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

Wednesday, May 12, 2021

12:02 p.m. to 4:20 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

She-Chia Chen, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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(Chairperson, pedsODAC)

Member and Head, Division of Solid Malignancies

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Professor of Pediatrics

University of Tennessee Health Science Center

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OCE, OC, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(10:00 a.m.)

Call to Order

DR. PAPPO: Good afternoon, and welcome to day number 2 of the Pediatric ODAC meeting. 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 email 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 12, 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: Thank you, Dr. Pappo.

Good afternoon. My name is She-Chia Chen, and I am the designated federal officer for this meeting. When I call your name, please introduce

yourself by stating your name and affiliation. We'll start with Oncologic Drugs Advisory Committee members.

Dr. Pappo?

DR. PAPPO: Hi. Good morning. I'm Alberto Pappo. I'm a pediatric oncologist at St. Jude, and I'm the chairperson for this meeting.

DR. CHEN: Dr. Cheng?

DR. CHENG: Good afternoon. Jon Cheng. I'm 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?

DR. ANGIOLILLO: Good afternoon. This is Anne Angiolillo, director of the Leukemia and Lymphoma Program at Children's National Medical Center in Washington, D.C., and professor of pediatrics at the George Washington University School of Medicine.

DR. CHEN: Dr. DuBois?

(No response.)

DR. CHEN: Dr. DuBois?

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

DR. CHEN: Dr. Dunkel?

DR. DUNKEL: Good afternoon. 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. My name is Julia Glade Bender. I am from Memorial Sloan Kettering Cancer Center in New York as well, where I'm a pediatric oncologist and vice chair for clinical research.

DR. CHEN: Dr. Janeway?

DR. JANEWAY: Hi. Katie Janeway. I'm a pediatric oncologist at Dana-Farber and Boston Children's.

DR. CHEN: Dr. Laetsch?

DR. LAETSCH: Hi. 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, parent of a child with cancer, and I work for Solving Kids' Cancer in New York.

DR. CHEN: Dr. MacDonald?

DR. MACDONALD: Hi. I'm Tobey MacDonald. I'm a pediatric neuro-oncologist 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: Ms. Preusse?

MS. PREUSEE: Hi. Courtney Preusse, acting consumer representative, and I also work for the Fred Hutch in Seattle.

DR. CHEN: And Dr. Seibel?

DR. SEIBEL: Hi. Good afternoon. I'm Nita Seibel, a pediatric oncologist in the clinical investigations branch of the National Cancer Institute.

DR. CHEN: Now we will go to FDA

participants.

Dr. Reaman?

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

DR. CHEN: Dr. Corrigan-Curay?

DR. CORRIGAN-CURAY: Yes. Hi. I'm Jacqueline Corrigan-Curay. I'm the director of the Office of Medical Policy. I'm also the acting deputy center director for operations in the Center for Drugs.

DR. CHEN: Dr. Donoghue?

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

DR. CHEN: Dr. Ehrlich?

DR. EHRLICH: Hi. This is Lori Ehrlich. I'm a pediatric hematologist/oncologist and clinical team leader in the Division of Hem Malignancies I at the FDA.

DR. CHEN: Dr. McMahon?

DR. McMAHON: My name is Ann McMahon. I'm in the Office of Pediatric Therapeutics at the FDA.

DR. CHEN: Dr. Mishra-Kalyani?

DR. MISHRA-KALYANI: Hi. My name is Pallavi Mishra-Kalyani. I'm a lead mathematical statistician in the Office of Biostatistics, Division of Biometrics V at the FDA.

DR. CHEN: And Dr. Rivera?

DR. RIVERA: Good afternoon. I'm Donna Rivera. I'm the associate director for pharmacoepidemiology in the Oncology Center of Excellence.

DR. PAPPO: Thank you.

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, 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 the meeting topic during the break. Thank you.

Dr. She-Chia Chen will read the Conflict of Interest Statement for the 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 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, will be discussed.

The potential for use of data sources to construct external controls to evaluate effectiveness of investigational products will be 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.

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 speaker, the agency has determined that the information to be provided by this speaker 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. Bruce Carleton has acknowledged being a principal investigator or co-investigator on several studies with the Canadian Institutes of Health Research, Genome Canada, Genome British Columbia, British Columbia Provincial Health

Services Authority, British Columbia Children's Hospital Foundation, and Health Canada.

Some of the studies include SEARCH & PREVENT: Active Surveillance and Evaluation of Adverse Reactions in Canadian Healthcare and Pharmacogenomics of Adverse Reactions Events Nationwide Team; Metabolomics for Prediction of Cisplatin Mediated Acute Kidney Injury: a Canadian Multicenter Adult and Pediatric Study; Hormonal Contraceptives and Risk of Pseudotumor Cerebri Syndrome in Women of Childbearing Age; Genomic and Outcomes Databank for Pharmacogenomic and Implementation Studies, GO PGx. He has also acknowledged being a scientific advisor for United Health Group's Pharmacogenomic Advisory Committee.

As guest speakers, Drs. Carleton 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 thanks to all of you for participating in today's virtual meeting of the Pediatric Subcommittee of ODAC, where we'll discuss the expanding efforts of the NCI's Childhood Cancer Data Initiative in aggregating and integrating demographic biologic, including genomic tumor characterization and clinical outcome data, and how CCDI might possibly serve as a resource for potential real-world data.

Real-world data from children and

adolescents with cancer can be obtained from multiple sources, and the potential for use of well-characterized and appropriately collected and standardized data to create sufficient evidence is of particular interest in pediatric cancer drug development in light of the rarity of specific cancers in children, which creates issues for clinical trials designed to demonstrate effectiveness, as well as sufficient numbers of treated patients on studies for evaluation of both short- and long-term safety.

Many clinical trials of new cancer drugs in children are designed with single-arm studies with plans to use historical or external controls; and real-world evidence might also contribute to the development of priors for randomized studies, incorporating a depth of Bayesian designs.

The availability of reliable sources of real-world data is pivotal to the potential of creating adequate real-world evidence, and the potential use of real-world evidence in regulatory decision making must be considered within the

context of FDA's framework on real-world data and real-world evidence.

The 21st Century Cures Act, passed in 2016, prompted a focus by the FDA on both real-world data and real-world evidence and their potential use in regulatory decision making in the development of a real-world evidence program, and we'll start today with a review of that framework.

As a result of several pediatric legislative initiatives over the past two decades, results of multiple pediatric clinical trials of new drugs have provided labeling information on effectiveness and safety.

Both the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act also require FDA to review case reports of adverse events associated with the use of medical products studied in children under these two pieces of legislation.

The review process conducted by FDA's Pediatric Advisory Committee contributes to the general knowledge of medical product safety in

children. Although real-world evidence has not been fully applied to address questions of medication safety in children, the emerging sources of data from clinical trials and observational studies of pediatric oncology, especially those incorporating lengthy longitudinal follow-up, as well as pharmacoepidemiologic investigations, might also provide opportunities for more efficient and accurate intermediate and long-term safety data of cancer drugs approved for use in children.

So again, I'd like to thank you for your participation. I look forward to presentations and hopefully a robust discussion. Thank you.

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

We will now proceed with FDA presentations, starting with Dr. Jacqueline Corrigan-Curay.

DR. CORRIGAN-CURAY: Thank you very much for inviting me to speak a little bit about the real-world evidence framework for FDA.

She-Chia, if you could please see if you could advance to my next slide?

DR. CHEN: Just a moment. Thank you.

FDA Presentation – Jacqueline Corrigan-Curay

DR. CORRIGAN-CURAY: Thank you very much.

Let me jump right in and speak a little bit about FDA's real-world evidence framework.

As just mentioned under 21st Century Cures, Congress passed us with establishing a program to evaluate the potential use of real-world evidence to support new indications for drugs already approved or to satisfy post-approval study requirements.

The first task for FDA was to develop a framework for that program, which was published in 2018 and described some of our priority areas, the challenges, and potential pilots. This framework guides our program right now. Congress also appropriated funds for demonstration projects, which I'll touch on, with the expectation that these activities would lead to guidance to be published by December 2021.

What you have in front of you are the definitions for real-world data and real-world evidence. These are FDA's definitions. I won't

read them to you. I'll just note under real-world data, we added the words "routinely collected" to distinguish from data that might be collected primarily from research. I would also note that we're not only talking about data that arises in the healthcare system, but data that can be generated outside of that system to inform on patient health.

Our definition of real-world evidence is, of course, regulatory-focused on potential benefits or risks of the medical product. And again, I'd like to just note that it is designed agnostic, and real-world evidence can be generated through randomized trials, through the use of external controls, and through the observational studies.

Our framework laid out three considerations which really guide the review of applications that come in, as well as the program. First is whether the real-world data is fit for use; can it answer the question that you're trying to answer; whether the trial or study design that's chosen to generate real-world evidence can provide adequate scientific

evidence to answer, or help answer, the regulatory question; and then whether the study conduct meets FDA's regulatory requirements, really focusing on any study monitoring and data collection issues.

Now, we have experience with real-world evidence. We've been using it for safety for over 10 years and generating really actionable evidence, including in the Pediatrics, as you can see, the article on the intussusception of the rotavirus.

It has not been used extensively in effectiveness, but certainly there are examples -- and these are just a couple of examples; there are more -- in which it has supported a finding of effectiveness, and many in the oncology area.

Our program is really built on four activities: engaging stakeholders, reviewing proposals, conducting demonstration projects, and ultimately on issuing guidance. While we focus on the postmarket evaluation in the phase 4 area, we realize that real-world data and real-world evidence are critical across the development

program.

So let's talk a little bit about data. You really cannot build quality real-world evidence unless you have quality real-world data, and that is really the starting point when you're thinking about a study for real-world evidence.

Now, this is just some unpublished data of endpoints in registrational trials, and first and foremost, you need to find out whether the measure of interest is going to be captured in real-world data and, importantly, is it captured consistently in a way that it is accessible?

So when you look at these endpoints, certainly hematology-pathology imaging are all things that are used in clinical practice, but is the frequency of the assessment adequate to discern effectiveness, and is there consistency in interpretation, for example, in imaging?

Certainly, certain clinical events like hospitalization may be much more reliable in real-world data, but you also notice that for FDA, we have a number of registrational trials that rely

on clinician-reported outcomes or patient-reported outcomes, not all of which will be used in clinical practice.

One of the things that we've been doing is really focusing some of our demonstration projects on the data. The transforming of RWE with unstructured and structured data to advance tailored therapy, or TRUST, is really based on the fact that there have been studies, which if you rely just on structured data -- for example, in HER -- you will get a very different cohort and sometimes not the cohort you're looking for. You really need to get into the unstructured data, which of course is much more difficult. This study will explore different ways for us to access that unstructured data using AI and other tools.

Now, another approach to this issue is the One Source approach, which is being done in the setting of the I-SPY breast-cancer platform trial, and also now in a COVID-19 trial. In this approach, it's really to change the HER but also to change the workflow, because changing the EHR

without the workflow can be frustrating for clinicians. To capture the truth, the One Source about the patient once has to be carried through the record because that's not only good for research, it's critical for quality care.

Other projects are, again, developing reusable frameworks for transforming raw data into fit for purpose and thinking about how this data will be structured for FDA submissions.

Now as I mentioned, sometimes the data isn't captured in the healthcare system, so we've also been focusing on tools that will allow us to fill in the gaps; in other words, can we develop mobile technology wearables and accelerometers that will really tell us how a patient is doing when they're outside the healthcare system?

FDA also was given a grant from HHS to develop the FDA MyStudies app. It is an FDA compliant platform that can be used to directly gather information from patients. It can be fed into their medical records, as well as into an eCRF. We're currently piloting in a randomized

clinical trial involving children with juvenile idiopathic arthritis, as well as with the Crohn's and Colitis Foundation to support the input from their patients into that registry.

Now, the other thing we think about, of course, is design, and this is just a schematic showing some of the possible designs using real-world data. If you look on the left side of this, this is really using traditional randomized trials but perhaps using real-world data to make them more efficient, and certainly is something that is incredibly important for us.

Then you look at trials in clinical practice settings, and that would be something like an RCT that might be using some endpoints or outcomes, or else a single-arm trial, as we're going to talk about, using external controls; then observational studies, of course, where you would not have any intervention, and you really rely on analysis of the data. This increasing reliance on the real-world data also creates increasing challenges in terms of causal inference, as well as making

sure you have real quality data.

That gets me to the point that the evidentiary standard for substantial evidence remains unchanged. The goal is to distinguish the effect of the drug from other influences, such as spontaneous change in disease course, placebo effect, or bias. So all the common practices that we use to do this must be attended to, and if they're not used, then we need to understand how we're controlling for some of the biases that those designs are meant to address.

We are doing some demonstration projects on design. We've just completed one using a randomized trial within the setting of the Sentinel Initiative. This was an educational intervention to increase the use of oral anticoagulants for patients at high risk of stroke, who had Afib. Unfortunately, it was not successful as a public health intervention, but it did show our ability to enroll 47,000 participants into a trial, to randomize them, and to capture their outcomes through this trial.

Now, the other area where there is great interest is can we use these data to really draw inferences about the effectiveness of medications? One of the ways we're trying to explore that is to try and use these methods to duplicate results from randomized clinical trials.

We're funding researchers up at Harvard to duplicate 30 clinical trials. The first cohort of those was published in December 2020, and it was a mix, as we would expect; because the point of this project is really not to say yes or no, but really to understand what questions are better answered or could be answered in this way.

If you're interested, we had a meeting in February, and the recording of that meeting is available, in which we brought this research and other research together to start to talk about what are the methods that we need to use and the questions that we can answer.

Of course, COVID-19 also really generated a lot of interest in real-world data. We really needed real-world data to understand this disease;

to prioritize research questions to be answered with clinical trials; and to help improve study design and support participant enrollment. FDA partnered with Reagan-Udall Foundation and Friends of Cancer in using real-world data in these many different ways.

Of course, what we've also seen is that data is accessible. There are data sets, there are statistical models, and it can become almost too easy at times to draw conclusions from data, and we have to be careful not to sacrifice methodologic rigor, or we can be led astray.

Looking forward, what we plan to do, and as outlined in the framework, is generate guidance in the topic areas that will inform our sponsors on how to use real-world evidence; in other words, what is a fit for use of real-world data for regulatory decisions? What kind of study designs using real-world data are appropriate to support effectiveness? What are the regulatory considerations, and what are appropriate data standards?

We have already provided a guidance on submitting documents using RWD and RWE to FDA. That's really more of a guidance meant to allow us to flag these submissions, so we can make sure the right people with the right expertise are weighing in.

I'd like to summarize by just saying that certainly FDA was accepting real-world and real-world evidence before the 21st Century Cures Act, but we continue to accelerate our review and evaluation. We continue to accumulate experience, and demonstration projects will advance our understanding.

The FDA guidance development will reflect learnings from applications and demonstration projects, and we will maintain evidentiary standards with real-world evidence and real-world data. Thank you for your attention.

DR. PAPPO: Thank you very much, Dr. Corrigan-Curay.

We will now proceed with FDA presentations, starting with Dr. Donna Rivera.

FDA Presentation – Donna Rivera

DR. RIVERA: Thank you, Chairperson and members of the committee.

Good afternoon. I am Donna Rivera, a pharmacist and pharmacoepidemiologist in the Oncology Center of Excellence. Today I'm going to speak about designing external controls using real-world data for pediatric cancer drug development.

Before we begin, I would like to start with the harmonized definition of externally-controlled trial. An externally-controlled trial compares a group of subjects receiving the test treatment with a group of patients external to the study, rather than to an internal group consisting of patients from the same population assigned to a different treatment.

(Pause.)

DR. CHEN: We are pulling up the slides right now; just one moment. Thank you, everyone.

DR. PAPPO: Thank you.

DR. CHEN: Dr. Rivera, the slides have

pulled up. You may advance it. Thank you.

DR. RIVERA: Thank you.

To set the stage for this discussion on external controls, a bit about the rationale for their use may be helpful. The clinical challenge that currently exists is interpreting time-to-event endpoints like progression-free survival and overall survival in single-arm cancer trials.

One potential solution that has emerged is the use of well-constructed, externally-controlled design. However, the primary methodological concern is ensuring the balance of prognostic factors and confounding influences for evaluation of treatment benefit in the absence of randomization.

For this presentation, I would like to focus on two aspects of external controls: study design and methodological approaches. Before we delve into these aspects, I would like to emphasize the challenges and intricacies of using an externally-controlled design.

The suitability of an external control arm

is reliant on many factors which require careful evaluation prior to study initiation. Because of the complicated nature, it is recommended to interact early and often with the relevant review division to seek guidance and assess upfront feasibility.

There are various ways to construct an external control, including what is referenced as the more traditional external control, which includes data from a non-randomized population outside traditional clinical trial enrollment. Additionally, there are also synthetic control arms which include observations that were not obtained by direct measurement, often simulated using advanced methods and modeling.

Time is an important factor in external controls. Temporal variations in external controls can include a concurrent control or a patient population treated during the same or similar time period, reflecting a similar standard of care and a historical control, or a non-contemporaneous patient population, whereas retrospective data is

used as a comparator. It is also possible to have combinations of these types of arms.

External control arms may be designed in various forms, and they can include data from previously conducted clinical trials, including pooled trial data. They can include real-world data from a single source or pooled data in a historical context, as well as prospective real-world data.

Additionally, hybrid perspective designs, such as those using concurrently randomized control data, as well as external control data, and other designs as mentioned by Dr. Corrigan-Curay, may be appropriate in this context.

Real-world data for external controls can come from a variety of sources, such as electronic health records, administrative claims, registries, and patient-generated health data. Registries and prospective designs may have proximal utility as sources for use in external controls.

In terms of uses for external controls, there are really two ways in which we think about

their application; either A, as a benchmark or natural history study as a type of epidemiological baseline; or as a comparator using individual patient-level matched data with formal hypothesis testing for statistical inference.

The optimal approach to obtaining interpretable time-to-event outcomes is to use a prospective randomized clinical trial. However, this is not always feasible, and when there is a clear rationale for the inability to randomize, the use of external controls may be a reasonable approach, meaning when randomized-controlled trials are infeasible or impractical, unethical, or there's a lack of equipoise.

External controls may be considered to generate supportive evidence. These may be particularly important in instances where objective response rate is challenging; for instance, in difficult-to-measure locations or for treatments where the cytostatic mechanism is unlikely to produce tangible response rate.

These situations can occur in pediatric

oncology, which is germane to our discussion today, as well as in other rare diseases or areas where there is a significant unmet medical need with limited treatment options or standard of care.

In terms of study conceptualization, studies may be designed in various ways. The more traditional and most widely used to date is likely the natural history or descriptive epidemiology type study that tends to serve as a benchmark. The external comparator type, which I just described, can be historical, synthetic, or a combination. They can also be applied in hybrid or pragmatic designs.

In evaluating fitness for purpose, as mentioned by my colleague, the following elements are important to consider: the data source, is the data appropriate for use as an external control; the patient population, is the control consistent in composition with the patient population in the investigational arm and can it serve as an appropriate comparator for the indication?

All of these questions are contingent upon

the source having sufficiently available data that can support adequate measurement, including that of endpoint. Furthermore, we will discuss these effects more specifically in the next portion of the presentation on methodological approaches.

Careful planning in the design phase prior to study initiation can ensure comparability of patient populations and data, such that the planned statistical analysis may adjust for potential biases for better estimation of the treatment effect and avoid artificially demonstrating a treatment effect that is not related to therapeutic intervention.

The protocol and statistical analysis plan should be finalized before the analyses begin and consider the following elements: assessing data quality and metrics of that data; cohort definitions; heterogeneity of real-world data; endpoint ascertainment and validation for both response and time-to-event endpoints; bias, including selection, confounding, and misclassification. All of these aspects are part

of evaluating fit for purpose: is the data complete, consistent, accurate, and longitudinal among other criteria?

These additional specific considerations may be useful when designing external control arms. The availability of key covariates, specifically patient-level data, on clinical and demographic characteristics, biomarkers, or other variables directly relevant to the clinical question of interest are important.

If a data source does not have relevant prognostic variables available, the source may not be fit for the purpose it is being intended to be utilized for in assembling an external control.

For example, in an evaluation of a biomarker-directed therapy, the accurate and reliable capture of biomarker testing data would be essential to select a patient population. Similarly, in a data set such as YourMedicare, the Medicare claims linkage is necessary to provide valuable data on treatment utilization that would not be evaluable without the linked data set.

Without careful attention to these factors, selection bias and confounding can render the results of the analysis comparing prospective trial data to an external control uninterpretable.

Evaluating the population of interest, external control arm patients should meet the same or similar eligibility criteria as patients in the trial or prospective study. The data source should be carefully selected. Prior to analysis of any pooled type of external control data, appropriateness and feasibility of such pooling should be evaluated.

Data missingness is a frequent and significant concern in the use of real-world data. Complete data, characterization, and evaluation of quality, as well as data provenance, should be reported. We encourage transparency in reporting. Specific methods for handling missing data in the external control group and any sensitivity analyses should be included.

Temporality is an aspect, mentioned earlier, that is a design decision. The selection of

retrospective or concurrent arms can have implications for data interpretability. For example, changes in standard of care can impact the usefulness of historical control arm.

In terms specifically of measurement, items to consider our comparability of data sources and elements; measurement of the drug and other concomitant treatments or treatment-related factors; measurement of outcomes, including differential capture of endpoints or follow-up data for outcomes such as survival, which should be as complete as possible with limited censoring or missing data.

There are many nuances between the systematic caption, evaluation of response, in a trial and that which occurs in routine clinical practice. Temporal issues, including those already mentioned and also including the selection of time zero, which is going to be covered more extensively in the following presentation, along with intercurrent events, may impact analyses.

A well-designed protocol and statistical

analysis plan, developed a priori, are essential to the use of external control designs for regulatory purposes.

To summarize and apply this discussion, I would like to discuss examples of where we have seen external control arms submitted to FDA for regulatory use. External control data has been submitted typically in the clinical scenario where there are limited or no randomized studies available to evaluate a time-to-event endpoint.

Use of single-arm studies is common in oncology because objective response rate has a high certainty that the effect is due to the therapeutic intervention, and thus a control group is not necessarily required.

Given this response endpoint a single-arm trial is interpretable and the endpoint can be used for either accelerated approval or regular approval, depending on the application, the use of external controls has been limited to providing exploratory supportive data to inform clinical context.

Regulatory decisions to this point have been primarily based on trial response data. Real-world data submissions, including external controls, have been limited by several factors, including inadequate information on patient demographic and clinical characteristics such as differences in treatment rates or differences in geography; lack of prespecified protocols to ensure selection of comparable patient populations, raising concerns about selection bias; and a lack of a priori formal statistical comparisons or a formal analysis plan to outline the statistical methodology. Variance in follow-up was another factor that contributed to overall concerns about measured and unmeasured confounding.

To reiterate, even when external control designs were submitted in oncology, regulatory approvals were based on the single-arm clinical trial data, where durable overall response rate in the context of acceptable safety was considered evidence of clinical benefit. However, we continue to work with the community to improve our ability

to rely on external control arms for situations where response rate is not available and randomization is impractical or infeasible.

As mentioned in the previous presentation, under the 21st Century Cures Act, the agency is opened to evidence development and trial design modernization evaluation.

To conclude, real-world data is being evaluated as a potential solution to the challenge of inability to interpret single-arm, time-to-event data. The greatest challenge remains in the uncertainty of whether the two populations are well matched for key prognostic factors because there is not randomization.

There are two design questions I hope you can take away from this presentation to ask when thinking about designing an external control using real-world data. The first, what is the real-world data study questions; and the second, is the data fit for purpose?

It is the second question about fit-purpose data. This is the most salient aspect for

discussion in the oncology drug development community, where efforts must focus in order to assure the use of external control arms can reliably provide substantial evidence of efficacy or effectiveness for regulatory decision making. Thank you to my colleagues, and thank you for the opportunity to speak on this emerging topic.

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

We will now proceed with the FDA presentation from Dr. Pallavi Mishra-Kalyani.

FDA Presentation – Pallavi Mishra-Kalyani

DR. MISHRA-KALYANI: Yes. Thank you very much, Chairperson and members of the committee. My name is Pallavi Mishra-Kalyani. I'm a lead mathematical statistician in the Division of Biometrics V in the Office of Biostatistics in CDER. Today my presentation will cover some of the statistical considerations for external control trials, particularly those in pediatric trials.

As mentioned by my colleagues who have presented in this session, randomized trials are generally the preferred option for providing

evidence of drug efficacy. We generally consider these to be the gold standard for comparing treatments, as we know that randomization will not only take care of confounding by known factors, but it will also remove any confounding by unknown factors.

However, there are cases where randomized control arm is not possible, and perhaps single-arm data might fall short in providing the evidence required for a particular type of treatment. And in that case, an external control may be an option for helping to estimate comparative treatment effect.

As mentioned previously, there are a lot of different ways that external controls could be utilized in clinical trials. Certainly they can be used to demonstrate natural history of disease or even provide some evidence towards the contribution of components to treatment effect. There may be a use for external controls for establishing efficacy from prior trials, so providing the null hypothesis, let's say, for a single-arm trial. And

finally, we may even consider using them to compare efficacy across treatment arms by supplementing or replacing concurrent controls in a prospective trial.

This last example would require the greatest amount of, I think, evidence regarding the external controls being appropriate for a particular scenario, and it's very true that the source of the data for the controls would determine the potential use.

So if data is only available from published literature, then we would not be able to use that type of data for a comparative efficacy analysis. However, if high-quality and complete patient-level data is available from prior clinical trial data, then we may be able to compare efficacy endpoints.

As my colleague Dr. Rivera described, the study design is incredibly important in an externally-controlled clinical trial. Principles of good study design include avoiding differences in the populations that result in groups that cannot be compared, such as measurable endpoints

temporality, availability of variables, amongst other items. Our basic goal in good study design is to minimize the need for analytic tools to deal with bias or confounding. We will not be able to remove all sources of bias and confounding just by design, but we can minimize a good deal of it.

Using the estimand framework in designing a study, and then the corresponding analysis plan, can allow for a detailed approach to determine the important aspects of the study. This would include the population of interest; the treatment or intervention to be studied; the endpoint or outcome that will measure the difference across groups; intercurrent events which occur post-randomization and can interfere with the interpretation of the results if not appropriately accounted for; and finally, the summary measure that's used to describe the actual treatment effect.

This estimand framework can be particularly helpful in studies of external controls or real-world data because it allows for a systematic approach to make sure that at the end of the day,

the design of the study is capturing the results that you would like to measure.

When designing or writing the statistical analysis plan for an externally-controlled trial, it's very important to prespecify all analysis plans and all approaches, and preferably done prior to any look at the outcome data of the external control. So if you're using data that has already existed either in a registry form or prior clinical trial, it's important to design this study and to design the statistical analysis plan without looking at the outcome data first.

Formal sample size and power calculations are still relevant. Even though we're not using them maybe to design a prospective study, it's still important to identify these operating characteristics of the study of interest, and it may be helpful to prespecify a stringent type 1 error or alpha rate to ensure that the comparison is appropriate.

Methods to control for various types of bias, including selection bias and confounding,

should be specified. Some types of bias cannot be addressed with analytic methods. That's why we try to minimize these in the design stage. But what we can do is consider sensitivity and supportive analyses to understand the effects of these potential biases; although we might want to consider hybrid designs where we look at both concurrently randomized control data as well as external control data together to compare to an experimental group, sometimes or usually with Bayesian statistical methods, as this allows for less reliance on external control data.

I described in the previous slide that methods to control for or address certain types of bias will be necessary in an externally-controlled trial. There are many different types of bias. I've listed three common ones here on this slide that should be considered.

Selection bias, which is the bias that exists when our comparative groups come from different populations or populations with different underlying distributions of characteristics, and

here we can use methods like balancing scores, basically propensity scores, and inverse probability weighting to make sure that our populations are comparable;

Confounding, which can exist when a certain characteristic is both related to the treatment receipt and the outcome of interest, and again, we can look at balancing scores and inverse probability weighting, as well as other methods like marginal structural models; and

Misclassification of the data, when data is not characterized in the most appropriate manner -- it may be missing or may be mismeasured -- we can try to measure this misclassification or validate measurements of external data by measuring sensitivity, specificity, positive predictive value, or negative predictive value.

I want to focus now a little on balancing scores because these tend to be very important in studies that incorporate external control data. The general idea is that we want to balance two

populations -- let's say here the experimental treatment and the external control -- so that whatever remaining differences are between the two populations can be attributed solely to the treatment effect.

The scores generally come from a model for the treatment group that includes covariates that may be related to both treatment assignment and outcome. We can use these scores in many ways. We can match, stratify, or weight in the analysis of treatment effect. But it's important to recognize that the use of these types of balancing scores, like propensity scores, require very strong assumptions, such as no unmeasured confounding, a sufficient overlap of the two distributions, and correct model specification for the balancing score. And some of these assumptions can be very difficult to verify, if possible at all.

In general, trials that compare an experimental arm to an external control require a high volume of good quality and complete data. We want to avoid bias in ascertainment and definitions

of data across treatment groups because even small discrepancies may make a very big difference in the comparability.

Good study design really cannot be underestimated here. They can help to avoid many of the pitfalls using non-concurrent or non-randomized data in external controls. Analytic methods can help to address bias or confounding that may remain after good study design, but they cannot eliminate the threat of bias completely. These methods require strong assumptions. But we can also rely on sensitivity analyses to assess how robust the results are to these assumptions.

Finally, I just want to give some final statistician thoughts on external controls. I would like to say that the burden of proof to demonstrate that external controls meet the bar for comparative analyses really should not be underestimated. We really set this bar high because we want to make sure that at the end of the day, whatever treatment effect we can measure from this comparison is really a measure of the

treatment effect and is not confounded by the many factors that do exist in the comparison to external controls.

So when considering a design that includes external controls, we should also consider other options that preserve the principle of randomization but may be a little easier, let's say, to incorporate in certain scenarios, particularly in pediatric trials where sample size may be limited. N to 1 randomization ratios; pragmatic trials; and decentralized trials may be very good options in these scenarios. They offer some flexibility in trial design, but preserve the principle of randomization.

Hybrid trial design is definitely a good option as well because it allows for both concurrent controls as well as external data to be incorporated. It minimizes the risk of relying on external controls completely However, if you do ultimately decide that an externally-controlled clinical trial is the best option, then all operating characteristics and statistical methods

should be prespecified to ensure the validity of the comparison.

Thank you very much for your time and I'm happy to take any clarifying question.

Clarifying Questions

DR. PAPPO: Thank you very much, Dr. Mishra-Kalyani.

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.

We will now start with questions. The first one is going to be Dr. Cheng.

DR. CHENG: Yes. Hi. Good afternoon. Jon Cheng, industry rep. I hope you can hear me ok. Thank you to the FDA for a very thorough and thoughtful presentation.

My question is, from the industry side, there's obviously high-level interest on synthetic controls, particularly the external control arm. My question is, particularly the hybrid design, is there a precedent or has there been good examples where one can be referred to as to how to utilize that so that there could be almost like a working guide; or are we still a ways away in having the electronic health records and individual patient data, even for some vendors like Flatiron, to be able to do it at the level of vigor that the FDA is hoping for?

DR. MISHRA-KALYANI: Hello. This is Pallavi Mishra-Kalyani. I will start with some response to this question, but I know that my colleague, Dr. Rivera, may also have some interesting comments

to add.

I don't believe at this point in oncology that we have an example of a hybrid design that we can point you to. I know that there are groups that are working on hybrid designs for various types of trials. Some of these have been presented publicly, and there have been papers on this topic.

I would say that the best option for someone who is considering a hybrid design is to bring that proposal to the FDA. We do have statisticians with experience in this area, and we can provide feedback on both the design and the analysis plan to ensure that, ultimately, you're on the best track possible to ensure comparison to both the concurrent control as well as the external control.

I'll add that this is a design that we think is really preferable to relying solely on external controls because if for some reason you are not able to meet the burden of proof to ensure that the external control data is compatible with the prospective data from the randomized portion of the study, you are at least left with, let's say, an

N to 1 randomization of the experimental arm to the control arm, and that certainly will help provide evidence for a comparative treatment effect, even if it may be somewhat underpowered to what you might have wanted for your hybrid design.

DR. CHENG: Thank you. I actually agree. I do think the hybrid seems like a good next-step for all of the reasons that were stated, but even then, the bar seems fairly challenging. So that's where a precedent or having that discussion would be helpful, so that you can validate the external control to be in line with what you expect to see in your contemporary randomized control, for example.

But the fact that there isn't maybe a precedent suggests that obviously more work needs to be done. And I was just curious as to it seems like there is an opportunity to do that, but it is a little bit dependent on how good the electronic medical records are at a patient level. So that's why I just had that background, but thank you for the answer.

DR. RIVERA: This is Dr. Rivera. Maybe just to add, I think part of what I concluded my presentation with was exactly that; that the community as a whole, there's a need for methodological development in this area because it is exactly to that point of the ability to validate and contextually understand what is being demonstrated.

So I would also encourage again and emphasize that contact with the relevant review division early and often is preferable to really try to understand this emerging area.

DR. CHENG: Yes. Thank you.

DR. PAPPO: Does that satisfy your question, Dr. Cheng?

DR. CHENG: Yes. Thank you.

DR. PAPPO: The next question is Dr. Janeway.

(No response.)

DR. PAPPO: Katie, are you on?

(No response.)

DR. PAPPO: Okay. We'll jump to Dr. Duncan,

and then we'll come back to Dr. Janeway.

Ira?

DR. DUNKEL: Thank you. This is Ira Dunkel, Memorial Sloan Kettering Cancer Center. My question and comments I guess are both for Dr. Rivera and for Dr. Mishra-Kalyani.

As a pediatric neuro-oncologist designing phase 1/2 clinical trials in ultra-rare patient populations, we're almost always forced to use historical controls rather than developing randomized studies. And I think that even with the data that we have from existing clinical trials, it's often very difficult, because of small numbers, to develop an appropriate historical control.

So should real-world data evidence be able to help us develop more robust historical controls, it would be really enormously beneficial.

I think the question part, maybe for Dr. Mishra-Kalyani, is that one thing that we're often struggling with is that as diagnostic tests are developed and tumorous subtypes are identified,

the historical control data may not always have all of the molecular subtyping of the tumors that we're using to develop the current studies.

I guess the point is that we're almost always being forced to come up with trial designs that have some imperfections in them because of tiny numbers of patients and lack of adequate historical controls. I guess the question is, how do you balance what is ideal versus what can truly be accomplished, given these limitations? Thank you.

DR. MISHRA-KALYANI: Thank you for that question. I think it's a very important one. Certainly, this is a major issue in most fields of oncology, most disease areas, because our science is getting better in that we're able to identify subtypes, we're able to identify genetic and molecular markers, biomarkers, and that certainly is helping us push the field into the future with specific information regarding these disease subtypes. However, it does make cross-trial comparison or cross-data source comparisons more

difficult because, as you mentioned, historic data does not always have that information.

I think that there are a couple of factors to consider. The first is whether or not a particular genetic or molecular subtype or biomarker is important with respect to prognostic or predictive value. Just knowing that something exists may be different from whether or not it actually makes a difference to the patient care. But certainly if we do know that it is important and a data source does not contain that information, then it most likely will not be a good data source for a comparative analysis.

I would add to that, that we find that external controls are probably going to be most useful in disease areas where there has not been much change in the science over time. For example, non-small cell lung cancer might be a difficult area to apply external control data because there are a lot of targeted therapies, and prior data sources may not have sufficient information with respect to the testing of patient tissue or samples

to identify particular subsets of patients, genetic markers, and molecular subtypes that are important for identifying the appropriate control population.

But in other diseases, there has not been as much, I guess, scientific progress. And for those diseases, the patient population is consistent over time, and the treatment for those patients in various disease settings is consistent over time. And in those cases, external controls may be more likely to be of use.

DR. DUNKEL: Thank you for the response, and thank you for the interesting presentations.

DR. PAPPO: We will now go back to Dr. Katie Janeway.

DR. JANEWAY: Hi. Hopefully you can hear me.

DR. PAPPO: Yes.

DR. JANEWAY: This is Dr. Janeway from Dana-Farber and Boston Children's. This is a question for Drs. Rivera and Mishra-Kalyani. Thank you to all three speakers for the very nice presentation. It's appropriate that I'm speaking

now, after the emphasis was placed on diseases where there has been very little progress, which is an area I work in, in osteosarcoma.

One question or one comment I have that I'd be interested in your thoughts about is we actually do have quite nice historical benchmarks that we have been developing the Children's Oncology Group over the last five years.

One nuance of using this evidence for clinical trial design that I'd like to understand better is the extent to which the people, the group developing the trial, need to have access to the actual data, the actual patient-level data, versus being able to use something that's sort of been presented in aggregate in a publication.

In other words, just to be very specific or give a case example, if a pharmaceutical company was interested in developing a product in osteosarcoma and wanted to use our historical benchmark data, would they have to access the patient-level data, or could they use what's been put in aggregate publication in a peer-reviewed

journal?

DR. MISHRA-KALYANI: Hi. This is Dr. Mishra-Kalyani, and I'll start. And I'll ask my colleague, Dr. Rivera, to also chime in, as I know that she will have a lot to add to this.

I think it really depends on the disease setting as well as the intent of the external control data. We really do require individual patient-level data that is very complete and of good quality to compare external control to experimental data.

However, if we are really only looking to make sure that we have the appropriate study design, or we have a very well understood natural history from various different data sources and data types, we can probably use a summary of the data that's available to create a benchmark to compare a response rate to or another endpoint that would be appropriate in a single-arm trial.

That being said, if you are trying to design a study, let's say, with a time-to-event endpoint like event-free survival, or overall survival, or

progression-free survival, it's very difficult to compare those two benchmarks. So then you would really need the patient-level data for a comparison.

I would say that which endpoint is most appropriate for your particular disease and treatment setting is something that you can discuss with the agency. We're happy to have those discussions, and depending on what the answer is, that will also dictate what type of external control, if any, is appropriate for that setting.

Dr. Rivera, would you like to add to that?

DR. RIVERA: Thank you, Dr. Mishra-Kalyani. Yes, I will add.

This is Dr. Rivera. Thank you for the question. I really agree that it's very contextually dependent on the regulatory purpose. As in my presentation, I kind of alluded to there are two types we most often see, one being that baseline, natural history type, and the second being that comparative type.

I think in an individual patient-level

context, if you're going to use it as a comparator and you want to do any type of characteristics of the patients for matching purposes, or any other statistical evaluations, and the true purpose is in that comparison of effectiveness or safety, then it would really be pertinent to have access to that individual patient level data. However, as my colleague has alluded to, it is dependent, and we would encourage discussion with the relevant review division.

DR. PAPPO: Does that answer your question?

DR. JANEWAY: It does, Dr. Pappo. I have a follow-up question, but I can probably save it for later in the day. Thank you.

DR. PAPPO: Thank you.

I'm next in the queue. I'm Alberto Pappo. I had a question. It's expanding a little bit on Dr. Janeway's question and also on Dr. Cheng's question. It's mostly directed, I think, to Dr. Corrigan-Curay.

Who makes the decision whether it's needed to have additional real-world evidence with a

specific compound? Is it usually investigator initiated, and they come to you, or they go to the company; or does the company acknowledge that it's a very rare disease, and that you need to have additional information?

The other question is, are most of the studies initiated by the drug company, and are they mostly observational? How do you assure that the quality of data is good enough to conduct such trial?

DR. CORRIGAN-CURAY: Well, thank you for that question, and certainly a lot to unpack there. Real-world evidence is seen as another way to reach substantial evidence of effectiveness. First of all, it's more likely to be used in the post-approval setting; that you're starting with an evidence base and then seeing if you can build on that evidence base using real-world evidence.

The applications that we're most likely to see are sponsors proposing, perhaps, to expand an indication. It may be a combination of other evidence and real-world data; it may be that

they're seeking to see if they can do it purely through an observational study; or perhaps, as has been discussed in the last couple of questions, as an external control.

There is great interest in using this for observational studies on the basis that if the data is collected and we discern causal inference reliably, then certainly that could be much more rapid than a clinical trial. But we've seen great challenges in having a sufficient quality of data to really understand and control for the different factors that go into why one patient will get one drug versus another.

So as we meet with sponsors -- and not only part of the real-world evidence subcommittee but obviously all the divisions -- and really exploring that data, and what it is that the data has reliably and what it is lacking, I would say that usually has been one of the greatest challenges, is you really often are lacking one or two elements that we think is really critical to have to be able to generate a comparable population.

I would say we're also very much encouraging to integrate this into randomized clinical trials and take the advantage of randomization, but trying to understand whether you can capture some of those endpoints through the real-world data.

I hope that answers your question, and I would invite my colleagues also to jump in on that.

DR. PAPPO: It does. Thank you.

In the interest of trying to keep us on time, I'm going to allow one more question, and that's going to be Ted.

DR. LAETSCH: Thank you, Dr. Pappo.

This is Ted Laetsch from Children's Hospital of Philadelphia. I think in light of our next speakers talking about the Childhood Cancer Data Initiative and Dr. Janeway's comments about historical control data developed through COG, but I recognize the importance of real evidence, particularly for rare pediatric tumors where randomized trials may not always be feasible.

There's been a lot of discussion about conversations with sponsors, but I wonder what also

conversations the FDA has had with other groups that gather this data to make sure that the data meets standards, so when sponsors come to these groups to ask about a potential control arm for their study, that we have the data that they need.

DR. RIVERA: Hi. This is Dr. Rivera. Maybe I'll start, and then ask Dr. Corrigan-Curay to also comment. I can say that the Oncology Center of Excellence does work collaboratively with a variety of these data groups in order to advance regulatory science exactly towards this purpose.

So we are engaged from the research aspect in understanding this data and further developing the methods with the goal of advancing the use of real-world data for regulatory purposes and improving patient access to therapeutics, so we definitely are aware of this and are taking it into account.

You also heard in the first presentation from my colleague that the overall agency is involved in a lot of demonstration projects and efforts related to a deeper understanding of

observational methods and appropriateness of use of real-world data to meet the substantial evidence standard, so I will turn it over to my colleague for any additional comments.

DR. PAPPO: Anyone else would like to expand on the answer?

DR. CORRIGAN-CURAY: Yes. Hello. I'm sorry I was muted. I would certainly say that we are supporting demonstration projects and that we make public the results we take two stakeholder meetings to really get the message out of what we think is quality data and how to generate that.

We've met with a number of small companies in the rare disease space who are trying to set up registries and other ways to generate quality real-world data in order to support applications. We've met with them. And certainly as our guidance comes out, that will also be for others than sponsors, but others who are trying to generate this type of data. Thank you.

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

DR. LAETSCH: Yes. Thank you very much.

DR. PAPPO: Okay. We will now proceed to additional speakers. Our next speaker is Dr. James Doroshow.

Speaker Presentation – James Doroshow

DR. DOROSHOW: Hello? Hi. This is Jim Doroshow. I'm the deputy director for clinical and translational research at the NCI, and it's a real pleasure to join you today. I want to thank the FDA for inviting me to present to the Pediatric Oncology Subcommittee. In my remarks, I will provide a high-level version of the NCI's effort to establish a childhood cancer data initiative and explain some of the initiative's activities and plans.

As everyone knows, cancers in children and young adults are rare and represent a small percentage of all of the cancers diagnosed annually in the United States, and this poses, really, many research challenges. There simply aren't enough data, even in very large pediatric cancer centers, to provide answers for these patients.

Through the Childhood Cancer Data Initiative, we are trying to build a community focused on childhood cancer care and research data. As an early step toward building this community, in July of 2019, we had our first NCI-supported symposium, and many ideas were shared through breakout groups, presentations, posters, and discussions to advance this notion. Fortunately, in 2020, the NCI was the beneficiary of a $50 million per year, over 10 years, congressional appropriation to really establish and to move the effort in pediatric data forward.

In June 2020, a group of 14 investigators and advocates participated in the ad hoc NCI Board of Scientific Advisors working group, and the group included advocates and experts in pediatric hematology/oncology, bioinformatics, clinical informatics, and drug development.

These individuals, with this diverse expertise in pediatric research, sought to define the pressing scientific questions that, if answered, would provide the opportunity to deliver

significant changes in outcomes for children with cancer. They also brought their experiences with many related childhood cancer data and research initiatives, their data repositories, tissue repositories, registries, as well as legislation such as the RAISE Act and the STAR Act.

The report that this group generated provided 24 distinct recommendations for NCI to consider in planning the implementation of the CCDI over the coming nine years. Those recommendations fell into seven primary sections and considered the current landscape of pediatric and AYA cancer research data, including areas of need and potential barriers to collecting and sharing the information in both a research and a clinical setting across many institutions. The group additionally provided suggestions for engaging with a wide variety of stakeholders to inform CCDI priorities, as well as ideas for innovation and transformation within this field.

I won't go through all of these recommendations, however, most of them can be

collectively summarized in five key recommendations. The CCDI activities the NCI has begun to pursue in the first two years directly address critical suggestions, and it's important to note that NCI has received these same recommendations in multiple forums validating their significance to the pediatric cancer research and care communities.

The feedback received at the CCDI kickoff symposium last year further affirms the goals and intent outlined in these recommendations. First and foremost, the NCI received strong encouragement from the community to provide adequate resources to reduce barriers and furthering of data sharing, broadly and openly, for cancer research through financial support, programmatic priorities, and thoughtful policy.

In addition, the recommendations included NCI taking a lead role in establishing a federated data infrastructure that identifies and connects data of all types, including clinical trials and outcomes, preclinical testing, molecular and

biomedical markers, and surveillance data.

It's really imperative that such an ecosystem will have the resources and the technology to manage, enrich, and analyze all of these different types of data to really enhance our ability to understand how to make progress in pediatric cancer. Further, maintaining a strong central resource catalog of all available pediatric data sets, bioassessments, tools, workflows, and resources, as it is being developed, should go a long way to serve immediate needs of multiple stakeholders across the pediatric gateway cancer and survivorship communities.

Keeping in mind the newly enacted law put forth in the RACE for Children Act, the working group recommended NCI look for ways to aggregate with preclinical testing and cancer model data in a way that could better inform rapid pediatric clinical translation, and particularly strategies that might identify or validate variants curated on the FDA Relevant Molecular Targets List to drive drug development in young patients.

Finally, more than half of the 24 recommendations, as well as their primary suggestion for transformative discovery, can be directly addressed through the development of a national strategy for biospecimen collection and archiving of germline and tumor samples from every child diagnosed with cancer, regardless of enrollment on a therapeutic trial.

The recommendations further encourage this strategy to include baseline genomic testing of all patients, including linking translational data to outcomes and providing deep sequencing of all relapse cases to ensure that we are learning from every patient, including those in underserved populations.

With those activities as a starting point, NCI is working to identify the many existing data types that we can build upon and to identify the gaps that need to be filled with an aim to make connections between data and people focused on helping children. Several important steps are needed to achieve these goals. We need to improve

the quality of the data, improve the consistency of the data, and most importantly, perhaps improve the accessibility of the data.

Childhood cancer data is often stored at a hospital or institution where the child is treated, and no single institution treats enough children to move all the research questions we have forward fast enough. We can learn faster to improve the future for children by connecting these data and sharing it with the entire cancer research community.

Although substantial progress has been made in the treatment of several types of childhood cancer over the past five decades, progress against other types has really been limited. One potential benefit of the CCDI is to make more rapid progress in improving existing treatments for childhood and AYA cancers and developing new therapies where none exist. Progress will also improve outcomes, quality of life, and survivorship.

The long-term outcomes of cancer go far beyond initial cancer treatment. Even when

long-term survival is achieved, many survivors may experience long-term adverse effects from the disease or its treatment. The late effects of childhood cancer therapy can have profound quality of life, physical, emotional, and other consequences for survivors, including a shortened life expectancy.

More research is needed to develop new and more effective and safer treatments. CCDI will facilitate the infrastructure that will allow researchers to learn from every child and cancer now and through their survival.

The current fiscal year is the second of ten years for which funds were allocated by Congress for this initiative. In the short time, we've seen the community come together to build the shared understanding of the challenges and opportunities that can be addressed by CCDI.

In fiscal year '20, NCI received $50 million to allocate toward enhancing the collection, sharing, and use of pediatric and AYA cancer research data. CCDI activities in fiscal year '20

focused largely on extending and augmenting foundational programs and in developing systems that will support future activities of the CCDI.

NCI allocated CCDI funds in 2020 for a range of research activities in childhood cancer and survivorship through intramural and extramural grants, contracts, and a system of administrative supplements. The 2020 activities started by building a foundation for data sharing, analysis, and access that will support and enhance childhood and AYA cancer and survivorship research in future years.

Now in our second year, CCDI leadership is actively planning research opportunities that will build upon advisory group recommendations, insight from diverse stakeholders in pediatric and AYA cancer communities, and CCDI activities initiated last year. The long-term vision for NCI and for the pediatric cancer community is to enhance data sharing, accessibility, and usability in a way that it's most beneficial broadly. We want to use this initiative in childhood and AYA cancers to serve as

an example for how the larger adult research and cancer community can also maximize their data to enhance benefit.

NCI has already begun efforts to develop a searchable online catalog to help users find and access existing pediatric data, tools, and resources. To this end, a landscape analysis of existing childhood and AYA cancer data and repositories was completed with the extra goal of understanding the potential for connecting or linking both systems and any analytic pipelines with NCI resources.

In addition, we are indeed creating an infrastructure for CCDI that will provide federated data from multiple community-driven and NCI-supported data resources, those that already exist and new resources under development. The first of these up and coming NCI-supported data resources for CCDI include a national childhood cancer registry of linked patient data and pediatric preclinical data commons that will maintain and analyze preclinical testing and cancer

model data.

CCDI was further able to support some administrative supplements to cancer centers and associated pediatric care centers and the initiative to link existing pediatric research and clinical care data, and tools, and pipelines for the development of NCI repositories and the National Childhood Cancer Registry.

Multiple supplements were awarded that included support for data and tools that will come from research on ultra-rare tumors or facilitate validation of clinical variants that could inform the FDA Relevant Molecular Targets List.

While efforts are underway to develop the National Childhood Cancer Registry and the Pediatric Preclinical Data Commons here at the NCI, we recognize that the CCDI activities starting in fiscal year '21 and moving forward will need to incorporate mechanisms to more actively federate with additional clinical and research data resources, both within and outside the NCI.

Our vision for establishing a wider

ecosystem includes many types of data from discovery science, patient care, population data, surveillance studies, and how that can be queried in a meaningful way by a variety of stakeholders.

Components of this federated pediatric care data ecosystem include an essential underlying data science infrastructure; enhanced cloud-computing platforms; and services that link disparate information stored in data repositories and registries.

Successful implementation of this infrastructure will require development and promotion of standards and tools for data interoperability, as well as a clear plan for sustainability and data governance to ensure the long-term health and function of this ecosystem.

A key objective for NCI through the CCDI is to make data more useful by creating easily accessible resources for translation and impactful analysis. CCDI has funded multiple efforts to develop and refine computational methods, analytic and management tools, and pipelines that can be

shared through NCI resources for use with a variety of clinical and research data sets. These projects include functional capabilities that address better interpretation of pathology images and patient reports; identifying and validating relevant molecular therapeutic targets; sustained data curation to repair various relevant data sets for integration with our NCI resources; and refining and scaling of natural language processing algorithms for real-time data capture.

CCDI has initiated efforts to enable data by creating user-friendly interactive data portals for resources and interfaces that are more readily accessible for multiple types of stakeholders. We're also taking steps to start developing frameworks for a harmonized pediatric data model and terminologies for pediatric cancer.

Traditionally, data has often been collected or generated for a specific need or hypothesis. However, the advent of larger data sets and innovative technologies is shifting this paradigm to include using data for novel discovery and

hypothesis generation as well. Creating more comprehensive and meaningful data sets through the CCDI will help the research and clinical care communities to better understand each type of data and its effects on pediatric cancer over time.

A critical objective for CCDI is to fill knowledge gaps in childhood and AYA cancers and survivorship by generating and augmenting key data sets for improved analysis. To further support and enhance essential NCI projects like Pediatric MATCH and the Childhood Cancer Survivor Study, CCDI has invested in molecular characterization and sequencing in germline and tumor samples of multiple tumor types, pediatric preclinical models, and secondary cancers arising in survivors.

We are supplementing research focused on germline genetic factors and environmental exposures from pesticides and agricultural toxins to further understand the biology of certain pediatric and AYA cancers, including risk and susceptibility in patients, survivors, and their

families. CCDI has additionally supplemented the development of molecular characterization of patient-derived cancer models and cell lines in pediatric brain cancer and solid tumors.

Finally, CCDI is committed to activities directly focused on biomedical research and clinical care that can be more readily translated into novel therapeutic options. These data types are critical to inform new treatments and improve the lives of patients and survivors.

Because NCI is fundamentally a research organization invested in many areas of cancer research, from epidemiology studies to preclinical and clinical models, we have a unique ability to facilitate the sharing of data that can be used to support the broader community in critical care and treatment for childhood and AYA cancer patients.

CCDI is supporting research and data collection that will help validate variants on the FDA's Relevant Molecular Targets List. We're also expanding the value of pediatric reference data through a robust Rare Pediatric Tumor Cell Atlas

and the abilities for translation of those data into the clinic.

CCDI has invested in pilot projects to improve and enhance efficiency of clinical trial data through comprehensive federal monitoring, safety reporting, as well as increased quality of data collected directly from patient-reported outcomes.

CCDI has invested in pilot projects, as well as seeking to improve therapies by supplementing research to explore clinical implications of specific treatments, including risks and benefits of pediatric proton therapy, genetic susceptibility, to adverse effects post-treatment.

In addition to planning these opportunities to federate data repositories and registries into the larger ecosystem, CCDI leadership is currently working on a strategy for implementation of a phased protocol that includes clinical and molecular characterization and rapid access to the resulting data with a goal of scaling to ensure availability to every child diagnosed with cancer

in this country.

In December 2020, Dr. Warren Kibbe and I presented NCI's strategic plan for CCDI in response to the CCDI working group recommendations, which included establishing a guidance structure to focus the ongoing and new activities, which you can see in this slide.

The National Childhood Cancer Cohort working group will focus on strategies to gather data from every child diagnosed with cancer, regardless of where they received their care, and includes the development of a national childhood cancer registry.

The Molecular Characterization Protocol working group will work to develop and implement a national strategy, building on existing efforts, including COG's Project Every Child, to offer appropriate clinical and molecular characterization to all children with cancer. This will include tumor and germline [indiscernible] characteristics and enable research using patient-level data in a secure and de-identified way.

The Data Platform working group is working to define a strategy and an approach to develop a platform to federate, aggregate, and integrate data from all relevant NCI-supported and community-based childhood data sources. This will be a system that can bring data of different types from different sources together in a way that incentivizes researchers to query the available data in new ways.

A cross-cutting issues team will address issues that affect each of the individual areas of focus in a collaborative and coordinated fashion, such as the use of data standards and data flow between systems, and the steering and engagement committees provide a high-level, strategic oversight in community outreach for CCDI to ensure that the initiative remains in line with the needs and priorities of the large childhood cancer community. Each working group is led by NCI staff and external experts, and all groups contain diverse expertise and advocates.

The Childhood Cancer Data Initiative is a

community effort committed to learning from every child by using data to improve treatments, quality of life, and survivorship. We're working to use each critical piece of data to help the research and clinical care communities understand how each cancer patient and their data can be used to improve the lives of children and of families everywhere. Thank you so much for your kind attention.

DR. PAPPO: Thank you very much, Dr. Doroshow. We will now proceed to the next speaker, Dr. Malcolm Smith.

Speaker Presentation – Malcolm Smith

DR. SMITH: Hello. I'm Malcolm Smith in the Cancer Therapy Evaluation Program at NCI, and I'll be talking on the National Childhood NCI targeted cancer data initiative with CCDI, and really drilling down on some of the things that Dr. Doroshow explained about how the CCDI project may be useful as a real-world and real-world evidence resource for pediatric oncology. And I do first want to thank Dr. Reaman and FDA for the

opportunity to speak at this important meeting.

As Dr. Doroshow explained, the Childhood Cancer Data Initiative is to learn from every child by better collecting data, multiple data types, improving quality, consistency, and the accessibility from every child; develop new treatments; and improve outcomes, quality of life, and survivorship.

The CCDI began planning this past year, and in year 1, some pilot projects were initiated, supplements, [indiscernible]. Some of these things are [indiscernible] during the presentation like the National Childhood Cancer Registry, the Pediatric Preclinical Data Commons, an Open Targets platform.

Supplements were given to cancer centers for submission of data to allow aggregation of patient-linked clinical and molecular data to begin to learn how we can take data from multiple cancer centers and [indiscernible].

[Inaudible – audio distorted] with Pediatric MATCH and doing the comprehensive genomic

characterization of approximately 500 patients with specimens from diagnosis and relapse, as well as germline, so we can learn more about the progression of genomic changes from diagnosis to relapse, and also more for the patients who did enter one of the therapeutic arms of Pediatric MATCH to learn more about the genomic correlates of response.

The CCDI has three major prongs that Dr. Doroshow described, and I'll be speaking to each of these, the National Childhood Cancer Cohort, the Molecular Characterization Protocol, and the Data Platform.

First, I'll speak on the National Childhood Cancer Registry. This builds on core data derived from cancer registries, state cancer registries, and the SEER registries. These data are extended and expanded to include additional relevant information such as detailed treatment data, genomic characterization, the trajectory of care from diagnosis throughout life, including second primary cancers and recurrent disease, and other

relevant factors related to risk and outcome such as residential history.

This registry will integrate within the CCDI federated data ecosystems, and in support it will include data on a broader set of patients and those covered at COG facilities. The majority of patients are seen at COG member institutions, but not all, and they learn more about who these patients are that are not seen at COG member institutions.

This is a conceptual framework for the National Childhood Cancer Registry. In the middle is the National Childhood Cancer Registry database, and this combines de-identified data submitted from SEER cancer registries, from the non-SEER registries, and it creates a virtual whole registry of de-identified patient data.

The data from the registries is supplemented, and if you look on the left side by other data sources, the ones that are in current use include LexisNexis for information about residential history and other items. There are

linkages to state vital records in the National Death Index and other linkages for demographic characterization.

[Indiscernible – audio distorted] -- how they can be incorporated into the National Childhood Cancer Registry. For example, additional state records like the birth records, blood spots; data from the Children's Oncology Group becoming part of the registry database; genomic and genetic data from multiple sources, and I'll say more about plans for Project [indiscernible] and data from [indiscernible] companies as well, about individual patient, there's clinical data, genomic data into this registry database.

This slide shows a schematic of how we envision the NCCR data products being accessed. Up at the top, you see the NCCR and its registry data, the virtual pool registry linkage, things like LexisNexis and other data sources coming into that.

The data outputs from that and the way the data can be accessed, some of these are similar to how data are accessed, for example, from the SEER

program now, so there will be published reports of the data, and there will be access to programs like SEER STAT, as you can see under number III under Canned Analysis.

But as well, there will be access to individual level data both for cloud analysis and for downloading individual level data for study. This would be for research projects that have undergone IRB review, but it will provide a way for the research community to access and make use of the data from the National Childhood Cancer Registry.

The next thing I'll talk about is the CCDI Molecular Characterization Project. Here, as Dr. Doroshow said, we do have a working group of experts charged with advising NCI on a national strategy for offering appropriate clinical and molecular characterization to every child with cancer so that every child would have access to the characterization needed for a precise diagnosis and information about prognosis, defining the potential from molecularly targeted therapies, as well as

creating a comprehensive molecular and clinical data set that would enable future discoveries. The working group will facilitate development of the Molecular Characterization Protocol that's described on the next slide.

This is a partnership with COG. The goal, again as Dr. Doroshow said, is to provide a nationwide genomic characterization platform to make state-of-the-art testing available to every child throughout the country, and then to develop ways to learn from every child by collecting the characterization data and clinical data for use by researchers.

This will be a pilot initially [inaudible - audio gap]. This may be as many as up to 3,000 patients per year. To walk you through how this is envisioned to work, the persons on the panel and in the audience who are COG members are well aware of Project Every Child. This is a non-therapeutic clinical trial that's offered to every child that presents to a COG member institution, and it allows for the collection of

data, clinical demographic data, on the patient and follow-up data on the patient, as well as the collection of tumor specimens and blood specimens for research purposes.

What's being built into Project Every Child by the Molecular Characterization Protocol is a specimen collected in Project Every Child and in the bio repository that will then be sent for clinical genomic characterization in CLIA-accredited laboratories; DNA analysis, either whole exome sequencing or NGS-targeted panels; RNA sequencing with a special focus on fusion; and then DNA methylation array analysis, which will be especially important for the CNS [indiscernible] patients.

These data will be available within 14 to 15 days, will be returned to the treating physician, and will be able to be used by the physician to either determine eligibility for a COG clinical trial, as well as to help guide the clinical care of that patient.

Another aspect of the molecular

characterization is that there's a research and discovery component shown at the lower-left side, where if there is nucleic acid remaining after the clinical characterization, then additional studies can be performed to better understand the cancer, whole genome sequencing, single-cell RNA analysis, and others.

Perhaps most importantly, the data -- the clinical demographic data, the follow-up data from the patient -- is collected through Project Every Child, as well as the molecular characterization data, and will be in an NCI data repository so that it can be made available to the research community to make discoveries relevant to the treatment, diagnosis, and prognosis of children with cancer.

Where we're at with this, the goal is to have the protocol molecular characterization aspect of Project Every Child activated in the second half of 2021. We're working with Leidos Biomedical to identify vendors for the sequencing, with plans for one vendor for DNA or RNA sequencing and DNA methylation analysis. There could be up to three

in total, or if one can do everything that would be great as well. The proposals have been received, and they're currently undergoing review through Leidos Biomedical.

So just to summarize this project, it will provide clinical genomic characterization, initially focusing on the CNS tumors, sarcomas and selected rare cancers; DNA sequencing; RNA sequencing and the DNA methylation arrays; and additional research and molecular characterization when there are bank specimens remaining after the clinical characterization. Then this data goes into the data repository so that it can be useful for future research.

Another thing I wanted to quickly discuss with you is the Pediatric Preclinical Data Commons and Open Targets platform. This is not necessarily useful for real-world data, though persons interested in real-world data as part of pediatric drug development will probably also be interested in this project as well.

What we're planning through CCDI to do is to

develop an open-target instance for childhood cancers. Open Targets is a large-scale, multiyear, public-private partnership that uses human genetics and genomics data for systematic drug-target identification and prioritization. There's the Open Targets platform that integrates public domain data to enable target identification and prioritization, and its genetic portal identifies targets based on GWAS and functional genomics.

The CCDI is supporting development of an Open Targets instance for childhood cancers, and this is being led by Leidos with Dr. John Maris and Deanne Taylor from CHOP, working on the project. The idea is there is an Open Targets pipeline, and through that pipeline, we'll be adding pediatric cancer data.

I show examples of the type of data that would be added: project genomic data; the Pediatric Preclinical Testing Consortium data; KidsFirst genomic data; other brain tumor genomics and clinical data; as well as adult reference data like GTEx and TCGA. Open targets have platform

data as well, as shown on the figure.

The goal would be, then, to use the Open Targets' analytic capabilities and the pediatric data incorporated into it to be able to address questions like: is there a genome target of interest that is not currently on the Relevant Molecular Targets List that perhaps should be added; if there's a new drug with a specific target being developed; are there specific pediatric cancers for which that drug and its target might be relevant; and for a research or science specific childhood cancer, what are the specific Relevant Molecular Targets List targets that might be most relevant to that childhood cancer?

This project is getting off the ground now, and we hope will be useful for pediatric drug development. Again, the idea is that there is an Open Targets platform and that we can add pediatric cancer data to that platform, curate the data, develop additional analytic capabilities to make use of the data, and really inform pediatric cancer target identification and prioritization.

Another thing to describe is the NCTN and NCORP Data Archive. This actually predates the CCDI project, but it's very relevant to the real-world evidence and real-world data discussion.

The NCTN/NCORP Data Archive is a centralized controlled-access databases that contains individual patient-level clinical data. It promotes the sharing of NCI-supported clinical trial data from the NCCN/NCORP programs and fulfills the requirements for data sharing, and it complements other NCI data sharing activities that focus on other things like genomics, or imaging data, or the sharing of specimens which uses a Navigator portal for disseminating that information.

The Data Archive includes clinical data from phase 3 trials from the NCTN program that were published as of January 1, 2015 and for the trials that had non-primary publications published as of April 1, 2018. The submissions of the data are due within six months of the earliest publication date, and for each trial, there's a clinical data set and

associated data dictionary and meta-data. The data sets are patient-level, de-identified and include values for all of the variables that were used in the publishing of these.

Access to the data requires completion of a data request form and a signed data use authorization form. But it's important to note that the NCI review of these forms is for adherence to legal and administrative requirements, and there's not a scientific review for the data requests.

This slide just shows the number of trials for which there are data in the NCTN/NCORP Data Archive. Of note here, there are 38 COG clinical trials for which data have been submitted. These are data from stage 3 COG clinical trials.

The last thing I want to discuss is the Childhood Cancer Data Platform, and this really is the glue that holds the whole thing together. It's designed to curate data from multiple children's cancer institutions and community-based and NCI-supported childhood AYA data resources; to make

patient-level data available from these sources; to provide easy access to enable deep analytics; to support interoperability among existing data resources and to provide tools and other resources to facilitate this; and to provide a central portal to find and analyze childhood and AYA cancer data.

The final point I want to make -- and these are really just some caveats or cautionary notes -- is I really think that the Childhood Cancer Data Initiative can make important contributions in providing real-world data, but there are challenges.

The challenge of small patient numbers really can't be overestimated. You have low incidence cancers, and for many of these, we further subdivide them by molecular biomarkers. Take a tumor like atypical teratoid rhabdoid tumors, or ATRT, it's already rare. And for a particular project or drug development program, it may be a particular subset, a molecularly-defined subset, of ATRT that's most relevant. So the small numbers are just extremely challenging.

There's a challenge with variable outcomes and diagnosis. Really, aside from DIPG, which has a terrible outcome, [indiscernible] -- for most other childhood cancers there is variability in outcomes. It depends on multiple things, some of which we understand, some we don't. But molecular factors, the tumor-staging factors, and the ability for surgical resection and [inaudible – audio gap] -- relapse. Much of the drug development we're talking about may occur in that setting.

So these challenges become particularly important, the prior therapy that patients, receive their prior response to therapy and, again, molecular factors [inaudible – audio gap] -- and then the overall general challenge of data collection after initial treatment failure.

When I spoke of the data archive, those were COG [inaudible – audio gap] patients newly diagnosed. There are fewer trials from children that relapse. There are far few patients that enroll on those trials, so there's limited data, and there are real challenges in collecting data

after the initial treatment failure.

The final point is the challenge of time required to identify sufficient numbers of cases in low-incidence populations and then follow outcomes over several years.

I bring this up because I do think the Molecular Characterization Protocol will be providing really useful information that could be helpful in providing real-world data for various projects. But if we started this year and we enroll them, it's going to be two or three years, at a minimum, before we begin to have the kind of follow-up that would be important.

Then because these are rare cancers, to get enough patients, it may take two or three years of enrollment to get sufficient numbers, and then another two or three years for adequate follow-up. These are all challenges just to be cognizant of when we talk about our ability to use data sources like these for real-world evidence.

My point in ending with this isn't to say that getting real-world, fit-for-purpose data from

childhood cancers through programs like the one I described is impossibly difficult because I don't believe that. But there are challenges in the pediatric setting that may not apply to the adult cancer setting, the more common adult cancers that may not allow quick, or easy, or cheap solutions; and furthermore, the time and resources that will be needed to prepare the high-quality data that will be required for the data to be used for generating real-world evidence.

So I again thank you for the invitation to speak and will be glad to entertain questions during the question period.

Clarifying Questions

DR. PAPPO: Thank you very much, Malcolm.

We will now take clarifying questions from the speakers. 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 that we can move on to the next panel member.

Now we will be ready for questions, and we're going to start with Will Parsons.

DR. PARSONS: Thank you. This is Will Parsons from Texas Children's Hospital and Baylor College of Medicine. This is a question for either Dr. Doroshow or Dr. Smith.

One comment first is I'm a strong proponent of the CCDI project and its potential to provide an invaluable framework for pediatric cancer research. I guess one question I was thinking about as I heard the presentation was whether you could comment a little further on how this CCDI pediatric cancer data ecosystem is anticipated to interface or complement similar adult initiatives, both within NCI as well as other institutes, such as

NHGRI.

It's critical to maximize the benefit of the data, not just for AYA patients, but also in terms of trying to make inferences about molecular data, responses to molecular therapies and immunotherapies, and then also potentially for cancer susceptibility questions, many of which are diseases that are more penetrant in adulthood.

Malcolm commented a little bit I believe on this, on probably the Open Targets project, but I'd be curious to hear a little more on your thoughts about interaction with the adult oncology world.

DR. SMITH: Dr. Doroshow, do you want to take the lead in answering that?

DR. DOROSHOW: Sure. I'll give it a shot since I'm a medical oncologist. Let me just say, to the best of my knowledge -- and I have been in charge of the Division of Cancer Treatment and Diagnosis for 17 years, and nothing even remotely like CCDI exists or is planned for adult malignancies, and it would be incredibly important to do so, if we could do so.

But really, one of the major features of the CCDI is as a test of whether or not we can get all of the various communities -- and they're a smaller number of pediatric communities -- to actually work together to make this goal happen, because if it's possible, it gives us a stimulus that would be very hard to resist; in particular, a stimulus to make public the enormous amount of data that exists.

I could offline talk for hours about how long it took to get the patient Navigator and the Archive up and running. It took a decade or more, and we only have phase 3 trials. So I think these are just enormously important activities, because if it can be shown to be done in the pediatric setting, then we have a way forward, I think, to do this in the larger adult cancer community.

DR. PAPPO: Does that answer your question?

DR. PARSONS: Yes, unless Malcolm had any other comments.

DR. SMITH: No, I don't have anything to add to that, Will. Thanks.

DR. PARSONS: Great. Thank you.

DR. PAPPO: Next is Dr. Reaman.

(No response.)

DR. PAPPO: Greg, do you have a question?

DR. REAMAN: Sorry. I'm unmuted.

It's Greg Reaman from the FDA, and I'd like to also extend my thanks and appreciation to both Malcolm and Jim for their presentations. I think the whole CCDI is really an unbelievable opportunity for the childhood cancer research community.

In exploring the potential for real-world data that might be able to inform external controls or historical external controls, I'm concerned that the NCTN Data Archive only includes phase 3 frontline trials and not other studies, and it's really those other studies of more novel agents, perhaps, that might be useful.

Are there any plans to extend the NCTN Data Archive to include phase 1/phase 2 studies? And could you also comment if this is the totality of NCI-supported studies? Some of the other early phases, the Clinical Trial Network, the PBTC, are

they all part of this in the childhood cancer data platform? Thanks.

DR. DOROSHOW: I'll let Malcolm address the second question. I think the first question is a great one and really a very straightforward answer, because we would do it in a heartbeat if we had the resources.

Actually, both the Navigator and the Archive were started with actually no additional resources, and I think that it would be enormously useful to put the phase 2 -- I don't know about the phase 1 data, but surely phase 2 --

DR. REAMAN: Phase 2.

DR. DOROSHOW: -- data would be incredibly useful. But without the resources to assist the groups to do what is a significant activity -- it costs money and people -- it's hard for me to mandate something like that without having the resources to try to make it happen.

DR. REAMAN: Okay. Thanks.

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

DR. REAMAN: It does. Thank you.

DR. PAPPO: Tobey, you're next.

DR. MACDONALD: Hi. It's Tobey MacDonald from Emory University. I guess I suppose this question's for both of the presenters.

Seeing that currently we at our single institution do a lot of sequencing action on all the cancer patients that come through, trying to then select a drug for the target remains very challenging. There's usually still a menu, and then cause-and-effect relationship is complex and difficult to assess.

So I wonder after all the characterization has been performed and the linkage to clinical data, is there an idea for a future effort to look more on a functional level to establish cause-and-effect resistance mechanisms, high functional screens either from targets or drug screens, that would complement all of this information? That's my question.

DR. DOROSHOW: Malcolm, do you want to give it a shot? Or I can; whatever you want.

DR. SMITH: Okay.

Well, I can say one thing about that. Certainly for Open Targets, there's an interest in having functional data incorporated into it for precisely the reasons you are describing, Tobey. There's a recognition of the importance of the functional screens and finding ways to incorporate them into the Open Targets platform.

In terms of other things beyond that, I would defer to Dr. Doroshow in terms of other programs that might extend in the direction that you're asking about.

DR. DOROSHOW: The most pertinent is a network that we formed with Moonshot money about four years ago to study drug resistance and functional genomics of drug resistance, and that has been very productive, all focused on adult cancers, just to make it clear, but focused in the way that you elucidate.

That has just been renewed, and it will be more focused on resistance rather than on mechanisms of sensitivity, and essentially a

hundred percent will focus on functional genomics. And there are more initiatives that are being considered about how to have a broader scope of functional genomic screens that are brought to bear across the board on a variety of diseases.

DR. SMITH: Tobey, I could add one more thing. Dr. Doroshow's comments brought to mind the pediatric oncoprotein consortium; again, another Moonshot initiative focusing on the Ewing sarcoma fusion; synovial sarcoma fusion; the [indiscernible]; the alveolar rhabdomyosarcoma fusion; and the fibrolamellar hepatocellular carcinoma fusion. I think that's all of them.

The grant, there are nine altogether. Probably most of them would have some genomic component of it. It is something where there's certainly interest in both generating more data and making that data available.

DR. MACDONALD: Thank you. That answers my question, and I continue to hope that it gets extended broader to the pediatric cancer. Thanks.

DR. PAPPO: Next is Ira.

DR. DUNKEL: Hi. Ira Dunkel, Memorial Sloan Kettering. This is a question for Malcolm.

Malcolm, you may have already addressed this and I missed it, so excuse me if you did. I'm wondering for the ultra-rare tumors, such as perhaps the TRT and subgroups that you mentioned, where accumulating data and/or tissue is going to be a longer term process, whether this system allows submission of data or tissue from international sites or consortia.

DR. SMITH: That's a great question, Ira. We don't have that built into any of the projects that I talked about, but I think if the data are available and there was willingness for submission, there would be interest in including that. If you know of specific things that we can contribute in that area, we'd certainly be glad to set up conversations about it.

DR. DUNKEL: Thank you very much.

DR. PAPPO: Tobey, is your hand still up or you have another question?

DR. MACDONALD: No more questions. Sorry.

DR. PAPPO: Okay.

Does anybody have any other questions? Otherwise, we can proceed with additional FDA presentations.

(No response.)

DR. PAPPO: Okay.

We will now proceed with an FDA presentation by Dr. Ann McMahon.

FDA Presentation – Ann McMahon

DR. McMAHON: Hello. Good afternoon. The title of my talk is Real-World Evidence to Assess Pediatric Medical Product Safety. I work in the office of Pediatric Therapeutics, in the Office of Clinical Policy and Programs, in the Office of the Commissioner of the FDA. This is my disclaimer, and this is my outline for the brief talk that I'm going to be giving. I will give an overview of pediatric real-world data and evidence with respect to safety, and give some examples.

The Pediatric Advisory Committee, or the PAC, was congressionally mandated in 2002. We mention it here to give you a background on how

pediatric product safety information comes to light generally at the FDA.

It was mandated that 18 months after pediatric labeling changes, FDA will conduct postmarketing safety reviews of those drugs with labeling changes and present the information to the PAC. OPT, my office, works with the Division of Pediatric and Maternal Health and the Office of Surveillance and Epidemiology to establish a more robust pediatric pharmacovigilance strategy. There may be a higher percentage of oncology products going to the PAC with the Research to Accelerate Cures and Equity, or RACE, for Children's Act.

With that background, I'll launch into my talk about pediatric RWD and RWE.

What are the special considerations in pediatric real-world data or real-world evidence? Data that may be especially important in children are birth date, gestational age, data related to families such as demographics and health status, and records outside the healthcare system such as school performance and school records.

Other special considerations in pediatric RWD/RWE are growth and development both in infants and children, measuring both weight and height, and performed by pediatric clinicians. In addition, other examples of important issues in pediatrics include large enough sample size to detect rare adverse events, as a number of people have talked about, and having a denominator that is actually within the database.

I want to give you some examples of pediatric-oriented databases in North America. Notice that these databases all used electronic medical records. All had inpatient data in the databases. A few had outpatient data as well, and all allowed calculation of incidence rates within the database. In other words, both numerator and denominator were present within the same database.

Notice also that most of the databases have the capacity for longitudinal data analysis, something that is particularly important in pediatrics and in oncology.

This slide shows some more attributes of

pediatric databases in North America. The biggest sample size is 6 million, so these are relatively small databases. With the exception of the Vermont Oxford Network, the date of earliest data collection was actually rather recent.

The following are two examples of studies highlighting pediatric RWD/RWE safety research. This is a use case of pediatric RWD safety. It is the study about the use of octreotide in infants and children. Octreotide is a synthetic peptide analog of naturally occurring somatostatin used off label in children less than 6 years of age for hyperinsulinism.

Notice that there is a lack of control data on efficacy or potential adverse events from off-label use. In this study, there were only 103 patients, and during the study period, 2 patients died, one from necrotizing enterocolitis 3 days after octreotide treatment. There were comorbidities in that patient that died of NEC, which included patent ductus arteriosus, respiratory distress, and heart block type 1.

There were 11 other serious adverse events in the 101 surviving patients.

This slide shows clinical information for infants treated with octreotide for hyperinsulinism. You can see that we do not have complete clinical information for every variable. In general, the patients were full term and the octreotide daily dose and duration were quite variable.

The next use case is a study of acute kidney injury during treatment with IV acyclovir for suspected or confirmed neonatal herpes simplex virus infection. The objective was to describe the epidemiology of and risk factors associated with acute kidney injury, or AKI, during acyclovir treatment in neonates.

This was a multicenter study. There were 1,017 infants, with the majority receiving short courses of acyclovir, and in the end, there were 4 associated outcomes with acute kidney injury after Cox regression. Confirmed herpes simplex virus disease was one; receipt of at least to

concomitant nephrotoxic medications was another; receipt of mechanical ventilation was another; and admission to an intensive care unit was another; so sicker infants and those exposed to nephrotoxic drugs were at high higher risk from acyclovir.

A group of us performed a systematic review of pediatric RWE safety and efficacy. The objectives were to describe the state of RWE in pediatrics by identifying observational studies published during 2016.

It was a systematic review. A small body of studies, 29, were categorized as using RWD to assess medication safety or effectiveness in children, and the studies varied in age, groups, diseases, conditions, and methods. Most studies relied on data collected at single institutions, and a quarter of these studies did not use well-established statistical methods to control for confounders.

Some takeaway points regarding pediatric RWD/RWE from this talk are in working with pediatric RWE/RWE, it can be difficult to adjust

for growth and development, and it can be difficult to obtain records outside of the medical record system, such as school records.

Confounding cannot always be fully controlled. As an example, in the acyclovir example, the sicker patients were more likely to have AKI, and it can be difficult to unbundle variables associated with, quote, "sicker" unquote, patients in such a study. Samples can be small in pediatric patients with rare diseases, especially if using medication off-label such as octreotide for hyperinsulinism.

In conclusion, RWD/RWE in pediatrics may be useful to fill in gaps in pediatric knowledge. RWD may help to identify a more diverse population from a demographic perspective. RWD may enable reflection of product use in the general population, and RWD may open up understanding of the variable nature of underlying illness outside randomized clinical trials. And this slide is for your reference. Thank you.

DR. PAPPO: Thank you very much for your

presentation, Dr. McMahon.

We will move to the next presentation by Dr. Bruce Carleton.

DR. CARLETON: Hello? Can everyone hear me alright?

DR. PAPPO: Yes.

DR. CARLETON: Great.

Guest Speaker Presentation – Bruce Carleton

DR. CARLETON: Thank you very much for the opportunity to speak to the committee today. I'm actually humbled by the opportunity and also excited about all of the work that's being done, both by government agencies and those external to government, to improve child health; and a special thanks to Dr. Pappo and Reaman for the invitation for today, and Dr. Chen and Yvette for helping me cross the technology barriers to be able to present this.

I want to talk to you a little bit about what we're working on in Canada. We are a very large country with actually quite a small population, so we relish the opportunity to work

with FDA and other agencies to improve child health, particularly in pediatric cancer.

The paradox of modern drug development, of course, is that the clinical trial population gives us information about population efficacy and safety, but it is actually the individual patients we treat, which vary widely.

In our country, in 2007, our regulator, Health Canada, did an analysis and showed that 50 percent of serious adverse events are only uncovered after the drug reaches the market. As such, I'm particularly interested in the three outcomes that are possible with drug therapy, obviously the drug working, the drug not working, or the drug causing harm, and these overlap.

This simplistic bell-shaped curve that I've drawn on response could be looked at very simplistically, as the top of the bell would be the average response, the right tail would be those that are super responders, and the left tail would be those who have no response. Perhaps harm can follow the same pathway, no response but serious

harm, average response and some harm, and super response and no harm.

All of these things overlap, and any outcome may not be sustainable over time. It's the heterogeneous disease experience of children with cancer that makes measurement of benefit-harm over short time periods.

In Canada, to address some of these issues, we built a network to look at biomarkers of drug response in children. Most of these patients are children with cancer. Rationale for that is that they actually experience a lot of the most serious adverse effect. Potent pharmacologic agents being used to prolong life can do that.

We have the centers across the country, from Victoria actually on Vancouver Island, which is represented and hard to see but on the left-hand side, which is actually larger than England on the scale here, all the way to St. John's Newfoundland. We have pediatric and adult centers. The pediatric centers are funded, so the people that do the data extraction and the clinical characterization, the

assessment of temporality between drug and outcome, are all paid by the network itself, which is grant funded by federal and provincial competitive. grants.

The recruitment of subjects has been much more robust than we expected, beginning in 2004. The intercept begins at zero because it's too hard to show that now over the course of time. I wanted to say that the curve looks like it's tapering a bit, and it is actually because what we're doing now is not just recruiting new subjects, but actually following longitudinally the subjects that we do have.

In some cases, our follow-up times are in decades. That would be an extreme case. But we do have up to 20-plus years of data for some of these patients and their drug outcome experiences.

One of the areas that we began thinking about when we started as a pharmacogenetics network was to look at cisplatin based upon the concern about hearing loss, which was more frequent and severe in children. In fact, our own real-world

data show that 37 percent of our patients developed CTCAE grade 3 or grade 4 since 2005. Most of these would be grade 3, but because platinums are heavy metals, one of our key outcomes is to characterize hearing loss over time, since you can detect platinums in the circulating serum of patients for decades after treatment. Most of the hearing loss that we see occurs within the first 4 to 6 months at the present time, but there is some suspicion of ongoing ototoxicity.

So we naturally began this, again, on the early 2000s by looking at patients with a variety of tumor types, something that many on the disease side might bristle a bit about, that we've combined tumor types. But we're interested specifically in ototoxicity from cisplatin. And of course controlling for dose and exposure, we were able to find some interesting data.

I want to point out the fact that this design is a bit rare in pediatric cancer. I continue to review papers that have control groups that include grade 1 toxicity. So they aren't

really controls if you're trying to find a variant that is related to toxicity, particularly if that variant is shared between patients who have mild toxicity and those that have more significant toxicity. But our design was to eliminate the mild toxicity cases from the analysis because we didn't know if they were just mild at a point in time.

In this early -- [inaudible – audio lost].

DR. PAPPO: Dr. Carleton, it looks like we've lost you.

(No response.)

DR. PAPPO: Dr. Chen or Joanna, can we check if he's connected?

DR. CHEN: Thank you for your patience. Please hold while we try to get Dr. Carleton back online. I can see he's connecting momentarily. Thank you for your patience.

DR. CARLETON: Hello? Can you hear me now again?

DR. PAPPO: Yes.

DR. CARLETON: Okay. I very much apologize, but technology. Sorry about that.

So getting back to this issue, what we identified in our early work within the network were these variants in methyltransferases, which were somewhat perplexing because how are methyltransferase variants related to cisplatin biotransformation? No one knew.

You can see that in the early phase, what we were thinking of was postulating mechanisms by which the loss of TPMT function or the loss of COMT function could increase cisplatin toxicity. This is early work where we're identifying biomarkers. They're very strongly associated with toxicity.

In this work published in Nature Genetics in 2009, we showed that if you increase the number of risk alleles, you increase the severity, the frequency, and the earlier onset of hearing loss, and that the differentiation between patients occurred very quickly in the days post-cisplatin starter therapy. You can see at the intercept that these lines differentiate very early, and I mentioned that earlier. Most of the hearing loss that we see tends to happen about 4 to 6 months

after treatment initiation.

As a result of some work that I did with the Office of Clinical Pharmacology and independent review of the data that we gave them, raw data, at FDA, there was a label change warning of the risk of genetic variants in 2012. But much of the work has continued since then, and I wanted to show you how we continue to use the real-world data to further explore and move towards treatment and management of this condition because that's really the goal of the network. It's not just to define genetic biomarkers; it's to understand the biology of harm, the biology of non-response, the biology of super response, for example, and then begin to move those ideas into clinical trials.

The next step in this process was to explore the impact of these variants on cellular responses to cisplatin to validate markers that we were finding that were highly associated with ototoxicity, and we did this by expressing them in two particular inner ear cell lines from the organ of Corti, murine cell lines, and then monitor the

impact by cytotoxicity and also activation of a cisplatin response chain that showed up in some of our early genome-wide work.

What we found was that the low-activity variant, star-3A [ph] for example -- and there are some other findings, but I only have a few minutes, so I'll just focus on this particular variant -- this particular low-activity variant, expression of this sensitized cells to cisplatin cytotoxicity and essentially creates a cellular phenotype consistent with higher effective cisplatin concentrations in the inner ear. This suggests that there is a role of TPMT in the cytotoxicity of cisplatin, and particularly its ototoxicity.

The next step was to look at TLR4 expression, which we knew, through work, was induced by increasing cisplatin concentrations. By showing this TLR4 induction, we began thinking about what this could mean in terms of preventing toxicity.

These particular low-activity star-3A

expressing cells showed significantly increased TLR4 response to cisplatin compared to the wild type, so that, again, suggests that we've got an interaction here that is particularly important in understanding toxicity from the original real-world evidence that we accumulated across Canada.

This work continues to develop, and one of our post docs, who is now a professor of immunology and medical microbiology at the University of Alberta in Edmonton, has continued the work that he started with us years ago.

What we're now looking at are a number of other studies that I want to show you; first that if we delete TLR4, we can increase the viability and decrease the apoptosis of cells, even at higher cisplatin concentrations. This was done with two methods, both flow cytometry and propidium iodide staining and Annexin V staining as well.

The next thing that is interesting is that when we delete TLR4, we actually decrease the reactive oxygen species generation and proinflammatory cytokine secretions in response to

cisplatin. This is important because the methyltransferase variants themselves are very much integrated into homocysteine and reactive oxygen species pathways, which are much more complicated than just a simple metabolic picture of cisplatin itself in terms of its pharmacokinetic biotransformation.

What we've now been doing is actually trying to inhibit TLR4 using a small molecule to actually prevent cisplatin ototoxicity in a variety of cell lines. This TAK-242 antagonist that we've recently published binds to the intracellular toll interleukin receptor in the domain of TLR4 and disrupts protein recruitment. This is very exciting news. Some data that we haven't presented today now is looking at whether this disrupts cancer cells cell lines at the same time, and it appears it does not.

These early works are moving us towards what we would like to do as a network, which is to move to interventional trials, trying ways to either protect against hearing loss from platinums or

designing new agents that avoid these pathways of toxicity.

We've also targeted five other critical pediatric oncology adverse drug reactions for work. I've shown you the number of patients here. We're very proud of what the network's been able to do; not just do we have solid numbers across Canada using all of our 16 oncology treatment centers, but we actually have a very high level of scrutiny and data for each of these cases.

I could tell you, for example, how many patients per center are included; how many patients were removed; why they were removed; how many genotyping failures have occurred; and why the failure occurred; for example, if they failed identity by descent analysis, which could indicate poor DNA quality, and if there's mismatched reported and imputed sex, for example.

We occasionally run into samples who are cousins or have a degree of relatedness to each other that we're not comfortable with in the analysis. We have an internal validation process.

All of the clinical data come through and are collected at individual sites, and are re-reviewed by an expert panel. So we sometimes remove cases that were originally thought to be, for example, pancreatitis and later turned out not to be.

So that's something that's been really, really important to our work, is to ensure that we have quality data and very deep phenotyping data about patients. Because this is an active surveillance network, we are not limited by just the data that we've collected. We can actually go back into the records and collect more data if needed, and sometimes that's necessary because the case definitions for these reactions advance over time.

Lastly, I wanted to mention that it's been my goal all along, since the early 2000s, to make these data globally accessible in a database that is both clinical and genomic, and all of the data would be there to facilitate new discoveries worldwide to replicate work that's been done elsewhere, to create new analytical methods, and

begin to further improve the safety of drugs in pediatric oncology.

I think it's important to note here that reproducibility is important, but I think it is less important than it is often cited to be. To quote I guess from the National Academies' recent editorial on this issue when they were looking at climate change, they mentioned in their report that "reproducibility" -- this is the PNAS editorial -- "is neither a necessary nor sufficient condition to ensure the validity of conclusions drawn from research because a study may be inherently flawed and inappropriate for supporting a conclusion, and yet could be fully reproducible."

So certainly reproducibility and replicability play an important role in achieving rigor and transparency. And for some other lines of inquiry, replication is one way to gain confidence in scientific knowledge, but for other lines of inquiry, direct replications may be impossible because of the characteristics of the phenomena being studied.

That's one of the issues that we run into in pediatric oncology with different centers treating patients actually quite differently in many cases, and we've run into this before; that it can be very difficult across centers to find exactly the same findings for the same patients.

I think that I'll conclude by saying that I agree with the National Academies that "the robustness of science is less well represented by the replications between two individual studies, or reproduction of one or more studies, than by a more holistic web of knowledge reinforced through multiple lines of examination and inquiry," and that's what we're doing with our real-world data in Canada with these cell studies, and soon clinical trials. Thank you very much for your attention.

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

We will continue to our next speaker, who is Dr. Doug Hawkins.

Guest Speaker Presentation – Douglas Hawkins

DR. HAWKINS: Thank you. It looks like my

slides have come up. I want to thank again the organizers for putting together this session. This has been very informative.

I'm going to provide some of the Children's Oncology Group's perspective on some of the uses and potential limitations of clinical trial data for the purposes of an external control. I'll also talk a little bit about some of our biology and registry studies, and then end by discussions of the COG registry, Project Every Child.

Many of you know a lot about COG, but just to make sure, COG was formed in 2000 as the merger of four legacy pediatric oncology groups. It's the one NCI-funded NCTN member that is devoted to pediatric cancer. There are four others in the United States devoted to adult cancers. There are over 200 institutions worldwide with most in the United States, but we have members in other countries, including Canada, Australia, and New Zealand.

We have conducted, since the inception of COG, over 300 clinical trials that included IND

agents, and we estimate that approximately 90 percent of children with cancer are seen at COG institutions, although this probably needs to be revisited.

This gives you an idea of the geographic reach of the COG centers within the Continental United States, and then to also look at this on the global level showing the member institutions in Canada, Australia, New Zealand, and one in Saudi Arabia. So this really is a geographically very diverse group.

I think in contrast to many cooperative groups that serve adult indications, we have a fairly good penetration or enrollment of children on clinical trials. This is a more recent analysis from 2004 to 2015, looking at enrollment on frontline COG studies using SEER data as the benchmark. You can see that in the youngest of patients, nearly 30 percent enroll on a frontline COG study, although this percentage drops off dramatically in the teen years, and then in young adulthood, but this involvement is variable across

histologies.

For the most common malignancies, including ALL and lymphoblastic lymphoma, in this era, nearly 60 percent of children in the United States enrolled on a COG frontline study compared to the SEER data. This dropped off dramatically across different histologies to a low of 3 percent. Again, this is just looking at the 0 to 9 age group, but similar data was seen in 10 to 19 years.

How this is achieved, I think it's really important to understand that COG is not a group of large elite institutions. The ability to enroll to COG studies is really the aggregate activity of hundreds of institutions.

This is looking at data. Each bar here is an individual institution, and they're given an inverse size. So these are the smallest institutions or the lowest accruing, and these are the highest accruing institutions over a three-year period on our frontline phase 3 and pilot studies. You can see that half of all the enrollments on COG studies are contributed by 46 of the largest

institutions. But in order to get the other half of our enrollments, it requires the aggregate activity of over a hundred institutions, small and medium-sized institutions, across the network.

So in other words, the enrollments on COG really require all institutions, both, small, medium, and large, and I think that's what gives us some of our geographic diversity.

Now I'm going to talk a little bit about some of the potential uses and limitations of our historical data from clinical trials for the purposes of an external control. To illustrate this, I'm going to take an example, which I think is one of the more extreme examples, of how it is really essential to make sure you control for a key biologic feature.

This is an older publication looking at infants with metastatic neuroblastoma. It's a fairly large cohort of patients. It looks like we have a fairly stable event-free survival curve. And if that's all you knew, you might be able to use this as your external control.

But there is one biologic feature that when added to this analysis showed dramatically different outcomes, and this may be one of the most dramatic Kaplan-Meier curves ever published, looking at the outcome for children who had MYCN non-amplified neuroblastoma versus those that had MYCN amplified neuroblastoma. And if one did not control for this one biologic feature, and one did not have these data reliably, it would be very hard to use the data set for the aggregate population as your external control. I just use this as a point of illustration of how essential some features are for control.

Also staying with the theme of neuroblastoma, therapy changes over time. This is a recent publication from the Children's Oncology Group, comparing children with high-risk neuroblastoma who either received two transplants versus one transplant. We see that therapies evolve over time and outcome evolves over time. So a historic control that might use patients who received a single transplant may not be relevant to

the therapy that's given currently, where tandem transplant has been adopted as a standard within the Children's Oncology Group.

There are other limitations to using COG data, and I'll go through them quickly. In some cases, the molecular marker of interest, the ones that you might want to control for, may not be present in all of our historic data sets. And again, staying with the neuroblastoma example, we know that ALK alterations are a major area of focus, and yet we don't have data on the ALK status in all of our patients, including our historic data sets.

COG has relatively limited late toxicity data, especially beyond 10 years from enrollment. Our data, when we collect them, are not collected necessarily with the idea of a regulatory filing, so when we're asked to provide historical data, it may not fit the need for a regulatory filing without a great deal of work.

I think in most cases, people are looking for outcome after recurrence. That's where you're

really trying to get a good historical control group. Within the Children's Oncology Group, we put very little effort into characterizing what happens to patients other than life status after recurrence, so how patients are treated and what other events they may have after an event is not well characterized other than life status.

I'm now going to talk a little bit about our biology studies and how these might be used as a source of non-clinical trial data, and I'll illustrate, again with an example of neuroblastoma, a biology study that's been open in the Children's Oncology Group for over 20 years.

Over 11,000 children have enrolled in this neuroblastoma biology study. It was used for the purposes of biobanking, central pathology review, as well as centralized tumor testing. Enrollment on this biology study was required prior to enrollment on our clinical trials, and this biology study captures the vast majority of children with neuroblastoma in North America. We estimate 70 to 80 percent of all cases in neuroblastoma and North

America are participants in this biology study. So this may be a real-world data set since it has such a large proportion of the total population.

This biology study comes with clinical annotation, including outcome data. There's a manuscript under review, where outcomes comparing those enrolled on the biology only were those who enrolled on biology plus clinical trials and showed that the overall survivals were relatively similar. So the biology study outcomes could be used as an internal standard, I think.

Another example of a biology study within COG is the renal tumor study. This was started in 2006. There are over 6,000 patients enrolled. It had a similar purpose of biobanking, central pathology, but also imaging review and centralized tumor testing. It was also required for enrollment on clinical trials.

Within the United States, we estimate that 90 percent of children with renal tumors, based on SEER data, have also enrolled on this renal tumor biology study, so it reaches a near population

sample, at least for the United States, and we have clinical annotation and outcome data.

We've done some preliminary analyses of limited subsets, looking at the lower stage patients, and the outcome for patients enrolled only on the biology study appears to be very similar to the clinical trial data. I think this reflects this uniformity of therapy used, at least within certain cohorts. So again, this could be used as an external control, at least for the purposes of these limited sets.

I'm now going to talk a little bit about Project Every Child. Dr. Smith covered this in some detail. This is a project that was started in 2015 within the Children's Oncology Group as a mechanism both of biobanking, of tumor and germline, and a way to facilitate epidemiology research by getting permission for future contact to collect a limited amount of clinical annotation with outcome data.

Since its opening, over 24,000 children have enrolled. We estimate, again based on SEER data,

that 45 percent of children diagnosed with cancer between birth and 14 years of age are enrolled on Project Every Child, and we have clinical annotation with outcome data, although the outcome data for Project Every Child has not been mined like it has been in the cases of neuroblastoma and renal tumors, as I illustrated.

This also has broad participation across the COG network, and this is a similar diagram that I showed you for clinical trial enrollments, now just showing it for Project Every Child. Again, the largest institutions, 52 contribute to half of all the enrollments on Project Every Child, but the remaining 50 percent of the patients come from 170-plus institutions, small and medium-sized, across the COG network. So there's broad participation across multiple institutions in Project Every Child.

Dr. Smith outlined in great detail, and I will not reiterate, how we're planning to leverage Project Every Child as a mechanism for consent; tissue collection that will then be analyzed

through a central battery of molecular characterization with a rapid return of results back to the treating institution for the purposes of refining diagnosis; identifying potential targets; identifying prognostic factors; as well as banking of residual material that can be used for other research discovery.

I think this is a great opportunity to the Molecular Characterization Project to leverage Project Every Child and some of the data it collects, as well as use it to return results to patients.

If I can conclude, I think the historical data that are available through COG clinical trials could potentially serve as an external control, but we have to remember careful caveats, including incomplete molecular annotation, particularly for variables of interest; making sure that the therapy that is delivered is comparable and that they haven't been changed over time; and recognizing that these data were not collected for the purpose of regulatory filing and might need significant

work before they're used for that purpose.

We have several large biology studies, and at least our preliminary analysis suggests that the patients who enroll in our biology studies have an outcome similar to those who have enrolled on clinical trials, and these could serve as an external control also.

Project Every Child I think had some potential that can be further mined quickly once we integrate some of the molecular characterization that will come forward with the Molecular Characterization Project. So thank you very much.

Clarifying Questions

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

We will now take clarifying questions for 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 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 that we can move on to the next panel member.

We will now open the session for questions. Dr. Seibel, you're first.

DR. SEIBEL: Thank you, Alberto.

My question is for Doug Hawkins, and that is you commented on the biology studies as well as Project Every Child. Can you tell us a bit more or provide more details about the follow-up for these patients; how granular this is?

DR. HAWKINS: Yes. I think for neuroblastoma, I believe the follow-up is similar. I've not seen the publication yet ready for Wilms' tumor to look at comparability of follow-up. For Project Every Child, I think this is an opportunity

for us to explore more. We simply have not looked in detail at the length of follow-up, and it is also more modern. The renal tumor in the neuroblastoma studies have been open for over 15 years now, whereas Project Every Child is only five since it first opened.

In terms of granularity of data, I think it's variable by diagnosis. In some cases in Project Every Child, there was moderately specific information and exposure information like treatments with different specific regimens or staging information. In other cases, the clinical annotation is more rudimentary, so I think it will vary by diagnosis.

I think what I look at as one of the goals is we need to look deeply into some specific diagnoses and see -- just like it's been done for neuroblastoma and Wilms -- how well do the data compare to contemporary clinical trial data.

DR. SEIBEL: Doug, for a patient who is on Project Every Child, who didn't enroll on a clinical study, does COG reach out to the

institution once a year to find out the status of that patient?

DR. HAWKINS: Yes. That's annual reporting of life status, including events, and life status is a requirement. It's part of our data currency. So that is an annual data currency expectation, and it's reporting life status and any events.

DR. SEIBEL: Okay. Thank you.

DR. HAWKINS: Sure.

DR. PAPPO: Donna, you're next.

MS. LUDWINSKI: Thank you.

Donna Ludwinski. This question is for Dr. Hawkins. Thank you very much for your presentation. I was curious. When you mentioned certain data elements that are missing in the biology study, particularly the neuroblastoma biology study, how feasible would it be to go back and reanalyze tissue, presuming there's tissue available, for those missing markers? You mentioned ALK, but also ATRX is a newer gene. Thank you.

DR. HAWKINS: Yes. Thanks. Thanks for your

question. Almost anything is feasible with adequate funding. I think one of the advantages of the biology study is that enrollment includes submission of tissue, therefore there should be some element of residual tissue in the bank.

Assuming we have an assay that can be applied to the tissue that's available, assuming there is residual tissue, and probably most importantly, assuming there is funding available to do that, I think it certainly is possible.

That won't help you if you're going to the biology study to look for the external control where you need existing data, but it might help us to improve the usability of the data from those biology studies as external controls if we've applied the appropriate biologic screening to molecularly annotate those samples.

MS. LUDWINSKI: Thank you very much.

DR. PAPPO: Ted?

DR. LAETSCH: My question is also for Dr. Hawkins.

Doug, I noticed that the enrollment on

Project Every Child varies based on diagnosis, and you highlighted neuroblastoma and Wilms' tumor where there is central pathology review offered to patients and sites.

I wonder if you could comment about the resources required to capture this same sort of granular data for the majority of the population in other tumors.

DR. HAWKINS: Yes. I just want to clarify, the data I showed about enrollment by histology was on clinical trials, and it was broken down into ALL, brain tumors, neuroblastoma, et cetera. But I think I could probably show similar data for Project Every Child also, that the percentage of enrollment probably varies from histology to histology.

Early on, ALL for instance, and still now neuroblastoma and renal tumors are excluded from Project Every Child since originally there was a separate ALL biology classification study. Now that ALL is included in Project Every Child and we have an upfront study which starts with submission

of tissue through Project Every Child as part of the review for ALL clinical trial eligibility, I suspect the enrollment for ALL has gone dramatically up, the percentage of enrollment.

I think for other diseases where there's no linkage to a clinical trial, the enrollments can be much lower, and I think rare tumors are a great example, where if there's not a clinical trial to which eligibility for the clinical trial is tied to the enrollment, the percentages can be lower.

We clearly have seen that on the neuroblastoma if you look at the percentage of children in North America enrolled on the neuroblastoma biology study. The same thing for renal tumors; when there's a link between clinical trial eligibility and enrollment on the biology study, enrollment in the biology study goes up dramatically.

DR. LAETSCH: Thank you.

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

DR. LAETSCH: Yes. Thank you very much.

DR. HAWKINS: Maybe I could add one other comment. I think the Molecular Characterization Project may totally change this dynamic because if there is the prospect of receiving a comprehensive molecular test, battery of tests -- DNA, RNA, methylation -- in a relatively rapid time period, I think there will be a powerful incentive to enroll on Project Every Child, particularly for the histologies included.

As Dr. Smith mentioned, CNS tumors soft-tissue sarcomas, and selected rare tumors, I think we're going to see a dramatic increase with that rapid return of results back to institutions and patients.

DR. PAPPO: Thank you.

Julia. You're next.

DR. GLADE BENDER: Thank you for these very interesting presentations. I may be asking a very naïve question, but Doug just mentioned again that external controls require previous, existing data. I just want to clarify that that is so; that there is no way to -- because there was an idea of a

hybrid data set with a concurrent group, and the question is whether, as Donna Ludwinski mentioned, certain things could be backfilled.

Then the other question is, is there any role in any of this for parents of potentially children who have died to donate tissue to help build databases, particularly harkening back to Malcolm's question of the rare tumors and the molecular profiling?

DR. HAWKINS: This is Doug Hawkins. I'm not sure that the question's entirely directed towards me, but maybe I could just address the last item that you raised, which is the potential to donate tissue for children who have died.

One of the administrative supplements that COG received related to STAR funding was to support tissue collection at the time of autopsy and as a strategy to try to increase the amount of tissue available for children for whom our therapy has failed. We are in the process of rolling that out to try to increase that submission, and I think having that tissue available would be hugely

beneficial for our biology purposes.

DR. PAPPO: Thank you, Doug.

Julia, does that answer your question?

DR. GLADE BENDER: Yes.

DR. PAPPO: Okay, and we have a final question for Dr. Reaman.

Dr. Reaman?

DR. REAMAN: Greg Reaman from the FDA. I was going to partially respond to Julia's question, and then ask Doug a question.

I think backfilling missing data is clearly one of the things that, from a regulatory perspective, we would be concerned about in the use of historical controls, where our concern is really eliminating any intentional or unintentional bias. Do you bias a historical control by only backfilling with patients who have tissue available so that you can come up with the control group that you want? So, in general, it would not be something that we would recommend.

Then for Doug, can you just clarify with Project Every Child, other than an annual

requirement to report life status, is there any mechanism for reporting detailed information on treatment, continued treatment, for patients who haven't been enrolled on a COG study, and if a relapse has occurred, what the new therapy is? How granular is the treatment intervention?

DR. HAWKINS: Thank you, Greg, for that question. I will say that we have not looked at the data sufficiently to answer that across all tumor types. I have looked within a couple of tumor types, and the data are pretty granular in terms of treatment exposures, initially.

I'll take the example of soft-tissue sarcomas. We ask people to declare did you use one of the following 10 common regimens, and if not, you could multi-select different drugs to put together a regimen.

So I think for many diseases, outside the context of a clinical trial, there's relatively granular data. But once an event happens, it's been our strategy not to collect more information other than life status after that event. And I

think that's a fundamental -- that's true for clinical trials and it's true for Project Every Child. Once an event happens, we simply track people for life status, not for subsequent therapy.

DR. PAPPO: Thank you, Doug.

Does that answer your question, Greg?

DR. REAMAN: Yes, it does.

Thanks, Doug.

DR. PAPPO: Okay.

We will now take a 15-minute break. 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 3:30. Thank you very much.

(Whereupon, at 3:12 p.m., a recess was taken.)

Open Public Hearing

DR. PAPPO: Okay. We are back, and we will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at

the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written and oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include a sponsor's payment of your travel, lodging, or other expenses in connection with your participation in this meeting. Likewise, the FDA encourages you at the beginning of your statement -- [inaudible - audio lost] -- financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the

issues before them.

(Pause.)

DR. PAPPO: Can you hear me?

DR. CHEN: Yes.

DR. PAPPO: Were you hearing everything I was saying about the open public hearing or was I just talking to myself?

DR. CHEN: I heard you.

MALE VOICE: We heard you.

DR. PAPPO: Okay, good. So we'll continue.

The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson, and thank you for your cooperation.

Speaker number 1, your audio is connected

now. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. ZUCKERMAN: Thank you very much. Can you hear me?

DR. PAPPO: Yes.

DR. ZUCKERMAN: Thank you.

I'm Dr. Diana Zuckerman. I'm president of the National Center for Health Research. Thanks so much for the opportunity to speak today. Our center is a nonprofit think tank that scrutinizes the safety and effectiveness of medical products, and we don't accept funding from companies that make those products.

My perspective is as a scientist trained in epidemiology and public health, and as a former faculty member and researcher at Vassar, Yale, and Harvard, and I've also worked at the Department of Health and Human Services, the U.S. Congress, and the White House, and I'm on the board of the Alliance for a Stronger FDA, which lobbies for more appropriations for the FDA.

I really appreciated this meeting. There's been so much very important information, and I just want to comment on a couple of things that were brought up.

The first one I want to talk about is this idea of focusing on real-world evidence when randomized-controlled trials are not possible, or either not possible, or not ethical, or both. And I think that's something we could all agree on, but in my experience, what is possible and what is ethical is in the eye of the beholder, and that's where things get very complicated.

I have seen instances where a company said they felt it would not be ethical to have a randomized-controlled trial or any kind of control group because they were so sure that their product was probably going to be effective and probably going to be safe. And while we understand that, and we understand, especially with studies involving children, the desire to give these kids any opportunity to get well, I do think that the ethical thing to do is to study it carefully, as

carefully as possible, before we start selling it to a larger number of patients, whether those patients are children or adults.

I also wanted to mention that the shortcomings of historical controls, which were described previously by some excellent speakers -- but just to say that one of the things to look at in historical controls, in addition to the fact that treatment protocols may have changed considerably, even after a few years, is how often historical controls are not as diverse in terms of race, ethnicity, and other issues as we try to make sure they are today. And that can also have quite an impact on their adequacy as a control group.

Then the last thing I want to mention is the prespecified statistical analysis plan that was brought up and how important that is for real-world evidence. I agree completely. Again, my concern is how often this doesn't happen in the real world of FDA reviews.

Even just recently when the FDA had a public meeting on cancer drugs that had been approved

through accelerated approval mechanisms, where there were prespecified statistical analysis plans for the confirmatory studies, the studies did not reach those prespecified criteria. And yet, the feeling was, well, there was a trend, and it was a non-significant trend.

But that desire to hope and the wishful thinking that this product would work makes it very difficult to stick with those prespecified statistical analyses plans even though the power calculation should have already been done. The companies had agreed to them, and yet there's tremendous pressure not just from the sponsor, but also often from clinicians and of course patients on advisory committees to disregard the fact that those prespecified statistical analysis plans were not followed, or they were followed, and the results are not adequate to confirm that the product had benefits outweighing the risks.

So again, I want to thank you for this meeting. I think it's been very informative, and the speakers have been excellent. And I just

wanted to add my support for those points. Thank you very much.

Clarifying Questions (continued)

DR. PAPPO: Thank you very much for your presentation.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. I will now go back and allow about 10 minutes for remaining clarifying questions for all 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. And as a gentle reminder, 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 that we can

move on to the next panel member.

So now we're open for questions for all of the speakers. I'll let you gather your thoughts for a couple more minutes, and if not, we'll move on to the questions to the committee and panel discussions.

Dr. Seibel?

DR. SEIBEL: Yes. I have a question, and probably this could go to any of the speakers during the first session. In the FDA briefing document, it refers to "the potential for use of well-characterized and appropriately standardized data to create sufficient evidence is a particular interest to pediatric cancer drug development in light of the rarity of cancer, in general, and the specific types of cancer, and in molecularly phenotype subtypes of cancer that occur in children."

My question is, has there been any discussions, and particularly with the NCI, about what are the standardized data that should be collected, particularly as we move ahead in the

Childhood Cancer Data Initiative?

Malcolm mentioned the supplements that have been given to cancer centers for some of those samples and results already, but to see if there is some type of standardized data collection so we will have what we need for the future.

DR. PAPPO: Any of the presenters would like to tackle that question?

DR. REAMAN: This is Greg Reaman.

Nita, maybe I can try and address that. The standardized data that I think was referred to was standardized clinical data, outcome data that might be used in the process of the construction of an external control. It was not really intended to specifically be related to genomic data that is either in the process of being collected or to be collected, but it was more related to how clinical data was collected, managed, submitted, and analyzed. So that was the reason for the use of the term "standardized."

DR. SEIBEL: But going forward, I do think it would be helpful to have -- if we're providing

supplements to get additional data on genomic characterization patients from cancer centers, that doesn't need to be just limited to the genomic data; it could include other data as well. So it would be important to have some idea of what would be basics, or minimum, that we should be asking for.

DR. REAMAN: I couldn't agree more. We haven't had those discussions, but I think recognizing the perceived high bar, if you will, for external controls and their use in regulatory decision making, I think having those discussions and providing some input as to the specific data, the quality of the data, the integrity of the data, how the data were managed, submitted, analyzed, I think would be appropriate going forward. Sure.

DR. SEIBEL: Thank you.

DR. RIVERA: Dr. Reaman, is it ok if I add?

DR. REAMAN: Yes, of course.

DR. PAPPO: Yes, please.

DR. RIVERA: Hi. This is Dr. Rivera. That's a really great question, and I think

highlights a salient point in the totality of the real-world data community, and that is the impact of standardization on the use of this data.

I think a lot of the potential for the use of real-world data is in the ability of us to be able to standardize, to characterize, and truly understand what the data represent, the validity of the endpoints, and then, of course, the interpretation of that data as fit for purpose, for example, in regulatory use.

Within the OCE, the Oncology Center of Excellence real-world evidence program, we are working on a lot of standardization type efforts, including the characterization of data quality, and specifically work on minimum data elements and endpoints.

So I think it is a great idea for us to think about how we can synergize with our federal colleagues as well in creating an ecosystem that can promote and include these conversations so that we can increase the ability for these much needed therapies for pediatric patients.

DR. SEIBEL: Thank you.

DR. PAPPO: Thank you very much.

Greg, did you have a question or it was just to answer Nita's query?

(No response.)

DR. PAPPO: Okay.

Questions to the Committee and Discussion

DR. PAPPO: Well, 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 questions to the committee and panel discussions. I would like to remind 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 proceed with question number 1. Question number 1 is, consider the potential of existing and future real-world data resources that may provide real-world evidence to support pediatric cancer drug development programs.

Consider potential uses to inform regulatory decision making, and consider specific pediatric cancer drug development programs that may benefit.

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

Steve?

DR. DUBOIS: Steve DuBois, Dana-Farber, Boston Children's. I think one area that this highlights is certainly the rare molecularly defined subgroup of a rare pediatric cancer. And having a well-characterized cohort of patients already identified with a specific molecular alteration where their clinical outcomes are well described would be incredibly helpful because that's obviously a classy example where randomization becomes very challenging.

So I think in our field, that I think is going to be an important contribution of these initiatives to develop more real-world data.

DR. PAPPO: I couldn't agree more. And perhaps some of the resources that are currently

being implemented for infrastructure like the CCDI will help facilitate the gathering of data for these very rare subgroups.

Dr. Janeway?

DR. JANEWAY: Yes. Katie Janeway, Dana-Farber, Boston Children's. I hope this is a well-formed comment. I'm sort of thinking about it as I'm speaking.

I think that for some of our rare unmet medical need cancers -- and obviously those of you who know me know that I'm thinking about osteosarcoma as I'm saying this -- some of those cancers are sort of stuck in a catch-22 in terms of what are limitations on our ability to create those high-quality data sets out of our patients who enroll in clinical trials.

So what do I mean by that? If we're looking, for example, at designing a new clinical trial for newly diagnosed osteosarcoma, just to take the example, we have limited information currently about genomic subtypes that predict response or resistance to treatment. And because

of that, we don't have biomarkers that we can justify performing on a clinical trial, therefore we miss the opportunity to require sample submission on the clinical trial, and it's hard for us to identify funding to support those efforts.

So I guess what my comment is, one of the challenges in a cancer type like that is obtaining the resources, both the samples and also the funding, to support the endeavor to generate the types of data sets that are going to be useful in the future.

DR. PAPPO: Thank you very much.

Dr. Laetsch?

DR. LAETSCH: Hi. Ted Laetsch. I agree completely with Dr. DuBois and Dr. Janeway. My additional comment was that I think Dr. Hawkins highlighted nicely how COG may have some resources to provide real-world data for newly diagnosed patients.

I think a number of drugs that are in development, most of them are initially at least studied in the relapse or refractory setting. So I

think developing additional resources in that setting will also be important, in addition to these resources looking at real-world data for newly diagnosed patients.

DR. PAPPO: Thank you, Ted.

Tobey?

DR. MACDONALD: Tobey MacDonald, Emory University. I would only add, as we touched upon before, that the functional genomics data that's currently underway in the adult population now, seemingly trickling down somewhat to some histologies in pediatrics, will be of incredible value as we now are developing our targeted therapeutic programs.

We currently have one target in the drug, and we still don't know or understand when the drug works or fails to work. These type of data would be helpful for that understanding, as well as to the next level. We need to have combined therapeutics, and the functional genomics hopefully will inform us of which drugs to pick.

DR. PAPPO: Thank you.

One more comment, Dr. Glade Bender?

DR. GLADE BENDER: Julia Glade Bender of Memorial Sloan Kettering. I just want to add to what Dr. Janeway was trying to articulate, which is what I think I was trying to articulate before, which is, really, that currently we're only supposed to collect data on trials where we have an objective, and in order to do that, then collect that data, we need to have that question funded as well.

So it becomes difficult to then have a complete data set to subsequently use as a future external control if we don't have all of that data.

I think that the general molecular profiling national trial will help a lot if there is tissue, but there won't always be tissue. If the standard of care is to continue to take as minimal a biopsy as possible upfront, then we will never get that data, and we will never be able to stratify patients molecularly to make sure that we have the right balance in our historical cohort.

So just wondering and remembering a prior

FDA ODAC meeting where I remember an impassioned public comment about biopsy and DIPG, that if we didn't do that, we would never be able to move forward; and thinking that if we want to move forward and make use of this real-world data, we're going to need to potentially change our practices of how we collect tissue.

DR. PAPPO: Thank you very much, Julia.

If I can summarize the comments, it appears that real-world data and real-world evidence are going to be very helpful in helping better define rare molecular subtypes of pediatric cancers.

Some of the current limitations include the quality of the data sets, specifically genetic data sets that could better help us predict response and identify biomarkers for future clinical trial risk stratification.

One of the main limiting factors is funding and resources, and this is something that needs to be expanded a little bit more. And another issue would be to expand studies to include functional genetics to try to better inform targeted therapies

for these patients.

Did I encapsulate everybody's comments ok, or did I miss anything?

(No response.)

DR. PAPPO: Alright. We will move to question number 2. Given the discussion of the FDA framework on the use of real-world data and real-world evidence on regulatory decision making, consider how best to assess the appropriateness of existing or emerging data sources as potential sources for real-world data. Discuss critical attributes of such data.

If there are no questions or comments concerning the wording of the question, we will now open the question for discussion. And I think this question pretty much expands a little bit on some of the points that were raised on the last one, but we will go ahead and take comments from Dr. MacDonald.

DR. MACDONALD: Sorry. That was a left-over hand raised up.

DR. PAPPO: Okay.

Anyone want to make any comments on this specific question or expand on this? I think that some of the issues were addressed on the previous one, but let's see if someone else -- Katie has a comment.

DR. JANEWAY: Yes. My only comment here -- sorry. Dr. Janeway, Dana-Farber, Boston Children's, still. I haven't moved yet.

So my only comment here was that there's been a huge emphasis in this discussion on the CCDI, which I think is great. It's a terrific aggregation effort and also an effort to fund generation of new data. But there are already some efforts [inaudible - audio gap] -- and I just think it's important to keep those in mind. I suspect they will be incorporated into the CCDI eventually or somehow accounted for in the catalog. But I just wanted to say that.

DR. PAPPO: Thank you, Katie.

Anyone else?

(No response.)

DR. PAPPO: I'm requesting to enter the

meeting. I guess they don't want me around anymore. Hold just for a second. Okay. I'm back in.

Katie's comment was to just take into consideration that there are other efforts to try to have data that includes clinical and genomic data, and those efforts need to be recognized.

If there's not any additional comments on question number 2, we will move to question number 3.

(Pause.)

DR. PAPPO: Do you want me to advance to question number 3 or do you just want me to read it?

Consider the real and perceived limitations of real-world evidence from existing and developing registries in pediatric cancer drug development as a result of the General Patient Data Regulations in the European Union?

Katie?

DR. JANEWAY: Sorry. I don't mean to keep commenting. Katie Janeway, Dana-Farber, Boston

Children's. We do have some experience in early conversations with our European colleagues in bone sarcoma, and the main issue here was GPDR [inaudible – audio gap] between the clinical data whether from the electronic medical record or registry, or a clinical trial, and data generated from patient samples.

So I think, given that people emphasized it with biomarkers and rare population subsets, this becomes a major issue.

It is going to be important for those rare subsets to aggregate data between U.S., Europe and, frankly, other countries outside of Europe as well, and the regulatory issues do become, in some cases, quite limiting.

DR. PAPPO: Thank you very much, Katie. I don't see that I've been admitted to the meeting again, but I know that Dr. Reaman was there and Dr. Seibel, so let's go with Dr. Reaman.

DR. REAMAN: Hi. Greg Reaman from the FDA. I just wanted to provide a little bit of context for this question, and I think Katie addressed it.

I had hoped that in the discussion of the CCDI, there may have been a little bit more of an idea as to how international cooperation/ collaboration might actually develop in a harmonized aggregated system of pediatric cancer data. But we are aware of concerns with sponsors who have attempted to depend on data from registries outside of the U.S. and the release of some of those data.

So it's something that I think just needs to be appreciated as a potential challenge, and it's a particular challenge because these regulations are actually directed at situations where there might be for-profit or a financial motivation for the release of the data outside of that institution or country.

I also wanted to just follow up with Dr. Janeway's question before about other resources. Bringing information to us about those other resources would certainly be helpful. That doesn't have to happen today or anything like that, but if there are resources for real-world evidence

that people are aware of, and maybe even been thinking about using, that would be helpful for the agency to have that information as well. Thanks.

DR. PAPPO: Thank you very much, Greg.

Dr. Chen, I cannot see anything except for the fact that I have requested entering into the meeting. Would you like for me just to log out or log back in, or can you help me before I ask Dr. Seibel to comment on this?

DR. CHEN: Yes. Thank you.

Dr. Pappo, go ahead and start with Dr. Seibel. We're working on it. Thank you so much.

DR. PAPPO: Okay, Nita. Do you mind going ahead, please?

DR. SEIBEL: Sure. Nita Seibel from NCI. I wanted to echo what Katie and Greg had said. The GPDR seems like it will be very restrictive and potentially block companies from transferring data to other companies or to share it, as well as patients have the right to the erasure of their data.

So I think this could really impact things, depending particularly on small populations, where it would be important to see what the European experience would be with a certain drug. So I think this will be an issue; although, Greg, you probably know much more about it than I do.

DR. PAPPO: Greg, would you like to expand on that?

DR. REAMAN: Sorry. Greg Reaman. I'm not sure that I can really expand on it. I don't think we've actually seen the negative impact that we're expecting to see. But I do know that there have been situations where institutions have not been able to provide data to sponsors that they originally had agreed to provide because of the new regulation. So I do suspect that it may become a bigger issue in the future.

(Pause.)

CAPT WAPLES: Hi. Good afternoon. This is Yvette Waples, the team lead for this meeting. We're just going to do a quick two-minute pause to try to get Pappo back on. Thank you.

(Pause.)

DR. PAPPO: Okay. Can you hear me now?

DR. CHEN: Yes, we can.

DR. PAPPO: Good. I'm sorry. I had to log back out and back in.

Dr. Chen, can you establish a chat with me again, please?

DR. CHEN: Sure. Just a moment.

(Pause.)

DR. PAPPO: Thank you for your patience.

(Pause.)

DR. PAPPO: Okay. I don't know if there were any other speakers in the queue after Dr. Seibel and Dr. Reaman.

Can you let me know, Dr. Chen?

(Pause.)

DR. PAPPO: From what I could gather, there may be some issues with the GPDR and that some of this data might be a little bit more restrictive. And given the regulations, it may affect the ability to obtain data, especially since some of this may be driven by pharma, and also given the

option of the patients not to share the data, if I understood that correctly.

Did I get that right or, Greg, do you want to add anything to what I said? It was kind of choppy, and I couldn't get all of the comments together. Sorry.

DR. REAMAN: I think you captured it pretty well, Alberto.

DR. PAPPO: Okay. Sorry. Thank you very much.

We will now proceed with question number 4. Consider possible mechanisms for how and by whom attribution of real-world data and real-world, evidence-generated adverse events of new cancer drugs can be accomplished, and data optimally aggregated to inform patients and providers.

Steve?

DR. DUBOIS: Steve DuBois, Dana-Farber, Boston Children's. This is a really tricky one. We completed a project here just looking at our local patients getting off-label use of targeted therapies, and it was a mountain of work for the

team extracting all of the data. We really focused on things that we thought would be clinically significant, such as admissions, ER visits, or urgent clinic visits. We weren't able to capture all grades of all AEs for this type of a project. I don't have a solution, but just to say out loud that this is really hard.

Dr. Seibel?

DR. SEIBEL: Oh, that might be left from before. But actually I do have a comment on this in that this is tricky, the whole idea of whether you could link medical records to registry.

Part of the issue with adverse events from new cancer drugs is what is the control for this? This has come up particularly with a drug that we're looking at with osteosarcoma and pneumothoraces. So what is our baseline to know if this is a new adverse event? It's something we need, but it is a challenge, I think, how to gather those data.

DR. PAPPO: Dr. Reaman?

DR. REAMAN: I apologize. [Inaudible –

audio gap].

DR. PAPPO: Yes. I think the question was also the possible mechanisms, so we recognize that there is a challenge, but does anybody have any potential idea of what would be a better mechanism to try to get this data?

Julia?

DR. GLADE BENDER: I think recognizing the challenges and given the very interesting discussion that we had yesterday regarding the Patient Voice, I wonder if there is any way to incorporate the Patient Voice in some of this adverse event capturing of real-world data; in particular, if we could figure out what were the questions that we wanted to ask of patients and picked from validated measurements such as some of the ones we learned about yesterday in PRO-CTCAE, and whether One Source could potentially be the patient themselves.

DR. PAPPO: Thank you.

So what I'm hearing is that everybody agrees that it's challenging to get this data right, and

perhaps one possibility would be to incorporate other data sets like Patient Voice to try to complement the data that is obtained to inform possible mechanisms for real-world data and real-world evidence for drug-generated adverse events.

Did I get that one right? Did I miss anything?

(No response.)

DR. PAPPO: It looks like we don't have any other takers, so that was pretty cool, and it went very, very smoothly, so we will now proceed with the FDA closing remarks from Dr. Greg Reaman.

Closing Remarks – Gregory Reaman

DR. REAMAN: Thank you, Alberto, and thanks to all of the committee for today's discussion. I thought this was an important issue to bring before the pediatric subcommittee, given that there are potential -- and I say potential -- opportunities for real-world evidence in facilitating pediatric cancer drug development.

As you heard, the issue is not new to the

agency. Real-world evidence has been used primarily in the postmarketing setting, but the 21st Century Cures Act did provide opportunities for real-world evidence to actually extend indications, or supplemental indications, for approved drugs.

Now with the RWE program, I think it's looking at areas that certainly need guidance and development, assessing fitness, or fit for purpose, of data to be used, a plan to accumulate experience through a demonstration projects, and then hopefully actually publish a guidance on how real-world evidence might be used in the construction of external controls.

I think one important thing was that the evidentiary standards for benefit-risk or for determining safety and effectiveness of new drugs can't be and won't be altered by the use or the consideration of external controls and studies of products.

This might be perceived as a high bar for external controls, but I think until we get this

all sorted out, it probably is going to require a great deal of discussion between investigators, sponsors, and regulators.

I'd point out that although many of our studies in pediatric cancer are single-arm studies, the need for control is really essential in those studies that have time-to-event endpoints. So there's still the opportunity for single-arm studies using objective response and duration of response as important endpoints to move promising agents forward.

I think we did hear about the challenges, and I think the opportunities are real. The challenges unfortunately are more real, particularly in the setting of non-contemporaneous or historical controls, the temporality of data, the changing biology, the changing standards of care, and issues related to biomarker analysis and genomic phenotyping.

I think, as has been pointed out in the CCDI discussion and by the committee, there are real promises I think with Project Every Child and

extending the opportunity for genomic sequencing and phenotyping of tumors for all pediatric cancer patients, and that might actually benefit external control development as well.

The issue of completeness of data and missing data is obviously an issue, ascertainment of data, and particularly outcome assessments. This is a problem that we have seen, where outcomes are assessed in the experimental group at specified intervals but not necessarily specified at particular intervals in the, quote/unquote, "external control group." So are results really and truly comparable?

Homogeneity of patient populations, and particularly looking at prognostic factors and the need for propensity score matching, I think the big message here is the need for granular patient-level data, and also the need for prespecified plans and prespecified statistical analysis plans.

It's really not appropriate to keep analyzing a proposed historical control until you come out with planned or anticipated results, and

then say that's the historical control group that you want to use.

So the message that I think is of greatest importance is there's really a need, if this is something that's going to be pursued, for early discussion, and early discussion with the real-world evidence program within the Oncology Center of Excellence, and discussions with the appropriate review divisions and their statistical colleagues.

I think there's also a need to evaluate the hybrid designs, so there may be opportunities to not just use an external control, but to use some real-world evidence to inform a Bayesian design as well. Obviously, there is no guidance at this time, at this point in time, and there's no precedent to use as a template. And you might actually take that as a call to arms, if you will, and help develop the precedent.

I think CCDI, as it was explained, has incredible promise to provide data with respect to a genomic characterization and its linkage with

Project Every Child. If there are patient-level clinical data that can accompany those phenotypic data, it could be a very valuable resource.

I think extending the NCTN Data Archive to earlier phase studies would be very helpful, and particularly the phase 2 or activity-seeking studies in the pediatric population could be very informative and helpful.

With respect to safety monitoring, I think the whole issue of attribution of an adverse event to a specific drug is somewhat problematic, but I think looking at targeted investigations and then evaluating potential pharmacogenetic correlations has some really promising opportunities for children with cancer and with pediatric cancer drug development.

So obviously this is a beginning, and I think it was a great discussion. I hope everyone found the information of interest and of use going forward. With that, I would just like to thank you all again for participating virtually in yet another pediatric subcommittee meeting. Thanks.

Adjournment

DR. PAPPO: Thank you very much for your comments, Greg. I want to thank all the panel members for your participation, also all the FDA staff for making this run very smoothly, and all the speakers and guest speakers, and hope to see you next year in person.

We will now adjourn the meeting. Thank you very much.

(Whereupon, at 4:20 p.m., the meeting was adjourned.)