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Stakeholder perspectives on implementing the National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

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Abstract

The National Cancer Institute (NCI) is developing a patient-reported version of its Common Terminology Criteria for Adverse Events, called the "PRO-CTCAE." The PRO-CTCAE consists of a library of patient-reported items which can be administered in clinical trials to directly capture the patient experience of adverse events during cancer treatment, as well as a software platform for administering these items via computer or telephone. In order to better understand the impressions of stakeholders involved in cancer clinical research about the potential value of the PRO-CTCAE approach to capturing adverse event information in clinical research, as well as their perspectives about barriers and strategies for implementing the PRO-CTCAE in NCI-sponsored cancer trials, a survey was conducted. A survey including structured and open-ended questions was developed to elicit perceptions about the use of patient-reported outcomes (PROs) for adverse event reporting, and to explore logistical considerations for implementing the PRO-CTCAE in cancer trials. The survey was distributed electronically and by paper to a convenience sample of leadership and committee members in the NCI's cooperative group network, including principal investigators, clinical investigators, research nurses, data managers, patient advocates, and representatives of the NCI and Food and Drug Administration. Between October, 2008 through February, 2009, 727 surveys were collected. Most respondents (93%) agreed that patient reporting of adverse symptoms would be useful for improving understanding of the patient experience with treatment in cancer trials, and 88%, 80%, and 76%, respectively, endorsed that administration of PRO-CTCAE items in clinical trials would improve the completeness, accuracy, and efficiency of symptom data collection. More than three fourths believed that patient reports would be useful for informing treatment dose modifications and towards FDA regulatory evaluation of drugs. Eighty-eight percent felt that patients in clinical trials would be willing to self-report adverse symptoms at clinic visits via computer, and 68% felt patients would self-report weekly from home via the internet or an automated telephone system. Lack of computers and limited space and personnel were seen as potential barriers to in-clinic self-reporting, but these were judged to be surmountable with adequate funding. The PRO-CTCAE items and software are viewed by a majority of survey respondents as a means to improve adverse event data quality and comprehensiveness, enhance clinical decision-making, and foster patient-clinician communication. Research is ongoing to assess the measurement properties and feasibility of implementing this measure in cancer clinical trials.

Implications

Policymakers: Patient self-reporting provides essential information about the safety and effectiveness of drugs and devices which can aid setting treatment and reimbursement priorities.

Researchers: Patient-reported outcomes provide reliable and valid accounts of the symptoms experienced by patients during treatment, which can provide important study data and prompt new research questions.

Practitioners: Systems that allow patients to self-report their own side effects in real-time to providers have been demonstrated to improve symptom control, patient satisfaction, patient-clinician communication, and to aid in clinical decision-making.

Keywords

Patient-reported outcomes, Symptoms, adverse events, Oncology, Cancer, Clinical trials, Toxicity, safety, Tolerability, Comparative effectiveness research, Cooperative groups, National Cancer Institute

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INTRODUCTION

The Common Terminology Criteria for Adverse Events (CTCAE) is a lexicon of individual items maintained by the US National Cancer Institute (NCI) in order to standardize documentation of adverse events (AEs) in cancer clinical trials [1]. Initially developed in 1984, it was substantially revised in 2003 to expand anatomic site specificity and include criteria for surgical effects, and was again revised in 2009 to harmonize terminology with the *Medical Dictionary for Regulatory Activities* [2, 3].

Each CTCAE item contains a term which represents a specific AE of interest and response options anchored to discrete clinical criteria which yield a severity grade between 1 and 5. As such, these items are used in clinical trials to document both the incidence and severity of AEs. Three general categories of AEs are included in the CTCAE: those based on laboratory reports (e.g., anemia); those based on clinical observations (e.g., retinal tear); and symptoms (e.g., dyspnea). All three categories of items are currently reported by clinicians.

Based on mounting evidence that clinician reporting of patients' symptoms underestimates the prevalence and severity of these symptoms [4–11], and recent guidance from the FDA regarding standards for the development of patient-reported outcomes measures [12], in 2008, the NCI contracted to develop patient versions of those items in the CTCAE which represent symptoms, which collectively would be called the "Patient-Reported Outcomes version of the Common terminology Criteria for Adverse Events" or PRO-CTCAE. In addition, the NCI contracted to develop a software platform for administering these items in clinical trials (although the ultimate intention of the PRO-CTCAE initiative it to move towards electronic administration of these items in clinical trials, paper versions consisting of PRO-CTCAE items will also be available).

As a part of the PRO-CTCAE initiative, the NCI wished to ascertain the extent to which various stakeholders involved in NCI-sponsored trials (particularly within the NCI's cooperative group network) recognize a need for such a library of patient-reported AE items and administration software. Stakeholders of interest included cooperative group committee leaders, study chairs/principal investigators, clinical investigators, research nurses, research assistants/data managers, patient advocates, and representatives of the NCI and FDA. Of particular interest were perceived barriers to implementing a system in clinical trials for electronically collecting patient-reported adverse symptom information and recommended solutions for overcoming these barriers.

METHODS

Survey–An anonymous survey was developed to capture impressions from various stakeholders involved in the conduct of NCI-sponsored clinical research about the perceived value, feasibility, and potential barriers to implementing an electronic software platform for capturing patient-reported adverse symptom events in multicenter oncology trials. Background questions queried participants' research role (s), affiliation(s) with cooperative groups, and educational degree(s). Additional questions pertained to barriers to PRO-CTCAE implementation at the patient-level and site-level, as well as overall impressions of the usefulness of such an approach to capturing adverse event information. These questions utilized a common response option format including *strongly agree*, *somewhat agree*, *neither agree nor disagree*, *somewhat disagree*, and *strongly disagree*. Two open-ended questions invited general impressions and recommendations for desirable system features. A copy of the survey is included as an APPENDIX.

Participants–Individuals were eligible to participate if they were clinical investigators (based at academic centers or community practices), data managers, NCI staff, FDA staff, cooperative group leadership, or patient advocates with direct involvement in the development, conduct, or analysis of cooperative group trials. Study recruitment targeted investigators in community oncology practices participating in NCI cooperative group research (i.e., Community Clinical Oncology Program sites); patient advocates registered with the NCI; investigators, data managers, and leadership of the Cancer and Leukemia Group B (CALGB) and Radiation Therapy Oncology Group (RTOG); FDA reviewers in the Office of Oncology Drug Products and Study Endpoints and Labeling Development staff; and NCI staff in the Division of Cancer Prevention (DCP) and Cancer Therapy Evaluation Program (CTEP).

Procedure–The survey was uploaded to a secure electronic distribution system, and an email soliciting participation was sent to distribution lists of the targeted participants. In addition, paper versions of the survey were distributed when disease committees convened at cooperative group meetings. Because paper surveys were handed out at multiple cooperative group meetings and were also circulated electronically, it is not possible to quantify the total number of distributed surveys. The survey indicated to respondents that it was anonymous, and no personally identifying information was collected. Data were collected between October, 2008 and February, 2009.

Analyses–Frequencies and proportions were computed for all survey items. Associations between participant role and various responses were examined with chi-square analyses. Since some participants endorsed more than one role, participants were categorized into mutually exclusive groups as *Researchers* (i.e., lead primary investigators, investigators), *Research Staff* (i.e., research nurses and research assistants/data managers), *Patient Advocates*, or *Regulators* (i.e., NCI and FDA representatives). Likert responses for each item were collapsed to create three response options (i.e., Agree, Neither Agree nor Disagree, Disagree).

Qualitative responses to the open-ended questions were evaluated in stages. First, responses were reviewed for content analysis. Three main themes were identified: general approval/disapproval of patient reporting for adverse event monitoring; concerns about a PRO-CTCAE system; and suggestions for functions of a PRO-CTCAE system. Next, responses were coded according to these major themes and grouped into subordinate categories. Finally, the frequencies of responses within categories were tabulated.

RESULTS

Participants–A total of 727 questionnaires were collected between October, 2008 through February, 2009, with the distribution of respondents including 26% researchers, 44% research staff, 14% patient advocates, and 16% regulators. Ten of the US NCI-sponsored clinical trials cooperative groups were included in the survey including the American College of Surgeons Oncology Group (ACoSOG); American College of Radiology Imaging Network (ACRIN); Cancer and Leukemia Group B (CALGB); Children's Oncology Group (COG); Eastern Cooperative Oncology Group (ECOG); Gynecologic Oncology Group (GOG); National Surgical Adjuvant Breast and Bowel Project (NSABP); North Central Clinical Trials Group (NCCTG); Radiation Therapy Oncology Group (RTOG); and Southwest Oncology Group (SWOG). Among the cooperative groups, CALGB (41%) and RTOG (34%) represented the largest number of respondents.

Perceived usefulness–Table 1 summarizes survey responses by participant role. There was strong consensus (93% overall) that patient reporting of adverse symptoms would be useful for improving our understanding of the patient experience with treatment in cancer clinical trials. The majority of respondents endorsed that such an approach would improve the completeness (88%), accuracy (80%), and efficiency (80%) of symptom data collection in clinical trials. More than three-fourths of respondents indicated that patient reports would be useful for informing treatment dose modifications and towards FDA regulatory evaluation of drugs.

Acceptability–Survey responses revealed that 89% endorsed, with 64% *strongly* endorsing, the need for a PRO-CTCAE approach to collect adverse symptom assessments directly from patients in clinical trials. Adverse symptom severity was regarded by 68% to be better understood by patients than clinicians, particularly among patient advocates, while research staff disagreed the most, $\chi^2(6, N=624)=54.64$, $p<.001$. Conversely, 86% of all respondents agreed that some symptoms may be better understood by clinicians due to technical training and expertise. Consistent with these results, 88% agreed that adverse events in clinical trials should be reported by *both* patients and clinicians.

Implementation barriers–Although 88% of respondents felt that patients in clinical trials would be willing to self-report adverse symptoms at clinic visits via computer, 88% believed that severe illness could be a potential barrier. Inclusion of proxy reporting by caregivers for patients too ill to self-report received support by 68%, particularly among patient advocates, $\chi^2(6, N=619)=15.08$, $p<.020$. A belief that patients enrolled in clinical trials would be willing and able to self-report weekly from home via the internet or via an automated telephone system was shared by 68%, but research staff were the most skeptical $\chi^2(6, N=625)=42.88$, $p<.001$. Most participants agreed that a potential barrier to patients self-reporting at clinic visits via computer is the scarceness in the clinical setting of computers that can be accessed by patients (70%). Other perceived barriers to this approach included limited time at clinic visits (58%), limited available personnel to assist patients (57%), and limited clinic space (50%). However, compared with research staff, fewer patient advocates thought that clinic time, personnel, or space were barriers. With no significant differences between groups, 43% of all respondents agreed that their workload would increase if patient reports were used for AEs while 42% neither agreed nor disagreed.

Importantly, 79% of participants perceived that all potential barriers were manageable if additional funds could be obtained. Regarding the method of patient reporting in clinic, 82% indicated that paper-based reporting was feasible, and relative to electronic reporting, more respondents thought portable devices (58%) were feasible compared with desktop computers (39%). Researchers endorsed the use of portable devices more than other groups, $\chi^2(6, N=565)=100.98$, $p<.001$.

Patient advocate respondents were more likely than other respondent types to endorse that patients would be willing to self-report from home between visits. Advocates were also more open to an approach in which caregivers reported on behalf of those too ill to report for themselves.

Qualitative responses–Of the total sample of 727 respondents, 292 respondents (40%) provided comments to the open-ended questions. Of these, 24% offered generally positive statements about a PRO-CTCAE approach. For example, "*Self-reporting of adverse symptoms is needed. This would improve the understanding of patients' reactions to new treatments or drugs and avoid the problem of patients not telling clinicians of problems because they do not want to 'bother' the doctor. It also makes the patient feel a part of the research process and not just a 'guinea pig' which is very important.*" In comparison, only 3% wrote general

Table 1 | Responses to stakeholder survey, by respondent role subgroup (N=727)

	All respondents	Respondent role subgroups				p < value
		Researchers[a] (N=189)	Research staff[b] *(N=316)*	Patient advocates (N=104)	Regulators[c] *(N=118)*	
In general, patients better understand the severity of their symptoms than clinicians						
N	624	178	288	86	72	.001
Agree	68%	80%	54%	81%	76%	
Neither	13%	12%	15%	7%	13%	
Disagree	19%	8%	31%	12%	11%	
Caregivers will be able to report on behalf of severely ill or debilitated patients						
N	619	175	285	86	73	.020
Agree	67%	59%	68%	83%	66%	
Neither	14%	18%	13%	7%	15%	
Disagree	19%	23%	18%	11%	19%	
Most patients in clinical trials would be willing to self-report symptoms from home on a weekly basis						
N	625	178	287	87	73	.001
Agree	68%	76%	57%	85%	70%	
Neither	14%	14%	15%	7%	19%	
Disagree	18%	11%	28%	8%	11%	
Limited space at my clinic site is a potential barrier to implementing a system for collecting data directly from patients						
N	577	174	286	65	52	.001
Agree	50%	48%	58%	26%	40%	
Neither	21%	13%	15%	54%	40%	
Disagree	29%	39%	27%	20%	19%	
Limited personnel at my clinic site is a potential barrier to implementing a system for collecting data directly from patients						
N	576	173	285	64	54	.001
Agree	57%	71%	53%	38%	58%	
Neither	18%	7%	15%	52%	32%	
Disagree	25%	23%	32%	11%	11%	
Limited time at my clinic site is a potential barrier to implementing a system for collecting data directly from patients						
N	577	174	285	64	54	.001
Agree	58%	69%	55%	44%	54%	
Neither	19%	9%	17%	44%	28%	
Disagree	23%	22%	27%	13%	19%	
Wireless laptop/tablet computer-based patient self-reporting is feasible at my site						
N	565	170	285	60	50	.001
Agree	58%	79%	55%	33%	32%	
Neither	23%	8%	20%	58%	46%	
Disagree	19%	13%	25%	8%	22%	

[a] Includes cooperative group committee leaders, study chairs/principal investigators, and clinical investigators

[b] Includes research nurses and clinical research assistants/data managers

[c] Includes representatives of the national cancer institute and food and drug administration

negative statements, such as, "*There are already several good systems for collecting data of this kind. I am not sure why additional systems are needed.*"

Respondents also commented on potential implementation barriers and provided suggestions to guide the optimal design of a system to capture patient-reported adverse events (see Tables 2 and 3). The most frequently reported potential barrier was a concern that patient self-reports could introduce inaccuracies into adverse event reporting because of reporting and recall biases, and lack of knowledge. Other cited potential barriers included unfamiliarity with electronic devices, lack of computer access at home, and limited acceptance of and adherence to reporting protocols by patients. Additional concerns were that such an approach might be a burden to patients, might generate "needless" data, diminish communication between patients and doctors, and cause patients to be overtreated for symptoms.

Multiple suggestions were offered to strengthen the development of patient-reported AE items and software, with representative examples shown in Table 3. The most common recommendation was to assure that any approach to patient self-reporting be

Table 2 | Common qualitative responses regarding potential barriers to implementing a standardized system for capturing patient-reported adverse events in cancer clinical trials (N=292)

Potential barriers	n[a]	Examples
Patient-related		
Inaccurate reporting	48	"Some under-report; others appear to over-report." "Patients may not give true statements due to fear they may have to come off study medications." "Patients not trained to identify many adverse events."
Computer literacy	24	"Patients, especially elderly, are not computer literate."
Lack of computer and internet access	17	"The only reservation is the availability for our patient access to computers at home and the physician office."
Acceptance/adherence	15	"Our patient population is a mixture of people who would love to do this and others who would not want to and be quite annoyed at the suggestion." "Worry about compliance with patients."
Patient burden	12	"I would like to see this not to become patient's burden."
Reading literacy	7	"Please be aware of the literacy limitations of other cultures and educational levels."
Appropriate for minorities	6	"We have a number of patients who have immigrated to our community from other countries. Many need one-on-one help in deciphering both the survey question and how they should answer."
Unable/illness	5	"The most seriously ill patients may not report and only those who are faring well in the trial may report, thus, skewing the results." "I don't feel that all patients would be able to self report."
Inaccurate proxy report	5	"Caregivers can over-state the patient's condition and even more frequently under-state the patient's condition."
Site-related		
Limited personnel	20	"I am concerned about the workload generated by this type of system". "Not enough time, staffing to facilitate."
Limited space	6	"This is a great idea, but in our sites, space is a big issue."
Funding insufficient	6	"Funding will not overcome the barriers."
Regulatory approval	2	"Too many regulations to allow this process in my setting."
Study-related		
Unnecessary data	8	"We have used a paper review of AEs. It has generated a lot of spurious data." "Does the FDA truly want everything a patient reports including something not related to any treatment?"
Data discrepancies	5	"I can see discrepancies between what a patient reports versus what a clinician would report."
Procedural difficulties	4	"It would be yet another area where we would have protocol deviations out of our control." "Electronic devices can often be misplaced, forgotten, or patients can forget to save the data."
Decline enrollment	3	"This self-reporting may be a factor that causes someone not to consent to trial."
Treatment-related		
Clinical relationship	6	"Patient self-reporting could be helpful but should not replace communication between doctor and patient. This tool can't be another reason for patients not to talk with their doctors."
Treatment implications	5	"Not every symptom needs a medical treatment." "I would be concerned that it may increase the dose modifications required."
Staff notification	2	"How does the clinician gain access to this information for patient care and dose modifications?"

[a] Some respondents identified more than one potential barrier

Table 3 | Suggestions by survey respondents for the design of a standardized system to capture patient-reported adverse events in cancer clinical trials (N=292)

Suggestions	n[a]	Examples
User friendly		
Understandable	41	"Clear definition of the concept measured." "Give examples." "Include pictures." "Simple short concise verbiage."
Easy to complete	40	"Touch screen system." "Drop down menus." "Quick to complete." "Easy to navigate." "Error correction."
General comments	37	"User friendly."
Patient Education	23	"We need much better patient education so that they feel comfortable reporting events." "Any reporting system has to be clear about the reasons for reporting symptoms in order to make sure that patients don't withhold things that might be relevant."
Readable	18	"Large font." "Minimal words per screen." "Instructions modified for people with visual impairment or reading disability." "Available in different languages."
Easy for administrators	13	"Easy to implement for sites." "Leveraging potential business of practice incentives to their use may prove to be a way to accelerate uptake."
Accessible/portable	12	"Development of portable electronic/tablet systems." "Accessibility is important to avoid biases."
Help support	6	"Help function should be available."
Cues/Reminders	4	"Auto calls or email to remind patients to self report." "Prompt when PRO measures are due and not obtained."
System features		
Reporting options	40	"It would be nice if patients were given a choice of electronic vs. paper." "There should be some open ended way for patients to report." "The option to self-report daily or more than weekly as needed."
Electronic reporting	32	"eTablets were used in a practice I worked in and greatly improved the assessment of the patients' symptoms and adjustment of treatment as needed." "Should make such a survey a web form." "Wireless." "PDA"
Involve clinician	27	"Best system is probably interactive between patients and staff." "Patient self-reporting should always be accompanied by clinician assessment simultaneously."
Outside clinic reporting	17	"Reporting between appointments would be very helpful." "Favor home reporting due to limited clinic time/space."
Data quality assurance	9	"Would also need to be reviewed by trials staff to ensure that patient is reporting all symptoms and events."
(Differentiate) proxy reports	6	"Caregiver or proxy reporting might be useful to avoid burden to ill patient or to avoid missing data however it would need to be coded differently." "For a pediatric population, the system would have to allow for parent reporting."
Patient privacy	4	"Assurance of privacy."
System development and implementation		
Validate	29	"A system such as the one proposed must be validated to withstand the highest level of scrutiny." "Use instruments that patients have reviewed and provided qualitative feedback on."
Standardize assessment	14	"Good idea but devil is in the detail. There should be a standard method of reporting." "Group common AE's together and do not "repeat" similar questions/events."
Minimize recall period	10	"Record the information at the time the symptom occurred."
Obtain additional information	7	"Include QOL and affective measures." "Include field to indicate interventions for AEs."
Longitudinal assessment	6	"What is of interest is change over time since it is recognized that some patients have poor baseline scores that are unrelated to study treatment." "We really don't know much about long term AE's."
Assess group/individual differences	6	"More work needs to be done to examine how different types of patients communicate with physicians or cancer care teams."

Table 3 (continued)

Funding	6	"Financial support."
User benefits		
Improve communication to site personnel	16	"Customized 'tell your doctor fields' would add to value for busy clinics and an automatic email and feedback to data mangers and investigators on trials." "Real-time feedback to providers."
Clinically useful	14	"Include some diagnostic queries." "Ability of health care personnel to access patient-reported symptoms to integrate these into clinical evaluation."
Helpful for patients	11	"System to categorize the adverse events over time for a patient to see a pattern or trend." "The system should be used to provide 24/7 coverage for patients."

[a] Some respondents identified more than one potential barrier

user-friendly. Patient reminders and feedback were proposed to increase adherence, and to facilitate patient care. Automated alerts to flag severe symptoms to research and clinical staff were deemed important. Respondents advocated that any patient-reported items and software should be appropriate for use in a range of patient populations, including minorities, pediatrics, disabled, non-English speaking, and those with lower literacy and educational levels. Similarly, system testing within a range of community settings and not just at large university-based clinics was encouraged. Respondents also recommended research on the interpretation of response choices as some felt that reporting differences may exist by treatment trajectory, symptom tolerance, severity of illness, location (e.g., home vs. clinic), cultural factors, and age (e.g., adolescents).

DISCUSSION

Diverse stakeholders involved with administration of clinical trials in the NCI-sponsored cooperative group network endorse development of a system to systematically collect patient-reported adverse event information. Across several respondent subgroups (i.e., cooperative group leadership, investigators, data managers, patient advocates, regulators), the PRO-CTCAE approach was viewed by most as a means to improve data quality and comprehensiveness, enhance clinical decision-making, and foster patient-clinician communication. Moreover, it was felt that patient-reported adverse event information should be incorporated into published study results and drug labels.

These findings reflect an overall movement in clinical research and drug regulatory policy towards favoring patient self-reports for those experiences best known to the patient, such as symptoms [3–5, 13–18]. Of particular note is the FDA's recent guidance for industry on patient-reported outcomes measures in medical product development to support labeling claims, in which patient-reported outcomes (PROs) are advocated for measuring subjective experiences of patients related both to treatment benefit and risk [12, 19]. Most HRQL and symptom instruments focus on treatment benefit, but the patient perspective on tolerability is rarely systematically captured. The availability of inexpensive technologies for administering questionnaires to patients (e.g., via computer, telephone, or other portable device), and widespread patient familiarity with these technologies, have made it feasible to collect information directly from patients during cancer treatment [20, 21]. A recent report by the Institute of Medicine highlights the need for data standardization and efficiency within the cooperative groups and the importance of engaging patients in the clinical trial enterprise; the approach of the PRO-CTCAE is consistent with this report's recommendations [22].

The results of this survey are being used to inform pilot feasibility studies of implementing PRO-CTCAE in NCI-sponsored clinical trials within the NCI's cooperative group network. In these pilot studies, selected PRO-CTCAE items are being administered electronically to patients enrolled in several multicenter clinical trials. Outcomes of interest include cost, logistical requirements for sites, acceptance by clinical staff and patients, and added value of collected information.

The PRO-CTCAE approach may yield benefits beyond screening for and characterizing adverse symptoms in clinical trials. Longer-term monitoring of patients' symptoms can be used to evaluate post-treatment patterns and timeframes for resolution of symptoms. It may also aid in symptom monitoring and management during routine chemotherapy care.

The stakeholder survey suggests that the largest perceived barrier to adoption of PRO-CTCAE in NCI-sponsored trials is the logistics around clinical implementation. When asked what resources would be necessary to facilitate computer-based administration of PRO-CTCAE items at clinic visits (i.e., at the point of care), many respondents suggested that additional computers, staff, and space would be necessary. This suggests that for an in-clinic electronic questionnaire administration model of PRO-CTCAE implementation to be successful, additional funds would be necessary to support site-level infrastructure. Alternatively, a model could be

developed in which patients do not rely on clinic-based computers to report, but rather would report between visits via home computers or an automated telephone system. Although training and backup data collection methods for non-respondents would still be necessary, much of this could be centralized or handled by site staff without requiring additional equipment or physical space at sites. Most respondents felt that such a remote-reporting model would be feasible.

Research staff (research nurses, research study assistants, data managers) generally had more concerns than other stakeholders about the logistics and resources necessary for adding this approach to the already-complex conduct of clinical trials. These are understandable concerns for this stakeholder group given limited resources at study sites for current data management needs and competing priorities in clinical trials [23]. Therefore, successful implementation of the PRO-CTCAE in cancer trials requires commitment of resources and education of research staff regarding its value as a data collection tool to improve the quality, comprehensiveness, and efficiency of AE data collection. Notably, clinical staff members who have actively participated in pilot studies including patient-reported AE data have highly endorsed its use [20].

Of note, patient respondents were more likely than other respondent types to feel that patients would be willing to self-report weekly from home between visits. This bodes well for the use of a between-visit approach to monitoring patient symptoms. It also reveals that clinical staff may underestimate the level of patient willingness or enthusiasm to self-report from home.

The success of broadly integrating use of the PRO-CTCAE items and software in cancer clinical research as tools for AE documentation and to enhance clinical decision-making will likely also depend on their integration with clinical workflow and in particular with other electronic systems used to manage clinical trials and electronic health records [24]. As such, an emphasis of the PRO-CTCAE initiative is integration with other clinical systems. [25]

To date, version 1.0 of the PRO-CTCAE items has been developed, encompassing 78 of the 790 items in CTCAE version 4. [26] Cognitive interviews have been conducted in a diverse sample of patients to assess the content validity of the items, [27] and a multi-center validation study to assess the measurement properties of the items is currently underway. [28] An online portal for administering these items to patients has been developed [25]. Prior work demonstrates the feasibility of collecting adverse symptom information directly from patients during cancer treatment [15, 20, 21], and additional feasibility studies in the NCI cooperative group network are ongoing.

In generalizing our findings, it should be recognized that a nonresponder bias may exist since our sampling procedures did not allow us to determine the response rate, and respondents comprise a convenience sample of those investigators, data managers, patient advocates, and regulators who were willing to participate. As a result, there may be unaccounted-for differences between survey responders and nonresponders in their perceptions about patient self-reporting of adverse events. However, given the size and diversity of our sample, we speculate that the high levels of overall endorsement observed in our study are comparable to the viewpoints of a majority of stakeholders.

As most participating investigators were academics and community-based practitioners working within the NCI's cooperative group network, their sentiments may not extend to industry, where most preapproval drug development is conducted. However, many academic investigators serve as thought-leaders and advisors to industry. Nonetheless, ascertainment of sentiments towards such systems among stakeholders in the pharmaceutical industry would necessitate additional study. Notably, other research is being conducted to evaluate the extent to which patient self-reporting of would affect the frequency of reporting of adverse symptoms in clinical trials compared with the current clinician-reporting approach. It has been hypothesized that the frequency of adverse symptoms not attributable to products being studied (e.g., related to comorbidities or "noise") would actually be reduced, while the power to detect adverse symptoms attributable to products themselves would be increased. Such properties would be appealing to sponsors and regulators, but these evaluations are pending.

The overall goal of a clinical trial is to collect valid and reliable data about the efficacy and adverse event profile of an intervention. This information is used by investigators to understand the properties of that intervention; by regulators to assess its overall value to the public; and by clinicians and patients during informed decision-making. It has become clear that the current mechanism for collecting adverse symptom event information in trials does not adequately represent the patient subjective experience with treatment. As a consequence, the information about tolerability that is available to investigators, regulators, clinicians, and patients when making decisions is incomplete. To alleviate this gap, an approach to systematically and efficiently collect patient-reported adverse symptom events is indicated, and the PRO-CTCAE represents one such approach. The ultimate goal of this work is to enhance the quality of information about the

impact of treatment on patients, to better inform decision-making and to improve patient safety.

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APPENDIX

DATE: _____/_____/_____ | | | | **(v11)**

PRO-CTCAE STAKEHOLDER SURVEY

NCI is developing a system for patients to report their own adverse symptoms in clinical treatment trials, called the PRO-CTCAE. This system will allow patients to self-report selected CTCAE symptoms electronically (by computer) or via paper forms at clinic visits. Clinicians and investigators will have access to this information for treatment decisions and/or documentation. We are seeking your input to assist us in understanding potential barriers to implementing such a system in the multicenter clinical trial setting.

1(a). What is your current role (check all that apply):
__Lead PI on treatment trial protocols
__Investigator on treatment trial protocols
__QOL/Symptom researcher
__CRA/RSA (Research Assistant)
__Research nurse
__Member of cooperative group committee
__Cooperative group leadership (Committee Chair, Executive Committee member, etc)
__NCI representative
__FDA representative
__Patient advocate
__Representative of industry sponsor

1(b). If you are affiliated with a clinical trials cooperative group, please check all that apply:
__ACoSOG
__ACRIN
__CALGB
__COG
__ECOG
__GOG
__NSABP
__NCCTG
__RTOG
__SWOG

2. Professional training:
__MD
__RN/NP
__PhD
__RPh/PharmD
__MPH or other Master's
__BA or BS

3. Have you worked with cancer populations?
__Yes __No

Please indicate how you perceive potential barriers to implementing a system for patient self-reporting of adverse events in the multicenter clinical trials context:

4. PATIENT-RELATED ISSUES	**Strongly Agree**	**Somewhat Agree**	**Neither Agree nor Disagree**	**Somewhat Disagree**	**Strongly Disagree**	
Most patients participating in clinical trials of cancer treatment would be willing to self-report adverse symptoms at clinic visits						4a
If patients feel well enough to attend a clinic visit, they are likely able to self-report their symptom burden						4b
Severe illness or debilitation is a potential barrier to patient self-reporting						4c
Caregivers will be able to report on behalf of severely ill or debilitated patients						4d
Caregivers should be allowed to report symptom burden on behalf of severely ill or debilitated patients						4e
Most patients in clinical trials would be willing to self-report symptoms from home on a *weekly* basis (ie, by computer, automated telephone system, handheld device, etc)						4f

5. CLINIC/STUDY SITE ISSUES	**Strongly Agree**	**Somewhat Agree**	**Neither Agree nor Disagree**	**Somewhat Disagree**	**Strongly Disagree**	
Limited *space* at my clinic site is a potential barrier to implementing a system for collecting data directly from patients						5a
Limited *personnel* at my clinic site is a potential barrier to implementing a system for collecting data directly from patients						5b
Limited *time* at my clinic site is a potential barrier to implementing a system for collecting data directly from patients						5c
Lack of computers for patients to use for self-reporting is a potential barrier at my clinic site						5d
The above potential barriers could be overcome with adequate funding						5e
My clinic site has research staff who could likely assist patients with self-reporting symptoms in clinical trials if such a system were adopted						5f
There are areas at my clinic site that could be configured for patient self-reporting						5g

	Strongly Agree	Somewhat Agree	Neither Agree nor Disagree	Somewhat Disagree	Strongly Disagree	
My clinic site has computers that could likely be adapted for use by patients to self-report symptoms in clinical trials						5h
My site would need to acquire new computers for patient-reporting if such a system were adopted						5i
Desktop computer-based patient self-reporting is feasible at my site						5j
Wireless laptop/tablet computer-based patient self-reporting is feasible at my site						5k
Paper-based patient self-reporting is feasible at my site						5l

6. YOUR OVERALL IMPRESSIONS	Strongly Agree	Somewhat Agree	Neither Agree nor Disagree	Somewhat Disagree	Strongly Disagree	
Systems to efficiently collect patient self-reported adverse events in clinical trials should be developed						6a
In general, patients better understand the severity of their symptoms than clinicians						6b
There are some symptoms which clinicians better understand than patients						6c
In clinical trials, adverse symptoms should only be reported by *patients* and should not be separately reported by *clinicians*						6d
In clinical trials, adverse symptoms should only be reported by *clinicians* and should not be separately reported by *patients*						6e
In clinical trials, adverse symptom information should be reported by *both* patients and clinicians						6f
Both patient-reported and clinician-reported adverse symptom information should be reported in clinical trial results, and in drug labels						6g
Patient self-reporting of adverse symptoms in trials would *decrease* my workload						6h
Patient self-reporting of adverse symptoms in trials would *increase* my workload						6i
Patient self-reporting of adverse symptoms from home between visits could provide valuable data for assessing drug toxicities in clinical trials						6j
If patient-reported adverse symptoms were included in drug labels, clinicians would use this information to help describe the consequences of treatment to future patients, and to shape treatment recommendations						6k

7. Patient self-reporting of CTCAE adverse symptoms would be useful for:

	Strongly Agree	Somewhat Agree	Neither Agree nor Disagree	Somewhat Disagree	Strongly Disagree	
Providing information to inform treatment dose modifications in clinical trials						7a.
Improving efficiency of data gathering in clinical trials						7b.
Improving the completeness of symptom data collection in clinical trials						7c.
Improving the accuracy of adverse event documentation in clinical trials						7d.
Providing information for FDA to use when evaluating the toxicities of drugs						7e.
Providing toxicity information for use in drug labels						7f.
Improving our understanding of the patient experience with treatment						7g.

8. General comments, suggestions, or feedback are welcome and encouraged:

9. What features would you want to see in a system for patient self-reporting of adverse events in clinical trials?

Please feel free to email any additional comments, or interest to become involved in this effort, to Laura Sit (sitl@mskcc.org).

Thank you for taking the time to share your viewpoints, which we hope to use to design a useful and valuable system.

1. National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. NIH publication # 09-7473. Published May 29, 2009; Revised Version 4.02 September 15, 2009 (available at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf, last accessed December 30, 2010).
2. Trotti, A., Colevas, A. D., et al. (2003). CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Seminars in Radiation Oncology, 13*(3), 176–181.
3. Trotti, A., Colevas, A. D., Setser, A., & Basch, E. (2007). Patient-reported outcomes and the evolution of adverse event reporting in oncology. *Journal of Clinical Oncology, 25*(32), 5121–5127.
4. Fromme, E. K., Eilers, K. M., et al. (2004). How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the quality-of-life questionnaire C30. *Journal of Clinical Oncology, 22*(17), 3485–3490.
5. Basch, E. (2010). The missing voice of patients in drug-safety reporting. *The New England Journal of Medicine, 362*(10), 865–869.
6. Pakhomov, S. V., Jacobsen, S. J., Chute, C. G., & Roger, V. L. (2008). Agreement between patient-reported symptoms and their documentation in the medical record. *American Journal of Managed Care, 14*, 530–539.
7. Schnadig, I. D., Fromme, E. K., et al. (2008). Patient-physician disagreement regarding performance status is associated with worse survivorship in patients with advanced cancer. *Cancer, 113*(8), 2205–2214.
8. Parliament, M. B., Danjoux, C. E., et al. (1985). Is cancer treatment toxicity accurately reported? *International Journal of Radiation Oncology, Biology, Physics, 11*(3), 603–608.
9. Basch, E., Iasonos, A., McDonough, T., Barz, A., Culkin, A., Kris, M. G., et al. (2006). Clinician versus patient self-reporting of symptoms during cancer treatment: a paired analysis using the national cancer institute's common terminology criteria for adverse events (CTCAE). *The Lancet Oncology, 7*(10), 903–909.

10. Bruner, D. W., Scott, C., et al. (1995). RTOG's first quality of life study–RTOG 90-20: a phase II trial of external beam radiation with etanidazole for locally advanced prostate cancer. *International Journal of Radiation Oncology Biology and Physics, 33*(4), 901–906.
11. Varricchio, C. G., & Sloan, J. A. (2002). The need for and characteristics of randomized, phase III trials to evaluate symptom management in patients with cancer. *Journal of the National Cancer Institute, 94*(16), 1184–1185.
12. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for industry: Patient-reported outcomes measures: Use in medical product development to support labeling claims. Issued December 2009 (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf, last accessed February 9, 2011).
13. Willke, R. J., Burke, L. B., et al. (2004). Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. *Controlled Clinical Trials, 25*(6), 535–552.
14. Bruner, D. W., Bryan, C. J., Aaronson, N., Blackmore, C. C., Brundage, M., Cella, D., et al. (2007). Issues and challenges with integrating patient-reported outcomes in clinical trials supported by the national cancer institute-sponsored clinical trials network. *Journal of Clinical Oncology, 25*(32), 5051–5057.
15. Velikova, G. L., Booth, et al. (2004). Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. *Journal of Clinical Oncology, 22*(4), 714–724.
16. Sloan, J. A., Cella, D., et al. (2005). Clinical significance of patient-reported questionnaire data: another step toward consensus. *Journal of Clinical Epidemiology, 58*(12), 1217–1219.
17. Lipscomb, J., Reeve, B. B., et al. (2007). Patient-reported outcomes assessment in cancer trials: taking stock, moving forward. *Journal of Clinical Oncology, 25*(32), 5133–5140.
18. Patrick, D. L., Ferketich, S. L., et al. (2003). National institutes of health state-of-the-science conference statement: symptom management in cancer: pain, depression, and fatigue, July 15–17, 2002. *Journal of the National Cancer Institute, 95*(15), 1110–1117.
19. Rock, E. P., Kennedy, D. L., et al. (2007). Patient-reported outcomes supporting anticancer product approvals. *Journal of Clinical Oncology, 25*(32), 5094–5099.
20. Basch, E., Artz, D., Dulko, D., Scher, K., Sabbatini, P., Hensley, M., et al. (2005). Patient online self-reporting of toxicity symptoms during chemotherapy. *Journal of Clinical Oncology, 23*(15), 3552–3561.
21. Abernethy, A. P., Ahmad, A., Zafar, S. Y., Wheeler, J. L., Reese, J. B., & Lyerly, H. K. (2010). Electronic patient-reported data capture as a foundation of rapid learning cancer care. *Medical Care, 48*(6 Suppl), S32–S38.
22. Committee on Cancer Clinical Trials and the NCI Cooperative Group Program, Institute of Medicine. (2010). *A national cancer clinical trials system for the 21st century: reinvigorating the NCI Cooperative group program*. Washington: Institute of Medicine of the National Academies.
23. Institute of Medicine, National Academy of Sciences. (2010). *A national cancer clinical trials system for the 21st century: reinvigorating the NCI cooperative group program*. Washington, DC: National Academies Press.
24. Buetow, K. H. (2009). An infrastructure for interconnecting research institutions. *Drug Discovery Today, 14*(11–12), 605–610.
25. Chilukuri, R., Gulati, M., Agarwal, H., Baumgartner, P., Reeve, B., Sit, L., et al. (2009). Software system for administering the Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE). Presented at the National Cancer Institute caBIG Annual Meeting, Washington, DC.
26. Basch, E., Reeve, B. B., Cleeland, C. S., Sloan, J. A., Mendoza, T. R., Abernethy, A. P., et al. (2010). Development of the patient-reported version of the common terminology criteria for adverse events (PRO-CTCAE). Presented at 2010 ASCO Annual Meeting, Chicago, IL. J Clin Oncol 28 (suppl; abstr e19605).
27. Hay, J., Atkinson, T. M., Mendoza, T. R., Reeve, B. B., Willis, G., Gagne, J. J., et al. (2010). Refinement of the patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE) via cognitive interviewing. Presented at 2010 ASCO Annual Meeting, Chicago, IL. J Clin Oncol 28:15s (suppl; abstr 9060).
28. Dueck, A. C., Mendoza, T. R., Reeve, B. B., Sloan, J. A., Cleeland, C. S., Hay, J., et al. (2010) Validation study of the patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). Presented at 2010 ASCO Annual Meeting, Chicago, IL. J Clin Oncol 28:15s (suppl; abstr TPS274).