Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Meeting
May 11-12, 2021

Location: Please note that due to the impact of the COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: On May 11, 2021, the subcommittee discussed 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 also focused on approaches to investigators and commercial sponsors to use the Pediatric PRO-CTCAE in toxicity assessment moving forward.

On May 12, 2021, the subcommittee discussed real-world evidence (RWE) for regulatory use in pediatrics, real-world data (RWD) resources, and RWD and RWE to advance pediatric safety assessments of oncology drug products in children within the context of the FDA framework for RWE. Potential data sources and publicly available platforms, including those made possible through the development and implementation of the National Cancer Institute's Childhood Cancer Data Initiative, were discussed. The potential for use of data sources to construct external controls to evaluate effectiveness of investigational products was considered given the frequent dependence on single-arm studies due to extremely small study populations, now exaggerated by molecularly defined subtypes of the rare cancer types that occur in children.

These summary minutes for the May 11-12, 2021 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) of the Food and Drug Administration were approved on June 30, 2021.

I certify that I attended the May 11-12, 2021 meeting of the pedsODAC of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/	**/S/**
She-Chia Chen, PharmD	Alberto S. Pappo, MD
Designated Federal Officer, ODAC	Chairperson, pedsODAC

Final Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Meeting
May 11-12, 2021

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on May 11-12, 2021. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary members were provided the briefing materials from the FDA. The meeting was called to order by Alberto S. Pappo, MD (Chairperson). The conflict of interest statement was read into the record by She-Chia Chen, PharmD (Designated Federal Officer). There were approximately 260 people online on May 11th and approximately 250 people online on May 12th. There was no Open Public Hearing (OPH) speaker presentation on May 11th and one OPH speaker presentation on May 12th.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: On May 11, 2021, the subcommittee discussed 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 also addressed the challenges of capturing this type of data across the age spectrum of the pediatric population and possible generalizability of the data. It considered approaches to address concerns about excluding the patient voice of young children deemed incapable of self-reporting. The subcommittee also focused on approaches to investigators and commercial sponsors to use the Pediatric PRO-CTCAE in toxicity assessment moving forward.

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Attendance:
ODAC Members Present: David E. Mitchell (Consumer Representative, participation in Day 1 Only); Alberto S. Pappo, MD (pedsODAC Chairperson)

ODAC Members Not Present: Jaffer A. Ajani, MD; Ranjana H. Advani, MD; Massimo Cristofanilli, MD, FACP; Jorge A. Garcia, MD, FACP; Susan Halabi, PhD; Philip C. Hoffman, MD; Christopher H. Lieu, MD; Anthony D. Sung, MD

ODAC Member Present (Non-Voting): Jonathan D. Cheng, MD (Industry Representative)

Temporary Members: Anne L. Angiolillo, MD; Steven G. DuBois, MD; Ira J. Dunkel, MD; Julia Glade Bender, MD; Richard Gorlick, MD (Participation in Day 1 Only); Katherine A. Janeway, MD, MMSc; Theodore W. Laetsch, MD; Donna Ludwinski, BSChE (Patient Representative); Tobey J. MacDonald, MD; D. Williams (Will) Parsons, MD, PhD; Courtney J. Preusse (Acting Consumer Representative, Participation in Day 2 Only); Elizabeth Raetz, MD (Participation in Day 1 Only); Nita Seibel, MD (Participation in Day 2 Only); Malcolm A. Smith, MD, PhD (Participation in Day 1 Only)

FDA Participants (Non-Voting): Gregory H. Reaman, MD; Vishal Bhatnagar, MD (Participation in Day 1 Only); Jacqueline Corrigan-Curay, JD, MD (Participation in Day 2 Only); Martha Donoghue, MD; Elizabeth S. Duke, MD (Participation in Day 1 Only); Lori Ehrlich, MD, PhD (Participation in Day 2 Only); Ann W. McMahon, MD, MS, FISPE (Participation in Day 2 Only); Pallavi Mishra-Kalyani, PhD (Participation in Day 2 Only); Meena N. Murugappan, PharmD, MPH (Participation in Day 1 Only); Donna Rivera, PharmD, MSc (Participation in Day 2 Only)

Designated Federal Officer (Non-Voting): She-Chia Chen, PharmD

Open Public Hearing Speakers: Day 1: None; Day 2: Diana Zuckerman, PhD (National Center for Health Research)

The agenda was as follows:

Day 1: May 11, 2021

Call to Order	**Alberto S. Pappo, MD** Chairperson, pedsODAC
Introduction of Subcommittee and Conflict of Interest Statement	**She-Chia Chen, PharmD** Designated Federal Officer, ODAC
Introductory Remarks	**Gregory Reaman, MD** Associate Director Pediatric Oncology Oncology Center of Excellence (OCE) Office of the Commissioner (OC) Associate Director Pediatric Oncology Office of Oncologic Diseases (OOD) Office of New Drugs (OND), CDER, FDA

FDA PRESENTATIONS

FDA Perspective: Patient Self-Reporting in the Evaluation of Cancer Drug Tolerability	**Elizabeth S. Duke, MD** Medical Officer Division of Oncology 2 OOD, OND, CDER, FDA
Patient-Reported Outcomes (PROs) in Pediatric Cancer Registration Trials – An FDA Perspective	**Meena N. Murugappan, PharmD, MPH** Research Fellow OCE, OC, FDA

Clarifying Questions

SPEAKER PRESENTATION

Patient Self-Reporting and Cancer Drug Tolerability: Lessons Learned from the Adult Experience with PRO-CTCAE	**Lori Minasian, MD** Deputy Director Division of Cancer Prevention National Cancer Institute (NCI) National Institutes of Health

FDA PRESENTATION

FDA's Project Patient Voice: Let the Children be Heard	**Vishal Bhatnagar, MD** Associate Director for Patient Outcomes OCE, OC, FDA

GUEST SPEAKER PRESENTATIONS

Rationale for the Development of Pediatric PRO-CTCAE	**Pamela S. Hinds, PhD, RN, FAAN** Executive Director Department of Nursing Science, Professional Practice, and Quality Outcomes Research Integrity Officer Children's National Hospital Professor of Pediatrics School of Medicine and Health Sciences George Washington University
Design and Evaluation of the Pediatric Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (Ped-PRO-CTCAE™) System	**Bryce B. Reeve, PhD** Director, Center for Health Measurement Professor, Population Health Sciences Professor, Pediatrics Duke University School of Medicine

Clarifying Questions

LUNCH

PEDIATRIC PRO-CTCAE: FUTURE DIRECTIONS BEYOND TOLERABILITY

GUEST SPEAKER PRESENTATIONS

Pediatric PRO-CTCAE: Future Directions Advancing Supportive Care Strategies - PROs	**Lillian Sung, MD, PhD, FRCPC** Professor, Department of Paediatrics Senior Scientist, Research Institute Canada Research Chair in Pediatric Oncology Supportive Care The Hospital for Sick Children Toronto, Canada
Facilitating Survivorship Care and Research	**Tara O. Henderson, MD, MPH** Professor of Pediatrics Interim Chief, Pediatric Hematology, Oncology and Stem Cell Transplantation Director, Childhood, Adolescent and Young Adult Survivorship Center Comer Children's Hospital University of Chicago
Incorporating Pediatric PRO-CTCAE in the National Clinical Trials Network (NCTN) Clinical Trials	**Douglas S. Hawkins, MD** Professor of Pediatrics University of Washington Chair, Children's Oncology Group Seattle Children's Hospital
Clarifying Questions	

BREAK

OPEN PUBLIC HEARING

Questions to the Subcommittee and Subcommittee Discussion	
Wrap-Up	**Elizabeth Duke, MD**
Closing Remarks	**Gregory Reaman, MD**

ADJOURNMENT

DAY 2: MAY 12, 2021

Call to Order	**Alberto S. Pappo, MD** Chairperson, pedsODAC
Introduction of Subcommittee and Conflict of Interest Statement	**She-Chia Chen, PharmD** Designated Federal Officer, ODAC

Introductory Remarks	**Gregory Reaman, MD** Associate Director Pediatric Oncology Oncology Center of Excellence (OCE) Office of the Commissioner (OC) Associate Director Pediatric Oncology Office of Oncologic Diseases (OOD) Office of New Drugs (OND), CDER, FDA

REAL WORLD EVIDENCE (RWE) FOR REGULATORY USE IN PEDIATRICS

FDA PRESENTATIONS

The FDA Real World Evidence (RWE) Framework and Considerations for Use in Regulatory Decision-Making	**Jacqueline Corrigan-Curay, JD, MD** Director, Office of Medical Policy Acting Deputy Center Director for Operations, CDER, FDA
Designing External Controls Using Real World Data for Pediatric Cancer Drug Development	**Donna R. Rivera, PharmD, MSc** Associate Director for Pharmacoepidemiology OCE, OC, FDA
Statistical Considerations for External Controls in Pediatric Trials	**Pallavi Mishra-Kalyani, PhD** Lead Mathematical Statistician Division of Biometrics V Office of Biostatistics Office of Translational Sciences CDER, FDA

Clarifying Questions

PEDIATRIC REAL WORLD DATA (RWD) RESOURCES

SPEAKER PRESENTATIONS

Childhood Cancer Data Initiative	**James H. Doroshow, MD** Deputy Director for Clinical and Translational Research, NCI National Institutes of Health (NIH) Director, Division of Cancer Treatment and Diagnosis NCI, NIH
The NCI Childhood Cancer Data Initiative (CCDI) and RWD/RWE Resources for Pediatric Oncology	**Malcolm A. Smith, MD, PhD** Associate Branch Chief for Pediatrics Clinical Investigations Branch Cancer Therapy Evaluation Program Division of Cancer Treatment and Diagnosis (DCTD), NCI, NIH

Clarifying Questions

RWE IN EVALUATING PEDIATRIC DRUG SAFETY AND INFORMING RESEARCH STRATEGIES

FDA PRESENTATION

Real World Evidence (RWE) to Assess Pediatric Medical Product Safety	**Ann W. McMahon, MD, MS, FISPE** Deputy Director of Science Office of Pediatric Therapeutics Office of Clinical Policy and Programs OC, FDA

GUEST SPEAKER PRESENTATIONS

Using RWD and RWE to Evaluate Pediatric Cancer Drug Safety	**Bruce Carleton, BPharm, PharmD, FCP, FISPE** Professor of Pediatrics, Medical Genetics, Population & Public Health University of British Columbia Chair, Division of Translational Therapeutics, Department of Pediatrics Faculty of Medicine Director, Pharmaceutical Outcomes Programme, BC Children's Hospital Senior Clinician Scientist BC Children's Hospital Research Institute Vancouver, Canada
Informing Pediatric Clinical Research Strategies and Drug Development Through RWE	**Douglas S. Hawkins, MD** Professor of Pediatrics University of Washington Seattle Children's Research Institute Chair, Children's Oncology Group

Clarifying Questions

BREAK

OPEN PUBLIC HEARING

Questions to the Subcommittee and Subcommittee Discussion

Closing Remarks — **Gregory Reaman, MD**

ADJOURNMENT

Questions to the Committee:

Day 1: May 11, 2021

Discussion of Issues Relating to the Development of Pediatric Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

1. **DISCUSSION:** 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 use.

   Subcommittee Discussion: *Some members of the Subcommittee agreed that PRO assessments can provide clinicians with a more better understanding of the burden of therapy in children. Some members of the Subcommittee members raised concerns about the diversity of the data, whether PRO assessments would accurately reflect comprehensive and equitable input across the spectrum of pediatric patients with cancer due to important factors such as socio-economic status, race/ethnicity, access to care, cognitive abilities, etc.*

   Subcommittee members also highlighted the possible role of PRO in determining how to move forward with a specific therapy that has a marginal effect on overall survival based on its impact on the quality of life. It was further commented that PRO-CTCAE might further inform clinicians early regarding adverse events that patients encounter and that could be addressed sooner to maximize supportive care for the children to improve drug tolerability and increase their compliance.

   Subcommittee members commented that assessment of PRO could potentially be valuable in randomized clinical trials and clinical care, but were uncertain regarding its value in single arm early phase clinical trials given that do not capture information regarding drug attribution and contribution of patients' underlying disease processes and concomitant medications. Please see the transcript for details of the Subcommittee's discussion.

2. **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 care-giver reports of "observable" symptoms (frequency, severity, and interference).

   Subcommittee Discussion: *Based on the context that PRO-CTCAE data are retrospective and descriptive, the majority of the Subcommittee members agreed that the PRO-CTCAE data would be beneficial to include children's voices, along with caregivers reported observable symptoms to evaluate symptom management. The importance of having both PRO data and caregivers' reports of observable symptoms was also discussed as this information is complementary and would help provide a more complete clinical picture. Some Subcommittee members noted concerns that a potential lack of concordance of the data might occur between patients and caregivers particularly for children under 7 years of age. Please see the transcript for details of the Subcommittee's discussion.*

3. **DISCUSSION:** Consider the logistical and operational challenges to collecting and analysis of data from patient self-report of symptoms.

   Subcommittee Discussion: *Some Subcommittee members raised a concern regarding whether use of PRO-CTCAE would require significant infrastructure and resources. The Subcommittee members noted that collecting this type of data might pose operational challenges and that perhaps some tools could facilitate incorporation of PRO-CTCAE assesments into clinical trials. Three main potential challenges were raised: 1) increased patient and caregiver burden, 2) the additional resources required for analyzing the collected data, 3) collecting the same adverse event data from different perspectives (patients vs. caregivers vs. clinicians) might lead to data discrepancies and consolidation issues. For large clinical trials, some Subcommittee members suggested considering collection of PRO-CTCAE data in a subset of enrolled patients (e.g., approximately 10-20%) to better assess the feasibility of PRO assessment. Some Subcommittee members suggested that that a separate subprotocol for PRO data collection and analysis might be necessary to maintain data integrity. Additionally, it was suggested that use of PRO-CTCAE be considered optional for patients to avoid increasing patient burden. Some Subcommittee members also noted the possible need to collect data at different time points during the clinical trial. Please see the transcript for details of the Subcommittee's discussion.*

4. **DISCUSSION:** 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.

   Subcommittee Discussion: *Some Subcommittee members recommended that the collected PRO-CTCAE data be accessible and this data could be a complementary way to look at burdens of treatments or side effects. The majority of the Subcommittee members agreed that it would be worthwhile to incorporate this data into the FDA's Project Patient Voice. Please see the transcript for details of the Subcommittee's discussion.*

5. **DISCUSSION:** Consider whether data obtained in real time from children's self-report of symptomatic adverse events (AEs) 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.

   Subcommittee Discussion: *The Subcommittee did not provide any recommendations or consideration for this discussion question as the majority of the Subcommittee members considered this question was similar to Questions 4 and 6. Please see the transcript for details of the Subcommittee's discussion.*

6. **DISCUSSION:** Consider how pediatric PRO-CTCAE might contribute to planning and implementation of supportive care and survivorship research strategies in children.

   Subcommittee Discussion: *The Subcommittee members noted that the pediatric PRO-CTCAE tool could contribute to implementation of optimal supportive care guidelines and*

development of research strategies for children. For example, it was noted that it may provide real-time data for management of acute side effects and perhaps for long-term side effect management such as mental health as a screening tool. Some Subcommittee members suggested that this tool might be useful to uncover some aspects of tolerability that might not have been correctly assessed in the past. Some Subcommittee members raised concerns regarding the complexity of use of PRO data in relation to insurance coverage, in addition to, ensuring sufficient and accurate data capture and availability to assist with making clinical decisions in real-time. Please see the transcript for details of the Subcommittee's discussion.

Day 2: May 12, 2021

Discussion of Real-world evidence (RWE) for regulatory use in pediatrics, real-world data (RWD) resources, and RWD and RWE to advance pediatric safety assessments of oncology drug products in children within the context of the FDA Framework for RWE

1. **DISCUSSION:** Consider the potential of existing and future RWD resources that may provide RWE to support pediatric cancer drug development programs. Consider potential uses to inform regulatory decision-making. Consider specific pediatric cancer drug development programs that might benefit.

   Subcommittee Discussion: The majority *of the Subcommittee members agreed that RWD and RWE would help better characterize molecular subtypes of pediatric cancers. Subcommittee members noted some of the current limitations include the quality of available datasets, specifically genetic data sets that could help predict better clinical responses and identify biomarkers for future clinical trials. Resources and funding were noted as other limiting factors and the Subcommittee agreed that this needed to be expanded. Some Subcommittee members commented that another issue was expanding studies to include functional genetics to better inform targeted therapies for pediatric patient populations. Please see the transcript for details of the Subcommittee's discussion.*

2. **DISCUSSION:** Given the discussion of the FDA framework on the use of RWD and RWE on regulatory decision-making, consider how best to assess the appropriateness of existing or emerging data sources as potential sources of RWD. Discuss critical attributes of such data.

   Subcommittee Discussion: *Some Subcommittee members noted that it is important to recognize that there are other efforts in pediatric oncology underway to include clinical and genomic data in addition to the the Childhood Cancer Data Initiative (CCDI). Please see the transcript for details of the Subcommittee's discussion.*

3. **DISCUSSION:** Consider the real and perceived limitations to RWE from existing and developing registries in pediatric cancer drug development as a result of the General Patient Data Regulations (GPDR) in the European Union.

Subcommittee Discussion: *Subcommittee members commented that there might be some issues with GPDR which might be more restrictive. Given the complexity of regulations in different countries, it was commented that this might affect the ability to obtain data. It was further commented some of these challenges might be driven by pharmaceutical firms being blocked from transferring the information and patient data to maintain privacy of personal data. Please see the transcript for details of the Subcommittee's discussion.*

4. **DISCUSSION:** Consider possible mechanisms for how and by whom attribution of RWD/RWE- generated adverse events (AEs) of new cancer drugs can be accomplished, and data optimally aggregated to inform patients and providers.

Subcommittee Discussion: *Subcommittee members suggested incorporation of the patient voice through validated tools such as PRO-CTCAE to provide patient input on adverse events to alleviate some of the existing challenges. It was further commented that the RWD and RWE could potentially be used to inform clinicians regarding adverse reactions to medications. Please see the transcript for details of the Subcommittee's discussion.*

The meeting was adjourned at approximately 2:15 p.m. on May 11, 2021 and approximately 3:30 p.m. on May 12, 2021.