FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE (pedsODAC)

Virtual Meeting

Tuesday, May 11, 2021

10:02 a.m. to 3:07 p.m.

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P R O C E E D I N G S

(10:00 a.m.)

Call to Order

DR. PAPPO: Good morning and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her e-mail and phone number are currently displayed.

My name is Alberto Pappo, and I will be chairing today's meeting. I will now call the May 11, 2021 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee to order. Dr. She-Chia Chen is the designated federal officer for this meeting and will begin with introductions.

Introduction of Subcommittee

DR. CHEN: Good morning. My name is She-Chia Chen, and I'm the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation. We will first start with Oncologic

Drugs Advisory Committee members.

Mr. Mitchell?

MR. MITCHELL: I'm sorry; slow to mute. I'm David Mitchell. I'm the consumer representative. I'm also a cancer patient with multiple myeloma.

DR. CHEN: Dr. Pappo?

DR. PAPPO: Good morning. I'm Alberto Pappo, a pediatric oncologist at St. Jude, and I'm the chairperson of the Pediatric ODAC.

DR. CHEN: And Dr. Cheng?

DR. CHENG: Good morning. I'm Jonathan Cheng, a medical oncologist by background. I work for Bristol Myers Squibb, and I am the industry rep.

DR. CHEN: Next are temporary voting members.

Dr. Angiolillo?

(No response.)

DR. CHEN: Dr. Angiolillo, I think you're on mute.

DR. PAPPO: Anne, can you hear us?

DR. ANGIOLILLO: Good morning. This is Anne

Angiolillo. I'm director of the Leukemia and Lymphoma Program at Children's National Medical Center in Washington, D.C., and also professor of pediatrics at the George Washington University School of Medicine and Health Sciences.

DR. CHEN: Dr. DuBois?

DR. DUBOIS: Steve DuBois, pediatric oncologist at Dana-Farber and Boston Children's.

DR. CHEN: Dr. Dunkel?

DR. DUNKEL: Good morning. This is Ira Dunkel. I'm a pediatric neuro-oncologist at the Memorial Sloan Kettering Cancer Center in New York.

DR. CHEN: Dr. Glade Bender?

DR. GLADE BENDER: Hi. I'm Dr. Julia Glade Bender, also at Memorial Sloan Kettering in New York. I'm a pediatric oncologist and vice chair for clinical research.

DR. CHEN: Dr. Gorlick?

DR. GORLICK: Good morning. I am Richard Gorlick. I am a pediatric oncologist and the division head of pediatrics at MD Anderson Cancer Center in Houston.

DR. CHEN: Dr. Janeway?

(No response.)

DR. PAPPO: Katie, can you hear us?

DR. CHEN: Dr. Janeway?

(No response.)

DR. CHEN: Dr. Janeway, I think you're on mute.

Okay. We'll go to our next.

Dr. Laetsch?

DR. LAETSCH: Good morning. I'm Ted Laetsch. I'm a pediatric oncologist at the Children's Hospital of Philadelphia at University of Pennsylvania.

DR. CHEN: Ms. Ludwinski?

MS. LUDWINSKI: Hi. Donna Ludwinski. I'm a patient representative and a research advocate for Solving Kids' Cancer.

DR. CHEN: Dr. MacDonald?

DR. MACDONALD: Good morning. This is Tobey MacDonald. I'm a pediatric neuro-oncologist and director of the neuro-oncology program at Emory University and Children's Healthcare of Atlanta.

DR. CHEN: Dr. Parsons?

DR. PARSONS: Hi. I'm Will Parsons, pediatric oncologist at Texas Children's Hospital and Baylor College of Medicine in Houston, Texas.

DR. CHEN: Dr. Raetz?

DR. RAETZ: Good morning. I'm Elizabeth Raetz. I'm a pediatric oncologist and division director at NYU.

DR. CHEN: Dr. Smith?

DR. SMITH: Good morning. I'm Malcolm Smith. I'm a pediatric oncologist at the Cancer Therapy Evaluation Program at the National Cancer Institute.

DR. CHEN: Dr. Janeway?

DR. JANEWAY: Yes, I'm here. I'm sorry. I had to step away for a second.

DR. CHEN: Can you introduce yourself and your affiliation, please?

DR. JANEWAY: Of course. I'm a pediatric oncologist at Dana-Farber and Boston Children's Hospital, and focus on osteosarcoma and precision oncology research.

DR. CHEN: Thank you.

Finally, we'll go to FDA participants. We'll start with Dr. Reaman.

DR. REAMAN: I'm Gregory Reaman, associate director for pediatric oncology in the FDA's Oncology Center of Excellence.

DR. CHEN: Dr. Bhatnagar?

DR. BHATNAGAR: Good morning. My name is Vishal Bhatnagar. I'm a medical oncologist and the associate director for patient outcomes in the Oncology Center of Excellence.

DR. CHEN: Dr. Donoghue?

DR. DONOGHUE: Hi, my name is Martha Donoghue, and I'm the acting deputy division director of the Division of Oncology 2 in the Office of Oncologic Diseases at the FDA.

DR. CHEN: Dr. Duke?

DR. DUKE: Hi. My name's Elizabeth Duke. I'm a medical officer in the Division of Oncology 2 at the FDA.

DR. CHEN: And Dr. Murugappan?

DR. MURUGAPPAN: Good morning. My name is

Meena Murugappan, and I am a research fellow with the patient-focused drug development team at the Oncology Center of Excellence.

DR. PAPPO: Thank you very much.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are

anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing this meeting topic during the break. Thank you.

Dr. She-Chia Chen will read the Conflict of Interest Statement for this meeting.

Conflict of Interest Statement

DR. CHEN: Thank you, Dr. Pappo.

The Food and Drug Administration, FDA, is convening today's meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all temporary members of the subcommittee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of

the subcommittee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that temporary members of the subcommittee are in compliance with the federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, temporary members of the subcommittee have been screened for potential financial conflicts of

interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

For today's agenda, information will be presented regarding the development and successful implementation of the Pediatric Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events, PRO-CTCAE, as a tool for eliciting the patient's voice in oncology clinical trials to more accurately determine tolerability and toxicity of drugs under investigation.

The subcommittee will also address the challenges of capturing this type of data across the age spectrum of the pediatric population and possible generalizability of the data. It will consider approaches to address concerns about excluding the patient voice of young children

deemed incapable of self-reporting. The subcommittee will also focus on approaches to investigators and commercial sponsors to use the pediatric PRO-CTCAE in toxicity assessments moving forward. This is a particular matters meeting during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the temporary members of the subcommittee, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all temporary members of the subcommittee to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Jonathan Cheng is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Cheng's role at this meeting is to represent industry in general and not any particular company. Dr. Cheng is

employed by Bristol Myers Squibb Company.

With regard to FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speakers.

Dr. Tara Henderson has acknowledged being a principal investigator or co-investigator for several studies, including Quality-Adjusted Cost Implications of Brentuximab Vedotin in Newly Diagnosed Pediatric Hodgkin's Lymphoma; Late Effects of High-Risk Neuroblastoma; AYA-RISE Intervention; Improving Delivery of Genetic Services to High-Risk Childhood Cancer Survivors; and the ASPIRES study.

Dr. Pamela Hinds has acknowledged being a principal investigator for multiple National Cancer Institute studies, including, Comparison of Symptom Toxicities and Neurocognitive Changes and Functional Outcomes in Pediatric Brain Tumor Patients Treated with Proton Versus Photon

Radiotherapy.

Dr. Bryce Reeve has acknowledged involvement on research grants regarding the development and evaluation of the pediatric PRO-CTCAE measure, which was supported by grants from the National Cancer Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

As guest speakers, Drs. Henderson, Hinds, Reeve, Sung, and Hawkins will not participate in committee deliberations, nor will they vote.

We would like to remind temporary members of the subcommittee that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the subcommittee of any financial relationships that they may have regarding the topic that could be affected by the committee's discussions. Thank you.

DR. PAPPO: Thank you very much, Dr. Chen.

We will proceed with FDA introductory remarks from Dr. Gregory Reaman.

Introductory Remarks – Gregory Reaman

DR. REAMAN: Thank you, Dr. Pappo, and good morning, and thanks to all of you for participating in today's meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee.

As mentioned, we will be discussing the development and potential use of the recently released pediatric PRO-CTCAE in the clinical research setting, particularly in the context of new drug development programs, and possibly in developing strategies for supportive care interventions and survivorship research.

We'll discuss opportunities and challenges in using these measures, capturing data across the entire age spectrum of the pediatric population, identifying acceptable assessment frequency in a core group of self-reported symptomatic adverse events and their severity, frequency, and degree of interference with daily activities that may be

incorporated in the OCE's project, Patient Voice, which we'll hear about later.

The 21st Century Cures Act directed FDA to systematically incorporate the patient experiences, needs, perspectives, and priorities into drug development and evaluation since the limited experience with cancer actually makes patients the true experts in their disease.

With successful use of patient-reported outcome measures that are fit for purpose, patients can provide unique and valuable information on symptoms and functional status that could possibly inform FDA's benefit-risk assessment of new cancer therapies.

Our focus today is on the use of PROs and will not include their potential use in evaluating efficacy, as the primary efficacy outcomes of importance in pediatric oncology are clearly objective: tumor response to a particular therapy; extending survival without evidence or recurrence of disease in cure. However, studies have reported that using PRO tools to monitor symptoms and toxic

effects during chemotherapy can improve adult patients' quality of life, decrease the number of hospitalizations, and actually lengthen survival.

In addition to their utility in clinical care, patient-reported outcome data can add value to the assessment of the risk-benefit profile of new therapies, and the Oncology Center of Excellence has highlighted the utility of patient-reported outcome data to further characterize the tolerability of anti-cancer therapies in adult cancer trials in an online program, Project Patient Voice, designed to augment the side effects information included in the U.S. prescriber information or product label.

Evidence for multiple studies suggest that clinicians and parents' ratings of children's symptoms clearly do not reflect the child's self-reported experiences, with parent and clinicians more often underreporting the burden of cancer and treatment on the lives of children and adolescents.

AE grading is based almost exclusively on

what is documented in patient charts and symptoms and are thus more likely missed compared with clinical or laboratory-based results. Despite these important findings and limitations, it really has become the norm to accept clinicians' graded symptomatic AEs as the sole source of safety and toxicity data in pediatric oncology trials.

So today, we will review FDA's perspective on the use of patient self-reported outcome data and its use in a regulatory setting. And again, our focus here is on self-report of symptomatic AEs, intolerability, and not efficacy.

We'll briefly review FDA's experience with pediatric patient-reported outcome data in pediatric oncology applications and how we might be able to extend the use of the patient-reported outcomes CTCAE, and extend that to children, and how the voice of children might really contribute to patient-focused drug development.

So with that, again, I thank you and look forward to today's presentations and discussions.

Thanks, Alberto.

DR. PAPPO: Thank you very much, Dr. Reaman.

We will now proceed with FDA presentations, starting with Dr. Elizabeth Duke.

FDA Presentation – Elizabeth Duke

DR. DUKE: Good morning. My name's Elizabeth Duke, and I'm a pediatric neuro-oncologist at the FDA. As Dr. Reaman said, I'll be starting the day off with an overview of patient self-reporting in the evaluation of cancer drug tolerability.

In cancer clinical trials, clinician-reported adverse events have long been used to characterize the safety of a given drug, however, we know there's more to the story for patients and their families.

As an introduction and to set the stage for the day, I'll review several definitions and a brief history of the use of patient-reported outcomes in drug development. I'll discuss how these patient-centered measures can add to our understanding of the tolerability of a given medical product and how this can supplement

traditional safety data.

I'll highlight some key elements of patient-reported outcome measurement selection for symptomatic adverse events when designing a clinical trial, such as item selection, completion rate, and assessment frequency. And I'll briefly summarize some of the key issues in pediatrics that Dr. Murugappan will discuss more in the next talk.

In general, assessment of clinical outcomes can be made through reports by a patient, a non-clinician observer, a clinician, or through performance-based assessments.

A patient-reported outcome, or PRO, is a measurement based on a report that comes directly from the patient about the status of their own health condition without amendment or interpretation by a clinician or anyone else. It can be measured by rating scale, counts of events, and absolute terms such as severity or frequency, or change from a previous measure, and this is what we'll focus on today.

Observer-reported outcomes are based on

observed signs or behaviors by someone other than the patient or provider; generally, a parent or caregiver who provides rating, but not interpretations. There are unique challenges to collecting this type of data, which we won't focus on today but can discuss more during the discussion period.

Clinician-reported outcomes are classically based on the common terminology criteria for adverse events, or CTCAE, grading system for oncology clinical trials, and performance outcome measures are based on standardized tests.

At the FDA, along with our charge of determining that a drug is safe and effective, we aim to approve treatments that meaningfully address the aspects of disease that are most important to patients and reflect their perspectives on the benefits and harms of treatment.

While we have standardized assessments with clinician-reported safety, we know that symptomatic toxicity can be underreported, and the symptoms that a clinician documents during a clinic visit

may not tell the whole story of the patient's experience.

Patients with the same disease and on the same treatment regimen may have vastly different experiences and the clinical meaningfulness of a given side effect may vary between individuals. And there are certainly cultural differences in how symptoms are perceived and externally expressed.

Patient-reported outcomes can provide additional information that is relevant to investigators, regulators, clinicians, and most importantly to other patients and their families.

Particularly in the field of oncology, there has been sustained research and policy work in this area for many years. In 2001, one of the early working group meetings attempted to harmonize efforts around methodologic standards for measuring and interpreting PROs in the drug evaluation process. As far back as 2013, this pediatric subcommittee of ODAC has discussed the topic of how the incorporation of PROs in cancer clinical trials might be used to facilitate cancer drug development

for children.

The establishment of the Oncology Center of Excellence and its Patient-Focused Drug Development Program, along with the 21st Century Cures Act, and most recently the launch of Project Patient Voice, which you'll hear more about from Dr. Bhatnagar, have resulted in the OCE's Pediatric Oncology Program, focusing its efforts on including the voice of children in pediatric cancer drug development.

PRO data can and has been used in product labeling. While most of these approvals included PRO measures related to efficacy, there is precedent for using PRO data to inform safety and tolerability.

In addition to the label, which is limited in its ability to convey this complex and often nuanced information, many people at the FDA are working on ways to communicate this data in other effective ways.

While in certain circumstances, clinical efficacy of a drug may be informed through PROs

through improvements in disease-related symptoms or functional impact, a universally important role for PRO is in the evaluation of symptomatic side effects and their impact. This is particularly relevant in pediatric where, historically, significant toxicity is accepted in pursuit of a cure. And thus, PRO measures can add to our understanding of tolerability.

Tolerability is unique from traditional safety data in that it reflects the degree to which symptomatic and non-symptomatic adverse events, associated with a given product's administration, affect the ability or desire of a patient to adhere to the treatment regimen, while reportable safety information involves clinical judgment and incorporates the overall adverse event profile, including labs, radiographic and clinical events, as well as reported side effects.

In order to objectively measure safety and tolerability, in addition to the historical clinician-reported and biomarker data, the FDA's Oncology Center of Excellence has worked to create

a core set of patient-generated symptoms and functional outcomes that can provide a consistent set of data elements to complement existing data from clinical trials.

You can see on the left in blue what we have standardized and done well historically in clinical trials, survival and tumor endpoints, along with traditional CTCAE safety results and other trial data, including dose modifications, dose discontinuations, and hospitalizations.

What the OCE would like to encourage is a rigorously assessed core set of patient-generated data, on the right in red, which can supplement the clinician-reported safety data with PRO measures of symptomatic adverse events and an overall measure of the impact of those side effects.

There are many deep and complex aspects to the patient experience, and those are extremely important to recognize and address. For the specific purpose in helping to determine whether a given drug is safe in the regulatory setting, the outcomes being measured should be closely related

to the treatment being evaluated and sensitive to changes in the toxicities of treatments.

Ultimately, the question is, how can regulatory bodies use these data for the narrow purpose of evaluating an anti-cancer treatment? In addition to providing a longitudinal characterization of symptoms and function to help assess risks and benefits in later-phase trials, we're beginning to explore the use of PRO data in early-phase dose optimization.

Typically, exposure-response analyses for safety are performed using pharmacokinetic data and clinician-reported CTCAE data on a high-incidence side effect. In one published analysis, FDA looked at a known exposure-response relationship focused on the side effect of diarrhea using PRO-CTCAE data.

The PRO-CTCAE is the NCI's openly available item library developed specifically for the assessment of symptomatic adverse events, which you'll hear more about very shortly from Dr. Minasian.

The authors here found that PRO-CTCAE results were able to replicate the exposure-response relationship and in fact appeared more sensitive, revealing a stronger association with pharmacokinetic drug exposure data compared to the standard clinician-reported CTCAE terms. While this is only one trial, the exploratory analysis suggested that PRO data may complement the assessment of exposure-response relationships for symptomatic toxicities compared to standard analysis using CTCAE alone.

PRO assessments can be deployed in many ways and for many purposes, so establishing consistency in how the information is captured and reported in cancer trials is important from a regulatory standpoint.

Some key aspects to this for trialists, including industry sponsors, academic institutions, and cooperative groups, include the careful selection of the most relevant symptoms in the context of the disease and product under investigation. There is no magic number to

include, but we recommend less than 50 items per visit and less than 10 total minutes of patient time per visit.

In addition to specific symptoms, including their frequency, severity, and degree of interference, one could consider an overarching question such as, "I'm bothered by the symptoms of my treatment," to show that a drug is comparatively more tolerable.

A high completion rate with as little missing data as possible is important since the absence of information does not equate to the absence of symptoms. Our goal is at least 80 percent at all time points up to 6 months. Their frequency of assessments is often weekly in those initial cycles of a trial, and then spreads out as patients get further along in treatment, increasing again at time points when there are expected fluctuations in therapy.

One challenge of infrequent assessments of side effects is that they may miss the period of worse toxicity, the classic example being a

once-per-cycle PRO assessment for an IV cytotoxic chemotherapy where the assessment occurs after the recovery period rather than during the day 7 to 14 nadir period.

On this slide, we provide just one example of a potential schedule of PRO assessments that can help patients and providers elucidate what side effects to expect and when they may occur, regardless of the therapeutic context. This particular example would be most suitable for the situation where the therapy is expected to have significant toxicity and that toxicity is cyclic.

Assessment frequencies should be modified based on the treatment regimen under study. The baseline assessment is quite helpful to assist in distinguishing disease versus drug-related symptoms, and an evaluation of patients without a given symptom at baseline can uniquely capture its evolution over time. At the time of consent, patients should be informed about what PROs will be collected, what it will be used for, and whether it would be monitored in real time.

The FDA is sensitive to the balance between what meaningful additional data this provides and what is reasonable and feasible for patients, and those are important conversations to have during the development phase of the trial.

This also raises the idea of different mechanisms of reporting, such as wearables and devices, for which a lot of work is currently being done. I'll also note that the FDA is open and willing to have meetings with sponsors focused on these aspects of clinical trial design prior to their initiation.

There are several aspects of PRO development that are unique to pediatrics, which I'll only mention briefly, as Dr. Murugappan will speak about these next. Important features include recognition of the patient's age and developmental level; use of appropriate language and concepts; being aware of their duration of recall to report certain symptoms; and how to capture the experience of younger children who cannot complete a given PRO measure.

Many neurocognitive domains are negatively impacted by cancer and cancer treatment, adding to differences based on age alone. A systematic standardized approach to capturing pediatric PRO data could greatly inform our understanding of tolerability in pediatric oncology clinical trials.

In conclusion, patient-reported outcomes are a type of clinical outcome assessment that have been studied for many years, and these data are increasingly being included to support regulatory decision making.

PROs can provide unique data complementary to traditional safety information. There are important aspects to consider for measurement selection such as the number and content of specific items; to study design, including assessment frequency; to data analysis, including what to do with missing data.

Today we'll be talking about the use of PROs in pediatric oncology clinical trials, in particular the pediatric PRO-CTCAE and how we can continue to move forward in increasingly

incorporating the patient's voice into pediatric cancer drug development.

That's the end of my presentation. I would like to thank the whole team at the FDA and particularly these individuals. Thank you.

DR. PAPPO: Thank you very much, Dr. Duke.

We will now take clarifying questions for the FDA presenters. Please use the raised-hand icon to indicate that you have a question and remember to clear the icon after you have asked your question.

When acknowledged, please remember to state your name for the record before you speak and direct your questions to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number if possible.

Finally, it would be helpful to acknowledge at the end of your question with a thank you and any follow-up question with, "That is all for my questions" so we can move on to the next panel member.

I will wait for Dr. Chen to show me anybody that is willing to ask any questions.

(Pause.)

DR. PAPPO: Hold on.

We will now proceed with the next presentation, and this is going to be Dr. Lori Minasian.

FDA Presentation – Meena Murugappan

DR. MURUGAPPAN: Good morning, everyone. My presentation is next. My name is Meena, and I am a post-doctoral research fellow with the patient-focused drug development team at the Oncology Center of Excellence. I'd like to take the next few minutes to share some findings from a recent review that we conducted at OCE to evaluate the use of patient-reported outcomes in pediatric oncology registration trials.

FDA is committed to ensuring that patients' experiences, perspectives, needs, and priorities are incorporated into drug development and evaluation. We recognize that patients are experts in their disease due to their lived experience with

the symptoms and treatment, and this includes children.

Experience in adult cancer clinical trials has shown time and again the benefits to collecting PRO data. It allows for more accurate and comprehensive reporting of symptomatic adverse events. This helps us better understand the overall impact of disease symptoms and treatment side effects from the patients' perspective, which can help inform FDA's benefit-risk assessment of novel therapies.

From a clinical perspective, we know that PRO data can play a vital role in facilitating shared decision making between patients and their clinicians regarding side effect recognition, management, and supportive care. Recent studies also suggest that using PRO assessments to monitor symptoms during routine cancer care can lead to an improvement in clinical outcomes like survival and reduce the risk for hospitalization.

However, despite these benefits observed in adults, adoption of PROs in pediatric cancer

clinical trials has been rare. This is concerning because a number of past studies have shown discrepancies between child self-report and caregiver or clinician report.

Caregivers may under- or overestimate symptoms and function relative to children, perhaps because their report is influenced by their own health state, experience with symptoms and functioning, and expectations for illness and symptom trajectory. Similarly, past studies have shown that clinicians may underreport the burden of cancer and its treatment on the lives of children and adolescents.

On top of this, adverse event grading is based on what is documented in patients' chart. Therefore, symptoms are more likely to be missed as compared to clinical or laboratory results. So it is essential to elicit the child's voice directly from the child, whenever possible, to accurately reflect their experience.

Given the growing recognition of the importance of PROs in pediatric oncology, in our

review, we decided to consider some key questions. First, what percentage of pediatric oncology registration trials have incorporated patient-reported outcome assessments? Next, which pediatric PRO instruments were the most commonly used? Were PRO endpoints approved for product labeling? And what are some opportunities to improve use of PROs in future pediatric oncology registration trials?

To conduct this review, we searched internal FDA databases and identified pediatric oncology product applications that had been approved between 1997 and 2020. We then reviewed sponsor-submitted documents like clinical study reports, study protocols, and FDA-approved product labeling to extract general information such as year of product approval, trial phase, study design, and sample size.

We also noted whether PRO data were collected and reported in each of the trials, and when PRO data were available, we recorded which instruments were used; what sort of role the PRO

had to play in the endpoint hierarchy; whether PROs were approved for inclusion in product labeling claims; and other indicators of PRO data quality like PRO assessment completion rate and use of anchor-based methods to detect clinically meaningful within-patient score changes.

So what did we find? Out of the 17 product applications that met inclusion-exclusion criteria, only four collected and reported PRO data, and all four of these products were approved in recent years, after publication of FDA's 2009 PRO guidance document.

These products were denosumab in 2013, tisangenlecleucel in 2017, larotrectinib in 2018, and selumetinib in 2020. Trials which incorporated PROs were generally stage 1 or 2 single-arm studies with sample sizes ranging from 28 to 88 pediatric participants per trial.

The median age of trial participants spanned from 5 to 16 years, and the most commonly used pediatric PRO instrument was the PedsQL Generic Score Scale, the standard version with a 30-day

recall period. Finally, PROs were treated as exploratory endpoints in all of these trials and were not subsequently included in product labeling.

Common reasons for non-inclusion of PRO endpoints in product labeling claims were related to limitations or challenges around study design and instrument selection. We found that PROs were often not associated with a clear research objective and corresponding statistical analysis plan.

We also found that some instruments were not fit for purpose. For example, the Brief Pain Inventory Short Form has only been validated in adults, and yet was used in a pediatric patient population. Similarly, we noted selection of PRO instruments like the PedsQL Generic Core Scale, standard version, which has a 30-day recall period. PRO instruments requiring patients to rely on memory over a lengthy recall period are likely to increase measurement error.

In addition, the PedsQL may not always be appropriate for the purpose of characterizing

tolerability and side effects of anti-cancer therapy. Domains like emotional, social, and full functioning are extremely important and contribute to health-related quality of life. For the regulatory context, however, these concepts can be impacted by many non-drug-related factors, and it is recommended that investigators select PRO instruments which ensure adequate measurements of physical functioning, disease symptoms, and symptomatic side effects. Finally, we noted use of proxy report for non-observable domains like pain.

Given these findings, we wanted to highlight some opportunities moving forward to enhance use of PROs in future pediatric oncology registration trials. First, we encourage use of patient self-report over caregiver report wherever possible due to limited agreement between child self-report and caregiver responses. For younger children or for those who cannot respond for themselves like infants, we encourage use of observer-reported outcomes rather than proxy report.

Proxy reports refer to responses by someone

who is not the patient responding as if that person were the patient. On the other hand, observer-reported outcome assessments, or ObsROs, limit caregiver responses to observable domains; that is, those events or behaviors that can be observed in patients who cannot reliably respond for themselves. For example, observers cannot validly report an infant's pain intensity, but can report infant behavior thought to be caused by pain.

ObsROs provide an opportunity to evaluate symptoms and function in even the youngest of children. To be able to reliably report as an observer, the caregiver should be cognizant of the patient's disease experience, which requires that they spend sufficient time with the patient to accurately reflect their observation.

Finally, we recognize the reality of pediatric oncology trials, where small single-arm trials are common. However, this should not preclude scientifically rigorous collection and descriptive analysis of patient self-reported symptom data to complement traditional safety data.

One example is use of the recently validated pediatric PRO-CTCAE, which focuses on disease symptoms and symptomatic side effects. The pediatric PRO-CTCAE enables self-report by children and adolescents aged 7 to 17 years. A corresponding caregiver version has also been designed for reporting in children younger than 7 years. Dr. Pamela Hinds and Dr. Bryce Reeve will share more about this measure during their presentation.

A near-term opportunity is to leverage OCE's Project Patient Voice platform to communicate such PRO data. Dr. Vishal Bhatnagar will speak further about this during his presentation later today.

With that, I would like to acknowledge the contributions of these individuals who made this work -- [inaudible – audio gap] -- the next speaker. Thank you.

Clarifying Questions

DR. PAPPO: Thank you very much, Dr. Murugappan, and sorry for the mix-up in the order of the speakers.

We will now take clarifying questions for FDA presenters. Please use the raised-hand icon to indicate that you have a question and remember to clear the icon after you have asked your question.

When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions" so we can move on to the next panel member.

I have Dr. DuBois?

DR. DUBOIS: Thank you. Steve DuBois, Dana-Farber. I have a question for Dr. Murugappan. I really appreciated your talk, and I wondered if you learned anything from the analysis that may help us think about how to avoid missed observations due to language barriers, literacy

barriers, or also barriers accessing technology to complete some of these instruments.

DR. MURUGAPPAN: Thank you for that very important question. Our analysis did not look into cultural and language barriers. I'm sure Dr. Pamela Hinds and Dr. Bryce Reeve can speak to the pediatric PRO-CTCAE, for example, which I know they're trying to validate in other languages. But our review specifically did not cover that topic, but it's definitely an important area for future research.

DR. DUBOIS: Thank you.

DR. MURUGAPPAN: Thank you.

DR. PAPPO: [Inaudible - audio gap].

Did you hear me? I'm sorry. I guess you didn't hear me.

Can you hear me now?

DR. CHEN: Yes, we can, Dr. Pappo.

DR. PAPPO: I apologize.

This was a question, actually, for either Dr. Duke or Dr. Murugappan.

What is the infrastructure that is needed to

conduct PROs? I know that most of these are patient-reported outcomes, but once the data is out for small institutions, are they going to be able to conduct the necessary analysis? Do you need a large infrastructure of CRAs, and could this impede the implementation of this in pediatric clinical trials?

DR. DUKE: Thank you. This is Elizabeth Duke. I might turn to Dr. Vishal Bhatnagar, who is spearheading a lot of these efforts.

Dr. Bhatnagar, would you mind commenting on that?

DR. BHATNAGAR: Sure.

This is Vishal Bhatnagar, associate director for patient outcomes. Thank you so much for that question.

I just wanted to ask a further clarifying question. When you say small trials and led by academic institutions, are you referring to assessment by academic institutions or use of the data by academic institutions?

Could you clarify, please?

DR. PAPPO: Assessment and use of the data by small institutions; so specifically, I'm talking, for example, about COG institutions that have 15 to 20 new patients a year, which they have already limited resources for CRAs and stuff.

How could that potentially impact the implementation of this and the analysis of PROs in those small institutions?

DR. BHATNAGAR: I see. Thank you very much for the clarification. What I would suggest for smaller institutions is to use widely available and publicly available free-for-use instruments for assessments. Part of the reason why we advocate for use of those is because of their availability and accessibility for smaller institutions.

Then furthermore, we at the FDA are happy to interact with institutions of all size. And investigators, if they are conducting clinical trials, they are very welcome to include questions regarding their PRO assessment strategy, even as early as the pre-IND meeting phase. So we're happy to support investigators big and small.

DR. PAPPO: Thank you very much, Vishal.

Next is Donna.

MS. LUDWINSKI: Thank you. Donna Ludwinski. I had a question about the research that exists so far with adults, that the assessment itself might add extra anxiety, depression, emotional reaction.

Dr. Duke had mentioned keeping it below 50 questions and 10 minutes. And if this is done on a weekly basis, reading a laundry list of negatively worded questions, including their emotional status, I'm just curious if there's any assessment of what additional distress that might cause.

DR. DUKE: Thank you. Elizabeth Duke. That's a good question.

I'm sorry. Did someone else want to answer?

MS. LUDWINSKI: I forgot to say thank you.

DR. DUKE: Oh, okay. No, that is an interesting question. I think for the most part here, we're focusing on symptomatic adverse events that are more in the category of objective: nausea and how many times have you had vomiting, and how

many times did you have diarrhea, for the most part.

But I hear you. I think that a lot of times, my sense in terms of taking care of patients is they want to be able to talk about that stuff, but others may have additional comments about that. But I would say, for the most part, these tend to be, at least for the symptomatic adverse events, more of the objective findings.

DR. PAPPO: Does that answer your question, Donna?

DR. LUDWINSKI: Yes. Thank you.

DR. PAPPO: Dr. Reaman?

DR. REAMAN: Thanks, Alberto.

Greg Reaman. I just wanted to go back to the first question that was raised about resources at smaller institutions in trying to implement this tool and collecting data, which is self-reported.

I think that is actually one of our discussion questions later today, but I just wanted to raise this because it would be helpful to know, hopefully with Drs. Reeve's and Hinds'

presentations, exactly what is required and how much effort is there in actually collecting these data at the institutional level and submitting it; and whether that is any more onerous than CRAs actually going through patient medical records, source documents, to elicit the kind of information on symptoms that patients might experience during therapy. Thanks.

DR. PAPPO: Thank you.

Any comments?

(No response.)

DR. PAPPO: We'll just wait to hear additional presentations.

The next one is Dr. Glade Bender.

DR. GLADE BENDER: Hi. Julia Glade Bender. Thank you very much for those interesting introductory talks. You mentioned the issues of being aware of the pediatric problem of small-trial patient numbers. In my experience, when proposing to incorporate a patient-reported outcome, the statistical plans always are told require large numbers.

There are some working groups working on the small numbers problem for things like molecularly targeted therapies, and I wonder if there are statisticians who are working on the problem of small numbers for patient-reported outcomes and whether there's a statistical resource for people who might be interested in incorporating these into trials.

DR. BHATNAGAR: This is Vishal Bhatnagar. I can take this question.

The purpose of the pediatric PRO-CTCAE, as well as the companion adult PRO-CTCAE, is really designed to help describe the patients' symptomatic adverse events that they encounter. We characterize this data as largely descriptive. So trials large and small can use this tool in order to just demonstrate the patients' experience while taking a certain therapy.

So for that reason, it is not necessary to have a statistical power or a certain sample size. We advocate for use of this descriptive tool for data regardless of trial size.

DR. GLADE BENDER: Thank you.

DR. PAPPO: We have time for two more questions so we can keep us on time.

The next one is Dr. Dunkel.

DR. DUNKEL: I'm sorry. Can you hear me?

DR. PAPPO: Yes.

DR. DUNKEL: Thank you.

Ira Dunkel, Memorial Sloan Kettering. This is a clarifying question for any of the speakers. I didn't quite understand how much existing data there are demonstrating that the PROs provide added benefit to the assessment, specifically for pediatric clinical trials, or whether there is a lack of such data at this point, and that would be one of the goals of the initial implementation of PROs in the first series of trials. Thank you.

DR. BHATNAGAR: This is Vishal Bhatnagar again. I can take this question as well. I think that Dr. Murugappan's presentation highlighted the lack of rigorous assessment of PRO in the pediatric space. And I think that there is certainly quite a lot of opportunity to better collect PRO in

children.

As far as how we would treat that data in terms of safety or efficacy, well-collected data, regardless of source, whether it's clinician, observer, or patient, well-collected data that's informative to any elements of safety or efficacy would be reviewed by FDA and certainly strongly considered.

I can point to various examples in adults where patient-reported outcomes have allowed for a better understanding of whether it's tolerability or toxicity. There are examples in labeling where visual toxicity, for example, was augmented with the patient report, and that certainly was considered as part of benefit-risk.

So I think that better-collected PRO certainly would be beneficial for FDA review as well.

DR. DUNKEL: Then maybe just one quick follow-up question to that. This sounds interesting, and I'm of course supportive of it, but if the initial implementation demonstrated that

there wasn't significant differences between parent reports or clinician reports versus the PROs, does the FDA have a thought or position as to what would happen next? Would the PROs continue to be used, and if so, would some of the other reports be de-emphasized?

I'm just trying to think about what is the branch point in the future once you know about added value that this would provide.

DR. BHATNAGAR: Sure. I think that there's a significant distinction between caregiver report and proxy report, and then also patient report, and then of course there's the clinician report. So I think that what we would need to see is adequate evidence for one over the other.

I think you mentioned sort of no significant difference between sources. Of course, we would need to see that evidence or data, and I think further work certainly needs to be done in that area. I think that will be discussed later on today.

DR. DUNKEL: All right. Thank you.

DR. PAPPO: Thank you.

If there are no additional questions -- I think, Greg, your hand is still raised. Do you have another question or can we move on to the next presentation?

DR. REAMAN: Sorry. I never lowered my hand. Yes, move on.

Thank you. Sorry for that, Alberto.

DR. PAPPO: Thank you very much.

We will now proceed to the next speaker presentation from Dr. Lori Minasian.

Speaker Presentation – Lori Minasian

DR. MINASIAN: Thank you. I am Lori Minasian. I'm a medical oncologist and the deputy director for the Division of Cancer Prevention, and I've been involved in the conceptualization and development of the adult version of the patient-reported outcomes for the common terminology criteria for adverse event reporting. I'm going to walk through some of the development, vision, and the use of the PRO-CTCAE in the adult scenario.

First, this was originally discussed and conceived in a meeting that was held between me and the NCI and the FDA, specifically looking at patient-reported outcomes and clinical outcome assessments.

It became very clear in the audience of clinical trialists, as well as FDA people, as well as patient advocates, that while NCI and the cancer community had collected health-related quality of life for many years, the information wasn't integrated into the clinical trials in a way that clinicians and patients could most effectively use it. So with that, then, we started to develop the patient-reported outcomes version of the common terminology criteria for adverse event reporting.

CTCAE is the lexicon for adverse event reporting that has been used in cancer clinical trials internationally for decades. It's designed for cancer-specific adverse events, and it has been revised over time. We're currently in the revision for version 6.

This provides a consistent method for

reporting and publishing safety data, and the grading of adverse events depends upon both the severity and the functional interference together. Not all adverse events in the library for CTCAE have all grades. The vast majority of adverse event items are in fact objective measures; laboratory values and others; 10 percent are subjective measures such as nausea, fatigue, pain, that are in fact amenable to patient reporting; and real-time patient reporting of symptomatic adverse events may improve the precision and reproducibility of symptomatic adverse events.

Clinician reporting of symptomatic adverse events in cancer clinical trials has been documented in multiple publications to underestimate both the frequency and severity of symptoms compared to patient-reported outcome measures. I've provided three of my slides, italicized, shorthand versions of a variety of publications to this effect.

The agreement between patient and clinician reporting is moderate

at best, with patients reporting greater severity of symptoms than is reflected in the clinician-graded events. And remember that most of these comparisons have been done with health-related quality-of-life tools, so it's a little bit like comparing a golden apple to a gala or Honeycrisp apple.

PRO-CTCAE is derived from CTCAE version 4.0. It's designed specifically from those items for patient-reported symptomatic adverse events, and it was designed for the opportunity to have patient and clinician reporting in a consistent way so that the patients can report the same items that clinicians report in a complementary fashion.

Seventy-eight items of the 780 items in CTCAE version 4 were deemed to be symptomatic adverse events and were used to create a library of 124 questions or items. This is an item bank that does not require that all items be used simultaneously in any one clinical trial. Just like with CTCAE, you don't necessarily report all of the adverse event items, you pre-select those

items specifically to the adverse events that the investigators wish to capture at baseline and monitor over time.

PRO-CTCAE has been available for public use since April 2016, although we've had investigators utilize and incorporate PRO-CTCAE items into trials while we were under its development. The complete library of items is listed at this website, and it is accessible to anyone. There are over 30 translated versions currently available and additional translations are actively being worked on as well.

This is the library. This is a slide that depicts the library for PRO-CTCAE, the adult version. You see a variety of different items, all of which can be mapped back to PRO-CTCAE. Under "oral" on the left, you can see "dry mouth" and you can see "mouth and throat sores." At the bottom of the right-hand, you see a table that says "attributes" where you have frequency, severity, amount, and interference.

Not every item has every attribute. Some

items only have one attribute. Dry mouth in particular only has S for severity, whereas another item, such as numbness and tingling, has both severity and interference associated with it.

The grading for CTCAE is different from the scoring of PRO-CTCAE. Clinicians provide one single grade for each adverse event item, and that grading requires that the clinician bundle together severity and interference. The distinctions between specifically grade 2 and grade 3 are specific to whether or not, and the degree to which, a patient may require a medical intervention.

Patients are only asked to score severity, frequency, and interference separately based upon whether or not that question item has those attributes associated with them. And currently, the patient score does not equal a clinician grade; rather this reporting of scores is meant to be descriptive reporting, currently.

There is ongoing work from investigators looking at building a composite score from the

patients individually scored questions into something that would be equivalent to a clinician grade, but we aren't there yet.

Here is a picture to help reinforce the difference between the grading of CTCAE and the scoring of PRO-CTCAE. Again, back to mouth sores, you can see for grade 2, the patient needs to have moderate pain not interfering with oral intake, but modifying their dietary indication, and a grade 3 would require either severe pain or oral intake.

So you can already see that, potentially, moderate pain that does interfere significantly with oral intake could be a grade 2, grade 3, depending on what the clinical scenario is for that patient. However, the patients are only asked to score what is the severity of the mouth sores, and then separately, to what extent or how much does it interfere with your usual or daily activities. So patients are asked to separate it out.

The adult version of the PRO-CTCAE has been incorporated in clinical trials, and a recent systemic review that was published this year, that

looked at PROs across multiple different instruments and tools from 2004 to 2018, demonstrated that PRO-CTCAE has currently been used in about 2 percent of cancer clinical trials, which is not bad when you consider that mostly it was publicly accessible and available in 2016.

So PRO-CTCAE is in fact feasible for collection in phase 3 trials, and there's a randomized phase 3 rectal cancer study published in JCO; the PROs were published in JCO, which showed excellent patient compliance.

This is a rectal cancer study where patients got daily radiation therapy, and for 20 weeks, the patients were recording and reporting on a weekly basis their scores to specific questions. They did not use the full library of PRO-CTCAE items. They chose a selected number that were highly relevant to the interventions that they were getting on both arms so that you could do a comparison across those two arms.

In addition, in a metastatic phase 3 castrate-resistant prostate cancer clinical trial,

patient-reported data actually improved the accuracy of symptomatic adverse event reporting.

In a different phase 3 radiation therapy study, the symptomatic adverse events that were reported by patients actually demonstrated greater granularity in bothersome toxicities. In particular, the study was using intensity-modulated radiation therapy to compare that to standard radiation.

Despite the fact that the clinician data, the CTCAE data, showed no difference in safety, the PRO-CTCAE data showed a reduction in symptoms, or symptomatic adverse events, as a consequence of the intensity-modulated radiation therapy. So that was a positive study.

Switching now from just the development of the tool and its use in clinical trials, the next real question is, how do we begin to think of analyzing it; how do we begin to think about using this tool for tolerability?

Currently, tolerability of cancer therapy has been developed over time to look specifically

in the phase 1 study in dose escalations, looking at the most single severe adverse event that occurs in cycle number 1. If there's no significant grade 3 or greater adverse events, then typically what you see in the publications is it's considered a tolerable regimen. However, this approach does not really capture the impact of chronic, low-grade or cumulative adverse events over time.

In 2017, NCI released under the Cancer Moonshot a funding opportunity to use, to analyze, clinician-reported CTAE and patient-reported PRO-CTCAE data, retrospectively, along with other clinical data and other PRO data to develop methods and approaches to understand and redefine tolerability in cancer treatment.

Making the point again of the need to collect longitudinal data for tolerability, here's an example of two different drugs and the relevance of the time profile to adverse event reporting. Drug X causes 5 percent dyspnea and drug Y causes 5 percent peripheral neuropathy. And in your standard tables, that's the only information you

will receive.

However, if you look longitudinally, drug X has that dyspnea in an acute fashion that resolves, resolves either with supportive care or on its own; whereas drug Y's peripheral neuropathy may not be reported in cycle number 1 or 2, but over time becomes progressive, cumulative, and chronic.

So the information that we get from the table doesn't provide us the full information that patients want to know with respect to what will happen to me when I take this therapy.

The Moonshot Consortium has been in progress, and a couple of items that have come out of it to date; the ToxT, which assesses longitudinal toxicity or trajectory over time. In addition, we've been exploring identifying cumulative toxicity, both the burden of single adverse events as well as multiple different low-grade adverse events becoming chronic.

A toxicity index has been explored along with some work currently being done to look at whether or not a single dominated chronic toxicity

versus multiple grade 1 or lesser toxicities actually impact the patient's willingness and ability to continue to receive chronic therapy over a prolonged period of time. More and more of our therapy is being given, whether it's oral therapy being given over multiple years or other therapies for a prolonged period of time.

Evaluating baseline factors is another aspect that we've been doing in the tolerability consortium because we've all recognized that individual patients respond differently to therapy. One of the findings has been to explore how baseline side effects, either from previous treatment, co-morbidities, or others, may impact and affect the development of treatment-emergent symptomatic adverse events, as well as potentially could predict treatment discontinuation of oral treatment.

The other thing that I would say is that in the spirit of exploring some of these lower grade toxicities, we've also seen focus groups around symptoms such as diarrhea, where the patient may

not have frequent loose stools, but in fact may have unpredictable loose stools. So even if it's twice a day, if it's unpredictable, it may in fact interfere with functions far more than two predictable loose stools or three predictable loose stools, in a way that makes for that patient the toxicity intolerable and puts them at risk for discontinuation.

A summary of the information that I've provided, in the use of the adult PRO-CTCAE, it is in fact very feasible to incorporate in cancer clinical trials. Patients have had terrific responses, and we've had excellent ability for patients to repeatedly fill out the assessments on a weekly basis, every two weeks, based upon the numbers and the time it takes to complete the assessments.

Patient reporting can complement clinician reporting in a way that provides valuable insight into tolerability, particularly when it comes to lower grade cumulative toxicities. Standard approach for the use and the analysis of the

PRO-CTCAE data are still under development, but we are very excited that over the next couple of years, we will develop standardized approaches for visual graphics, for visual display, as well as methods for determining tolerability.

Tolerability methods are in fact being developed and evaluated using retrospective trial data, and our next goals moving forward are to incorporate them as endpoints prospectively in cancer clinical trials.

This is the pediatric version of the library for PRO-CTCAE. It's blue, where the adult version is red, but it has a similar structure to it. It is also available at the website, and I will let others after me, including Dr. Pamela Hinds and Dr. Bryce Reeve, explain in detail the development of the pediatric PRO-CTCAE. But the expectation is, as we develop the methods for tolerability for the adult version, they will also be available for the pediatric version. Thank you.

DR. PAPPO: Thank you very much, Dr. Minasian, for an excellent presentation.

I just want to let you all know that we're going to have a chance to ask clarifying questions after we proceed with three additional speakers. So we will now proceed with an FDA presentation by Dr. Vishal Bhatnagar.

FDA Presentation – Vishal Bhatnagar

DR. BHATNAGAR: Thank you.

Good morning. My name is Vishal Bhatnagar, and I'm a medical oncologist and the associate director for patient outcomes in the Oncology Center of Excellence. I have the privilege today to provide an overview of an important OCE pilot initiative called Project Patient Voice, and we'll discuss ways in which this online resource can be useful for describing the pediatric oncology patient experience.

As we've heard today, there are areas of opportunity for the assessment of pediatric patient-reported outcomes. The goal of my presentation is to describe how we've developed Project Patient Voice and highlight how this important tool can be used to advance the

dissemination of well-collected, meaningful pediatric patient-reported outcomes.

Before I walk through the development and features of Project Patient Voice, I'll provide some context for why we developed this resource.

In 2016, the 21st Century Cures Act clearly laid out the importance of submitting patient experience data as part of marketing applications. This law directed FDA to systemically incorporate patients' experiences, needs, perspectives, and priorities into drug development and evaluation.

PRO is increasingly being provided as complementary information to clinician-reported outcomes, including information on treatment-related side effects and disease-related symptoms. However, there are vast differences in the approach to collection and analysis of PRO data between sponsors, disease areas, and as we've heard today, patient populations.

Even if a sponsor provides high-quality PRO data that is meaningful, the product label is not the best place to communicate this important

information. The product label has limited space and has design limitations, including lack of color, which is a challenge when trying to communicate complex patient-experience data to clinicians and patients.

Project Patient Voice is an Oncology Center of Excellence pilot project that was developed to meet these challenges. We developed Project Patient Voice as a publicly available resource for patients and healthcare providers to have access to high-quality, longitudinal, patient-reported symptom data that was collected from registrational trials. We also hope to raise the bar and demonstrate the feasibility of collecting and analyzing this level of patient-reported outcomes data.

We launched Project Patient Voice in June 2020, and the response has been overwhelmingly positive from patients, advocacy organizations, and even industry sponsors. The visualizations and content for Project Patient Voice took over a year to develop, and along the way, we worked with

patients and advocates seeking feedback throughout.

The link is provided on this slide. The website is also easily accessible via search engines and through the main Oncology Center of Excellence website.

This is the landing page for Project Patient Voice. Each of the numbered green arrows here on the screen point to clickable features and important elements of the website that I'll highlight.

First, we included responses to frequently-asked questions, including the purpose, the source of information, and the potential limitations of this website. Clicking on any of these questions will expand the accordion to show the response and additional resources.

At arrow 2, we provide contact information for the public to share feedback on all elements of the website. Receiving feedback directly from the public is one important way that we've ensured that the website is relevant and meaningful to patients. At arrow 3, there's a link to the first trial

that's included on the website, or a 3. As we add data from additional trials, they will be listed in this table.

Fourth, we include a link to the product label that corresponds to this trial. The label describes the trial more in depth and serves as the primary source for safety and efficacy information. Project Patient Voice is meant to be a complementary source of information to be paired with the product label, so we wanted to ensure that the label was readily accessible from this website.

Fifth, in the top-left corner, we included a link to an interpretation guide, a way for patients, caregivers, and healthcare providers to better understand the visualizations provided for each trial.

Once you click on the study you're interested in within the table on the main Project Patient Voice page, you're taken to a description of that trial that the patient-reported outcomes were collected in. This information about the trial is included in the product label, however, we

also provide it here for context.

Besides the trial descriptions, we also provide information on the instrument, also referred to as a questionnaire, survey, assessment, or measure, that was used to collect the patient-generated information.

For AURA3, PRO-CTCAE was used to collect patient-reported symptoms. At the top of the page, you'll notice a disclaimer that is repeated throughout the website and essentially makes clear to patients and the public that Project Patient Voice is intended to be used alongside a healthcare professional when discussing cancer treatment, and is not meant to be a patient's sole source of decision making.

Our intent is to create a website that patients and healthcare providers can use together as a starting point to discuss specific treatment side effects, but from the patient's perspective.

After the description of the study design and population, listed in a table are the various patient-reported symptoms that patients were asked

about during the trial, according to the instrument used. For each of the symptoms, the number of patients who are asked is listed in column B, and in column C, we list the proportion of patients who had that symptom even before treatment began. We felt it was important to include this because we recognize that patients may go on to a trial with residual symptoms from previous treatment or have symptoms related to their underlying condition.

In column D, we have the proportion of patients who had any worsening of the symptom from baseline, and in the final column, we have those patients who worsened to the worst two categories for a particular symptom.

For example, taking nausea, in the chemotherapy arm, 32 percent of patients reported nausea before beginning chemotherapy, 77 percent had some worsening from baseline, and 39 percent of patients reported frequent or almost constant nausea at some point in the trial.

We recognize this is a lot of information, but the intent is to provide a high-level overview

of patient-reported adverse events and allow patients to then hone in on specific symptoms that may be important to them. In fact, if you click on a specific symptom, it takes you to a symptom-specific page that provides visualizations and additional details.

Here's an example of one of the visualizations. Continuing with the symptom of nausea, patients were asked on an almost weekly basis the frequency of their nausea, and they could respond, never, rarely, occasionally, frequently, and almost constantly, as you can see in the color key at the bottom of the chart.

On the left side of the bar chart, we have the patients who are treated with Tagrisso; on the right, those that were treated with chemotherapy. At each week, we see the proportion of patients who reported not having nausea in green, so at week 5 in the chemotherapy arm, 49 percent of patients reported no nausea.

This type of visualization can provide a week-to-week snapshot to show the trajectory of

symptoms in a group of patients over time. These bar charts are available for each symptom on the website.

We also have a set of visualizations for the subset of patients who didn't have a particular symptom at baseline. In this case, we have the group of patients who didn't have nausea going into the trial. For example, those patients without nausea in the chemotherapy arm at baseline, 10 percent had almost constant nausea at some point during the trial. We think pulling out the subset of patients who are asymptomatic at baseline and seeing their experience is one way to isolate the effect of the drug on patients.

As I mentioned before, the development of this website and visualizations took over a year, and we sought input within and outside of FDA from various groups, including patients, academics, and with close collaboration with our first industry partner, AstraZeneca.

There were a few technical challenges that are worth noting. First, we needed to ensure that

patients knew exactly what this data is and what it isn't. So throughout, we made it clear that this is information that's not meant to replace the clinician-reported data provided in labeling, but instead provides another perspective on the same symptoms.

The next major consideration was that we interacted with patients and advocates on ensuring that the text on the website was at an appropriate reading level. This is highly complex, technical data, so we needed to find the right balance in terms of efficiently yet clearly communicating the results for understanding by a broad audience.

We also needed to ensure that those with visual impairment could have access to the data, and this informed our color choices and also led us to include downloadable Excel files that can be fed into document readers and text-to-speech can be employed. Finally, we also needed to work closely with the industry sponsor to reach agreement on these visualizations.

We hope to include more trials, and we need

to set criteria for inclusion to ensure high-quality data is provided. Our intention is to include only data from registrational trials used to support regulatory approval. The quality of patient-reported outcomes should be high and should have adequate rationale for patient-reported, treatment-related symptoms assessed.

Importantly, the PRO assessments should be at an adequate frequency and more frequent at the start of therapy, when new treatment-related symptoms are most likely to occur. The completion rate for the data should be high, meaning that a high proportion of patients who are provided a survey actually complete it.

Although the current example on Project Patient Voice is a randomized trial, we would consider inclusion of PRO from single-arm trials, as the data is meant to be descriptive of the treatment being administered.

Although the current focus of Project Patient Voice is to provide patient-reported side effect data, we're exploring ways to include other

types of patient-reported outcomes data, including physical function. We're hosting an FDA workshop in July to further discuss how physical functioning data can be analyzed in a way that would be useful for Project Patient Voice.

Now that I've walked through the capabilities of Project Patient Voice, I'd like to provide conclusions to contextualize Project Patient Voice to the pediatric population. First, regardless of the populations studied, PRO data should be collected and analyzed in a way that's meaningful and interpretable for patients and healthcare providers.

As I've shown, FDA's Project Patient Voice is a novel way to disseminate high-quality PRO. As we'll discuss today, there are opportunities to improve collection of PRO in children. Better collection of patient-reported tolerability from children enrolled in registrational clinical trials can lead to inclusion on the Project Patient Voice website. This data can be informative to children, parents, caregivers, and healthcare providers as

descriptive, complementary information before and during treatment, based on our experience in adults.

There were many people within and outside of the FDA who contributed to the development of Project Patient Voice, but listed here are the FDA colleagues who worked on this project. Thank you for the opportunity to present Project Patient Voice, and I hope that this tool can someday be used by children, parents, caregivers, and pediatric healthcare providers in the future. Thank you.

DR. PAPPO: Thank you very much, Dr. Bhatnagar, for your excellent presentation.

We will now proceed with the first guest speaker presentation by Dr. Pamela Hinds.

(No response.)

DR. PAPPO: Pam, we can't hear you. You're probably muted.

DR. HINDS: Are you able to hear me now?

DR. PAPPO: Yes, perfect.

DR. HINDS: Great. Thank you so much. Are

you able to see the slides?

DR. PAPPO: Yes.

Guest Speaker Presentation – Pamela Hinds

DR. HINDS: Alright. Well, you're ahead of me. I'm not able to see them quite yet, but I'm going to go ahead and get us started.

My name is Pam Hinds, and I am a nurse scientist here at Children's National Hospital in Washington, D.C., and I'm incredibly excited about today's workshop. I bring you greetings from both myself and Dr. Bryce Reeve, and multiple PIs, for the work that we are about to report regarding the pediatric PRO-CTCAE. And I am also incredibly grateful for the funding that we have received for this work from the National Institutes of Health and, in particular, from the National Cancer Institute.

I'm not able to see my slides, so if you'll forgive me, I'm going to go ahead and continue to the next slide. My purpose and my comment is that I'm going to describe to you why we even took on the initiative of creating a pediatric PRO-CTCAE

item library for children 7 to 17 years of age and their caregivers for their subjective treatment toxicities.

On the next slide, if I could see it, I'm taking you to an internationally, well-regarded website, which is the Children's Oncology Group website. And if you are able to see that slide, what you will notice is that there are very important statistics that are being shown, including the annual diagnostic rate for children and adolescents with cancer globally and within the United States; how many of those children will survive this illness and how many will not.

You'll also notice information from the enrollment from clinical trials. And on the very next slide, what you will see are important statistics about the effects of treatment. This follows children and adolescents into adulthood. But what you will not see on this slide are very important details about subjective treatment toxicities that children and adolescents in treatment for childhood cancer can and likely will

experience.

Now, what makes that so surprising as you look at the very next slide, which is a snapshot of the CTCAE, is that this manual directs us to report completely the impact of our cancer therapies. But one-third, in accordance with the definition of subjective treatment effects, are included in the CTCAE. That means that only the person, in this instance the child or adolescent, experiencing that AE can report it.

What we have learned, with over five decades of research with children and adolescents on the next slide, is that they are very willing to report their experience of subjective treatment toxicities. In the month before, most commonly reported by children and adolescents are fatigue, pain, sadness, depression, and worry, and there's two other subjective AEs that are reported just slightly less commonly, and that would be insomnia and worry.

But here's the problem. None of these subjective AEs are routinely collected across our

nation or other nations. That means, then, that the subjective treatment toxicities are underreported. That means they're undermanaged. And when we are mandated to report the impact of our therapies to the NCI, we then are incompletely reporting the full impacts of our therapies.

If I may take you to the next slide, what we can tell you from our research and the research of others is that if we don't ask, children and adolescents don't tell. In fact, up to 90 percent of children in treatment for childhood cancer will not report any burdensome symptoms if they are not asked.

When we interview them and their parents about why they don't tell, they indicate to us that they thought this kind of subjective treatment adverse event was to be expected, anticipated, not to be complained about because it was unavoidable and untreatable. And many of those assumptions are in fact not true. We are, with supportive care, able to manage many of these subjective treatment toxicities that are being experienced.

But if I take you to the next slide, I should be honest and share with you that there are some in pediatric oncology who honestly don't trust a child's voice to honestly report, and there are some who honestly believe the child voice is not necessary. But what we know is that children are able, are willing, and even detailed in their explanations of their subjective treatment toxicities. However, we have to ask the question, is anyone else able to answer on behalf of the child if we don't trust the child's voice or we don't think it's necessary?

What we can share with you is that even under the best of circumstances, using the most validated of measures, the highest agreement that we typically get between caregiver -- [inaudible - audio gap] -- from the family and child is never higher than low-moderate, and the agreement on subjective treatment events with agreement between child and clinician is rarely higher than low agreement. And it doesn't matter the subjective treatment toxicity that we are

measuring; the agreement is very low.

We've already spoken well, as demonstrated on the next slide, about the contributions from the U.S. Food and Drug Administration, both with the guidance they have given us related to PROs, the firm definition, guidance in how to achieve reliability and validity with measuring PROs, and now the current Project Patient Voice. Suffice it to say that we in pediatrics are incredibly grateful to the leadership shown by the FDA and other government offices.

If I may take you to the next slide, and that is the slide of the theory of unpleasant symptoms. Now, it looks quite complicated, and indeed it probably is. It represents the experiences of children and adolescents who are experiencing subjective treatment toxicities. And what you'll notice is that there are multiple influences upon them and their experience.

Symptoms for subjective treatment toxicities have strong characteristics: presence, absence, frequency, interference. And indeed, we do know

children are able to report, as demonstrated on the next slide. You may now think that I only want the child's voice during cancer treatments, but in fact, we need more than that voice.

What you'll notice on the next slide is the addition of the caregiver voice. Just as it is only the child voice that is able to tell us about that internal experience, that for many of us is unseen, it is the caregiver voice, the person who is very close to the ill child or adolescent, who is able to give us comparator information; how the child is now before the previous diagnosis or the previous course of therapy.

So as good as it is to have both voices, I would take you to the next slide, and would indicate to you that, in fact, we need three voices. We need the expert clinician. Just as the child can only speak for self and the caregiver can only be the voice to provide comparisons about this child, it is the expert clinician who can provide the comparison of this child to all other children on the same protocol being treated for the same

diagnosis, and at the same point in therapy. So much like Dr. Minasian mentioned, the need to look at how to combine the voices, we in pediatrics are at the very same point of wanting to combine.

Now, on the next slide, I take you right back to the CTCAE, or the manual from the NCI, and on the subsequent slide you will see after working with 187 pediatric oncology clinicians, our study team learned from them 62 subjective treatment toxicities that they would trust from the child voice as young as age 7 and older.

What you will notice on the top of that slide is what's called core items, and those core items, according to these experts, should be measured often because they are that commonly occurring across treatment protocols. What you will also notice, I am sure, is the medical terminology that is present on this slide.

If I may take you to the next slide, what we needed to do, then, was to take those medical terms and use cognitive interviewing with four very different age groups of children and adolescents,

and learn from them child-friendly words to replace what would be called medical jargon. And we were very able to do this after two rounds of cognitive interviews.

Dr. Reeve is going to go into detail with you about how we validated the measures, the items, but what I'd like to do is to take you into the future for just a moment and talk about the value that we can get, not just from the individual pediatric PRO-CTCAE item, but from something -- [inaudible – audio lost]

DR. PAPPO: Pam, it looks like we lost you.

(No response.)

DR. PAPPO: Pam, we can't hear you.

(No response.)

DR. CHEN: Dr. Hinds, can you please click the phone icon to connect with us again? Thank you.

(No response.)

DR. REEVE: This is Bryce Reeve. I'm the next speaker. I don't know. If we go to the next slide, I can try to make the point. I'll never

make it as well as Dr. Hinds, but I'm happy to do that --

DR. HINDS: Hi, Bryce.

Are you able to hear me now?

DR. REEVE: Yes, we can, Pam.

DR. PAPPO: Yes, we can hear you now.

DR. HINDS: That is great. And I'm so sorry. I don't know how to explain that, but I apologize to all of you.

I'm hopeful that you are on the same slide that I am on, and that is the slide with profiles.

Are you able to see the profiles?

DR. PAPPO: Yes.

DR. HINDS: If you're with me, you are seeing three profiles, and these are really representing the future to you of where we are going with our policies, with single items from the pediatric PRO-CTCAE. What we want very much to be able to be sure of with our analyses are exactly what Dr. Minasian talked about, the characteristics of each one of our CTCAE attributes, but in addition, can we look at, is the cancer experience

unique to each child?

What you see before you is a latent group analysis -- [inaudible – audio feedback].

DR. PAPPO: We have quite a bit of --

Pam, are you still on?

(Pause.)

DR. HINDS: Hi there. Can you hear me now?

DR. PAPPO: Yes.

DR. HINDS: I'm so sorry. I keep getting bumped out, but I think I'll be really fast.

Just to share with you, in the future what we are trying to do is to give both an item analysis and its attributes, as well as the possibility of an AE-suffering profile, meaning that we believe the cancer experience differs for each child.

On the slide in front of you, what I hope you see are three very different profiles representing high presence of AEs, moderate presence of AEs, and low presence of subjective AEs.

In brief, these are the scores from

477 children and adolescents at the same time point, indicating how many AEs they were experiencing. And what I would share with you is that almost 23 percent of children were in the high-suffering or high-AE prevalent profile, and that meant that the mean number of AEs that they were experiencing, 11 out of 16 AEs.

I'm going to very briefly take you to the next slide, which shows you why we're excited about this finding. And that is that with a much more established set of subjective patient-reported outcome measures, the pediatric PROMIS measures, similarly we found multiple profiles and quite similar profiles of high, moderate, and low suffering.

I believe that if you go to the next slide, you will see a closing quote from a 9 year old I was interviewing during our cognitive interviewing phase, when I said to her, "Were any of the questions that I asked you today hard?" And she said, "Easy peasy." And I said, "Oh. Why do you think the questions were easy?" And she said,

"Because it was mainly stuff about myself, and I know everything about myself."

On the next slide, Bryce and I would like to give thanks to everyone on our team, across the nine sites. And on the next slide, in particular, we would like to pay homage to the site PIs at every one of our nine sites who had the courage and commitment to see this study through. And I thank every one of you for your support of the patient voice. Thank you.

DR. PAPPO: Thank you very much, Pam.

We will now proceed with our guest speaker presentation by Dr. Bryce Reeve.

Guest Speaker Presentation – Bryce Reeve

DR. REEVE: Thank you so much, and good day, everyone. My name is Bryce Reeve, and I'm professor of population health sciences and also professor of pediatrics at Duke University School of Medicine. At Duke, I am also the director for the Center for Health Measurement. I do want to recognize, as Dr. Hinds did, our support through grants from the NCI, as well as the NIAMS, help

support this work to develop and evaluate the pediatric PRO-CTCAE.

This is a schematic of our timeline for development and evaluation of the pediatric PRO-CTCAE. Importantly, what I want to note is that we started this project about five years after the start of the adult project, so therefore we were able to leverage the infrastructure as well as lessons learned from the adult project to help develop the pediatric PRO-CTCAE.

In developing the pediatric PRO-CTCAE, we followed recommended guidelines from the FDA and from other organizations such as ISOQOL and ISPOR. But importantly, what I want to emphasize as well is we did not just simply take the adult measure and adapt it to pediatrics.

Importantly, we built the pediatric PRO-CTCAE from the ground up, starting from the very first step the adults did in terms of identifying symptoms, to ultimately testing this, specifically in children and adolescents.

The first phase -- and Dr. Hinds alluded to

this -- is that we wanted to make sure we understood what were the range and types of symptom AEs we wanted to capture off of the CTCAE system. So we engaged 187 experienced pediatric oncology clinicians through a Delphi-like process to help identify, again, what types of symptom AEs included in the CTCAE were amenable to child self-report and relevant and important to assess, whether they be prevalent, which are the symptoms included at the top of the screen, or more rare type of symptoms at the bottom part of our screen. And I know Dr. Hinds went through this, so I will move on in this part of the presentation.

Now that we know the range of all the 62 symptom AEs we want to assess with the pediatric system, our next goal was to be able to draft the questionnaire, the pediatric PRO-CTCAE. And again, we followed best practices for designing questionnaires with specifically children in mind.

As part of the development, the first thing we needed to make sure was that we translated medical jargon into child-friendly terms. So

you'll see at the top there, fatigue was characterized by feeling tired and nausea was characterized by feeling sick to your stomach.

We also wanted to look at different attributes of each symptom AE experience, again consistent to what the adults did. As you'll see on your screen, we have questions for the frequency of the symptom; how often did you have something like pain; severity of the symptom; how bad was your pain; interference of the symptom; how much did pain keep you from doing things you usually do; or potentially presence of symptoms; did you have pain, no or yes.

Not every symptom has all these attributes. At most, a symptom like headache might have three attributes, and for others, they might only have one of these particular questions depending on what's important to capture to help inform toxicity and tolerability assessment of these symptom AEs.

For the pediatric PRO-CTCAE, we use a 7-day recall period, which children were able to accurately reflect in their answers. And as you've

heard, in addition to the self-report pediatric PRO-CTCAE, we also developed and tested a parallel caregiver measure that simply follows the exact same type of questions, but of course replaces the pronoun "you" with "your child."

The next step, after we designed it in the best way we could, following guidelines, with our vast pediatric oncology experience working with children there, we still need to make sure that these questions were understandable to children. So we did cognitive interviewing, which is a set of one-on-one interviews with children and independently for caregivers to make sure that the child can both understand the questions being asked and provide a valid response or valid answer that reflects their own symptom experiences.

Now, importantly, for any type of pediatric measure, we wanted to make sure that this measure, this system, was just as accessible and valid for the younger age groups as they are for the older adolescents.

In both this phase, our qualitative phase,

and in our quantitative phase, you'll see that we stratified our evaluation in different age groups. For cognitive testing, we stratified by 7 to 8 year olds, our youngest kids, 9 to 12 year olds, and 13 to 15 year olds. After two rounds of cognitive testing, we found that these questions, again, were content valid and understandable, again, even to the youngest kids in our study.

Then we transitioned over to our quantitative or psychometric testing, and we included in our evaluation over 480 children, and in parallel we also collected data from their caregivers and clinicians. These kids were diverse in race, ethnicity, cancer type, and treatment received. These kids were with the first cancer diagnosis and completed at least one month of frontline treatment. And again, we purposely sampled kids in different age groups to do the quantitative validation in each of those age groups, 7 to 12, 13 to 15, and 16 to 18 year olds.

We collected data from children, from caregivers, and from clinicians at two assessment

points just prior to a treatment initiation, what we call T1 or baseline. Then just subsequent, within 7 to 17 days for chemotherapy, or about 4 weeks later for radiation, did a second assessment and collection of pediatric PRO-CTCAE data and complementary information that helps us validate the system.

While I'd love to present lots and lots of slides to you on this, my time is limited, but I'll just give you the summary. In terms of the convergent validity, we found that the pediatric PRO-CTCAE, the self-report questions, were very strong related with similar symptoms that are captured through either the Memorial Symptom Assessment Scale, or MSAS, or through the PROMIS pediatric measures.

In terms of known-groups validity, we found that the pediatric PRO-CTCAE items were able to differentiate children by their Play-Performance Scale, Lansky, so it differentiated children with very poor performance versus children with normal play performance, as well as the pediatric

PRO-CTCAE was able to differentiate kids that were receiving medications versus not receiving medications for symptom control. I'll actually present some of those findings on subsequent slides.

In terms of change-over-time responsiveness, we found that the pediatric PRO-CTCAE consistently showed changes consistent with what the Memorial Symptom Assessment Scale found over time. And for test/retest reliability, in a small subgroup of 46 kids of ALL in their maintenance phase, we found that there was consistent agreement when the child completed the measure, about 5 to 7 days apart, in terms of consistency in reporting their symptom level over time, when their health has not changed.

I felt like I had to show some results, so this is the known-groups analysis, comparing kids who took a particular medication within the past 7 days and what their subsequent symptom scores were. For example, for nausea, we asked the parents to let us know if their child took an antiemetic to help reduce their nausea.

What you see for the orange bar, the orange bar represents when a child took a medication to help control their symptoms. The blue bar represents when the child did not take a medication for that symptom control. So again, what we see for nausea, the level of symptom burden for nausea on pediatric PRO-CTCAE was much higher for kids that had to take a medication like antiemetic than those kids who did not.

Then if you look across your screen for constipation, for diarrhea, mucositis, and neuropathy, again we see that, consistently, those that had to take a medication for symptom control reported worse symptoms compared to those kids who did not take a medication.

This finding also carried through for other symptoms, so what you'll see again is you see high differences for those kids that had to take medications for headaches, pain, and insomnia. While there is sort of a trend for depression and anxiety, this was not statistically significant, but I feel like I need to present all information

and data. These kids are on anti-depressants, which typically take a while for them to actually start reducing sadness or anxiety.

In summary, what we have found over our qualitative and our quantitative phases of development and testing of the pediatric PRO-CTCAE and the caregiver version is that we've found that there's significant evidence for content validity, construct validity, responsiveness to change, and test/retest reliability.

We feel, based on these findings, that this evidence supports its use in pediatric oncology trials. As you've heard from our colleagues, Dr. Minasian, the pediatric system is available to the public for free on the NCI website, right alongside the adult measure.

On the last slide -- and hopefully you'll have access to our slides there -- you'll see for each phase of our testing, we have multiple publications that document the evidence: two publications for our concept elicitation phase; three publications for cognitive testing; three

publications for our quantitative phase; and then lastly, we did do work to take the pediatric PRO-CTCAE response pattern and translate that to a CTCAE-like metric. It's not equivalent, but similar to a CTCAE grade that might help in terms to improve some understanding of the data from the clinician perspective.

With that, I thank you for your time and look forward to our discussion.

Clarifying Questions

DR. PAPPO: Thank you very much, Dr. Reeve, for that excellent presentation.

We will now take clarifying questions for speaker, FDA, and guest speakers. Please use the raised-hand icon to indicate that you have a question, and remember to clear the icon after you have asked the question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

If you wish for a specific slide to be displayed, please let us know the slide number if

possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions" so we can move on to the next panel.

With that, I will open this session for questions. We have about 20 minutes for questions.

Dr. Chen, if you could guide me on who has their hands up.

Can you all hear me okay?

DR. CHEN: Yes. Hold on.

Hi. Dr. Pappo, just a moment.

DR. PAPPO: Dr. Janeway?

DR. JANEWAY: Yes. This is a question for Dr. Bhatnagar from the FDA regarding the Project Patient Voice. My question is whether the online version of the product label, which I usually access through the FDA website DailyMed, will be able to link out to this very nice representation of patient-reported data?

DR. BHATNAGAR: Hi, Dr. Janeway. Thank you for that question. So yes, as you mentioned,

there's multiple FDA methods to access product labeling. On Project Patient Voice, as I pointed out, we do have a conduit to lead to product labeling. However, we don't have any current plans for things like Drugs@FDA or other FDA-labeling websites to link to Project Patient Voice.

However, I do think that as more trials get added to Project Patient Voice, we'd certainly pursue having a way for the product labeling sites to link to Project Patient Voice. Thank you for that.

DR. PAPPO: Does that answer your question, Dr. Janeway?

DR. JANEWAY: Yes. Thank you very much.

DR. PAPPO: I have a question for Dr. Hinds and Dr. Reeve. That PRO-CTCAE has a very wide range of ages, from 7 to 17, and I was wondering if you'd been able to look at the percentage or the level of symptom rating and reporting; if there's a difference between younger patients and older patients, and the pattern, and how you can discern whether that is just a reporting issue based on the

age versus the actual side effects of the drug.

The other question I have is if you've looked at the caregivers' reporting versus the patients' reporting, what is usually the concordance rates, and what happens when there's a discordance between what the patient is saying and what the caregiver is saying.

DR. HINDS: Dr. Pappo, can you hear me?

DR. PAPPO: Of course, yes.

DR. HINDS: Thank you so much for that. We have not yet looked at the age-specific differences that you are suggesting, but I can say we have looked at profiles from our latent group analyses, latent profile analyses. There are no age-specific differences, meaning that children are distributed across the three profiles within the age groups that we have measured.

What I can say to you is that we have looked at concordance between parent and child, and it is somewhat higher than the reports that I shared with you earlier, but it is still low-moderate to high-moderate; so better but not on target where

one could replace the other.

Our past work, preceding the pediatric PRO-CTCAE indicated that with strong training, repeated measurement within a short period of time, 10 days, we are able to bring parent and child closer to being in higher agreement with each other.

Dr. Pappo, there was an earlier question about language translation for the pediatric PRO-CTCAE. May I just share with you that on the website, the NCI PRO website, there are of course English and also simplified Chinese and Italian translations.

With much appreciation to NCI, in particular Dr. Sandy Mitchell, the translations that are planned for this year of the pediatric PRO-CTCAE item libraries include Spanish, German, Danish, Korean, and French, and that's Canadian French and France French, and then Canadian English and Australian English. Thank you so much for the question.

Bryce, would you like to add anything?

DR. REEVE: Yes. Thank you, and thank you very much for the question. And thank you, Dr. Hinds, for a great answer.

So I'll build off Dr. Hinds' answers overall. The first question was regarding the age issue, and there are two important intersections of that: whether there are differences in terms of how they answer or report on the measure itself that has a validity question about it; and then secondly, in terms of age experiences and whether children younger or older have different experiences of symptoms and how we can disentangle those particular issues overall.

On the first issue, psychometrically what we did, if you remember, for both a qualitative and our quantitative phases, is that we stratified by age group. Again, the younger group -- for example, our quantitative testing was 7 to 12 year olds, and then 13 to 15 and 16 to 18.

Importantly, when we did our validation testing, looking at correlations or known-groups differences, we looked at each age group, narrow

age band, to make sure that patterns of correlations, patterns of known-groups validity, are consistent across age.

Now, a lot of our recommendations are across it because, basically, we found that the performance of the pediatric PRO-CTCAE worked just as well in the younger kids as it did in the older kids. So we feel strongly about that. Of course, we always welcome more and more validation information, but that was an important question we need to address through our study design.

The other related question is, does the children's experiences of symptoms vary by age? As Dr. Hinds says, we're still at this point -- we have a study we're doing analysis for, looking at our leukemia and lymphoma kids. We're also looking at hard tumors, and we're looking at how age may be associated or not associated with different age experiences, as well as by gender, race, and other important characteristics.

The last thing I wanted to comment on, the question was on correspondence between the child

and the caregiver. In our study, we collected data from the child using pediatric PRO-CTCAE; we collected data from the caregiver using our caregiver version of the pediatric PRO-CTCAE; and we collected data from the oncologist on the CTCAE.

We are in the process of writing results, so I won't give specific information, but as Dr. Hinds alluded, the caregiver had higher associations with the child self-report than the clinicians, and the caregivers' association in terms of agreement was in the moderate range at best.

Now, when we looked at the agreement between the child and then clinicians, at best, the agreement was fair. A majority of the time for these symptom AEs, the agreement was in the poor. When we looked at magnitude of differences, we found that the caregivers were much closer in terms of magnitude with the children's self-report. Sometimes they underreported; sometimes they're over, but it was much closer.

Consistently, for all the clinicians, their CTCAE gradings relative to the pediatric PRO-CTCAE

were much lower. At times, they're marginal compared to what the children are self-reporting. So again, I think this will support and hold up the value of making sure we capture that child's voice.

DR. PAPPO: Thank you very much. That is all for my questions.

Dr. Reaman?

DR. REAMAN: Yes. Thank you. I was just going to ask either Dr. Hinds or Dr. Reeve if they have any information on actual uptake of the use of the instrument in clinical trials, either single institution or in a multicenter setting, if they could just enlighten us on what the use of the instrument has been to date.

DR. HINDS: We do, Greg, and thank you so much for that question and all of your comments today. We do have embedded items. In fact, it's the core at one institutional study, not a clinical trial, but a research study.

We have embedded items in two phase 1 institutional studies. We have items embedded in one collaborative cooperative group study. And I

think Dr. Sharon Castellino may be on the line today representing that joint approach with COG and SWOG.

Quite recently, with then COG, a new Hodgkin's protocol has been approved and will include pediatric PRO-CTCAE items from the patient and parent perspectives.

Bryce, do you want to add to that?

DR. REEVE: I think you covered it really well. Our validation paper was published in 2020 last year and has now just subsequently been made available on the NCI website within this last year. We don't have, of course, the uptake because, again, the adults do.

But we're super excited about these early adopters, and I think that will help inform the implementation part of this process, what we can learn to help embed these measures into pediatric trials, and maximize the relevance of the data and minimize missing data.

DR. HINDS: Yes.

DR. REAMAN: Thanks very much. I'm aware of

the report of the validation. I know this is a recent release, so I commend you for the uptake, which I think is pretty impressive, actually, for this short period of time. So hopefully it's the beginning of a trend here in incorporating the use of these pediatric PRO-CTCAEs. So thanks.

DR. HINDS: Thank you.

DR. PAPPO: Thank you very much.

Just a quick reminder to state your name for the record before you speak.

Next question is Steve DuBois.

DR. DUBOIS: Thank you. Steve DuBois, Dana-Farber, Boston Children's. I have a question for Dr. Minasian related to the implementation of the PRO-CTCAE.

It seems to me that there's potentially three models of integrating data from the PRO-CTCAE with routine CTCAE reporting. One could think about separate reports for each of the tools. One could think about a single report in which the PRO-CTCAE is reviewed by the clinician grading the patients' AEs and modifying how they maybe

initially graded or coded an AE in the CTCAE.

Then one could also think about solely using the CTCAE for objective data and replacing the subjective elements of the CTCAE with PRO-CTCAE.

I imagine that there's pros and cons of each of those, but what are your thoughts, and what's the vision for how this would be implemented, or has been implemented? Thank you.

DR. MINASIAN: Thank you, Dr. DuBois, for the question. Yes, in fact, we have been thinking about this during the development and have had definitely different kinds of discussions about this.

To date, we're starting with the separate reports. There have been a couple of studies where clinicians have been shown the patient reports prior to making their final grade. And in fact, in the one study, it was clear that the clinicians actually did in fact change and modify some of their CTCAE grading and were actually quite pleasantly surprised to have that information, too.

I think many of us clinicians have had the

circumstance where we've talked to the patient, had one particular answer, and then later the nurses have called us from the chemo room and told us, oh no, Mr. so-and-so or the patient's having one symptom than we had originally elicited in the exam room. So I think some of this has to do with eliciting the questions explicitly rather than just asking for the patients to think of the symptoms or the experience themselves.

The third rationale, or the third scenario you said, of completely having clinicians do the objective and then the patients doing the subjective, I think is something that we've discussed a little bit for the future.

But I come back to the idea that the safety reporting really is the clinician's responsibility. And what we've seen in many of these different studies is the clinicians really are thinking about what is the medical impact of this particular event. Do I need to have an intervention? Do I need to stop therapy? Do I need to do something to prevent things from worsening?

So I think there's value in having clinicians do that grading, which bundles everything together that is distinctly separate from the complementary issues for the patients' response. Maybe in a distant future, we might figure out a very nice way to have one or the other, but I think for now, we have so much more information we need to understand about how clinicians grade, the use of the grades, and how patients respond prior to doing scenario 3 of only having patients do the subjective reporting.

DR. DUBOIS: Thank you so much. That makes perfect sense.

DR. PAPPO: We have time for one more question, and remember we can ask additional clarifying questions in the afternoon.

Tobey, go ahead.

DR. MACDONALD: Thank you. Tobey MacDonald, Emory University. Thanks for the great presentations. The questions, I have two for Dr. Reeve and Dr. Hinds, perhaps together, whether you have any complementary data in the grading

system as to what might be most important to the child. We see the graph of representation of severity, but sometimes in my own personal experience, it's really something like hair loss that actually is the key focus of that child, leading to a psychological ill-being, if you will.

So that's the first question, whether you have that information or whether you would include it. Second, similarly with clinicians, we make the attribution to the drug, and whether there would be the possibility of asking the child whether they think this is related to the drug or not. Again, because of the psychological impact, whether they think this drug or intervention is causing this symptom I think could have broad implications. Thank you.

DR. HINDS: This is Pam Hinds, Tobey, and thank you for the question. I think it's extraordinarily important, and if I may link it back to the attributes as well that we are measuring for each one of the subjective AEs. We are still looking at frequency, there's intensity,

there's interference, the more troubling characteristics for children and does that differ by gender, by age group.

So we are still at that level of data analysis and really appreciate your point, is it a single AE that makes all the difference for child or an adolescent? Could it be the cumulation over time? Could it be the collective addition of low-grade but still multiple AEs?

Those analyses are very much ongoing and very important, which I think comes back to how important it is to have the multiple voices inform supportive care decisions; the child voice, which can tell us, with emphasis, the importance of each AE, not just the presence, but how extensive the interference is for them in their activities of daily living or their view of self.

So I appreciate the question. It's very much an ongoing analysis.

Bryce, would you like to add to that?

DR. REEVE: Yes. Thank you, Pam, and thank you, Dr. MacDonald, for your really good questions.

I think you're exactly right about the impact issue overall. Any hair loss is a huge impact on their lives. And the same thing for nausea and vomiting; no kid -- I think they have slight types of nausea, but that is much more impactful, whereas a lot of kids live with fatigue and can tolerate maybe higher levels of fatigue overall.

As Dr. Hinds described, the good news is that, just like the adult measure, the pediatric measure not just looks at severity and frequency, but also looks at impact on the things they usually do in the day there. So we can look at, again, not just how severe it is, but from the child's perspective how it impacts their day, and we continue to explore that as well.

If you'll note in the last slide of my references, Molly McFatrich, who works at Duke University, led a study. And we actually worked with -- I can't remember the exact number -- a Delphi-like process, and were working with pediatric oncology clinicians where we were looking and seeing how can we weight and value, for each

symptom, the severity, frequency, interference to derive something that's somewhat like a CTC but not equivalent to a CTCAE, but how can we derive a single-summary score.

All the clinicians put much more value on the impact on their daily lives as helping to evaluate and judge the magnitude of that CTCAE grade there. But that's something, again, I think we can continue to look at in our analyses overall.

The attribution is a great question overall. I think -- and others can clarify as well -- that even in adults, there are questions about how people can actually attribute what is actually the cause of something like severe fatigue overall.

I think patients have a really good insight and perspective, that we need to think about better ways to capture that. A lot of it, of course, is based on study design, so importantly we recommend that you collect a baseline because, as was mentioned earlier, all kids are experiencing symptoms of fatigue, anxiety, depression. All these things are present even before the

intervention itself, so having that baseline allows us, when intervention is, to look at differences, and that might inform the attribution.

We don't currently have questions that ask the kid or the parent what is the cause of your pain or nausea there, but I think that's something worth exploring in future studies.

DR. DUBOIS: Thank you.

DR. PAPPO: Well, thank you very much.

We will now take a 25-minute break for lunch. Panel members, please remember that there should be no chatting or discussion of the meeting topic with anyone during the break, and we will resume at 12:50 Eastern time. So enjoy your lunch or your bathroom break, and we will see you in a little bit.

(Whereupon, at 12:26 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:50 p.m.)

DR. PAPPO: Hello, everybody, and welcome back. We will now reconvene and proceed with a few more guest speakers. The next presentation is by Dr. Lillian Sung.

DR. SUNG: Good afternoon.

May I start?

DR. PAPPO: Yes, please.

Guest Speaker Presentation – Lillian Sung

DR. SUNG: I'd like to first start by thanking Greg for this invitation, and I really wanted to congratulate Pam and Bryce for their creation and validation of the pediatric PRO-CTCAE.

Are my slides up?

DR. PAPPO: Yes.

DR. SUNG: Thank you.

I was asked to talk about potential future directions for advancing supportive care strategies as it relates to patient-reported outcomes, and specifically the pediatric PRO-CTCAE.

The number of potential directions is

clearly infinite, but I wanted to maybe address three particular areas that the PRO-CTCAE team could consider. The first is helping clinicians know how to respond to symptoms; the second is to begin to quantify short- and long-term impacts of symptom assessment; and the third, clinical trials to evaluate the impact of administration of the PRO-CTCAE.

In terms of helping clinicians know how to respond, clearly identifying symptoms alone is insufficient. Clinicians need to be able to act upon those symptoms and apply preventative and intervening actions. And as Pam alluded to earlier, interventions are available for symptom control.

But how should clinicians know what interventions to apply? One could turn to clinical practice guidelines, which are defined by the Institute of Medicine as statements that include recommendations intended to optimize patient care. These are statements that are informed by systematic reviews of the evidence and evaluation

and assessment of the benefits and harms of alternative options.

But there are challenges in the delivery of intervention according to clinical practice guidelines, and those relate to, are there guidelines available for all the symptoms addressed by the PRO-CTCAE; how can we enhance access to guidelines to address these symptoms; and how can we improve guideline-concordant care?

The problem of development of guidelines has been recognized by others, which has led to the creation of the International Pediatric Oncology Guideline Network. This is a network co-led by Lee Dupuis in Toronto and Wim Tissing in the Netherlands, and this group is important because it ensures that there is minimum duplication in efforts to create guidelines. It also ensures those guidelines are widely disseminated and allows the sharing of methods for their development and implementation.

Then once those guidelines are developed, how can we enhance access to them by healthcare

providers? This is an example of a repository of supportive care guidelines that's housed within SPARK, or Supportive Care Assessment and Recommendations for Kids. A similar repository exists within the Children's Oncology Group. But the important thing is, there needs to be an easy way for healthcare providers to access these guidelines to help manage their patients.

We know that the existence of guidelines alone will not lead to their implementation, so we need tools to help clinicians know what interventions should be implemented. We have started to work on what we call these supportive care pathways, where we are translating recommendations from guidelines directly into a format which facilitates healthcare providers to know what preventative or treatment options are available to treat a specific condition.

What you are seeing here is a care pathway for cisplatin-induced ototoxicity. We appreciate that there should be a generic care pathway, which are the direct translations of the guidelines, but

that each institution will need to adapt that generic format for their institution that considers their resources, values, and preferences.

The second larger bucket that I wanted to address was quantifying short and long-term impacts of symptom assessment. Some short-term impacts could be if we know about symptoms, do healthcare providers document them; do they act; does it lead to better symptom control and quality of life; and does it lead to better resource utilization?

In terms of long-term impacts, we could be looking at, does it improve survival; does it improve long-term psychosocial and financial morbidity? And I know that Tara will be addressing survivorship in a later talk, but I just wanted to touch upon symptom intervention and survival briefly.

To do so, I just wanted to introduce you to a symptom screening tool named SSPedi or Symptom Screening in Pediatrics tool. It is different than the PRO-CTCAE because this tool was developed for clinical implementation and symptom screening, not

for utilization within clinical trials.

SSPedi has 15 symptoms that were identified by children and their parents as being the most important to them, and SSPedi is rated on a 5-point degree of bothered Likert scale, that was the construct that was considered most important.

This instrument is meant for children 8 to 18 years of age, and because we know many children who are 8 cannot read very well, this instrument has an audio function that allows the entire instrument to be read aloud or specific questions. Because the symptoms themselves can be more difficult to understand, it also has a help function that gives children synonyms for symptoms that were derived primarily from children themselves during cognitive interviewing.

Using SSPedi, we determined how often do we treat severely bothersome symptoms, and we did that by asking children to self-report their degree of bother for the 15 symptoms. Here, I've just listed the first two within SSPedi. We took children who said they were severely bothered by a symptom, and

then we performed medical records review to look at whether or not there was any intervention for that symptom within a 2-day window before they reported, to a 2-day window after they reported.

In brief, if you look on the right-hand side of this slide, there are 8 symptoms that were treated less than 20 percent of the time when children self-reported they were severely bothered by a symptom. You can see that many symptoms are never or hardly ever treated, including fatigue.

Then what about long-term outcomes such as survival? Well, as Lori alluded to earlier, there are data from adults. And this is a study from Ethan Basch, who randomized adults with metastatic solid tumors to routine symptom screening versus standard of care, and he demonstrated in this publication in JAMA that routine symptom screening can improve survival for these adults.

Well, can we do something similar for children? We can think about approaches such as linking symptom screening data with alternative data sources to start to understand the impact in

the long term in a cost-effective manner. For example, in Canada, for all the studies that are using SSPedi, we are explicitly obtaining consent to link their data to a national pediatric cancer registry called the Cancer in Young People Canada, which is a population-based registry that has included all children with cancer in Canada since 2001.

For the Children's Oncology Group, one could consider obtaining explicit consent to link data across studies so that you could measure long-term event-free and overall survival in a subgroup of children who are enrolled on subsequent clinical trials.

The third or final point is can we conduct clinical trials to evaluate the impact of implementation of the PRO-CTCAE or symptom assessment? Here, I would advocate that we could think about individual patient-randomized trials or cluster-randomized trials. Individual patient trials are perhaps easier to perform, and they're probably okay to evaluate the impact of symptom

screening on feedback to clinicians. But they're probably less well suited if we want to change clinician behavior and that one could consider cluster trials.

I wanted to show an example of a cluster-randomized trial that has been supported by an NIH RO1 and a CIHR grant, where the objective is to determine if symptom feedback to healthcare providers, given at least 3 times weekly, and locally adapted symptom management care pathway, can improve self-reported symptom scores over 8 weeks. This is a trial that will be enrolling children 8 to 18 years of age who are English or Spanish speaking and newly diagnosed with cancer with a plan for any treatment.

The way this study will work is that there will be 20 sites randomized to either intervention or control group. For patients at intervention sites, those patients will be enrolled. They will have SSPedi prompted to be completed 3 times weekly for 8 weeks, and those with severely bothersome symptoms will have email alerts to their healthcare

providers. Those sites will also have symptom management care pathways adapted and implemented.

The control sites will have usual care, where the children will have assessments at baseline, week 4 and week 8, and that's conducted for both groups. The primary outcome is a total symptom score using SSPedi, fatigue using the PROMIS measure, and a quality-of-life measure.

We will also be measuring symptom documentation and interventions, as well as healthcare utilization, and one could imagine a similar type of study could be conducted using the PRO-CTCAE as well.

In conclusion, I've shown some possible future directions for the PRO-CTCAE. The first is possibly to help clinicians know how to respond to identified symptoms and to improve guideline-concordant care. The second is to start to measure the short and long-term benefits of routine symptom detection using the PRO-CTCAE, and finally to design clinical trials to measure the benefits of PRO-CTCAE implementation.

I'd just like to thank the many colleagues and my study team for the work that I've presented today. Thank you.

DR. PAPPO: Thank you very much, Dr. Sung.

We will now proceed with a guest speaker presentation from Dr. Tara Henderson.

DR. HENDERSON: Good afternoon. Can you all hear me?

DR. PAPPO: Yes.

Guest Speaker Presentation – Tara Henderson

DR. HENDERSON: Hi. My name is Tara Henderson. I'm a professor of pediatrics and the interim chief of Pediatric Hematology, Oncology, and Transplant at the University of Chicago. I'm going to be discussing facilitating survivorship care and research today.

In general, I want to discuss how survivorship outcomes are critical when considering pediatric clinical trials and how PROs are essential to these data, and some of the barriers or considerations to their collection using specific experiences in the COG infrastructure.

And like Lillian, I would like to thank Greg for this wonderful workshop and also congratulate Pam and Bryce on their spectacular work.

I want to start with, as we all know, childhood and AYA cancer is a success story, in large part to a lot of the work at the FDA, the NCI, as well as universities and the COG nationwide due to laboratory discovery, intense therapy, clinical trials, supportive care, as well as new therapies.

With this success, we've learned a new model of research, and that's survivorship and outcomes research. My colleagues, Smita Bhatia and Les Robison, really have developed beautiful graphics that I think about whenever I'm thinking about my career, and work, and survivorship outcomes. I think this is an important graphic to keep in mind when we're considering new drug development and data collection in children.

You can see that after cancer diagnosis and treatment, we're now developing a large population of cancer survivors, and we need to examine their

health-related and quality-of-life outcomes. With this data, we've been able to, and continue to, identify high-risk groups to both develop evidence-based clinical care guidelines, but also to develop intervention strategies and clinical trials of efficacy to improve their outcomes as survivors. Once we've done that, we are now working to implement those interventions and then feedback, and what we've learned to new treatments and thinking about a better cure.

As many of you know, the cost of cure in pediatric oncology is significant. In the childhood cancer survivor study, in survivors diagnosed between 1970 and 1986, 30 years after their cancer, 75 percent of survivors have at least one chronic health condition, while two-fifths have a severe life-threatening condition, and this is 8 times more likely than their siblings.

I want to point out that with these chronic health conditions, there's significant premature late mortality. You can see the blue and yellow lines here represent the general population

mortality rates and the red and gray represent the age-matched childhood cancer survivor study survivors since 5 years since diagnosis. You can see the premature mortality continues to fall off well beyond 10 and 15 years after diagnosis. This is due to second cancers, cardiac disease, and pulmonary disease. But what I want to note is that this represents an over 10-year loss in life expectancy.

We've also learned from that model I showed you that we have improving outcomes with advances in cancer treatment. Greg Armstrong published a seminal paper back in 2016, where he looked at the 15-year cumulative mortality in the 1970s, 1980s, and 1990s for a decade of diagnosis, and saw that this 15-year mortality fell off with time.

This reflected both risk stratification of therapy, for example, in acute lymphoblastic leukemia and Hodgkin's disease, which was learned through understanding the long-term outcomes of these patients, as well as screening of late effects, treatment of late effects, and supportive

care.

When we're considering survivorship, the long-term, self-reported outcomes are critical for clinical trial development. There are two ways I want to point out. Many pediatric diseases now have cure rates over 90 percent, but we're bringing novel therapies to upfront treatment that have unknown late effect profiles and yet are being explored in upfront therapy. In ALL, there's the example of blinatumomab, and in Hodgkin's lymphoma, we're bringing brentuximab vedotin as well as PD1 inhibitors.

Then there's also the example of more difficult-to-treat pediatric patients, where it's critical when describing both incremental advances in survival to also think about the long-term outcomes of these new therapies. My example is high-risk neuroblastoma, where we're bringing forward immunotherapy, MIBG therapy, isotretinoin, and tandem transplant, et cetera.

Currently, we get our outcomes data mainly from two sources. There's the retrospective cohort

studies. The NCI-funded U01 cohorts include the Childhood Cancer Survivor Study and the St. Jude Lifetime Cohort, which includes self-reported medical conditions, health-related quality of life, as well as psychosocial outcomes. But recently-treated patients are not included in these cohorts.

For example, the CCSS only includes patients treated up to 1999, and the St. Jude Life Cohort only includes patients treated up to 10 years ago, so many of the long-term effects of novel and newer agents haven't been described.

We also have the infrastructure of the survivorship and outcomes studies in the Children's Oncology Group. The COG has a dedicated survivorship committee, and there really is a rich portfolio. But it's important to note that studies generally are not embedded in clinical trials. It requires re-contact of patients through individual sites where there is significant loss to follow-up and heterogeneous site participation. So in sum, it requires significant research infrastructure and

per-case reimbursement.

I wanted to show you two examples of survivorship studies that have been embedded in the Children's Oncology Group trial consortium to talk about what are the resources needed and what to think about as we move forward with putting PROs and thinking about PROs long term for these patients.

The Late Effects After Higher Neuroblastoma Study, which is the LEaHRN study, has the COG name of ALTE 15N2. When we wrote this study, the goal we had was to describe the burden of long-term toxicity in the emerging population of high-risk neuroblastoma survivors. We wanted to both describe the prevalence of late effects, the risk factors for those late effects, the impacts on health-related quality of life, and to explore the impact of newer therapies on late effects.

This is our study design, so basically I want to show you that we had to identify patients centrally by COG. So we were looking at patients that were enrolled on the COG Neuroblastoma Biology

Study and were deemed high risk after January 1, 2000. The patients had to be at least five years from diagnosis and two years from cytotoxic therapy.

These eligible patients were recruited by sites once the sites opened the study and were given a list of the patients. In some, an enrollment occurred locally, and then there were multiple study procedures, including clinical laboratory studies, provider history and medical assessment, as well as patient and parent quality-of-life demographics and family history collection. We also did medical record abstraction, as well as did biologic specimen submission.

Actually, I wanted to show our enrollment on this study. We opened in June of 2017, and we had 91 institutions enrolling. Of those 91 institutions, there were a total eligible of 900 patients, and we enrolled 359. I'd like to say our enrollment is what we predicted, but honestly that is only 40 percent of the eligible patients,

so it would be ideal if we could even have more of those patients. But you can see here that we had an excellent accrual rate, even at the time of the COVID-19 pandemic.

We enrolled patients that were a median of 2.6 years, about 2.6 years at the age of neuroblastoma diagnosis, currently about 12 years, and about 9.3 years from their initial diagnosis. We found some critical patient-reported outcomes that I just wanted to show you.

We recently presented this at the Advances in Neuroblastoma Research meeting this past January, and showed through the patient-reported outcomes that 61 percent of our patients participated in special education; almost half required special education for hearing-impaired individuals; and 14 percent needed to repeat a grade.

We also collected other very important PRO quality-of-life measures, including the Behavior Assessment System for Children, the Behavior Rating Inventory of Executive Function, the PedsQL, as

well as the Scarring, Disfigurement, and Body Image measure.

I just want to summarize to say what was it about this study that enabled us to be successful in enrolling patients and collecting data in this infrastructure? First, we had significant funding. This is a consortium study funded through the St. Baldrick's Foundation, where we had funding along the lines of an NCI RO1. We received per-case reimbursement for every patient, and that was generous, and we also had BCP [ph] credits in addition to our per-case site reimbursement.

One of the keys was we had a central project manager at the University of Chicago who has trained sites. She has frequently and consistently updated and communicated with sites, and identified missing data, and educated those sites.

The other thing that we have identified as a positive was the age of the population, so we think these patients were younger, and many of them have not aged out of the pediatric hospital, which some of our childhood cancer survivors have. We also

have a highly sick population, so we think they're interested in coming back to the doctor's. We had an unbelievable partnership with the neuroblastoma committee and also partnerships with families.

I wanted to show another example of an embedded outcomes study in the Children's Oncology Group where we were trying to get at some later outcomes, not as far out as the LEaHRN study, but it was in an upfront clinical trial.

In the recently closed high-risk Hodgkin's lymphoma trial, AHOD1331, this study was to assess event-free survival and toxicity of a novel regimen incorporating brentuximab vedotin in the chemotherapy backbone of doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide. In this study, we were able to embed health-related, quality-of-life aims, and those were for a chemotherapy-induced peripheral neuropathy, study as well as a cost-effectiveness analysis.

Consent for these embedded studies were included in the overall trial consent, and at the time of enrollment, again, we had a central CRA at

the University of Chicago that was alerted to the patients being enrolled. At that time, the University of Chicago CRA sent both age and language-specific assessments, so back to the language question that was asked before.

We had our PROs translate it into French and Spanish in order to include many of our sites in Canada that were only French speaking, as well as some of our patients that speak Spanish. Baseline measures were completed prior to the start of chemotherapy, and then all the measures were uploaded via RAVE and transferred to the University of Chicago.

What I want to point out here is even with our significant ancillary funding in this study, we did very well up front with collecting at baseline and through the time of the chemotherapy treatment. You can see our compliance rates were over 90 percent. And even at the end of therapy, we're still over 80 percent. But for our cost-effectiveness study, we really wanted to get at some of the relapse and longer term outcome aims,

and you can see that the assessment compliance really dropped off as we got to 36 months off of treatment.

So we asked ourselves why are these completion rates in AHOD1331 falling with time, and we think that this is because these measures were completed on paper. It really was site-dependent based on there were some smaller sites with less resources and didn't have the support to collect and upload the data.

Lastly, the Hodgkin's lymphoma population is really more an AYA population, so we know that the follow-up with the cancer center falls off post-therapy, and this is a period of transition and moving, and sometimes difficult to trace these patients.

I think the important thing to ask, if we're going to be thinking about PROs in the clinical trial infrastructure is, can we develop innovative approaches to embed survivorship outcomes? The AHOD2131 study is an early-stage Hodgkin's lymphoma trial that's in development, and Pam alluded to it

earlier. This is a large upfront trial of 1800 patients with newly diagnosed stage 1 or 2 Hodgkin's lymphoma, a disease where the cure rates currently exceed 90 percent.

This study has been a great collaboration with the NCI and the Adult National Clinical Trials Network, with the primary aim to examine whether the three-year progression-free survival is superior with immuno-oncology versus standard approaches.

There was significant interest and support from the NCI in 12-year outcomes, including PROs. We believe that PROs will be important to study the late impact of the immuno-oncology approach that we know is not well understood, but the question still remains as we develop this trial, is how do we accomplish this?

Some ideas about collecting PROs, I've gone down many avenues to think about this. First, there's the ALTE05N1 protocol, developed by Smita Bhatia, which is the Umbrella Long-Term Follow-Up Study, which is a tracing mechanism to find our

long-term survivors. This study requires significant resources. You do have to support the Long-Term Follow-Up Study, and it's not a data collection mechanism, and at this point, patients are not enrolled at the time of diagnosis.

Another idea we examined was the Passport for Care. This is the Texas Children's Hospital developed web-based platform that enables survivors and their providers to develop care plans and for the care plans to be shared with primary care providers. But unfortunately, again, this current system is not compatible with enrolling all clinical trial patients. In order to have the Passport for Care, each individual institution must have a data-use agreement and a contract.

So we believe that we need to think about the development of an electronic mHealth application or platform, where we can think about how to collect PROs longitudinally, where the data would be provided to patients along with education and potentially to their providers, and it's kept data compliant. But we need to think about both

innovation as well as investment because this would need to be both developed and then thought about, the sustainability of such a platform.

In summary, with the continuing advancement in cures in pediatric cancer, it's imperative that we examine both the short- and long-term outcomes of these young patients. Both cohort studies and our current cooperative group survivorship studies have limitations.

A novel and modern approach to following patients enrolled in upfront clinical trials in order to collect PROs is needed. With the support from national agencies, perhaps collaboration with technology development can result in innovative approaches.

Thank you so much for your attention. I just would like to thank all of my collaborators for this study. Somehow, I forgot to put that slide in the uploaded version. Thank you very much.

DR. PAPPO: Thank you very much, Dr. Henderson, for your presentation.

We will now proceed with our final guest speaker presentation, by Dr. Doug Hawkins.

DR. HAWKINS: Thank you, Alberto. I assume people can hear me?

DR. PAPPO: Yes.

Guest Speaker Presentation – Douglas Hawkins

DR. HAWKINS: I want to thank, again, the organizers, especially Dr. Reaman, for this symposium. I think it's been really very useful, and I appreciate the opportunity to speak on behalf of the Children's Oncology Group about how COG may work towards incorporating pediatric PRO-CTCAE into our clinical trials.

These are the topics I want to cover, and I'm going to start with an example from my own clinical trial experience that, in retrospect, I wish that we had already incorporated pediatric PRO into the trial because I think it would have really informed the interpretation of the trial.

This is a study that I was the chair of for children with intermediate non-metastatic rhabdomyosarcoma. It's a study that ran for six

years, and it's a fairly simple study where it compared two chemotherapy regimens. One backed the standard at the time, and one backed with the addition of vincristine irinotecan.

The randomization happened up front. It was 42 weeks of total therapy. The VAC/VI arm did have lower cyclophosphamide, but it's important to know that the two arms were quite different. The standard arm would be expected to have fairly emetogenic chemotherapy every 3 weeks, often requiring hospitalization, and the irinotecan-containing arm would have additional GI toxicities with the drug given in clinic or sometimes inpatient for 5 days in a row every 6 weeks, alternating.

This is the study design, and at the end of the day, the two arms looked very similar. This wasn't an equivalent study, but the two arms had somewhat similar oncologic outcome; although there was a difference in the toxicity as was reported by the institutions.

This is how we reported the data, where we

looked at the maximum grade of toxicity experienced in a 15- or 12-week reporting period, but only grades 3 and 4. And when we compared the different regimens, we could see a higher level of diarrhea, particularly in the earlier phases, in the patients who received irinotecan. That was expected, given the toxicity of irinotecan.

There was somewhat more oral mucositis early on the irinotecan arm. That was the phase when radiation was given, and almost half of the patients on the study had parameningeal primary tumors, so their mouth would likely be within the radiation field. But there were differences in hematologic toxicities with less hematologic toxicity on the VAC/VI arm.

So using the institutionally reported toxicity, looking at the worst toxicity experience, but only grade 3 and 4s in a reporting period, we concluded that there was somewhat less hematologic toxicity on the VAC/VI arm, and then that would be preferable to bring forward to future studies.

But as I reflected on this experience, and

now thinking more about the potential for including pediatric PRO into our studies, we really didn't know which regimen was better tolerated. We certainly didn't know which regimen interfered with daily routine more. We didn't know whether there were any differences. We didn't examine differences by age or other parameters that might favor one of these two regimens over the other.

Although the oncologic outcomes for the two regimens were similar, it really was not clear, now that I look at it in retrospect, which was the preferred regimen. So obviously, I'm preaching to the choir to the people in this seminar, but I think this experience, or my own clinical trial experience, really showed how we did not have the opportunity to collect the relevant information about tolerability between these two treatment arms.

Now I'm going to talk a little bit about current or planned COG studies that intend to incorporate pediatric PRO-CTCAE into the studies. The first is a study that was actually started

within SWOG, for which SWOG is the lead group, but for which COG has been very involved in the planning and the implementation, and that is the study for advanced-stage Hodgkin's lymphoma.

This is a randomized phase 3 study where all patients receive a common chemotherapy backbone of AVD, and patients either receive the immuno-oncology drug, nivolumab or brentuximab vedotin. And this study from its outset was open to patients 12 years and older.

One of the secondary aims for the study was to compare the patient-reported symptoms by arm, and from the early design, the 12- to 17-year-old patients in the study would be evaluated by the ped PRO-CTCAE, and the older patients by PRO-CTCAE. This gave an opportunity to collect the data and do assessments across the whole AYA spectrum, including younger AYAs and older AYAs.

This study really gave an opportunity for the cooperative groups, the COG and adult cooperative group, to plan and to tailor this approach based on the age. In planning the study,

they had to agree to the items that would be included. They had to identify relevant items that were important on either treatment arm, either the nivolumab or brentuximab arm, as well as items that might be specific to the unique toxicities to be expected with each novel agent, including those with nivolumab or brentuximab.

In matching and developing this total set of items, there was an active decision to make sure we had matched pediatric PRO-CTCAE items so that they could have strong alignment between the two measures, despite the difference in age group.

I think this study is still ongoing. The study is still accruing. But I think this is an example where it has been successfully incorporated into a clinical trial, including pediatric patients. As of the last update I got, there were over 300 patients enrolled on study, and the completion rate across multiple cycles was really quite high.

So I think this demonstrates that in the cooperative group setting, this data collection is

possible, even though the data is collected at the end of each cycle, at the end of treatment, and then followed up at scheduled times. There may be some follow-up, as Dr. Henderson mentioned, with later time points, but I think this is feasible in the cooperative group setting.

I think it does raise the intriguing question that, if these two treatment arms with these two novel agents have similar oncologic outcomes, we might look to the patient-reported outcome, the patient experience, to determine which would be preferred, or maybe there would be differential groups that would prefer one regimen over the other, based on their symptom profile.

Now, Dr. Henderson already alluded to this study that's in development. She focused mostly on the application to late effects, but I think we could also focus on the ability of patient-reported outcomes to inform our interpretation of early and short-term follow-up toxicity.

This is a study which has been developed jointly between the entity and groups. COG will be

the lead, and it has been approved by the COG Scientific Council, and it's now going on to further review. This study will give all patients with early-stage Hodgkin's lymphoma the standard chemotherapy. They'll be assessed for response, and then there will be a comparison with either standard chemotherapy or immuno-oncology combination therapy.

One can imagine that given the high outcome, in general, for patients with early-stage Hodgkin's lymphoma, the two arms may end up being very similar. But there may be dramatic differences in the lived experience toxicity, both during treatment as well as short-term off therapy, that would favor one regimen over the other. With these newer agents, we truly need to look at novel ways of assessing toxicity to make valid comparisons of which regimen would be preferred.

As Dr. Henderson mentioned, this will require some new approaches, particularly for some of the long 12-year follow-up data, to really have complete data capture. And I think this is also an

opportunity to think about how the data can be captured electronically to reduce some of the site burden, as well as to improve the overall compliance with the observations.

So those are the two studies, and they both are developed within Hodgkin's lymphoma. I think that's a population that really lends itself to this data collection. We already have very high early outcomes. We want to see which treatment has a greater burden for patients, and the best way to answer that question is to get the data directly from patients, as you've heard before.

I just have a few closing thoughts about implementation of patient-reported outcomes into cooperative group clinical trials. I gave the example of when we're doing studies that will be conducted across the NCTN network, it's very important that we align as closely as possible the ped PRO as well as the adult PRO so that we can have comparable data across the AYA population.

I think we'll need to be selective in the specific items that are included, and also there

may be studies that lend themselves more to incorporation of robust patient-reported outcome data, particularly if we expect that there will be differences in the experienced toxicity profile between two or more treatment arms.

I think there remains a perceived notion that there is an increased burden on institutions to implement patient-reported outcomes, and I think Dr. Henderson described how funding can help. Providing additional funding to the sites can overcome some of that perceived notion that there is increased burden on the sites.

I think if we really want to capture data and particularly not have the drop-off over time, electronic data capture will be a very important part of implementation, both to reduce site burden but also to increase the total compliance with the observations. So with that, I will end. Thank you.

Clarifying Questions

DR. PAPPO: Thank you very much, Doug.

We have about 15 to 20 minutes for

questions. We will now take clarifying questions for our guest speakers, Dr. Sung, Dr. Henderson, and Doug Hawkins. Please use the raised-hand icon to indicate that you have a question, and remember to clear the icon after you have asked a question.

When acknowledged, also please remember to state your name for the record before you speak and direct your question to a specific presenter if you can. If you wish for a specific slide to be displayed, please let us know the slide number if possible.

Finally, it would be helpful to acknowledge the end of your question with thank you, and the end of your follow-up question with, "That's all for my questions" so we can move on to the next panel.

We will start with Dr. Gorlick.

DR. GORLICK: Thank you, Alberto.

It's Richard Gorlick at MD Anderson Cancer Center. This is a question for the speakers, but I'm not sure which one.

A question that I have is, throughout these

presentations, there has been very little discussion about how the implementation of the PROs themselves may have a risk of impacting on the pediatric patient's cancer experience.

Can anybody talk to what the risks are of implementing PROs? Thank you.

DR. SUNG: This is Lillian. Maybe I can take a start at that. It's a great question. I think just to rephrase your question, it's whether or not measuring PROs can have adverse effects and unintended consequences.

So indeed, we have thought about that in implementing these PROs, both in terms of could this cause distress and could this be burdensome to clinicians in terms of receiving their reports. We have tried to evaluate this. In over a thousand children that we have implemented PROs in, we have yet to identify an adverse event from measuring PROs. We have done qualitative interviews with clinicians to understand is it burdensome to receive symptom reports, and how do you incorporate that into your workflow.

I agree that this is something we need to continue to monitor. I am actually probably more worried about the clinician workflow and whether or not we could have unintended consequences in terms of clinician burden. But that's my own experience with PROs. I'll let Tara and Doug perhaps comment.

DR. HENDERSON: I think it's an excellent question that I didn't respond to because I was actually thinking. I think that we recognize that, both, there could be a burden, but also there could be concerning findings in some of the scoring, and that we need to ensure, if we're going to find out any of these issues, that it's acted upon.

We included in our development of both the LEaHRN study and the 1331 embedded studies that if there was distress or scores that indicated significant distress, that either the study PI needed to be notified, and then that PI needed to notify the physician. But there had to be a mechanism in place where you assured that the loop was closed on the distress in these patients.

I'm curious in terms of when Pam and Bryce

developed the PRO-CTCAE, how they managed that issue.

DR. REEVE: This is Bryce Reeve. Thank you so much, Tara, for calling on us.

Our study was outside the context of the clinical trial, but like any research study, we have protections in place to make sure the child, especially if the child reported something that's distressing, received active follow-up attention and care.

It reminds me of one of our cognitive interviewing a child, an 8-year-old boy. One of our questions was asked; in the past 7 days, have you hurt yourself? Something like that. I don't remember the exact wording.

The child actually did say yes, and the interviewer probed the child on why he answered that question. And his response was that he was experiencing cognitive -- brain fog, where it's hard for him to focus, and he was trying to hit his head to help himself concentrate on his task.

The interviewer said would it be ok if I

tell your parent and your doctor about this, and the kid was ok. And both the parent and the clinician were shocked to hear what this kid was experiencing, and subsequently they actually changed the dose, the regimen, of the chemotherapy to help accommodate that child.

I think that's just one as a case study, but I think it also can highlight the value of routinely collecting this information and having systems in place to be able to respond quickly, as you would with adult patients, to make sure that these very distressing symptoms are addressed quickly. And I think to the extent that we can address these symptoms quicker means that those kids can probably stay on their drug for a longer case there, so I see a positive.

Now, all these questions about implementation are extremely valid. We are thinking about these issues. We know that these are the next steps, and luckily we're learning a lot from the adult trials to think about what we need to address and consider for pediatrics.

DR. PAPPO: Thank you.

Does that answer your question?

DR. GORLICK: Yes. Thank you.

DR. PAPPO: Julia Glade Bender?

DR. GLADE BENDER: Hi. Julia Glade Bender from Memorial Sloan Kettering. This was a fabulous session, and it's really got me thinking. I was thinking about Dr. Hawkins' last talk, and really about how we would use these PROs.

The question is, if we run a trial, and the answer is that the arms are equivalent, then is there a standard of care or are there two standards of care, which have different toxicity profiles? This causes the downstream question of -- first of all, institutions like to have a standard of care because they feel that if they follow a standard, they will deliver it more faithfully.

It may create an increased burden on families down the road to decide which standard they want based on the toxicity, hearkening back to the Patient Voice website, which is fabulous, but as I said, it can really affect decision making if

we find out there's more than one standard.

I'm not sure that's a question, but that's what I was thinking.

DR. PAPPO: Any of the speakers want to expand on that observation?

DR. HAWKINS: This is Doug Hawkins. Maybe I could expand on that. I think you're exactly right. It is not uncommon that we run a trial and some arms look similar, and how people choose to go forward is variable. Sometimes we pick the arm which has the longer track record, the one that's been longer. If two arms look similar in terms of outcomes, you pick the one that has been established for longer.

But also I think sometimes we pick one based on our perceptions of the burden of care. If there are two treatments that have vastly different exposures of drugs that we know have specific late effects, alkylating agents, anthracycline, we might pick the one with the lower of those two exposures, but you're really trading off two different exposures. In the example I gave, was it more

irinotecan or more cyclophosphamide? Which would you prefer to have?

I think reasonable people could likely look at those and make different decisions. But the data we've had before was not informed as robustly as it should be by the patient's lived experience of toxicity. We've looked at overall rates of grade 3 and 4 toxicity.

So I think this will make that discussion more complicated, but there may be more informed choices about picking one regimen over another based on actual evidence of the burden of care for a patient.

DR. HENDERSON: This is Tara. I agree with Doug. When I think about toxicity and we take it from the late-effects frame of reference, I think taking leukemia as an example, as our paradigm, while toxicity at the time of the trial could be the tiebreaker for equivalence, really, in our patient population, given how long these patients are going to live, the longer term outcomes could actually be the tiebreaker.

I'm thinking leukemia, when you got cranial radiation and our patients would get second malignancies, and metabolic syndrome, and growth problems, and that fed back and informed how we created our new trials.

Now with neuroblastoma, Julia, I know you'll appreciate this with the high-risk patients, the significant late toxicity we're seeing, not just the upfront toxicity, is something to consider. I didn't spend as much time on 2131 and, Doug, as you were presenting it, I'm like, "I probably should have talked about that a little more since I've been living and breathing that trial."

But that's another example where we're looking at the upfront toxicity of immunotherapy and balancing that with what we know are late cardiac toxicities. But we don't know the late toxicity of immunotherapy. That's why I think electronic data capture is important, but I think we have to be even more innovative than just electronic data capture because if we don't understand what's going on later in these patients

as well, we really won't know the true tiebreaker of equivalence.

DR. SUNG: This is Lillian. Maybe I could just add one point to this conversation, and that's related to the idea of conditional recommendations and guidelines, which I think is a little bit about what Julia's talking about, where there are multiple valid options.

For conditional recommendations, we really distinguish between options that an institution might want to adopt uniformly even though different institutions might want to make different decisions versus decisions you would apply at an individual patient level.

There are some things, such as fever and neutropenia management, that even though there are multiple right options, you may want to standardize to try to improve the quality of care; so just to bring in that distinction between institutional versus patient-level decision making when there are multiple options.

DR. PAPPO: We will proceed with the next

question.

Katie Janeway?

DR. JANEWAY: Hi. Yes Dr. Janeway from Dana-Farber and Boston Children's. This is definitely not my area of my expertise, so forgive me if this question reflects some ignorance.

I've heard PROs discussed in a number of different contexts. I've heard them discussed as a way to manage disease symptoms to identify patients for interventions for symptom management. I've heard it discussed to identify disease symptoms to help us understand treatment effectiveness. I've heard it discussed to capture treatment side effects to better understand the patient's perspective on side effects. Then finally, we heard from Tara, Dr. Henderson, about better understanding the burden of treatment over time and survivorship.

I guess my question is, are there different PRO measurements that are measures; or tools that are best to optimize each of these uses; or can you use the same tool and it just depends on how you

analyze the data?

I guess the final -- it's really three questions -- or it's one question. That's one question. Then my second question is, are we trying to decide which of these uses or approaches is most important or do we think they're all equivalent? And I'll stop there. Thank you.

DR. HENDERSON: Well, I can start. I think there's the PRO-CTCAE, which we're trying to incorporate into upfront trials and make it as a standard. I think when we think about survivorship and what's been done up to this point, Katie, I think your question about are there different measures for different time points, the answer is yes.

Actually, there are measures for different symptoms that you're looking at. When we are looking at PROs in our different studies, we are looking at specific PROs for neuropsych outcomes, for chemotherapy-induced peripheral neuropathy, et cetera. So the longer term outcomes are a little bit different, and you do have to think

about what are some of those questions you're asking.

I know there's an attempt in many of the committees -- for example the adolescent and young adult committee -- to develop a standard battery of PROs so that if we are looking at an AYA trial, we don't have to reinvent the wheel at every time point for that age group, which I would argue would probably be a great thing to facilitate getting more of our trials in COG to have these different PROs. But I would defer to Doug on his thoughts as well.

DR. HAWKINS: This is Doug. I guess I would have to say I don't know that we have enough experience yet to know what the right approach is. You alluded to the AYA committee trying to develop a standard battery that could be plug and play across multiple studies.

I think, in general, that would be helpful. It probably will shorten our timeline to making decisions and incorporating PRO into our studies. The only question will be, are there agent-specific

toxicities? Are we anticipating that the toxicity of agent X will always involve a specific toxicity and that we have to make sure that item is included? That may not be true. Maybe there's enough of a broad core group of items that would capture the experience, the differential toxicity experience, across multiple agents.

DR. HENDERSON: Funny you bring that up, Doug. We have been talking to the AYA committee and want to incorporate some of those standard measures. But my hope is actually that we work with experts in PROs in the immuno-oncology world, both adult and pediatrics, because in the adult world, there's been some measures to look specifically at toxicity associated with immuno-oncology approaches.

So we want to bring some of those measures to complement some of the standard battery ideas that we are going to use. So we're very cognizant to think about making sure that the patient-reported outcomes are also reflecting the therapy that we're using.

DR. SUNG: This is Lillian. I certainly agree with all of that, and the only other thing I would add is I've never thought about PROs as being specific to measuring disease or treatments. It really depends on the disease and the treatment.

The additional thing is that I think the ideal PROs will depend on what you're trying to measure. So if you're really looking for a screening type of instrument, that's very different than if you're focused on pain. If you're focused on pain, then you probably want to measure specific to pain, or fatigue, or whatever the outcome you're interested in.

So I guess I would just say I don't think there is one instrument that covers all PRO needs. It depends on your purpose for measuring it.

DR. REEVE: This is Bryce Reeve. I'm sorry. I'm not one of the speakers. But just to build on that, I've worked both on the PROMIS pediatric as well as the pediatric PRO-CTCAE, and I often get asked that particular question; when do I use one versus the other overall?

As Dr. Sung said there, it's really on the context of use and what you're trying to collect in terms of the patient experience. And particularly we're talking about use of the pediatric PRO-CTCAE, as Dr. Minasian said there, as a descriptive system to be able to look at either drug tolerability or drug toxicity, not just cross-sectioning it over time.

So we're talking about, within particular clinical trials, based on the drug being tested, the mechanism of action there, that there would be selection of a core set of symptom AEs that can be pulled out of the pediatric PRO-CTCAE library to be able to, again, document tolerability, toxicity, and things like that.

However, if the goal of a trial was to have a measure of benefit or efficacy and wanted to include as a primary or secondary outcome a specific, maybe, symptom; or even functioning, a symptom like fatigue, or a pain, or functioning like physical functioning, the PROMIS pediatric measures might be a better useful system because

it's not really a descriptive system. It actually gives you a very reliable valid assessment to look at specific changes over time and a very high reliable measure that will give you confidence, whether there is or isn't a particular drug benefit.

That to me is a key differentiation, where the PRO-CTCAE is for AE tolerability assessments, whereas something like PROMIS could be used as an outcome and in a measure in a study.

DR. PAPPO: We're going to move to the next question.

Greg?

(No response.)

DR. PAPPO: Greg, do you have your hand raised? I thought you did.

DR. REAMAN: Sorry. I did have my hand raised, and I also was muted, so I apologize.

This is Greg Reaman, and I just wanted to expand a bit on the responses to Dr. Janeway's question, which is quite insightful. But our primary reason for bringing this topic was really

to evaluate the potential of the pediatric PRO-CTCAE in assessing tolerability and really providing an opportunity for children to be heard, heard and listened to, in the context of the patient-focused development activities and initiatives at the FDA.

But in thinking about it, I was thinking that there were perhaps additional opportunities for implementing or including the PRO-CTCAE in pediatric cancer clinical trials. Given that as pediatric oncologists, we're always resource constrained, are there other things that we could glean, other pieces of information that we could glean, that would ultimately benefit, number one, the conduct of a clinical trial, the support of patients during a clinical trial, or even inform clinical trial strategies going forward?

That's kind of the reason for this discussion, so I apologize, Katie, if we kind of confused things. But this was just to have a broader discussion, thinking really out of the box here, are there opportunities for thinking about

CTCAE and patient self-reports, particularly from children, in a broader clinical investigation perspective. Thanks.

DR. PAPPO: Dr. Minasian, do you want to add a comment to Greg's comment?

DR. MINASIAN: Thank you. Yes. The speakers that have answered Dr. Janeway's question have done a terrific job. I wanted to add a couple of different pieces to this.

One, NCI, which sponsors and funds the NCTN and NCORP, we are actively exploring a way to simplify and incorporate electronic PRO collection across all of the funded NCI clinical trials networks. So that is one thing we are working towards. That's about all I can say at this time.

We've been hearing a lot about different infrastructure requirements. Clearly, when there is the opportunity to have that, we've seen excellent responses from patients and very high-quality data.

The second aspect I would say is the question about which PROs to capture at which point

in time. In a way, we do a comprehensive assessment of what biomarkers to collect and what specific context for use. PROs are no different. PRO-CTCAE was specifically designed for the collection of symptomatic adverse events and was really intended to be used alongside of CTCAE, whereas the PROMIS tool, which is also NIH developed, was intended to create a [indiscernible – audio feedback] -- with different other constructs.

I think we will begin to see, and have already seen, the collection of multiple different PRO tools for different purposes inside the clinical trials. So PRO-CTCAE, you might choose, as Doug Hawkins beautifully described, a selection of specific items to collect, but you might also want to include a health-related quality-of-life tool that collects information once every three months, even if you're collecting a shorter amount with the PRO-CTCAE maybe every week during the therapeutic intervention.

Your choice of PROs is going to be dependent

upon what your question is in the clinical trials and what specific information you want to collect and analyze. If you're concerned about short-term toxicities and long-term toxicities, that's how you design the PRO to be incorporated.

In addition, you can collect different PROs. It doesn't have to be just one tool. It can be multiple tools that in an electronic collection can facilitate so that the patient just sees those questions that they're supposed to respond to at that point in time. Thank you.

DR. PAPPO: Thank you very much.

Donna, would you like to ask a question?

MS. LUDWINSKI: Thank you. Donna Ludwinski, patient representative. I just had a quick question -- and I think Dr. Sung would be appropriate -- about the results of any PRO assessment.

Are those routinely returned to the parents, especially when it comes to interpreting some of the things that we talked about before, like Dr. MacDonald brought up hair loss and feeling sad;

or the fact that the dog died; or the girlfriend broke up?

How is the parent involved in the interpretation of these, and are they given the results of these assessments?

DR. SUNG: Thank you for the question. That's a great question. I can tell you the approach that we've taken, and that may not be the right approach, but it's the one we've taken.

What we have done is, if you're a patient and you're self-reporting your symptoms, that patient can have access to their own scores at any time. They can track them. They can print them. They can do whatever they want.

If you're a parent reporting on behalf of your child, you can see the scores that you report for your child. We have not let the parent see the child's scores or vice versa. Again, that may not be the correct decision. It's the one we took to start with.

The only thing I wanted to also mention is we haven't actually approached how we get the

results to the healthcare providers, but that's actually been an enormous challenge for us because of privacy regulation around, first of all, how do you get the data and where do you store the data in multiple countries.

We have solved that by having country-specific databases, so we have U.S. data in U.S. databases; Canadian data in Canadian databases. And we have solved the e-mail problem via e-mail relay and other approaches that allow e-mails to be sent from an institution to their providers from some website.

I'm sorry. That wasn't exactly your question, but I just wanted to highlight that that was a challenge if we are returning symptoms as well. So just to summarize, patients and parents don't get an e-mail of their own summaries, but they can log in and see them at any time. But they can only see the scores that they report on behalf of themselves or their child.

MS. LUDWINSKI: I see. Thank you very much. That really helps.

Do the parents consent to this, and then --

DR. SUNG: Exactly. The parent consents, and they can see any score that they've ever reported. Correct.

MS. LUDWINSKI: Thank you very much.

DR. SUNG: You're welcome.

DR. PAPPO: Would anybody like to add anything to what Lillian said, addressing Donna's question?

(No response.)

DR. PAPPO: We are scheduled for a very short break, about 10 minutes. The good thing is that we do not have an OPH session, so we will have plenty of time to continue with clarifying questions.

It's 2:00 right now. We will be back at 2:10. I know that I have Malcolm, Ira, and Tobey in the queue for questions. So as soon as we come back, I promise you that I will let you ask your question.

So see you back in 10 minutes.

(Whereupon, at 2:00 p.m., a brief recess was

taken.)

DR. PAPPO: Just a reminder that there is no open public hearing session today. I also want to remind you that we have six questions at the end, so that will take a little bit of time.

We have about 15 more minutes or so for questions. We will now take the remaining clarifying questions for all of the presenters. Please use the raised-hand icon to indicate that you have a question, and remember to put your hand down after you have asked your question.

Please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number if possible.

As a gentle reminder, it would be helpful to acknowledge the end of your question with a thank you and end your follow-up questions with, "That is all for my questions" so we can move on to the next panel member.

Following the order that we had earlier, the

next question comes from Malcolm Smith.

DR. SMITH: Thanks, Alberto.

This is Malcolm Smith, and my question is for Lillian Sung. I wonder if you can address whether there are plans for SSPedi to be utilized as a clinical tool and integrated with the medical record for kids. And if that's a part of it, is it a plan for a research tool to a clinical tool?

DR. PAPPO: Lillian, are you on?

(No response.)

DR. PAPPO: Let's give Dr. Sung a couple of minutes.

(Pause.)

DR. PAPPO: Lillian, were you able to hear Malcolm's question?

(No response.)

DR. PAPPO: It appears that Dr. Sung is not on, so we're going to wait for her to log back in.

The next question comes from Dr. Laetsch.

DR. LAETSCH: Thank you, Alberto.

I'm Ted Laetsch. I want to congratulate all the speakers for great presentations, and I think

we've seen some really interesting applications of PROs in randomized trials. My comment and question was that I think a majority of drugs that have been approved for pediatric oncology recently have been approved in non-randomized studies.

Do the speakers have thoughts about how best to analyze PRO data from those studies where there's not a comparison and where there may not have historical data on the same patient population?

DR. BHATNAGAR: Hi, this is Vishal Bhatnagar from FDA. I can start the conversation about non-randomized trials, and take it even one step further in regards to potentially thinking about open-label trials, in general; not just single-arm trials but open-label trials as a whole, whether they're randomized or not.

When it comes to the patient experience as far as tolerability, we think that taking a look at the patient experience in single-arm trials is very valuable. We're really just trying to get a sense for symptoms and side effects. Then, when it comes

to looking at things outside of symptoms, for example, physical functioning, we really do take into consideration patients' baseline as a internal comparator.

DR. PAPPO: Hello?

DR. LAETSCH: Yes?

DR. PAPPO: Does that answer your question, Ted, or anyone else want to tackle Ted's question?

DR. LAETSCH: That answers my question unless someone else wants to comment. Thank you.

DR. PAPPO: The next question is from Elizabeth Raetz.

DR. RAETZ: I'd like to thank all the speakers for really fantastic talks. This is an area that is newer to me, so again, please forgive me if this is a naïve question, but it could be to any of the panelists.

In thinking about the information and dose modification guidelines, if this information is available in real time, and clinician-assessed CTCAE toxicities, if there is discordance, is there a thought about how the patient experience and

reported symptoms might influence dose modification guidelines or how that's handled, if that information is also available in real time?

DR. MINASIAN: This is Lori Minasian. I'm happy to answer or at least take an initial stab at the question. I think part of this is because of the way of the grading. In our clinical trials, we clearly identify grade 2 or 3 as leading to specific dose modifications, dose interruptions. It is designed specifically for patient safety. It's done in real time.

Historically, our PROs have not been done in real time, and we're trying to change that because of the dramatic data that's been demonstrated over the past few years that show that if you respond in real time, you will in fact have better patient outcomes, better survival, and better control of symptoms.

I want to go back to the example that Bryce Reeve gave when he talked about the cognitive interviewing of a young 9 year old who answered a question that he felt was relatively

straightforward about hurting himself, and he said that he was hitting his head to concentrate. When the clinician and the caregiver probed the patient further, they got additional information that changed their whole approach to his therapy.

So part of this whole construct right now is to generate the data so that we can better understand how to intervene sooner, yet still allow us the opportunity to give our patients the appropriate treatment over time.

I don't think we're ready right now at this point in time to say that patients' scoring of their symptomatic adverse events, right now, should automatically lead to a protocol-defined change in therapy. However, what it should lead to in real time is for the discussion with the clinicians, so that the clinicians can in fact make the appropriate decision. Maybe it is just a grade 1. Maybe it is a grade 2. Maybe there does need to be an intervention, but it still resides with the clinicians.

So at this point in time, we're still

exploring. We need to capture all the data to better understand what and how we can do it. We're not ready to take that step right now, but we think over the next few years, as we get more information, we'll be able to better take care of our patients, as well as be able to better define the algorithms and the paradigms for how we would change things over time. Thank you.

DR. HINDS: Dr. Pappo, this is Pam Hinds. May I please add?

DR. PAPPO: Yes, please.

DR. HINDS: Thank you so much. And I apologize to all of you. I've been on mute. It's a challenge to be unmuted.

I'm going to go back just a few questions and come forward to share with you that in timing children in completing the core item of the pediatric PRO-CTCAE, it's less than 10 minutes.

What I would respond to in terms of the single-arm designs, we've done many of these, typically phase 1/phase 2's. And they always have multiple data points, typically six, and

purposefully selected data points for where we anticipate having more or less of an AE that we are concerned about, or the cumulative effect that we can compare back to baseline; so carefully selected data points with real purpose and definition.

I think a lot of what we're talking about is what I call precision-supportive care. That high-risk group, we call them the high-suffering group; so the ability then to identify that group and to implement a change in supportive care from what we might consider to be the standard -- which tends to be described in each clinical trial protocol -- to a higher level of supportive care that is tailored to the particular AE or, in general, AEs if it is the cumulative effect of the AEs.

From a totally different set of PROs, where we find we are the least concerned about disrupting care is getting the PROs answered within 24 hours before the actual clinical appointment. Thank you very much.

DR. PAPPO: Thank you very much, Pam.

If that clarifies your question, Ted, we're going to move to Tobey MacDonald. He has a question.

DR. MACDONALD: Hi. Tobey MacDonald, Emory University. Pam actually may have partly answered this question. It might be naïve, and I may have, quite frankly, missed it.

For those who implement the PRO tool, you mentioned that 24 hours before the clinic visit. I wonder, is this across the board. The unified type of assessment tool, or much like a roadmap, everyone across sites is giving the assessment at the same point in time. Is it done always at the comfort of your own home? Do people do it in the clinic, waiting room, in the presence or absence of the parent, before bad news or a scan, et cetera?

Obviously, all these things could potentially influence this objective response. I don't know if you have data to show whether there is an impact between patients, and maybe the same patients serially, and whether this is administered in the same exact fashion or not. That's my

question.

DR. HINDS: Tobey, this is Pam Hinds, and I really value that question. What I can share with you, with single-arm, phase 1/phase 2 studies, trials, we have purposefully given the PRO tool before any information was given about status of response or disease condition. That's the one standardization with our measurement approach that we have used, so no information about disease status and treatment response would be in hand when we gave the PROs. That's the only condition we've actually put on.

DR. PAPPO: Does that answer your question, Tobey?

DR. MACDONALD: Yes, thank you for that part. Again, but I don't know -- are these always in the same location and also in the presence or absence of the parent? I know you said the parents don't have access to the answers, but if the parent's there, I often feel a lot of times when I'm asking children about their symptoms, sometimes they look at the parent before they give any

answer. So I'm wondering, is this in isolation or not?

DR. HINDS: Tobey, this is Pam Hinds, and I apologize for not having addressed that. We have looked at the possibility of method confound, not with pediatric PRO-CTCAE, but with the PROMIS pediatric measures. That has to do with doing it by phone or doing it electronically with the children, and sending the link directly to the child or making a phone call directly to the child with, of course, parent agreement.

We did not find score changes or differences between the two methods with the PROMIS pediatric measures, and those measures most typically were depressive symptoms, anxiety, pain, fatigue, and mobility; so no difference in that particular example.

There are children who will ask to have the items read, and they point to the answer when the parent is in the room. We always give them that option if they are actually already present for an appointment, and they indicate that they would like

privacy with their responses.

Typically, with a 5 to 7 year old, I will say with a PRO, "Would you like me to be your secretary? I can read to you, and you can give me your answers, and you can point or you can say them out loud." And they smile, giggle usually, like having a secretary, and then give me their answers.

It is true, and according to five of our research studies -- not clinical trials -- that children who are newly diagnosed between the ages of 5 and 6, at the time of diagnosis and within the first 30 to 40 days, will look to the parent at least 35 percent of the time according to our field notes. But as soon as they reach three months or more with their experience with treatment and PROs, they are much more likely, greater than 70 percent according to our field notes, to be able to answer for themselves, by themselves.

DR. MACDONALD: Thank you, Pam. That's very interesting.

Questions to the Subcommittee and Discussion

DR. PAPPO: Thank you.

I think we're going to move on because we have six questions. I want to thank all the presenters for their outstanding presentations, and our panel for a very lively discussion.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will proceed with the questions to the committee and panel discussions. I would like to remind the public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

We will now start with the questions. I don't know if you're going to show the questions or you just want me to read them.

Are we going to show them or I just read them? I'm just going to read them.

Okay. The first question is, consider how patient self-report by children of symptoms attributable to a drug in a clinical trial might inform patients, parents, and providers about its

tolerability and decisions regarding its use.

If there are no questions or comments concerning the wording of the question, we will now open the question for discussion.

(No response.)

DR. PAPPO: I think I will start by saying, and thus will summarize what Pam Hinds said, that I think the PROs basically give you an overall idea of the full impact of therapy. It complements our toxicity grading. It complements what the parents say. It gives you just the full impact of what the therapy burden is for these children.

So that's my two cents, but I'm happy to hear any additional discussions or points on this question.

Dr. Angiolillo?

(No response.)

DR. PAPPO: Dr. Angiolillo, do you want to comment on that question?

DR. ANGIOLILLO: Hello? Can you hear me now?

DR. PAPPO: Yes, we can.

DR. ANGIOLILLO: Thank you.

The presentations were excellent. I was probably having computer difficulties earlier. I had a question, but I can fold it into this question.

My concern is this, the diversity of the data. How is one assured that we're hitting all patient populations, i.e., socioeconomic, intellectual, privileged? Some children have learning disabilities, i.e., how do I know it's just not the privileged white person who has access to Zofran and Kytril? Basically, their reports of nausea are going to be very different than ones that are challenged. That's my question.

DR. PAPPO: Okay.

Julia?

DR. GLADE BENDER: Julia Glade Bender. Considering this self-report in a clinical trial, I think this gets at what Dr. Janeway was saying before, and hearing about upfront trials versus phase 1 trials. I think it's very context-specific. I can imagine in an upfront

trial, again, real-time reporting might help with trial compliance if we could treat child symptoms during the trial and potentially effect better outcomes for everybody.

What I'm having more difficulty with is, in a phase 1 study, we talk about the dose that we choose as a maximum tolerated dose, but if we're deciding that, based on toxicity from the observer doctor, if I'm understanding things correctly, we're actually determining the maximum safe dose as opposed to the maximum tolerated dose, as we think that tolerated is a subjective finding.

I think, in many ways, it will inform dose modification, but I hope it doesn't actually inform dose in phase 1 because tolerability may be different individually. So I'm hoping that it does inform how we use drugs, but maybe not determining a maximum tolerated dose that everybody will receive.

DR. PAPPO: Are you referring to that as to how we approach the side effects of the drug and how we intervene with that, based on the PRO-CTCAE

that we could act earlier to address those specific symptoms?

DR. GLADE BENDER: That's exactly what I mean. If it was available in real time, it would help with trial compliance, helping kids to stay on study and receive potentially a drug in an easier way for them, and maximize supportive care. But if it's being used to determine whether the drug is tolerable or not in an early-phase setting, that I'm more worried about because that may have more to do with supportive care than it does to do with the actual dose of the drug.

DR. PAPPO: Thank you very much for the clarification, Julia.

Steve?

DR. DUBOIS: Steve DuBois, Dana-Farber. I guess I'm thinking of this question, really, from the provider perspective. As I'm thinking about options I'm offering to my own patients, I think this type of information could be incredibly valuable.

Particularly, I take care of a lot of

patients with multiply relapsed cancer, and a lot of the interventions we might be thinking about may have only a modest impact on event-free survival or have a relatively modest response rate. But if I had data that patients on the drug maybe felt better than patients who weren't on the drug, even if progression-free survival wasn't much improved, if patients are feeling better, that I think would be helpful.

Likewise, if an agent has only a modest oncologic improvement in outcomes, something like EFS, PFS, or response rate, but makes patients feel terribly, that likewise is incredibly important data for prescribers to have, and maybe for the FDA to have when they're reviewing an application for an agent that maybe has a modest EFS improvement or a modest response rate improvement. If patients feel pretty badly on it, is that really worth it?

DR. PAPPO: So is it fair to say that PROs could potentially help you better evaluate quality of life in patients that are receiving experimental therapies, and guide you a little bit more as to

whether there's really a true impact of this drug on the patient and not necessarily related to progression-free survival or overall survival?

DR. DUBOIS: Correct.

DR. PAPPO: Thank you for the clarification.

Ira Dunkel?

DR. DUNKEL: Thank you, Alberto. I think my points have been made by others, but just very quickly, I think the presentations have been very compelling, that the PROs are valuable in a randomized clinical trial, in survivorship, and in clinical care.

I'm still a little less certain about a single-arm early phase study, how much additional benefit the PRO provides for clinical study data, given what I felt was a pretty important point that Tobey made earlier about the lack of attribution and the possible contributions of the underlying disease process and concomitant medications. Thank you. I'll stop there.

DR. PAPPO: Thank you, Ira.

Greg?

DR. REAMAN: This is Greg Reaman, and I just wanted to clarify that real-time assessments are probably not an anticipated context of use for the pediatric PRO-CTCAE. So as far as real-time dose modifications or protocol modifications based on patients' self-report, I don't envision that happening.

That's not what we would envision Project Patient Voice to be either, but this is really an opportunity to better inform patients, families, and prescribers, as Steve mentioned, about the tolerability; not necessarily toxicity, but the tolerability of specific products that might be used in the pediatric population.

I will point out also that I think there may actually be a use for these kind of data in the single-arm trial setting, maybe not in the phase 1 setting because it might be difficult to really isolate the adverse event related to a specific product, given a patient's condition.

Nevertheless, we really want to see what the tolerability of these agents are, unaccompanied by

other agents or modalities that might be used in combinatorial approaches as we generally use in pediatric oncology.

But to address Julia's concern, we don't see a role for these being used in real-time decision making.

DR. PAPPO: Thank you for that clarification, Greg.

I'm going to allow one more comment for this question, and that's Tobey MacDonald.

DR. MACDONALD: Thank you. Just going back also to the importance I think of the attribution of the symptoms, and particularly in this question 1, about drugs in a clinical trial, I think that makes a big difference whether you're giving drug outside a trial or in a trial. You can imagine a phase 1 trial from a psychosocial standpoint will score lower, I assume, in a phase 2 and likewise in an upfront phase 3 trial.

Certainly, when you think of PKs being conducted maybe over two days, there may also be a psychosocial component there when the PKs are done,

if they look like, oh, someone would be doing better as they stayed on the drug in their reporting. So I think it is a critical element of teasing apart whether the symptoms that are being reported are particularly for this drug, it's thought, or is being on this trial, which is, I think, a clear distinction.

DR. PAPPO: Thank you very much.

If I could briefly just summarize our discussion, I think one of the issues was whether we're going to be hitting the right patient population versus diversity of data, multiple socioeconomic status, race, et cetera, access to care, and whether the PROs are actually addressing all of the different patient populations.

The second issue is that the PROs are perhaps most important to determine whether you're actually affecting quality of life. You may have a marginal effect on event-free survival and overall survival, but you're actually impacting quality of life, and that may be a good measure to move forward for that specific agent.

There was some controversy as to whether PROs will be of importance or help in single-arm studies. There was a little bit of divided opinion, but apparently they could potentially help single-arm phase studies.

Finally, another important issue will be the attribution of toxicity, whether the drugs and PROs, in this patient population.

Did I summarize that okay or does anybody have any additions to what I just said?

(No response.)

DR. PAPPO: If not, we're going to move to the second point for discussion.

Since only children greater than 7 years of age are able to reliably self-report symptoms, discuss the role for supplementing experiences of younger children using caregiver reports of observable symptoms; for example, frequency, severity, and interference.

(No response.)

DR. PAPPO: I think I'm getting someone that's going to give us -- okay; no one at the

moment?

Julia?

DR. GLADE BENDER: I think with the context that this is not real-time but data to be looked at retrospectively and meant to be descriptive, I think the implication is that all data is good data, and that it would be helpful to at least give the younger child a voice by including caregiver reports of observable symptoms.

DR. PAPPO: I agree. Thank you very much.

Donna?

MS. LUDWINSKI: Thank you. Donna Ludwinski. Similar to what Dr. Glade Bender just said, it seems to me that this is just capturing data that the parents would be reporting anyway, on a continuous basis with the child's oncologist.

I guess I always thought that sort of data was collected in some fashion of another; in the records, surely. But it seems to me it wouldn't really change anything because that's how parents communicate with the oncologist.

DR. PAPPO: But you agree that reporting the

experiences from the caregiving experience would be an important measure to complement the data that we get from PROs, from patients?

MS. LUDWINSKI: Yes.

DR. PAPPO: Okay. I've been asked to remind you to please say your name for the record.

Elizabeth, you are next.

DR. RAETZ: Hi. Elizabeth Raetz from NYU. I agree that it would be helpful; anything to supplement the amount of information that you have and, really, it seems like the only option that would be practical for children less than 7 years of age.

The only thing that I was a little bit struck by in the presentations was the lack of concordance between what patients and their caregivers reported. That might presumably be less in a younger age range, but that would be one caveat that I was a little bit surprised by and might have some implications.

DR. PAPPO: Thank you very much.

To summarize this discussion, everybody

agrees that all data is good data and that it would be important to have caregiver reports of observable symptoms to supplement the data that is provided with the PROs.

There's a concern about the potential concordance between the PRO, the patient, and the caregiver, but that was talked about a little bit in the presentation of Dr. Pam Hinds. But that's just a fact. I don't think there's anything that we can do about that.

Did I summarize this discussion for the second question correctly or does anybody have anything to add?

(No response.)

DR. PAPPO: It looks like we're ready for discussion question number 3. Consider the logistical and operational challenges to collecting and analysis of data from patient self-reported symptoms.

That is a point that I had raised a little bit earlier; if this would require a significant amount of infrastructure and how is this data going

to be collated. Even if it's reported by the patients or by the caregiver, how is this data going to be incorporated into the clinical trial database, and would this require a significant amount of resources or not? And I don't think we had an answer from our presenters.

Does anybody want to add or expand on this?

Donna, I think you're next.

MS. LUDWINSKI: I am so sorry. I forgot to put my hand down from the last question. Sorry.

DR. PAPPO: Steve?

DR. DUBOIS: Steve DuBois, Dana-Farber. This question sort of gets at a question I had asked earlier, where you're collecting data on the same adverse event, but from, in one case, the clinician's perspective, and from the other, the patient's perspective.

I think there's the real potential for some operational challenges, trying to sort out, well, what is the source of truth? If you've got discrepant data coming from two different ways of capturing the same adverse event, there's some site

operational challenges of what will I enter into the case report form. But also, I imagine for the FDA reviewing a potential regulatory filing, trying to sort out, well, what is the truth?

So I think that there are still some challenges here to be worked out in terms of what ends up getting reported, what ends up getting reviewed and, quite frankly, what ends up in the label.

DR. PAPPO: Thank you.

Malcolm?

DR. MACDONALD: Malcolm Smith. I think Lori Minasian mentioned some electronic tools for reporting. Having tools that would facilitate data collection would certainly be useful, and incorporating them into the research record, there will be additional resources needed for analysis and collection of the data at the specific centers. So those things will happen and will be needed.

One thing that we talk about sometimes is whether we can use a subset of patients rather than all the patients on the clinical trial and

concentrate resources that is a subset of institutions, or a subset of patients, to make the collection of the data more feasible.

If we're doing an ALL trial with 2,000 patients, maybe we don't need the PRO-CTCAE data on all patients, but maybe 10 percent, 20 percent of those patients would be adequate to understand the intervention and its effects by the PRO-CTCAE tool. Thank you.

DR. PAPPO: Thank you very much, Malcolm.

Katie?

DR. JANEWAY: Yes. Dr. Janeway from Dana-Farber, Boston Children's. My comment is about the burden to the patient and the parents. I know that 10 minutes was discussed, but all of us on the phone who see patients in clinic and enroll patients on trials, you're already asking for about 10 minutes, then you're adding another 10 minutes.

So I think that should be considered, and particularly thinking about are all of the time points needed; for example, what is your objective; do you need to follow the patient out for a long

period of time after completion of the trial; those sorts of questions.

Then a related comment to this is whether any work has been done on ascertainment bias, meaning do you lose the patients who are doing well, and do you then perhaps overcount for outcomes? I guess the opposite could occur, too, although I think it's more likely that you lose the patients who are doing well. They have things to do, places to go, and aren't spending another 10 more minutes in clinic getting a transfusion anyways, so why not answer the form?

DR. PAPPO: Thank you very much.

Ira?

DR. DUNKEL: Ira Dunkel, Memorial Sloan Kettering. I think two brief points. One is that I can imagine there being enormous numbers of protocol violations occurring when patients don't occasionally do the reporting at the time frame, which could have downstream consequences with lots of need for IRB reporting of this. So I would hope that, if it's implemented, somehow we could avoid

that potential problem.

Then piggybacking on what Katie just said about patient or family burden, it seems to me that this probably should be, in most cases, an optional part of the study the family would consent to, so that those who felt that this was a burden were not mandated for doing the 10 minutes a week, or 10 minutes a month, or whatever it was. Thank you.

DR. PAPPO: Thank you, Ira.

Steve?

DR. DUBOIS: Sorry. I'll lower my hand. Sorry.

DR. PAPPO: Sorry.

Malcolm?

(No response.)

DR. PAPPO: Malcolm, do you have any additional questions or just lowering your hand?

DR. SMITH: No. I'm sorry. I'll lower my hand as well.

DR. PAPPO: Thank you very much.

If I could briefly summarize this, collecting this data may have some operational

challenges. There are several electronic tools that could facilitate the collection for these specific objectives, and we will definitely need infrastructure to do this. For very large trials, we may select to have just a small sample population, 10 or 20 percent of the large population, in very, very large studies.

There's also an issue of what is considered, quote/unquote, "the truth?" When you have three different sources of data, how do you do this, or how do you use this data for regulatory purposes if you have discrepant reporting on a variety of different toxicities?

Also, another issue would be the burden to the patient and the parent additionally filling out all of these reports and the impact that it may have on the patients, and the potential for ascertainment bias. The other comment that was brought up more recently was whether this PRO should be as an optional portion of the protocol for the families, whether they want to actually participate or not in this portion of the protocol.

Did I summarize pretty much everything ok or does anybody have any additions that I didn't specifically address?

(No response.)

DR. PAPPO: If there's no further discussion of this question, we will continue to question number 4. Consider how best the constellation of self-reported symptoms in children and adolescents should be selected to be used in extending FDA's Project Patient Voice to children.

I think I have Katie.

DR. JANEWAY: Yes. Dr. Janeway, Dana-Farber, Boston Children's. I think if you're going to do all of this work and collect all this data, making it accessible in that manner, it's great. It's a very nice way, a different and complementary way, to look at burden of treatment or side effects.

DR. PAPPO: I completely agree with you.

I believe that Dr. Bhatnagar also wants to say something.

DR. BHATNAGAR: I don't. I lowered my hand.

I think that was in reference to the last question. But I will take this opportunity to thank the panelists and the committee for their words in regards to the purpose of today and also Project Patient Voice specifically.

I just will also take this opportunity to add another layer of information to this specific discussion question.

Currently, the index study for Project Patient Voice has a listing of 28 symptoms, and that's quite a lot. We fully recognize that ascertainment of 28 symptoms in a trial may be a lot. So I guess one added dimension for this question is, what's the appropriate number of symptoms that should be assessed in a sort of run-of-the-mill trial? Thanks.

DR. PAPPO: Thank you very much.

I don't see any other discussions. I think everybody agrees with Dr. Katie, who brought this up. I think that incorporating this into Project Patient Voice would be worthwhile, expanding the access of this information.

So if there are no additional issues with this question, we will now move on to question number 5.

Consider whether data obtained in real time from children's self-report of symptomatic adverse events could possibly impact the conduct of a clinical trial or inform an individual study participant's clinical management. Consider specific assessment and reporting requirements to be included in the protocol.

If there are no questions or comments concerning the wording of this question, we will now open this question for discussion.

I thought that Greg had said that we would not plan to use this in real time, but I will let either Greg, Julia, or somebody else comment on this.

DR. REAMAN: Alberto, I can just speak to this -- this is Greg Reaman -- to not cause any confusion. We were just trying to make the point that, given the fact that we wouldn't expect this information to alter the course of a study, or to

impact or result in a dose modification or change in dosage, that that had to specifically be stated in the protocol. So that's all that's really meant by this question.

DR. PAPPO: Thank you for the clarification.

Any comments on that question? Katie?

DR. JANEWAY: My apologies. I forgot to lower my hand.

DR. PAPPO: I'm sorry.

Does anybody else want to raise their hand?

(No response.)

DR. PAPPO: I guess you all are tired.

Okay. We have one more question, question number 6.

We will now proceed to the next question, which is the last question, question number 6. Consider how pediatric PRO-CTCAE might contribute to planning and implementation of supportive care and survivorship research strategies in children.

Malcolm?

(No response.)

DR. PAPPO: I have Malcolm and then Julia.

Malcolm, would you like to comment?

DR. SMITH: I'm sorry. I didn't lower my hand again.

DR. PAPPO: Julia?

DR. GLADE BENDER: I think the points made here today are that maybe this is the most powerful use of the PRO-CTCAE now. If we collect the data prospectively, we will learn to ask questions better and provide better supportive care around certain regimens and trials, and looking forward to survivorship.

As we said before, the difference is going to be measuring and weighing acute side effects versus long-term effects, but we'll need the data to be able to address those questions. I think it will contribute very positively to the planning of supportive care and survivorship research in the future.

DR. PAPPO: Thank you, Julia.

Tobey?

DR. MACDONALD: Thanks. Tobey MacDonald, Emory University. I think from a neuro-

oncologist's perspective -- and this probably overlaps with question 5 as well; I just couldn't raise my hand quick enough for that -- I believe that both psychological and cognitive impacts of our treatment are grossly underestimated, and that this tool could be very important for uncovering some of those questions that we never get to ask our patients. This would be both in the acute setting and of course in the long-term setting of what the impact is on those two very critical elements.

As a wise colleague said to me, without mental health, there is no health. We're very good at picking up diarrhea, vomiting, and all of that, but I think that could be a very important part of this endeavor.

DR. PAPPO: Thank you, Tobey.

Donna?

MS. LUDWINSKI: Donna Ludwinski. Thinking about the survivorship research, and specifically Dr. Henderson's LEaHRN study, it made me curious if the 359 were truly representative of the 900 that

were actually eligible; so this survivorship research, using this strategy, making sure it's representative of the whole group, like Dr. Janeway said about those who are doing well might not really want to be bothered. So how do we interpret the results, then, in that long-term research setting?

DR. PAPPO: Thank you.

Katie?

DR. JANEWAY: This is Dr. Janeway from Dana-Farber. I just wanted to respond to the comment before this one, which is, I don't disagree that learning and mental health issues are a major issue in our patient population, both patients, and treatment, and in survivors.

I guess it makes me nervous to enhance ascertainment and then act on them in real time, given limited resources in that particular arena, both in our own clinics and then also even referring to local providers, given insurance reimbursement for mental health care and all of that; just a note of caution, not that we shouldn't

find out. It just can be hard to act on in a way that you might ideally like to.

DR. PAPPO: Tobey, I don't know if your hand's still up because you want to answer or you just forgot to put it down.

DR. MACDONALD: It's actually both, and I agree with you, Katie. What I meant was, as a screening tool, I think there are red flags we miss. There are those who are really in danger. I'm not talking about subtle impairments of psychological health. There are some that are in the red zone, that I think it would be very important for us to be alerted.

We have other mechanisms to do that, but the more screening we have, the better off we will serve our patients, in my opinion, and getting them the support that they need.

DR. PAPPO: If I can summarize the brief discussion on question number 6, I think that we all agree that the PRO-CTCAE may contribute to help planning and implementing supportive care guidelines and survivorship research strategies for

these children. But this tool may help uncover some elements that have not been correctly assessed in the past, although there's a role of ascertainment for these specific areas.

I think that's all I have.

Do you have anything else I need to say or did I miss anything?

(No response.)

DR. PAPPO: Alright.

We are getting to the end of this. We will now proceed with the FDA wrap-up comments from Dr. Elizabeth Duke, followed by FDA closing remarks from Dr. Greg Reaman.

Wrap-Up – Elizabeth Duke

DR. DUKE: Thank you, Dr. Pappo. This is Elizabeth Duke from FDA. I really just want to thank all of the speakers today. We really heard several excellent talks and appreciate the robust discussion.

Just as a recap this morning, building on the current experience with PROs in pediatric oncology clinical trials, and then the use of the

PRO-CTCAE in adult trials, we heard about the rationale on development of the pediatric PRO-CTCAE.

Then this afternoon, we heard about the potential uses of PRO data in identifying symptoms acutely and in the long term, and the incorporation of some items in two COG studies, both of early and advanced stage Hodgkin's lymphoma, as well as a few other ongoing studies.

As Dr. Pappo summarized, there were several important topics that were raised during discussion. We talked about optimizing item selection, identifying agent-specific toxicities, and capturing the importance as well as attribution of a given symptom; and then understanding differences and experiences between younger and older children and how to best measure that; capturing any undue burden on patients or providers, and the potential for differences in capturing data in heterogeneous populations; thinking about the use of the data in conjunction with the standard CTCAE; timing of PRO measurements

and how they can be used in the interactions between patients and their providers.

In terms of next steps, it sounds like the pediatric PRO-CTCAE is already in the early stages of being used currently in clinical trials to help capture tolerability, as the data is complementary to phase 2 reporting. Based on the discussion, it does sound like there would be utility for moving it forward in a variety of settings, thinking about embedding in trials with an eye towards both acute symptoms and survivorship outcomes, and then also how do we utilize technology to our advantage and operationalize these measures.

So again, thank you so much. For closing remarks, I'll turn it over to Dr. Reaman.

Closing Remarks – Gregory Reaman

DR. REAMAN: This is Greg Reaman. I'd also like to commend all of you as advisors for the robust discussion, and I'd like to thank all of the presenters for what I thought was really terrific quality of the presentations. Again, I commend the investigators that have been responsible for the

adaptation of the PRO-CTCAE for children. I guess I shouldn't call it adaptation because it really was a redesign and reconstruction that has gone on over a number of years.

I'm pleased that there does seem to be agreements for the potential of expanding tolerability information for children through Project Patient Voice, and I feel very strongly that children, families, and prescribers, that actually provide care for those children and families, really have the right to access as much information as possible that is going to inform their treatment decisions.

I think there are a number of logistical issues to think out. I'm pleased to hear that there is activity at the NCI about actually somehow making a collection of patient-reported outcome data as it relates to adverse events with the clinician-entered routine AE reporting, and somehow make that a little bit easier and streamlined going forward.

I was very pleased to hear that there are

already examples of implementation, and particularly in the area of symptoms related to immuno-oncology agents, despite the fact that there's limited utility to date. There are some diseases for which there is significant promise, and the significant promise is, really, I think related to the fact that known long-term toxicities associated with radiation therapy might be mitigated by the use of some of these drugs. So knowing what they do in the long term is clearly important as well.

I think we have a lot of thinking to do about retrospectively collecting this data from patient self-reports, and I think there really are opportunities for prospectively using those data to inform supportive care and survivorship research strategies, and actually to facilitate survivorship research.

So again, I'd like to thank you very much for a productive session and discussions. Thanks.

Adjournment

DR. PAPPO: Thank you very much, Greg. And

again, I want to thank all the members of the public and the FDA staff, the speakers, the guest speakers, and the panel members for attending this phenomenal meeting.

Tomorrow, we're going to meet at noon, and I believe we're going to be talking about real-world data to generate appropriate real-world evidence for various pediatric cancer drug development efforts. So I will see you all tomorrow, and we will now adjourn the meeting, and thank you very much.

(Whereupon, at 3:07 p.m., the meeting was adjourned.)