids patients in navigating the health care system and its related services and decisions) to integrate information, resources, and general support for patients.

Many of the challenges to integration and use were specific to a given stakeholder group. For example, regulators reported that evaluating adjuvant therapy requires them to make challenging and sometimes data-limited decisions to balance the risk of potential toxicity with the risk of potentially lethal tumor recurrence in a patient who is assumed to be cancer free. Clinicians uniquely described concerns about variability in practice caused by a lack of standardized approaches for treating AE symptoms in general. For some therapies, this concern was combined with the need to reduce AEs without reducing the efficacy of adjuvant therapy. Payers uniquely identified their limited ability to approve personalized treatment approaches that are not supported with consistent and highly documented results. They also cited challenges in initiating or publicizing evidence-based changes in practice based on their internal data sets because these are confidential to the individual patients and cannot be shared or integrated readily.

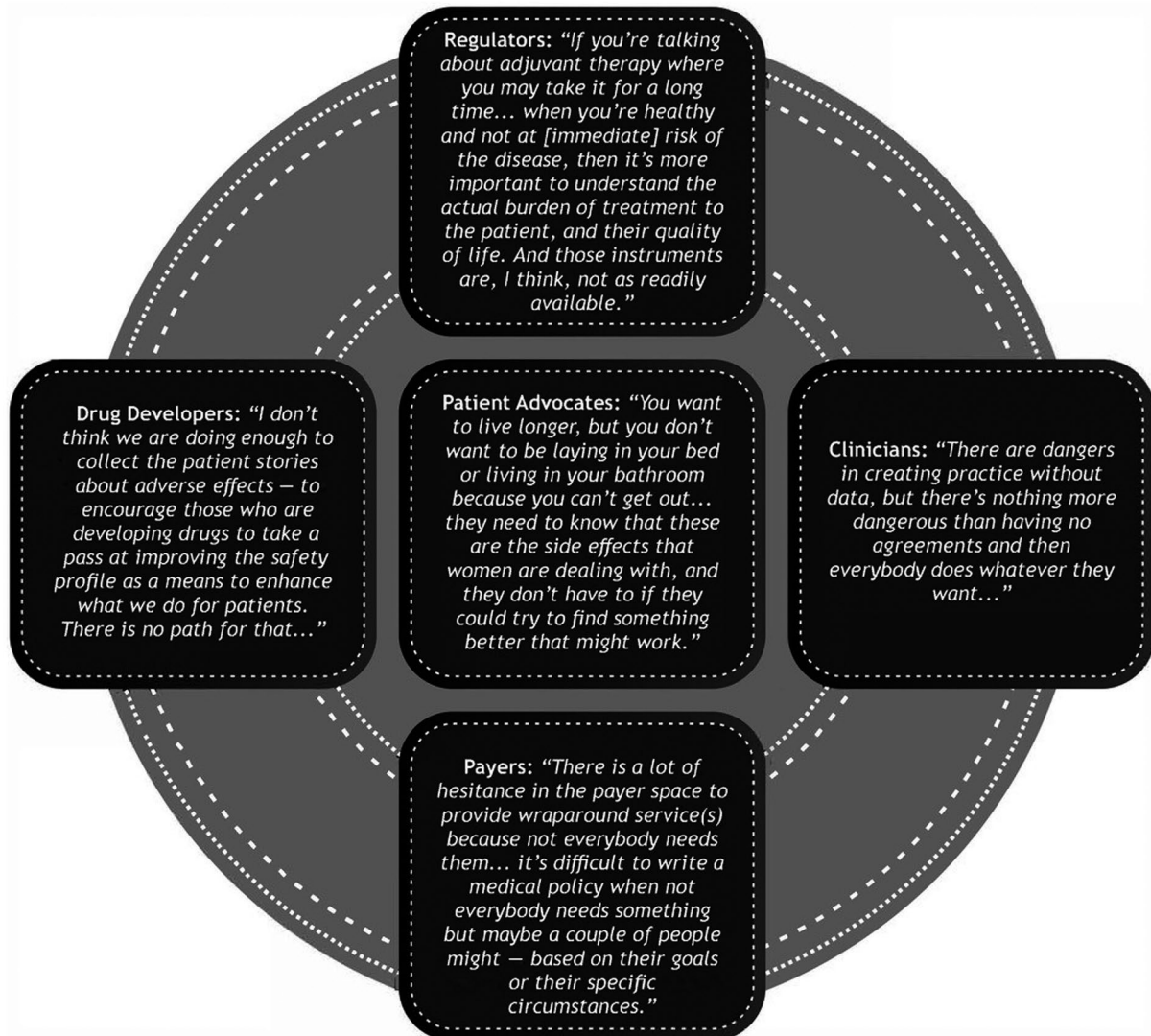


Figure 2. Exemplary quotes regarding the effects of integrating and applying information concerning adverse events.

Cultural and Economic Impacts on Information Regarding AEs

All stakeholder groups called for the greater frequency, breadth, and depth of discussions of acceptable risk: benefit tradeoffs for adjuvant therapies in both the public and private sector. Perspectives centered on financial, ethical, and cultural considerations (Fig. 3). Drug developers believed that establishing economic preferences for adjuvant therapies with less severe AE profiles could drive innovation in drug design. However, they also noted that documenting such preferences likely would require broad and long-term data collection efforts currently considered to be infeasible (as described above). Clinicians focused on the overall cost of care for patients

and the negative effects costs can have on a patient's decision to adhere to therapy or to pursue appropriate treatment. Payers described how the high prices of oncology drugs affected their ability to cover patient needs and emphasized that the payer business model limits “personalized” approaches to coverage. Patient advocates noted the disparities between the amount of money “flowing through” the US health care system and the poor overall breadth and quality of care for patients receiving adjuvant therapy. Drug developers and regulators generally did not comment in this arena.

Stakeholders also called for challenging the cultural values underlying a broad range of current practices. Regulators charged with evaluating the risk:benefit

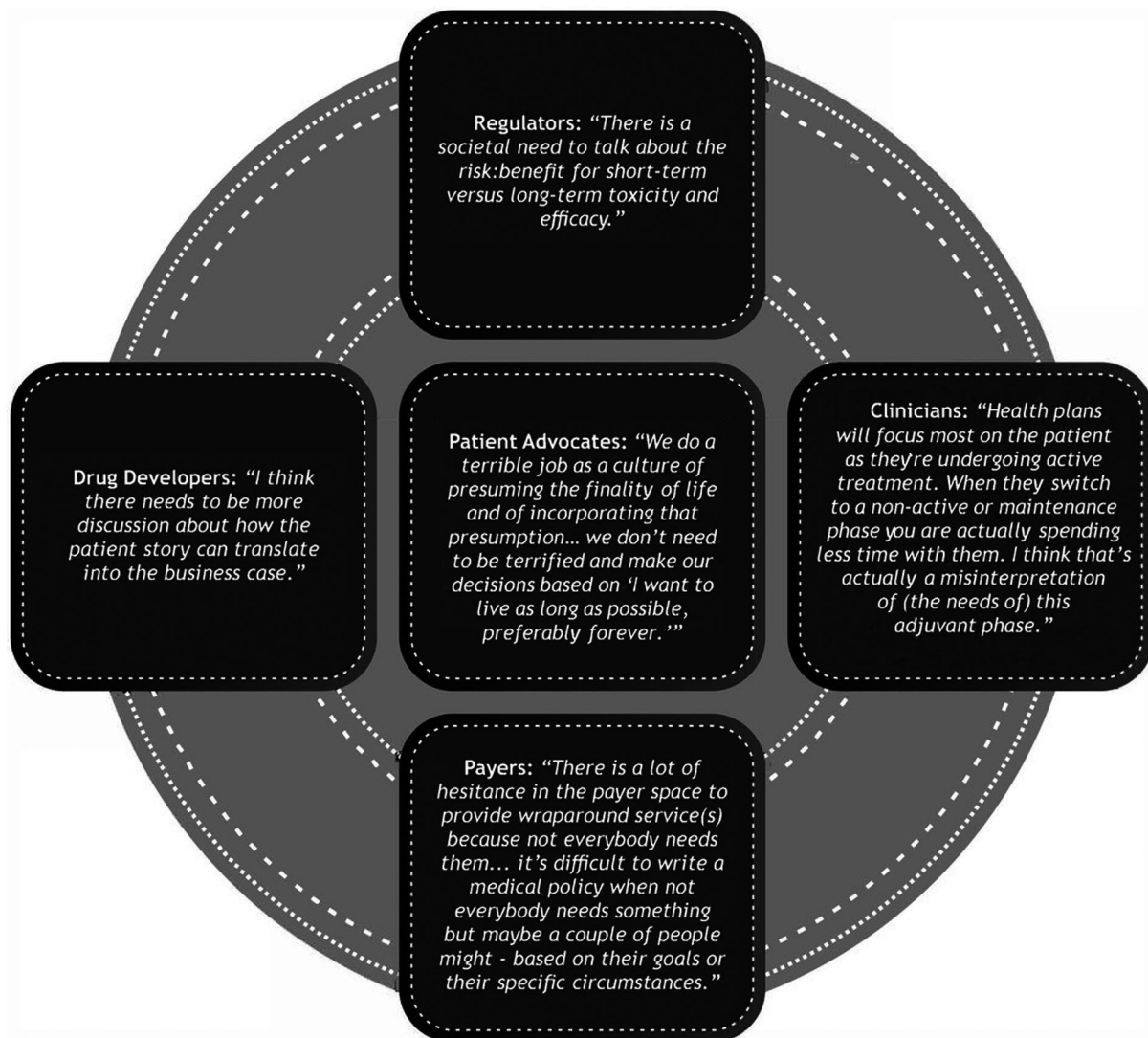


Figure 3. Exemplary quotes regarding the values and cultural aspects affecting the distribution of information concerning adverse events.

tradeoffs for approving adjuvant drug therapies suggested that renewed discussion regarding acceptable burdens and tradeoffs for patients receiving adjuvant therapy are needed given current survival rates and the growing evidence of the effect of AEs on patient quality of life. Many drug developers echoed this observation and stated that a societal or regulatory shift in acceptable risks and benefits likely would be necessary to change adjuvant drug design, testing, or data collection. Patient advocates also called for a broader cultural understanding of the long-term effects of some adjuvant therapies. They also cited the “there’s-a-pill-for-that” culture as contributing to additional treatment burden (time, cost, and side effects)

for patients without focusing on reducing AEs and their effects on activities of daily living and quality of life. However, few stakeholders who commented in this theme suggested ways to facilitate these new conversations.

Several of the groups noted that fully considering a patient’s need to understand AEs can get lost in the larger culture and priorities of primary cancer treatment. To this end, several payers expressed dismay that their case management support services are discontinued or reduced when a patient moves from primary treatment into adjuvant therapy. They believed that this reduction reflects an inherent misalignment in the health care payer system design and misrepresents the importance

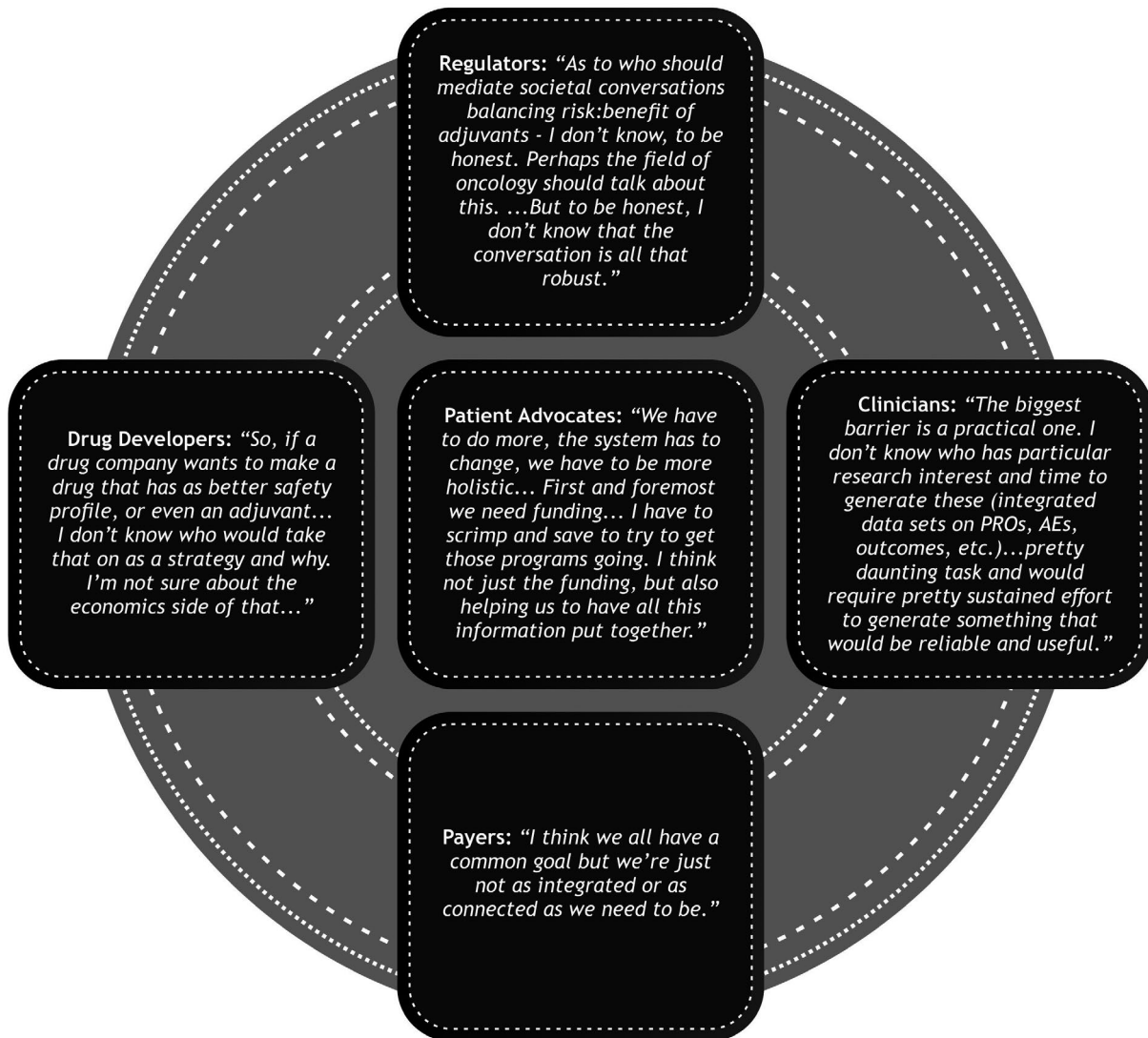


Figure 4. Exemplary quotes regarding the alignment and ownership of interstakeholder and intrastakeholder efforts to improve the use of information concerning adverse events. AEs indicates adverse events; PROs, patient-reported outcomes.

of adjuvant treatment adherence and supportive care on quality of life and outcomes.

Patient advocates, regulators, and clinicians all described the uniqueness of adjuvant treatment and its decision points when compared with the setting of metastatic cancer treatment. They noted the complexity of making decisions to initiate or maintain adjuvant treatment with the potential for AEs when tumors are absent or negligible (and often after a taxing initial course of therapy).

Perhaps the most profound observation, raised by patient advocates, was the need for greater cultural openness to clinician-patient discussions around death. They stressed that until we acknowledge the inevitability of

death despite the best therapy, candid and honest discussions of the tradeoffs between quality and quantity of life will be impossible.

Alignment and Ownership of Interstakeholder and Intrastakeholder Efforts

Frustration at the lack of coordination in meeting shared goals was a pervasive undercurrent in these interviews. In both implicit and explicit ways, stakeholders also reported a lack of clarity around who is responsible for the many diffuse issues described herein and thus who can or should provide the resources to address them (Fig. 4). However, stakeholder-specific contexts did vary.

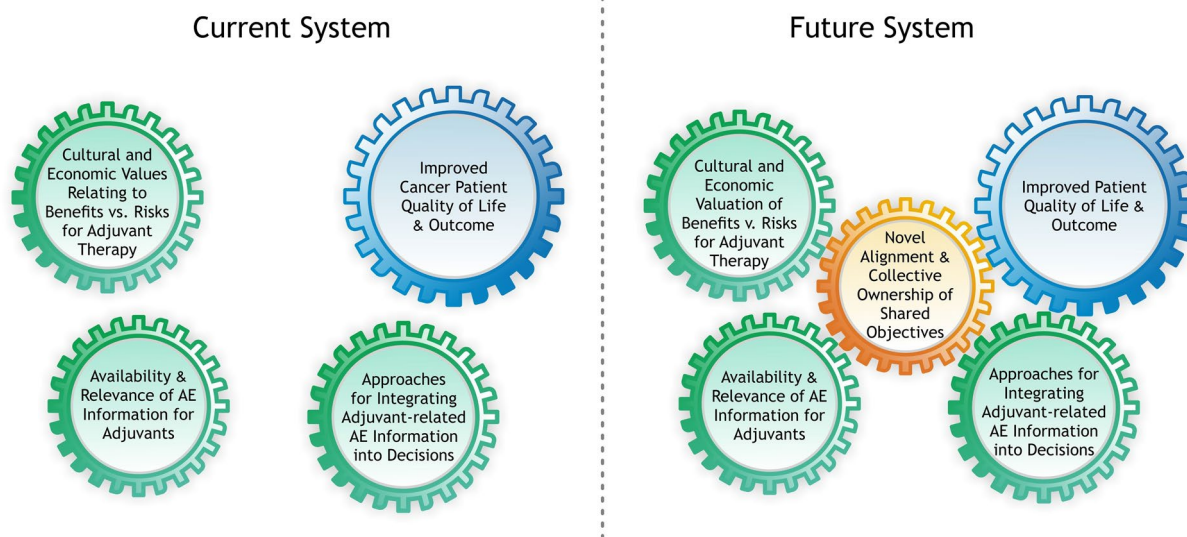


Figure 5. Current and future systems with which to improve the use of information regarding adverse events to inform patient care.

Drug developers and regulators highlighted the uncertainty around who would begin and sustain conversations to improve the use of AE information in the design and evaluation of adjuvant therapies. Clinicians, by contrast, focused most on the potentially overwhelming challenge of heterogeneous and rapidly changing information, preferences, administrative requirements, and fiscal constraints as they use AE information to design robust and patient-centered standards of practice. Payers expressed a more generalized uncertainty around the viability of opportunities for multistakeholder engagement. Finally, but in no way last, patient advocates focused on the challenge of identifying resources to facilitate both broad discussion forums as well as to implement specific research tasks and programs.

DISCUSSION

We believe the results of the current study provide new insights into intrastakeholder and interstakeholder perspectives regarding the breadth of challenges to the development and use of AE information to improve adjuvant therapy, and offer a compelling call for further action. This call to action is timely in light of the growing cross-sector focus on actively connecting patient experience with drug design, approval, and delivery using tools such as the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and a May 2019 draft guidance from the US Food and Drug Administration (FDA)

regarding the use of real-world data and evidence in drug evaluation.¹⁸⁻²⁰

We also believe the specific needs identified in the current study provide starting points for those seeking to better understand, support, and/or engage with their peers in future actions to improve outcomes for patients receiving adjuvant therapy. The consistency in the themes reported across stakeholder groups, despite the very different modes of operation, funding, composition, and spheres of influence of these stakeholders, suggests that future efforts to collectivize or synergize change initiatives could be effective. Despite this shared appetite for progress, a key takeaway from the current study is that even broadly desired change in the use of AE information in the adjuvant setting often has been stymied. Our identification of a lack of clear ownership to pursue or resource this change represents a significant new, if challenging, opportunity to affect systemic progress (Fig. 5). To the best of our knowledge, there currently are no ongoing efforts to broadly address these ownership and alignment deficiencies. Addressing this gap will require innovative approaches to realize cross-stakeholder motivation, management, and resourcing.^{21,22} Programs such as the former Biden Cancer Initiative that loosely collectivized disparate efforts and motivated independent groups toward a shared set of goals may provide inspiration and learnings. A similar, but more focused, approach could be effective in promoting systemic progress against the issues identified herein. We recommend

the formation of a novel multistakeholder leadership team to champion a new collective initiative operated under the auspices of a multidisciplinary nonprofit or a broadly chartered government entity (eg, the Health and Environmental Sciences Institute, the FDA Oncology Center of Excellence, etc). Even with limited resources, a focused leadership team could catalyze impactful efforts across the community by promoting the broader awareness of current gaps. By encouraging stakeholders to self-identify with a shared mission of improving the quality of life among patients who are receiving or have received adjuvant therapy, new collaborations, synergies, and patient benefits may be realized, even in the absence of formal program structures and agreements.

Limitations

The current qualitative study was designed intentionally to generate rather than test hypotheses, and thus it was limited to providing directional insights that inform future action. Its emphasis on breadth (eg, perspectives across a broad range of stakeholders of significance to the cancer care arena) versus depth also limited the study representation of variance within a given stakeholder category.

Conclusions

The results of the current study identified 4 themes that, if addressed, could improve outcomes for patients with cancer and cancer survivors by improving the collection and use of information regarding adjuvant treatment-related AEs. The lack of ownership of the collection, sharing, and dissemination of AE information relevant to adjuvant therapy is both a systemic hurdle to change and an opportunity to focus organizational, intellectual, and financial resources on improving outcomes for patients receiving these therapies.

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CONFLICT OF INTEREST DISCLOSURES

Syril D. Pettit's employer, the nonprofit Health and Environmental Sciences Institute, receives some of its charitable donations from sectors referenced in this research, including pharmaceutical companies as well as government agencies such as the US Food and Drug Administration. The work described in the current study was conducted in Dr. Pettit's capacity as a doctoral student at the University of North Carolina Gillings School of Public Health and was not directed or funded by the Health and Environmental Sciences Institute. No funding was received or provided for the research in this study and no conflicts are reported. Steven E. Lipshultz has received National Cancer Institute grant 1R01 CA211996-01; has received National Institutes of Health grants HL072705,

HL078522, HL053392, CA127642, CA068484, HD052104, AI50274, HD052102, HL087708, HL079233, HL004537, HL087000, HL007188, HL094100, HL095127, and HD80002; has received grants from Pfizer, the Michael Garig Fund, the Women's Cancer Association, and Sofia's Hope Inc; has acted as a paid consultant for Clinigen; has acted as a paid member of the Data Safety Monitoring Board for Axio Research; and has received honoraria from Biomed Central for work performed outside of the current study. Ethan Basch has received grants from the National Cancer Institute and the Patient-Centered Outcomes Research Institute; has acted as a paid expert consultant on research projects for Memorial Sloan Kettering Cancer Center, the Dana-Farber Cancer Institute, the Centers for Medicare and Medicaid Services, and RTI International (formerly Research Triangle Institute); and has acted as a paid scientific advisor for Noona Healthcare, Sivan Healthcare, and Self Care Catalysts. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Syril D. Pettit: Study design and conceptualization, methods, data collection, data coding, analysis, interpretation, and writing—review and editing. **Pamela Silberman:** Study design and conceptualization, methods, data interpretation, content review, and revision. **Kristen Hassmiller Lich:** Study design and conceptualization, methods, data interpretation, writing, content review, and revision. **Rebecca Kirch:** Study design and conceptualization, methods, data interpretation, content review, and revision. **Steven E. Lipshultz:** Study design and conceptualization, methods, data interpretation, writing, content review, and revision. **Randall Teal:** Study design and conceptualization, methods, data coding and analysis, data interpretation, and content review and revision. **Ethan Basch:** Study design and conceptualization, methods, data interpretation, content review, and revision.

REFERENCES

- Denlinger CS, Carlson RW, Are M, et al. Survivorship: introduction and definition. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2014;12:34-45.
- Office of Cancer Survivorship. Definitions, statistics, and graphs. National Cancer Institute. <https://cancercontrol.cancer.gov/ocs/statistics/statistics.html>. Accessed July 29, 2019.
- National Cancer Institute. Adjuvant therapy. NCI dictionary of cancer terms. www.cancer.gov/publications/dictionaries/cancer-terms/def/adjuvant-therapy. Accessed July 23, 2019.
- Cleeland CS, Allen JD, Roberts SA, et al. Reducing the toxicity of cancer therapy: recognizing needs, taking action. *Nat Rev Clin Oncol*. 2012;9:471-478.
- Pettit SD, Kirch R. Do current approaches to assessing therapy related adverse events align with the needs of long-term cancer patients and survivors? *Cardio-Oncology*. 2018;4(5). doi:10.1186/s40959-018-0031-4
- Allen JD, Stewart MD, Roberts SA, Sigal EV. The value of addressing patient preferences. *Value Health*. 2017;20:283-285.
- Shingler SL, Bennett BM, Cramer JA, Towse A, Twelves C, Lloyd AJ. Treatment preference, adherence and outcomes in patients with cancer: literature review and development of a theoretical model. *Curr Med Res Opin*. 2014;30:2329-2341.
- Genova C, Rossi G, Rijavec E, et al. Releasing the brake: safety profile of immune check-point inhibitors in non-small cell lung cancer. *Expert Opin Drug Saf*. 2017;16:573-585.
- Yang GS, Kim HJ, Griffith KA, Zhu S, Dorsey SG, Renn CL. Interventions for the treatment of aromatase inhibitor-associated arthralgia in breast cancer survivors: a systematic review and meta-analysis. *Cancer Nurs*. 2017;40:E26-E41.
- Langer SW. Dexrazoxane for the treatment of chemotherapy-related side effects. *Cancer Manag Res*. 2014;6:357-363.
- Seruga B, Sterling L, Wang L, Tannock IF. Reporting of serious adverse drug reactions of targeted anticancer agents in pivotal phase III clinical trials. *J Clin Oncol*. 2011;29:174-185.
- Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. *Adm Policy Ment Heal*. 2015;42:533-544.

13. Marshall MN. Sampling for qualitative research. *Fam Pract*. 1996; 13:522-555.
14. McAlearney AS, Reiter KL, Weiner BJ, Minasian L, Song PH. Challenges and facilitators of community clinical oncology program participation: a qualitative study. *J Healthc Manag*. 2013;58:29-44; discussion 45-46.
15. Chapman AL, Hadfield M, Chapman CJ. Qualitative research in healthcare: an introduction to grounded theory using thematic analysis. *J R Coll Physicians Edinb*. 2015;45:201-205.
16. Bradley EH, Curry LA, Devers KJ. Qualitative data analysis for health services research: developing taxonomy, themes, and theory. *Health Serv Res*. 2007;42:1758-1772.
17. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. 2007;19: 349-357.
18. Basch E, Schrag D. The evolving uses of “real-world” data. *JAMA*. 2019;321:1359-1360.
19. US Food and Drug Administration. Submitting documents using real-world data and real-world evidence to FDA for drugs and biologics: guidance for industry. DRAFT GUIDANCE. <https://www.fda.gov/media/124795/download>. Accessed May 29, 2019.
20. Chung AE, Shoenbill K, Mitchell SA, et al. Patient free text reporting of symptomatic adverse events in cancer clinical research using the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Am Med Inform Assoc*. 2019;26:276-285.
21. Rittel HWJ, Webber MM. Dilemmas in a general theory of planning. *Policy Sci*. 1973;4:155-169.
22. Weber EP, Khademian AM. Wicked problems, knowledge challenges, and collaborative capacity builders in network settings. *Public Adm Rev*. 2008;68:334-349.