FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM) AND THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE (PDAC)

Tuesday, November 19, 2024

8:30 a.m. to 4:53 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Jessica Seo, PharmD, MPH

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE MEMBERS (Voting)

Maryann Amirshahi PharmD, MD, MPH, PhD, BCPS, FACMT, FACEP, FASAM, FCP

Professor of Emergency Medicine,

Georgetown University School of Medicine

Department of Emergency Medicine,

MedStar Washington Hospital Center

Washington, District of Columbia

Michael C. Dejos, PharmD, MBA, BCPS, CHOP, CPPS
System Medication Safety Officer
Methodist Le Bonheur Healthcare
Assistant Professor
University of Tennessee Health Science Center
Memphis, Tennessee

Sascha Dublin, MD, PhD
Senior Scientific Investigator
Kaiser Permanente Washington Health Research Institute
Seattle, Washington

James Floyd, MD, MS
(Acting Chairperson)
Co-Director, Cardiovascular Health Research Unit
Professor of Medicine
Adjunct Professor of Epidemiology
University of Washington
Seattle, Washington

John B. Hertig, PharmD, MS, CPPS, FASHP

(via video conferencing platform)

Associate Professor

Department of Pharmacy Practice

Butler University College of Pharmacy and

Health Sciences

Indianapolis, Indiana

Elizabeth Rebo, PharmD, MBA, CPPS

Executive Director, Pharmacy Quality and Medication

Safety

National Pharmacy Services

Kaiser Permanente

Downey, California

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

MEMBERS (Non-Voting)

Jens-Ulrich Stegmann, RN, MD

(Alternate Industry Representative)

Senior Vice President

Global Head Clinical Safety and

Pharmacovigilance, EU QPPV

GlaxoSmithKline (GSK)

Wavre, Belgium

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

MEMBERS (Voting)

Walter S. Dunn, MD, PhD

Assistant Clinical Professor

University of California Los Angeles

Department of Psychiatry

Director, Mood Disorders Section

Director, Interventional Psychiatry Service

West Los Angeles Veterans Affairs Medical Center

Los Angeles, California

Jess G. Fiedorowicz, MD, PhD

(via video conferencing platform)

Head and Chief, Department of Mental Health

The Ottawa Hospital

Professor and Senior Research Chair in Adult

Psychiatry, Department of Psychiatry

University of Ottawa

Ottawa, Ontario

Rajesh Narendran, MD

Attending Psychiatrist

Resolve Crisis Services

UPMC Western Psychiatric Hospital

Professor in Radiology and Psychiatry

University of Pittsburgh School of Medicine

Psychiatric Molecular Imaging Program

University of Pittsburgh

Pittsburgh, Pennsylvania

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

MEMBERS (Non-Voting)

Carla M. Canuso, MD

(Industry Representative)

Vice President, Head of Neuropsychiatry Clinical Development

Janssen Research and Development, LLC

Titusville, New Jersey

TEMPORARY MEMBERS (Voting)

Jacob S. Ballon, MD, MPH.

Associate Professor

Co-Division Chief - Division of General Adult Psychiatry and Psychology

Co-Director, INSPIRE Clinic

Department of Psychiatry

Stanford University

Stanford, California

Michael Brisbin

(Patient Representative)

Odessa, Missouri

Megan J. Ehret, PharmD, MS, BCPP
Professor, Co-Director Mental Health Program
University of Maryland, School of Pharmacy
Baltimore, Maryland

Jeremy G. Perkins, MD, FACP, COL, US Army (ret)
Deputy Director, Hematopoietic Stem Cell Program
Murtha Cancer Center,
Walter Reed National Military Medical Center
Hematology-Medical Oncology Service
Department of Medicine
Associate Professor of Medicine,
Uniformed Services University of the Health
Sciences (USUHS)
Bethesda, Maryland

Brian W. Salvas, PharmD, RPh
Vice President Pharmacy Innovation and Engineering
CVS Health
Woonsocket, Rhode Island

Gopal Vyas, DO

Clinical Assistant Professor

Department of Psychiatry

University of Maryland School of Medicine

Maryland Psychiatric Research Center

Baltimore, Maryland

FDA PARTICIPANTS (Non-Voting)

Gerald Dal Pan, MD, MHS

Director

Office of Surveillance and Epidemiology (OSE)

CDER, FDA

Irene Z. Chan, PharmD

Director

Office of Medication Error Prevention and Risk

Management (OMEPRM)

OSE, CDER, FDA

Teresa Buracchio, MD
Director
Office of Neuroscience (ON)
Office of New Drugs (OND)
CDER, FDA

Cynthia LaCivita, PharmD
Director
Division of Risk Management (DRM)
OMEPRM, OSE, CDER, FDA

Tiffany R. Farchione, MD
Director
Division of Psychiatry (DP)
ON, OND, CDER, FDA

Bernard Fischer, MD
Deputy Director
DP, ON, OND, CDER, FDA

Marc Stone, MD

Deputy Director for Safety

DP, ON, OND, CDER, FDA

Carolyn Tieu, PharmD, MPH

Team Leader

DRM, OMEPRM, OSE, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. FLOYD: Good morning, everyone. We'll go ahead and get started. It's 8:30. I want to first remind everyone to please mute your line when you're not speaking, and also, please silence your cell phones and any other devices. For media and press, the FDA press contact is April Grant. Her email is displayed, and if you have any questions, please contact her.

My name is James Floyd, and I'll be chairing this meeting. I'm now going to call the November 19, 2024 Joint Drug Safety and Risk Management Advisory Committee and Pharmacologic Drugs Advisory Committee meeting to order. We'll start by going around and doing introductions, stating your name and affiliations, and I'd like to start with our FDA colleagues to the left and go around the table.

Teresa Buracchio, Director of the Office of

Neuroscience in CDER.

DR. CHAN: Irene Chan, Director of the Office of Medication Error Prevention and Risk Management.

DR. DAL PAN: Gerald Dal Pan, Director of the Office of Surveillance and Epidemiology.

DR. LaCIVITA: Cynthia LaCivita, Director of the Division of Risk Management.

DR. TIEU: Carolyn Tieu, Team Leader, Division of Risk Management.

DR. FARCHIONE: Tiffany Farchione, Director of Division of Psychiatry.

DR. FISCHER: Bernie Fischer, Deputy Director of Division of Psychiatry.

DR. SEO: Dr. Hertig, if you can go ahead and introduce yourself.

DR. HERTIG: Good morning. John Hertig, Associate Professor at the Butler University College of Pharmacy and Health Sciences.

DR. FIEDOROWICZ: Jess Fiedorowicz, University of Ottawa.

DR. PERKINS: Jeremy Perkins. I'm a

hematologist/oncologist at Walter Reed National Military Medical Center.

DR. EHRET: Megan Ehret, Professor at the University of Maryland, School of Pharmacy.

DR. DUBLIN: Sascha Dublin, Kaiser Permanente Washington, pharmacoepidemiologist and general internal medicine physician.

DR. SEO: Jessica Seo, DFO, FDA.

DR. FLOYD: James Floyd, Professor of Medicine and Epidemiology at University of Washington and Acting Chair for this meeting.

MR. BRISBIN: Michael Brisbin, patient and clozapine patient representative.

DR. NARENDRAN: Raj Narendran, psychiatrist, UPMC, University of Pittsburgh.

DR. DUNN: Walter Dunn, psychiatrist, Greater Los Angeles VA, University of California, Los Angeles.

DR. BALLON: Jacob Ballon, Associate Professor of Psychiatry at Stanford University.

DR. SALVAS: Brian Salvas, pharmacist and Vice President of Pharmacy Innovation and

Engineering for CVS Health.

DR. DEJOS: Mike Dejos, System Medication Safety Officer for Methodist Le Bonheur Healthcare in Memphis, Tennessee.

DR. REBO: Elizabeth Rebo, Executive Director of Medication Safety for National Pharmacy Services at Kaiser Permanente.

DR. AMIRSHAHI: Maryann Amirshahi, Professor of Emergency Medicine at Georgetown University School of Medicine and Medical Director of the National Capital Poison Center.

DR. STEGMANN: Jens Stegmann, Senior Vice President, Head of Clinical Safety and Pharmacovigilance at GSK, non-voting industry representative.

DR. CANUSO: Carla Canuso, Neuropsychiatry Clinical Development, Janssen Research and Development, non-voting industry representative.

DR. FLOYD: Great. Thank you.

For topics like this meeting today, there are often a variety of opinions, some of them are strong; and our goal is that this meeting will be a

fair and open forum for discussion in that people can express their views without interruption. So this is a gentle reminder that people should speak into the record only if recognized by the chair, and that's me. So 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 take place only during the open forum of the meeting. We know that sometimes the media are anxious to speak with FDA about these proceedings, but the FDA also will refrain from discussing details until after it's over. Also, the committee is reminded to please not discuss meeting topics during the breaks or the lunch. Thank you.

Dr. Seo will read the Conflict of Interest Statement.

DR. SEO: Thank you, Dr. Floyd.

Before I read the Conflict of Interest Statement, I'd like to take a moment to have our

FDA participant, Dr. Marc Stone, introduce himself into the record.

DR. STONE: Hi. I'm Marc Stone. I'm the Deputy Director for Safety in the Division of Psychiatry.

DR. SEO: Thank you, Dr. Stone.

We also have another panelist. Dr. Vyas, if you could state your name and affiliation for the record.

DR. VYAS: Hi. I'm Gopal Vyas. I'm a psychiatrist with the University of Maryland School of Medicine and have been using clozapine for some time.

Conflict of Interest Statement

DR. SEO: Thank you.

The Food and Drug Administration, or FDA, is convening today's joint meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting

members of the committees are special government employees 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 committees' compliance with the 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 members and temporary voting members of the committees are in compliance with 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 their 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, members and temporary voting members of the committees have been screened for potential financial conflicts of interests 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.

Today's agenda involves discussion of the re-evaluation of the Clozapine Risk Evaluation and Mitigation Strategy, or REMS, and possible changes to minimize burden on patients, pharmacies, and prescribers while maintaining safe use of clozapine. This is a particular matters meeting during which specific matters related to clozapine REMS will be discussed.

Based on the agenda for today's meeting and

all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(1) to Dr. Walter Dunn. Dr. Dunn's waiver involves stock holdings in a party to the matter and six competing firms. The aggregate market value of his financial interest in the common stocks of the seven firms is between $25,000 and $75,000. The waiver allows Dr. Dunn to participate fully in today's deliberations.

FDA's reasons for issuing the waivers are described in the waiver document, which is posted on FDA's website on the advisory committee meeting page, which can be found at www.fda.gov and by searching on November 19, 2024, DSaRM. A copy of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting

members to disclose any public statements that they have made concerning the clozapine REMS. With respect to FDA's invited industry representatives, we would like to disclose that both Dr. Carla Canuso and Dr. Jens-Ulrich Stegmann are participating in this meeting as non-voting industry representatives, acting on behalf of regulated industry. Dr. Canuso and Dr. Stegmann's role at this meeting are to represent industry in general and not any particular company. Dr. Canuso is employed by Johnson & Johnson and Dr. Stegmann is employed by GSK.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms 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 committees of any financial relationships that they may have with the firms at

issue.

Thank you, and I'll turn the floor back to Dr. Floyd.

DR. FLOYD: Thank you. We'll now move along to the FDA introductory remarks and a history of clozapine regulatory history, starting with Dr. Farchione.

FDA Opening Remarks - Tiffany Farchione

DR. FARCHIONE: Good morning, everyone. My name is Tiffany Farchione, and I'm the Director of the Division of Psychiatry here at FDA. We're here today for a joint meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee. FDA is convening this advisory committee meeting to discuss the agency's re-evaluation of the Clozapine Risk Evaluation and Mitigation Strategy or the Clozapine REMS.

Clozapine is an atypical antipsychotic that is approved for treatment of treatment-resistant schizophrenia and for reducing suicidal behavior in patients with schizophrenia and schizoaffective

disorder. Since its initial approval in 1989, prescribing, dispensing, and treatment with clozapine required enrollment of prescribers, pharmacies, and patients, and a restricted distribution program to mitigate the risk of severe neutropenia. Generic versions of clozapine were eventually approved, each with their own restricted distribution program. In 2015, these separate programs were transitioned to a single shared REMS. It is that shared REMS program that is the topic of today's AC.

To set the stage, let's first talk about clozapine's place in our treatment armamentarium, starting with its indication for treatment-resistant schizophrenia. Schizophrenia is a serious and persistent psychiatric disorder, and estimates of the international prevalence of schizophrenia among non-institutionalized persons vary but are generally less than 1 percent.

Schizophrenia can impact all aspects of an individual's life. Social, educational, and occupational functioning; physical health;

self-care; and quality of life are all impacted. As a result, schizophrenia is the 12th leading cause of years lost to disability worldwide. The clinical presentation of schizophrenia includes positive symptoms like delusions and hallucinations, negative symptoms like blunted affect and avolition, and cognitive impairment, and chronic treatment is typically required for symptom control.

Antipsychotic pharmacotherapy is the mainstay of treatment for schizophrenia, though it's generally recognized by clinicians that antipsychotics have their greatest benefit on positive symptoms and don't significantly improve negative or cognitive symptoms.

The majority of patients with first-episode psychosis will respond to their first antipsychotic treatment trial but, unfortunately, a significant subset of individuals with schizophrenia will continue to experience psychosis despite adequate trials of antipsychotic treatment. For those patients, subsequent treatment with a different

non-clozapine antipsychotic is less likely to result in significant symptom improvement, and based on recent meta-analyses, roughly 22 to 37 percent of individuals with schizophrenia are estimated to meet criteria for treatment resistance.

Treatment-resistant symptoms have a large impact on individuals with schizophrenia, their families and caregivers, their treatment teams, and society. Individuals with treatment-resistant schizophrenia generally exhibit more severe positive and negative symptoms, worse neurocognitive functioning, lower quality of life and community functioning, and higher healthcare costs compared to those who respond to antipsychotic medications.

Treatment-resistant symptoms require a substantial amount of time and resources for patient care activities, which may impact the healthcare delivery system. As disease progresses over time, the negative effects on families and caregivers also grow, including decreases in family

cohesion and flexibility.

Clozapine is the only antipsychotic medication approved for treatment-resistant schizophrenia. Its efficacy and treatment-resistant schizophrenia compared to other antipsychotic medications has been evaluated in published studies, in meta-analyses, and systematic reviews of schizophrenia clinical trials. Importantly, in the clinical study that supported marketing approval in the United States, clozapine demonstrated significantly greater efficacy compared to chloropromazine in treating the symptoms of treatment-resistant schizophrenia. It won in a head-to-head comparison.

This study included subjects with schizophrenia who had inadequate response to previous trials of at least three different antipsychotics and inadequate response to a 6-week trial of haloperidol in a single-blind, lead-in phase. At the end of the 6-week, double-blind treatment period, 30 percent of the subjects in the clozapine group, compared to 4 percent of the

subjects in the comparator group, met the criteria for treatment response.

Clozapine is also the only medication approved for reducing suicidal behavior in patients with schizophrenia and schizoaffective disorder. It's important to note that the rates of suicidal ideation and behavior, including suicide attempts and deaths by suicide, are higher in people with schizophrenia and schizoaffective disorder compared to the general population. Treatment with clozapine can be effective in reducing rates of suicide and suicide attempts in people with schizophrenia, even in those who have not met formal criteria for treatment resistance.

Clozapine's efficacy in reducing suicidal ideation and behavior was demonstrated in a multicenter international trial, comparing the risk for suicidal behavior in individuals with schizophrenia or schizoaffective disorder at high risk of suicide who were randomized to either clozapine or olanzapine; and in this study, subjects treated with clozapine had statistically

significantly longer delay in time to recurrent suicidal behavior in comparison with olanzapine.

The probability of experiencing either a significant suicide attempt, including completed suicide or hospitalization because of imminent suicide risk, was lower in the clozapine group, around 24 percent, compared to around 32 percent in the olanzapine group at week 104.

Despite being the only approved drug for treatment-resistant schizophrenia, drug utilization data analyses indicate that just under 148,000 patients were dispensed a clozapine outpatient prescription in the United States in 2023. For comparison, assuming that just under 2 percent of the U.S. adults have a lifetime history of schizophrenia, and assuming that 22 percent to one-third of those individuals would meet criteria for treatment resistance, that gives us an estimated 814,000 to 1.2 million patients likely to meet the criteria for treatment-resistant schizophrenia and who could potentially be eligible for treatment with clozapine.

Underutilization of clozapine has also been documented through VA and Medicaid claims. So although clozapine won't be appropriate for every patient with treatment-resistant schizophrenia, these data indicate that clozapine use is low in the indicated population.

The benefits of clozapine must of course be considered in the context of its risks. Although severe neutropenia may be the most well-known risk with clozapine, it's also associated with numerous non-neutropenia related risks. These risks are not the focus of the clozapine REMS, but they do weigh heavily on the burden of patient management and may impact a prescriber's decision to treat a patient with clozapine. We do outline these risks in the briefing document, and they are, of course, listed in the clozapine prescribing information, but the non-neutropenia related risks will not be the focus of today's meeting.

The focus of today's meeting is the risk of severe neutropenia and the Clozapine REMS Program that is intended to mitigate that risk. As I

already mentioned, clozapine has been available via a restricted distribution program since its initial approval in 1989 and via the Clozapine REMS Program since 2015. The exact monitoring requirements have changed over time in response to new data and new analyses, with the broad outline of the current requirements listed on the slide here.

Both the initial transition to the single shared system REMS and the subsequent 2021 transition to a new REMS administrator were fraught with challenges, but recognizing that these challenges had the potential to cause treatment interruption and barriers to patient access, the FDA has exercised enforcement discretion for certain aspects of the REMS throughout this period. As a result, the REMS has never been fully implemented or functioned as intended.

So just to set the stage for today's discussion, I want to briefly introduce the elements of the current Clozapine REMS Program. These will be described in detail later this morning. The REMS is designed to identify severe

neutropenia early so that prompt intervention can be taken to reduce serious outcomes, including infections and deaths associated with clozapine use. It includes prescriber certification; pharmacy certification; documentation of safe-use conditions; patient monitoring; and a patient registry.

The goal of the REMS is to mitigate the risk of severe neutropenia associated with the use of clozapine, but as I've noted a few times, the clozapine REMS has never been fully implemented, and neither the agency nor the CPMG have been able to determine the contribution the clozapine REMS has had on mitigating the risk of severe neutropenia; in other words, we don't know if the REMS is meeting its goal. We are also aware that there are concerns about the burden the REMS may have on stakeholders and patient access.

So in light of the agency's continued exercise of enforcement discretion and concerns regarding patient access, we've been conducting a re-evaluation of the clozapine REMS to inform

possible changes, including consideration of elimination, to minimize the burden on patients, pharmacies, and prescribers, while maintaining the safe use of clozapine.

Finally, I want to present our questions to the committee. At the end of today's meeting, these are the issues on which you will be asked to opine. We will ask how reassured or concerned you are that the current and potential clozapine healthcare providers have sufficient knowledge and access to resources about the risk of neutropenia and need for ANC monitoring. We will also ask how reassured or concerned you are that current and potential clozapine healthcare providers will perform ANC monitoring without the requirements of the REMS.

We'll ask whether you think the requirements for the prescriber to document ANC results and the pharmacy to verify the ANC results through the REMS are necessary to ensure safe use. And finally, we'll ask whether the requirement to educate healthcare providers on the risk of severe

neutropenia and the need for ANC monitoring through the REMS is necessary to ensure safe use. So as you listen to the presentations today, please bear these questions in mind.

With that, I want to welcome you again to today's meeting. I'll now pass the mic to Dr. Leah Hart for some additional introductory remarks on clozapine's regulatory history. Thank you.

FDA Clozapine Presentation - Leah Hart

DR. HART: Good morning. My name is Leah Hart, and I am a risk management analyst in the Division of Risk Management. This morning, I will be presenting on the regulatory history of the risk mitigation strategy for clozapine, including changes to approve labeling and information about the REMS approval and modifications. Currently, there are multiple clozapine products available, including two marketed under new drug applications. Generics of clozapine have been available since 1997 and are marketed under abbreviated new drug applications. There are currently eight clozapine abbreviated new drug applications available.

In 1989, because of the risk of severe neutropenia, Clozaril was approved with a boxed warning for agranulocytosis. The prescribing information at that time instructed the prescriber to obtain baseline and weekly monitoring of white blood cell counts, hereafter referred to as WBCs, throughout treatment and for 4 weeks after discontinuation. The 1989 prescribing information gave thresholds for interrupting and discontinuing treatment, as noted in the slide.

The 1989 FDA approval of clozapine included the Clozaril Patient Management System, which was a restricted distribution system. This restricted distribution system included documentation of the weekly monitoring of WBCs and enrollment of prescribers, pharmacies, and patients into the Clozaril National Registry. Furthermore, there was a prescription day supply limit that was tied to the weekly WBC monitoring frequency.

The Clozaril Patient Management System also included a national non-rechallenged master file, which was a list of patients who had experienced

severe neutropenia while on clozapine to ensure those patients were not re-challenged. This list was maintained by Novartis, the manufacturer of Clozaril, and the requirement was that the file must be checked prior to dispensing clozapine to patients.

Between 1989 and 2015, multiple generics were approved, and with each generic, another registry was developed. At the time of the shared system approval in 2015, there were six registries, and providers and patients were enrolled in multiple registries depending on the product dispensed to the patient.

Since the 1989 approval of Clozaril, there have been changes to the clozapine labeling that reduced the monitoring frequency over time. After a 1997 Psychiatric Drug Advisory Committee meeting, the prescribing information and restricted distribution program requirements were updated to change the required WBC monitoring from weekly to every 2 weeks after 6 months of continuous clozapine therapy.

In 2003, the Psychiatric Drugs Advisory Committee reconvened to discuss WBC monitoring with clozapine. As a result, in 2005, the prescribing information and restricted distribution program requirements were updated to decrease the frequency of WBC and absolute neutrophil count, hereafter referred to as ANC, monitoring to every 4 weeks after a patient maintained a normal WBC and ANC for the first year of treatment.

In September 2015, the prescribing information was updated to monitor for neutropenia using ANC only rather than WBC and lowered the ANC value at which therapy should be discontinued. The National Non-Rechallenged master file was eliminated, and contraindications to treating patients with pre-existing conditions, or using concomitant drugs known to cause neutropenia, were removed. With this label modification, separate ANC thresholds were added for patients with benign ethnic neutropenia.

I will now pivot to a review of the timeline of milestones since the approval of the shared

system REMS in 2015 to present. There have been two REMS major modifications since the original approval in 2015. The first modification was approved in January 2019 with an implementation in February 2019, and the second was approved in July 2021 with an implementation in November 2021. As noted in the slide, the FDA has exercised enforcement discretion at various time points between 2015 and the present as the CPMG work toward full implementation of this REMS.

The FDA determined it was necessary to combine all clozapine products into a shared REMS to reduce the burden on the healthcare system and increase the safe use of clozapine. In September 2015, the clozapine REMS was approved, and the goal was to mitigate the risk of severe neutropenia associated with the use of clozapine by educating prescribers and pharmacists about the risk of severe neutropenia and appropriate monitoring requirements; informing patients about the risk of severe neutropenia and appropriate monitoring requirements; ensuring compliance with the

monitoring schedule for absolute neutrophil count prior to dispensing clozapine; ensuring the prescriber documented a risk-benefit assessment when the ANC fell below the acceptable range for those patients continuing clozapine therapy as described in the prescribing information; and establishing long-term safety and safe use of clozapine by enrolling all patients who receive clozapine in the registry.

Stakeholders in the REMS included prescribers, pharmacies, patients, and the clozapine REMS manufacturers. We'll be focusing on the prescriber, pharmacy, and patient requirements in this presentation. There were approximately 50,000 registered prescribers who needed to certify in the clozapine REMS.

To become certified to prescribe clozapine, the prescriber needed to review the prescribing information and the guide for healthcare providers; successfully complete a knowledge assessment; and complete the prescriber enrollment form. The prescriber enrollment form included a list of

responsibilities that the prescriber had to agree to in order to become certified in the clozapine REMS.

Before initiation of treatment, the prescriber agreed to counsel the patient on the risks associated with clozapine, including severe neutropenia, and the program requirements included reporting signs of infection. The prescriber was able to determine if the patient should receive the guide for patients and caregivers based on clinical judgment. The prescriber enrolled the patient by completing and submitting the Patient Enrollment Form.

The prescriber had to obtain a baseline ANC and monitor ANCs according to the monitoring frequency outlined in the prescribing information. The ANCs had to be documented in the REMS within 7 days of the lab draw date. If a patient's ANC fell below the acceptable range, the prescriber could determine if the benefits outweighed the risks of developing severe neutropenia, and provided authorization to the REMS in the form of a

treatment rationale.

Approximately 28,000 registered pharmacies needed to certify in the clozapine REMS. An authorized representative carried out the certification process for the pharmacy. That person reviewed the prescribing information and the Guide for Healthcare Providers, successfully completed a knowledge assessment, and enrolled the pharmacy. The Pharmacy Enrollment Form outlined the pharmacy's requirements in the REMS.

With every dispense, the pharmacy had to obtain a REMS dispense authorization. This REMS dispense authorization verified that the prescriber and pharmacy were certified; the patient was enrolled; the ANC was current and in an acceptable range; or the prescriber had provided a treatment rationale to allow for dispensing. Approximately 90,000 patients needed to be enrolled into the clozapine REMS. Patients who were prescribed clozapine, or caregivers, needed to be counseled on the risks as well as the REMS requirements, unless the prescriber's clinical judgment was that the

patient's adherence to the treatment regimen would be negatively impacted. The patient had to have a baseline ANC.

Patients had to get regular ANC testing as directed by their prescriber. According to the 2015 prescribing information, the initial monitoring frequency was weekly during 0 to 6 months of treatment. If a patient maintained a normal ANC for 6 months, the frequency dropped to every 2 weeks between 6 to 12 months of treatment and further decrease to every 4 weeks thereafter if the patient maintains a normal ANC for an additional 6 months.

In the first 90 days after approval of the shared system REMS, implementation proved challenging for the CPMG to transition. These implementation issues resulted in long wait times for participants and disrupted access to clozapine for both pharmacies and patients. Prescribers were required to certify in the REMS by November 23, 2015, and pharmacies were required to certify by December 14, 2015.

Because of the implementation challenges experienced by the CPMG and to prevent further interruptions in treatment, in November 2015, the agency announced that the prescriber and pharmacy REMS certification deadlines were extended. At that time, the agency communicated to the CPMG that it would not take enforcement action if the REMS requirements were not met, so the applicants allowed dispensing of clozapine without meeting the REMS requirements.

It became apparent that full implementation would require a slower, more stepwise approach than originally anticipated. Between 2015 and 2016, the CPMG continued to work toward full implementation of the REMS. In May 2016, the CPMG released changes to the REMS system to allow pharmacies who were participating in the REMS to verify patient enrollment through a dispense authorization.

The dispense authorization signaled that the patient had been enrolled and had an acceptable baseline or most recent ANC even if the ANC was not current, or the patient had a treatment rationale

on file from the provider even if other safe-use conditions were not verified. However, the REMS did not restrict distribution to only certified prescribers and pharmacies; therefore, pharmacies could obtain clozapine from the wholesaler and dispense without participating in the REMS. Furthermore, the requirement for current ANC was not implemented.

With changes to the REMS dispense authorization discussed in the previous slide, the CPMG conducted an analysis that led them to determine that an estimated 52 percent of patients prescribed clozapine would not receive clozapine if the REMS required documentation of a current ANC. This emphasized the challenge of getting prescribers to comply with documentation of current ANCs. Denying clozapine to patients who may have had a current ANC in the acceptable range but not documented in the REMS system was especially concerning to the agency; therefore, the FDA continued to exercise enforcement discretion with regards to the requirements for documentation of a

current ANC.

From 2016 to the beginning of 2019, CPMG continued to work towards implementing the approved REMS while trying to minimize access issues for patients; then in January of 2019, the FDA approved a REMS modification. The key highlights of the modification were that prescribers and pharmacies had to be certified by February 28, 2019 or they would no longer be able to prescribe and dispense clozapine.

Inpatient prescribers were not required to be certified if they were prescribing for patients already enrolled in the program. If a patient's absolute neutrophil count is not current, this would not prevent clozapine from being dispensed; and if a prescriber was not certified, the pharmacist could use clinical judgment to dispense and provide prescriber information to the REMS through a dispense rationale. This was especially important to try to minimize access issues for patients. The pharmacist would obtain a dispense rationale and provide prescriber information to the

REMS for subsequent outreach to the prescriber.

The FDA remained concerned that patients would be denied access to clozapine if the requirements for prescribers to document a current ANC in the REMS system as a condition of dispensing was implemented; therefore, the FDA continued to exercise enforcement discretion for this requirement in 2019. Although the documentation of ANC monitoring was not enforced, FDA communicated in a CDER statement that monitoring was still to occur as described in labeling.

Subsequently, in March 2020, the agency released guidance for industry and healthcare professionals for certain REMS requirements during the COVID-19 public health emergency. Prescribers could consider whether there were compelling reasons not to complete the REMS required laboratory testing during the public health emergency and use their best medical judgment in weighing the benefits and risks of continuing treatment in their absence.

In July of 2021, the FDA approved a REMS

modification to the REMS that took effect in November of that same year. The purpose of this modification was to address the continued prescriber challenges with ANC reporting frequency and to change to a new REMS administrator. The program changes included reducing the frequency that prescribers were required to report ANCs to the REMS for all patients to monthly via a patient status form, regardless of the patient's monitoring frequency. This change did not reduce the monitoring frequency as described in labeling, just the documentation of that required monitoring.

This modification also implemented a new process for how pharmacies verified that the safe use and requirements were met before dispensing. This change to the verification process was necessary because the processes and information technology platform used by the previous REMS administrator that supported the major operations of the program would be different under the new REMS administrator.

With the REMS modification in July of 2021,

the goal remained the same as that approved in 2015, but there was a change to the third objective. Note that objective number 3 is changed from ensuring compliance with the monitoring schedule for absolute neutrophil count prior to dispensing clozapine to ensuring prescribers submit documentation that periodic monitoring of patients is performed to identify severe neutropenia. This documentation is done through a patient status form.

With the REMS modification in July 2021, there was a change to prescriber requirements regarding how the ANC is documented. Rather than the prescriber having to document the ANC according to the monitoring frequency, which could be up to weekly, the prescriber was required to document ANC results once monthly via the Patient Status Form. The Patient Status Form also collects additional data on clozapine-related neutropenic adverse events.

With the REMS modification in July 2021, there were changes to what the REMS dispense

authorization verified. Specifically, it now verified that a patient's status form was completed within the last 37 days for subsequent dispensings. Although the Patient Status Form should be submitted every 30 days, this allowed for a 7-day grace period. The REMS dispense authorization also verified that the prescriber had authorized continuation if one or more labs was missing, or had provided a treatment rationale if the ANC was below the acceptable range.

If the Patient Status Form was overdue and the pharmacist was in possession of a current ANC that was within the last 30 days of the attempted fill, and that ANC was within an acceptable range for the patient, the pharmacist could submit that ANC to the REMS and proceed with dispensing.

Implementation of this modification necessitated all stakeholders recertify or re-enroll in the REMS. During the implementation of this modification, challenges with the new system resulted in disrupted access to treatment for many patients. In November 2021, the FDA again

exercised enforcement discretion. This allowed wholesalers to ship clozapine to non-certified pharmacies. Pharmacists could dispense without a REMS dispense authorization, and dispensing could occur without verification of safe-use conditions.

Stakeholders continued to experience ongoing difficulties with the clozapine REMS after the July 2021 modification, including issues with patient access to clozapine for patients recently discharged from an inpatient setting. The approved REMS states that a pharmacy may provide a 7-day supply upon discharge from an inpatient facility. As a result of the ongoing difficulties, in November of 2022, the agency stated it did not intend to object if inpatient pharmacies dispensed a day's supply of clozapine that aligns with the patient's monitoring frequency upon discharge from an inpatient facility.

This slide estimates patient participation in the REMS based on monthly estimates of patients who had a dispensed clozapine prescription from U.S. outpatient pharmacies compared to the number

of patients who received a REMS dispense authorization from an outpatient pharmacy by month for the time period of November 2021 through June 2024. Based on this data, we estimate that 25 to 35 percent of the patients dispensed clozapine may not be participating in the REMS.

This table shows that starting in 2015, there have been various times when the agency has exercised enforcement discretion for the verification of safe-use conditions. Since the approval of the 2021 REMS modification, none of the requirements have been enforced, and this continues to present day.

In summary, the approved REMS has evolved since 2015, and the requirements of the REMS as outlined in the 2021 modification approval are not currently implemented. The requirement for the patient to have a current ANC documented in the REMS has never been implemented. Today, prescribers, pharmacies, and patients do not have to participate in the REMS in order for the patient to obtain clozapine. This concludes my

presentation.

DR. FLOYD: Thank you for the presentations.

Both FDA and the public believe in a transparent process for information gathering and decision-making. To ensure this transparency, the FDA believes that it's important to understand the context of an individual's presentation. For this reason, we encourage all participants, including the industry's non-employee presenters, to advise the committee of any financial relationships they have with industry, things like consulting fees, travel expenses, honoraria, and also equity interest.

Likewise, the FDA encourages you at the beginning of your presentation to advise if you do not have any such financial relationships. If you choose not to address this, it will not preclude you from speaking.

We will now proceed with presentations from the Clozapine Product Manufacturers Group.

AUDIENCE MEMBER: Louder, please.

DR. FLOYD: I want to take a moment to ask

people in the back not to shout out when they're not called on by the chair. Thank you.

Industry Presentation - Jason Gross

DR. GROSS: Good morning, and thank you, Dr. Floyd. I'm Jason Gross, Vice President of Scientific Affairs at HLS Therapeutics, who markets Clozaril. I've been involved with clozapine for most of my career, most recently as a member of the CPMG since 2015. Before this, I also led the approval of the first generic of clozapine in 1997.

I'd like to acknowledge members of the FDA, the committee, and especially the healthcare professionals, patients, family members, and patient advocates attending today. We respect that members of today's audience have a personal investment in schizophrenia, which has redefined their lives. As I look around the room today, I may be dating myself, but I started my career at the FDA, and it's a pleasure to see so many people that I've come to know and respect over the years.

The clozapine REMS is sponsored by the clozapine manufacturers who are listed here today.

We appreciate the opportunity to discuss the clozapine REMS and how we can come together to balance the need to protect patient safety and the need to ensure the access to this life-saving treatment. It's important that we begin by recognizing who we are here to help. Approximately 1 percent of the worldwide population is living with schizophrenia, and it ranks among the top ten leading causes of disease-related disability.

Between 22 and 40 percent of people suffering with schizophrenia will fail to respond adequately to standard antipsychotic treatment. This is generally referred to as treatment-resistant schizophrenia. Symptoms include distortions in thinking; perception; emotions; language; sense of self; and behavior. People living with schizophrenia often have challenges with work, maintaining healthy relationships, and caring for themselves.

First discovered in 1958, clozapine is the only approved product for treatment-resistant schizophrenia. It has been transformative for

treatment-resistant patients and their families, and yet, as you will hear from from my colleagues today, it is vastly underutilized and is the only product that has been indicated to reduce suicide risk and improve overall mortality in this patient population.

Clozapine improves functioning, reduces the persistence of psychosis and the risk of relapse, hospitalization, suicide, violence, and aggression, thereby improving patient well-being and family interactions. It's important to note clozapine is not a medication that can be stopped and started without challenges. Even a brief disruption from obtaining medication or missing doses can lead to a wide spectrum of somatic and psychiatric symptoms, including agitation; nausea; vomiting; insomnia; and withdrawal-associated catatonia; and even psychoses. Further, even if one day's dosage is missed, the medication should be retitrated as defined in the product label.

Despite its life-saving benefits, clozapine also carries a risk of severe neutropenia, which

can lead to serious infection and death. The risk of neutropenia was first identified shortly after clozapine was introduced in Austria and Switzerland, and led to the withdrawal in 1975 after physicians in Finland identified a cluster of 16 cases of neutropenia, which led to the deaths of 8 patients. After clozapine's withdrawal, physicians were no longer able to restabilize patients who had been successfully treated with clozapine, which was a cause of concern.

In 1984, a study to re-evaluate the efficacy of clozapine in patients who do not respond to other treatments was initiated. Following the overwhelming positive results of this landmark study, the FDA approved clozapine in 1989. This approval was contingent on a required clozapine patient management system to assure the safe use of the product. The condition of ANC monitoring is still noted in the current product today. I'm pleased to say that one of the four primary investigators from this landmark study is here with us today, Dr. John Kane, and you will hear from him

later.

The risk mitigation programs run by different manufacturers of clozapine were placed with a shared REMS in 2015, and this REMS was modified in 2016, as you heard today. For today's discussion, we'll call this the Legacy REMS. In 2021, the Legacy REMS were replaced by a Modified REMS designed to ensure that a patient either has a current acceptable ANC value on file when you receive clozapine or that the clinician has determined that there's a benefit of continued treatment, which outweighs the risk despite the lack of an acceptable ANC.

When enrollment of physicians, pharmacists, and patients in a Modified REMS did not occur as quickly as anticipated, the FDA implemented what is termed enforcement discretion to allow continuity of care while participants move from Legacy REMS to the Modified REMS. We also held listening sessions with stakeholders and made updates based on their feedback to ease stakeholder burden. Then we were informed that as part of its re-evaluation of the

REMS, the FDA planned to host an advisory committee meeting, which brings us here today.

Today, the advisory committee has been asked to discuss possible changes to minimize burden on patients, pharmacies, and prescribers while maintaining the safe use of clozapine. As you will hear, participation by healthcare providers and patients in the Modified REMS meets or exceeds that of the Legacy REMS.

When a stakeholder participates in the REMS, the REMS provides a resource to document compliance with monitoring requirements as specified in the label. Enforcement discretion and other REMS design and implementation factors limit abilities to collect data, and knowledge surveys, while better than previous surveys, continue to reveal gaps and understandings that can be addressed.

A review of the adverse event reporting data from the FDA FAERS database and sponsor pharmacovigilance reporting shows no evidence of a change in the clozapine safety profile. While the REMS plays an important role in ensuring patient

safety, we acknowledge stakeholders have made it clear that it can be difficult to obtain clozapine and maintain continuity of care. These stakeholder concerns are very important, especially since even a brief disruption in treatment can lead to challenging outcomes. While some of these stakeholder burdens may be attributed to the REMS, many other concerns are related to misconceptions about the REMS and other issues related to how healthcare providers and insurance companies implement treatment practices for clozapine.

Regardless of the cause, all stakeholders can and should collaborate to reduce burdens and ensure continuity of care. CPMG is committed to working with the FDA and our stakeholders to address challenges while maintaining the safe use of clozapine.

Here's our agenda for the rest of this morning's presentation. You'll hear from Dr. John Kane from the Zucker School of Medicine at Hofstra/Northwell. He will discuss clozapine's role in treatment-resistant schizophrenia, the

risks associated with clozapine with disruptions in treatment, and how regulators around the world have sought to balance risk management and patient access. You'll also hear from Dr. Robert Cotes from the Emory University School of Medicine. He'll provide his clinical perspective on treating patients under the REMS program.

You'll also hear from Mr. Jim Shamp from our REMS administrator, UBC. He'll give more detail on the REMS goals, operations, and a summary of our program assessments. And finally, I'll return to present our adverse event data, what we've learned from stakeholder feedback, and what we see as a potential area for improvement. Further, we have two additional experts with us to help answer your questions, Ms. Kelly Coombs and Dr. David Sykes.

Now, I'd like to turn my podium over to Dr. Kane to discuss the clinical background for clozapine and schizophrenia.

Industry Presentation - John Kane

DR. KANE: Thank you, Dr. Gross.

I'm John Kane, Professor of Psychiatry and

Molecular Medicine at The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell in New York. I'm very pleased to be here today. I thank the FDA for holding this meeting, and I look forward to the discussion.

Forty years ago, I was the principal investigator of the study that led to the FDA's approval of clozapine, and remarkably, more than three decades later, clozapine is still the only drug, the only medication, with FDA approval for severely ill patients with schizophrenia, who failed to respond adequately to standard antipsychotic treatment. I'd like to disclose that I'm a paid consultant to CPMG, I have received honoraria for lectures from HLS, and I am a consultant to Teva. The views expressed here are my own.

Clozapine has really been a cornerstone of schizophrenia treatment for several decades. This is illness which affects 20 million people globally. The lifetime risk of developing schizophrenia is a little under 1 percent, and

although we have several antipsychotic drugs available as first-line treatments, the prevalence of treatment-resistant schizophrenia remains high.

We define treatment resistance as the persistence of positive symptoms such as delusions or hallucinations despite two or more trials of first-line antipsychotic drugs. In reality, treatment resistance has been defined differently across a range of studies, and therefore, we consider a range of estimates for the prevalence of treatment-resistant schizophrenia; but it's important to emphasize that even at the very first episode of this illness, approximately 20 percent of patients are treatment resistant, and that prevalence increases to as high as 40 percent with more chronic illness.

There are enormous potential benefits of clozapine for patients with treatment-resistant schizophrenia as evidenced by numerous studies and meta-analyses that have been conducted over the past 30 years. There's evidence for a reduction in the persistence of psychosis and the risks of

relapse; hospitalization; violence; aggression; mortality; suicide; family burden, and importantly, there's evidence for improved functioning, as well as a reduction in direct and indirect economic costs associated with treatment-resistant illness.

Clozapine remains the only medication approved for treatment-resistant patients, and as I said, this has been the case for more than three decades. And despite that, it is seriously underutilized. In addition to underutilization, we see that patients who do ultimately receive clozapine face inordinate delays, not just weeks or months, but years. Patients undergo trials of multiple antipsychotics, or combinations of antipsychotics, before receiving a trial of clozapine, if they ever do.

And not only do these delays leave patients with unresolved symptoms, but data suggest that significant delays in introducing clozapine are associated with poor treatment response to clozapine once it is initiated. Since we do not have good predictors of clozapine response,

patients need to undergo a therapeutic trial to determine the potential benefit for them; therefore, clozapine should be considered, offered to any severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment.

A study of clozapine use in 17 countries demonstrated that the U.S. had some of the lower clozapine utilization rates when compared to other countries, particularly in the privately insured cohort. The highest rates of clozapine use were in Finland and New Zealand. In my opinion, the U.S. is not lagging behind just because of REMS requirements, as other countries have similar monitoring requirements. I believe that there are a number of other factors that contribute to the underutilization of clozapine, including lack of adequate training for psychiatric residents and other clinical team members.

Diniz et al. reported that 22 percent of individuals with schizophrenia experienced treatment resistance at the very first episode, and

this increases is to as high as 39.5 percent among more chronically ill individuals, and this does not even include the indication for suicidality. Fewer than 5 percent of U.S. patients are being treated with clozapine. The utilization gap therefore suggests that as many as 8 times more individuals could benefit from a trial of clozapine. Patients and families should be given the opportunity to receive a trial of clozapine.

A study of 50 state Medicaid programs from 2015 to 2019 demonstrated considerable state by state variation in clozapine use, as much as 13-fold from one state to another. This is unlikely to be accounted for by differences in patient populations. It really underscores the challenge that we have in implementing evidence-based medicine in a consistent fashion, across a range of geographic regions, treatment facilities, and health systems. There are a number of factors that play a role in the underutilization of clozapine, some of which we've listed here, but as I would suggest, the major factors really

involve clinicians; attitude; knowledge; lack of training; inadequate motivations or incentives; et cetera.

While the focus of today's discussion is severe neutropenia, clinicians manage a variety of potentially serious side effects associated with clozapine, including myocarditis and cardiomyopathy; seizures; pneumonia; gastrointestinal hypomotility; weight gain; and metabolic syndrome. Per the label, we monitor these side effects and others.

The risk of clozapine-induced neutropenia clearly decreases over time. Most serious neutropenic events occur within 18 weeks of initiating treatment, and the incidence becomes negligible after 2 years. In many countries, weekly blood monitoring is reduced after the first 18 weeks to once every 4 weeks, and the question has been asked whether it could be ceased entirely after 2 years unless clinically indicated.

The long-term risk in absolute terms compared with the magnitude of the advantages of

clozapine, including life expectancy, should be considered. Clozapine is grossly underutilized, and reducing the burden of long-term neutrophil monitoring could help facilitate long-term clozapine use without incurring significantly greater risk of severe neutropenia.

Neutropenia related death is rare. A meta-analysis of 36 studies involving over 260,000 clozapine-treated patients found the prevalence of neutropenia to be 0.4 percent and related deaths 0.05 percent; so clearly, the incidence of fatal outcomes has been dramatically reduced since the risk of clozapine-induced severe neutropenia was first identified several decades ago.

The stringent requirements for reporting blood monitoring is considered a factor that leads both patients and clinicians to underutilize or discontinue clozapine. Previous studies have suggested that flexible neutrophil monitoring may contribute to longer term clozapine maintenance. When we examine global monitoring, we see that the U.S. requires weekly monitoring for the first

6 months, every 2 weeks for months 6 to 12, and then monthly thereafter. Many other countries around the world require a weekly monitoring for the first 18 weeks, and subsequently monthly monitoring. A single international guideline could help to address the underutilization of clozapine while simultaneously addressing safety concerns.

It's critical that we recognize clozapine's potential role in improving the lives of patients with treatment-resistant schizophrenia. People live longer; experience a reduction in persistent psychosis; a reduction in the risk of suicide; reduced risk of relapse and hospitalization; a reduction in the risk of violence and aggression; improved psychosocial and vocational functioning; a reduction in family burden; and a reduction in direct and indirect costs.

It's also important to emphasize that for a subgroup of individuals with clozapine, treatment can be absolutely life-changing. Regrettably, we do not have good predictors of clozapine response. The overemphasis of risks and the burden of

lifelong reporting requirements can discourage patients from trying clozapine; therefore, in my discussion with patients and families, I emphasize that to determine their individual benefit to risk ratio, they will need to experience the potential positive impact that clozapine can have on their lives and the lives of their loved ones.

Thank you, and now I'd like to invite Dr. Robert Cotes to the podium to share his perspective on prescribing clozapine under the REMS. Thank you.

Industry Presentation - Robert Cotes

DR. COTES: Thank you, Dr. Kane.

I'm Robert Cotes, Professor of Psychiatry and Behavioral Sciences at Emory University School of Medicine. I'd like to thank the FDA and CPMG for this opportunity. I want to extend my heartfelt thanks to everyone here with a shared interest in clozapine, particularly those individuals with schizophrenia and their families. I look forward to learning from you later today.

I'm a clinician, educator, and researcher

focused on clozapine. I developed the clozapine program in 2012 at Grady Memorial Hospital that now serves 130 individuals on clozapine. We serve a large uninsured population. From 2020 to 2024, I served as Physician Expert for SMI Adviser, a 6-year grant from the Substance Abuse and Mental Health Services Administration, which was led by the American Psychiatric Association. There, I co-chaired the National Clozapine Center of Excellence and answered hundreds of consultation questions from prescribers about clozapine. I'm a paid consultant for CPMG. The views expressed in this presentation are my own, and I have no financial interest in the outcome of today's meeting.

Prescribing clozapine takes a team effort. The label requires monitoring, and the REMS ensures compliance. It occurs in a delicate and complicated system that involves the patient, prescriber, pharmacies, lab testing facilities, insurance, and distributors. Any breakdown in any part of this highly interconnected system related

to the REMS itself, or misconceptions about the REMS, can result in missed clozapine doses, which can have significant consequences for patients.

Some patients have prescribers, phlebotomy, and pharmacy all available in the same location, but more commonly, patients have to create their own system that requires coordination. Our clozapine program, for example, works with over 30 different pharmacies across the state and 15 different labs in unique configurations. The lack of standardization can also make errors resulting in missed doses more likely.

The patients and the families are at the center of this system. Before clozapine, patients have suffered considerably and have often failed multiple antipsychotics and ineffective combinations of other antipsychotics. They are usually at their wit's end. They often have to go to great lengths to find a prescriber who will initiate or continue clozapine. Many times the patient, their family, or caregiver must actually advocate for their loved one to start on clozapine.

Once prescribed, patients and families must then coordinate the logistical steps of maintaining access to clozapine. Patients may face cognitive symptoms of the illness, transportation barriers, and may or may not have family or caregiver support. They then must navigate this process at least monthly, continuing indefinitely, which can place considerable stress on patients. Finally, a question to consider is the patient's voice. Should patients have a role in choosing what level of risk they are comfortable with in this process?

Prescribers can be hesitant to start clozapine, or if they do use it, they can find it a challenge to continue. Antiquated notions remain about clozapine being the last resort rather than the only effective medication after two antipsychotic failures. Many prescribers lack the necessary familiarity and knowledge to identify TRS patients or to use clozapine effectively. Prescribers often make assumptions about which patients may benefit from clozapine and which patients have the necessary support to be adherent

with monitoring.

Some of these assumptions are incorrect, making prescribers unwitting gatekeepers as to which patients receive clozapine and which do not. When discussing clozapine with their patients, prescribers may not have the skills or time to convey its unique benefits without overfocus on the adverse effects. Finally, using clozapine takes additional steps from the prescriber, which are often not reimbursable.

There are challenges at the pharmacy as well, and patients often get stuck waiting there. In large chain pharmacies in particular, there can be discrepancies between the requirements of the REMS and pharmacy corporate requirements or what is required from the pharmacy benefit managers. For example, even if the patient status form is completed, some pharmacies require a faxed copy of the blood work, which is not required by the REMS. Pharmacies may have difficulties reaching prescribers if they are needed urgently to complete a patient status form, write a prescription, or

provide an ANC. Finally, if there is evidence of an active ANC, the pharmacist could use a dispense rationale, but sometimes this does not occur.

The laboratory where patients have their blood drawn is sometimes an unexpected area of difficulty. Although points of care testing is accurate and can be helpful, it is used infrequently in many settings. If patients are using a community lab, they often have to navigate the hours when the lab is open and may have to make appointments with the lab rather than walking in. Many labs will not accept the standing order and require an order to be faxed monthly, adding to system burden.

Additionally, when yearly labs, like a hemoglobin A1C or lipid panel, are added on, sometimes the ANC is not obtained. Finally, if using external labs, the lab exists in a separate electronic record requiring clinicians to toggle between multiple systems and windows. At any point in this cycle, if there is a break in the chain, missed doses of clozapine can occur, which can have

catastrophic consequences, often undoing considerable hard-earned progress.

As part of the evaluation of eight REMS programs, one study found that 60 percent of clozapine prescribers agreed, or strongly agreed, with the statement that "safe-use requirements often delayed patients in receiving their medication." The consequences of missed clozapine doses include a spectrum of issues from the need to retitration, which is not an exact science; psychological distress; physical discomfort; and clozapine withdrawal symptoms. Symptom exacerbation may occur in around 20 percent, potentially leading to psychiatric hospitalization or more serious outcomes.

Taken together, as a frontline clinician in 2024, prescribing clozapine is, well, hard, but not as hard as the journey for the patient. Coordinating care across settings is challenging, and transitions in care are an area of vulnerability. Our current system is not designed to handle this complexity, and specialized

clozapine clinics like mine are few. All of the barriers we discussed today exacerbate healthcare disparities as to who starts and who stays on clozapine.

The current situation feels untenable. In community mental health, where burnout is high and clinicians are often overwhelmed, managing clozapine requires a culture of urgency and the need to respond to emergencies. I frequently get calls on nights and weekends from patients at the pharmacy needing urgently to get their clozapine.

Also, I want my patients to call me if they develop signs and symptoms of neutropenia or an infection any time. I can see why it is difficult for patients to find a prescriber. To address some of these concerns, in my clinic, there is a 100 percent philanthropically supported staff member to manage clozapine for 130 patients during working hours, but most programs do not have such a luxury.

Let's again put this risk into perspective. Although clozapine is associated with severe

neutropenia in 1 out of 108 patients, death due to severe neutropenia is rare. One out of 7700 patients who receive clozapine are expected to die due to severe neutropenia. On the other hand, think of the benefit of greater clozapine use to appropriate patients. Clozapine is the only medication expected to work for TRS. Additionally, the InterSePT study found that treating just 12 patients with clozapine rather than olanzapine will show benefit for clozapine to reduce suicidal behavior.

Clozapine REMS has codified hematologic monitoring into the consciousness of psychiatrists and other prescribers. Monitoring has likely saved the lives of patients early during the course of their treatment; yet I wonder if it serves us in its current form. From my perspective, there are things that could make this better for everyone, and I sincerely hope that things change.

The key question for me, which the committee will be asked to vote on today, is, are the requirements for the prescriber to document ANC

results and the pharmacy to verify the ANC through the REMS necessary to ensure safe use? Other changes that could be considered could include time limit on centralized reporting in line with emerging data; a prescriber look-up to help connect patients to care; a focus on education about clozapine and the REMS; addressing misconceptions; and allowing greater flexibility to manage transitions in care.

I look forward to today's discussion. Thank you. I'll now turn it over to Jim Shamp from UBC to discuss the operations and assessment of the REMS.

Mr. Shamp?

(Applause.)

Industry Presentation - James Shamp

MR. SHAMP: Thank you, Dr. Cotes.

I'm Jim Shamp, Vice President of Data Intelligence and Program Analytics at UBC. I have over 20 years of experience working on risk management programs, including the clozapine REMS. I'll cover several topics, including an overview of

the REMS design and operation; the rationale for enforcement discretion and its impact on data collection; and a review of the assessment data from the Modified clozapine REMS, and in some cases, the Legacy clozapine REMS. I'll cover demographic data on patients and prescribers; data on the use of key REMS reporting tools; metrics to assess adherence to the REMS and how well the REMS is understood by prescribers, pharmacists, and patients.

So let's start with the REMS design and operation. As a reminder, the goal of the clozapine REMS is to mitigate the risk of severe neutropenia associated with the use of clozapine. It's important to understand the goal is not to prevent severe neutropenia but to ensure monitoring, identify low ANC values, and allow informed risk-benefit decision-making about continuing clozapine when this occurs.

The objectives of the REMS are to educate prescribers, pharmacists, and patients about the risk of severe neutropenia and appropriate

monitoring requirements; ensure that prescribers submit documentation showing that patients' ANCs are being monitored to identify severe neutropenia; ensure that prescribers are documenting a benefit-risk assessment for patients whose ANC values fall below the acceptable range; and to establish the long-term safety and safe use of clozapine by enrolling all patients taking clozapine into a registry.

The REMS educates, informs, and ensures safe use among the four key stakeholder groups. According to the requirements of the REMS, prescribers must be certified. They must enroll all patients in the REMS and submit each patient's ANC results monthly using a patient status form. Patients must be enrolled and comply with the ANC testing requirements. Pharmacies must be certified, and they must verify that the patient is enrolled and authorized to receive clozapine. And finally, wholesalers must enroll in the REMS and establish processes and procedures to ensure the drug is distributed only to certified pharmacies.

Here's how the process works. The prescriber and patient discuss clozapine, then the prescriber educates the patient on the risk of neutropenia and the need for ANC monitoring. Prior to treatment initiation, the prescriber orders lab testing for the patient and the patient completes the testing. Once this occurs, the prescriber enrolls the patient in the REMS.

The patient is now authorized for a dispense and can pick up clozapine from a certified pharmacy. The patient must comply with ongoing ANC testing according to their monitoring frequency, and their prescriber must submit the ANC values using the patient status form monthly. This cycle of office visits, blood draws, and prescription pickups continues indefinitely.

Recognizing the importance of continuity of care, several features were proactively designed into the Modified REMS. These features provide the opportunity for patients to receive clozapine even if the patient has a missing or abnormal ANC value, if they have a missing patient status form, or if

they are not enrolled in the Modified REMS.

These include a reason for missing lab, which allows a patient to receive clozapine without an ANC value as long as the prescriber provides authorization and a reason for the missing value; a treatment rationale which allows a patient to receive treatment even if they have an abnormal ANC value, as long as the prescriber documents that the benefits of continuing treatment outweigh the risk of neutropenia; a dispense rationale which allows a pharmacist to dispense clozapine to a patient who does not have a current patient status form, as long as a current and acceptable ANC value is available; and a transition dispense rationale. This was designed to be a temporary measure to let the pharmacist dispense to a patient who was enrolled in the Legacy system without being enrolled in the Modified REMS as long as a current and acceptable ANC value is available.

We also established a robust reminder system to prevent disruptions in care. The reminders, shown here, are designed to alert the prescriber if

a patient is in interrupted status or requires a patient status form. If in an interrupted status, the prescriber may choose to complete a treatment rationale if the benefits of continuing clozapine outweigh the risk of neutropenia, or choose to keep the patient in an interrupted status until the patient's ANC value returns to a normal level. This allows steps to be taken to ensure continued treatment.

Now, let's turn to the rationale for the enforcement discretion and its impact on data collection. As Dr. Gross mentioned earlier, the Modified REMS was approved on July 29, 2021. This required that all existing stakeholders re-enroll in the Modified REMS prior to its planned launch in November of 2021.

We opened a transition contact center and launched a new website to answer questions and assist stakeholders in enrolling. We also ran two outbound call campaigns, which were directed at prescribers with 10 or more patients in the Legacy system, authorized representatives for chain and

corporate pharmacies, and wholesalers and distributors. In addition, we completed email and hard copy outreach to prescribers, pharmacies, designees, and wholesalers prior to the launch of the Modified REMS.

Despite these efforts, participation in the Modified REMS fell below the levels seen in the Legacy REMS. Many prescribers, pharmacies, and patients were not prepared for the Modified REMS, which caused an increase of calls to the contact center, resulting in long wait times and difficulties for pharmacies and prescribers to certify. In some cases, this prevented patients from obtaining their prescriptions.

To ensure continuity of care, the FDA initiated enforcement discretion in November of 2021. Under enforcement discretion, pharmacists can dispense clozapine without obtaining an authorization, and wholesalers can ship to pharmacies without confirming the pharmacy is certified.

In 2022, additional discretion was exercised

to address the concern that inpatient pharmacies are only allowed to dispense a 7-day supply of clozapine to the patient upon discharge. With this additional discretion, inpatient pharmacies can now dispense a quantity of clozapine upon discharge that is in line with the patient's monitoring frequency. In the weeks following the launch, CPMG and the FDA worked to address concerns and enroll and certify stakeholders. Participation is now equal to or greater than the number under the Legacy REMS.

Enforcement discretion affects data collection. It allows a pharmacist to dispense without obtaining a REMS dispense authorization and wholesalers to ship to uncertified pharmacies. As soon as this is allowed, stakeholders are able to bypass all REMS requirements. The effect is that clozapine can be dispensed without the REMS having any visibility and no data are collected, which makes any analysis of the data difficult.

For example, we can't be sure when a patient started therapy, and we can't calculate time to

onset of severe neutropenia. As a result, we align with the FDA that there are challenges to determine the contribution the REMS has had on mitigating severe neutropenia. Understanding these limitations, let's now look at data we have captured.

We'll begin with the review of who is enrolled or certified in the REMS. In the most recent reporting, there were more than 154,000 patients enrolled in the Modified clozapine REMS. Over 96 percent of these patients were still active in the REMS. The 30 to 39 age group had the largest percentage of patients, and most were between 20 and 69. More patients were male, most patients were not Hispanic or Latino, and Caucasians make up 70 percent of the patients, and Black or African American make up 16 percent of the enrolled patients.

As of the most recent reporting period, there were over 58,000 certified prescribers. The majority of these prescribers were physicians. The number of certified prescribers was similar between

geographic regions, but we acknowledge that there are differences in population sizes and geographic areas of these regions, and we note that patients still report difficulty finding certified prescribers.

Now, let's look at the use of the key reporting elements of the REMS: the Patient Status Form, the REMS Dispense Authorization, the Dispense Rationale, and the Treatment Rationale. The Patient Status Form is the primary communication tool for a prescriber to submit patient data to the REMS. It documents ANC values, and when necessary, it documents the prescriber's assessment of appropriateness of continuing treatment. It also collects whether the patient experienced any adverse events due to clozapine-induced neutropenia. In the most recent reporting period, there were over 1.7 million patient status forms submitted for almost 121,000 unique patients who participated in the REMS.

The REMS dispense authorization verifies for the pharmacist that a patient is enrolled and

authorized to receive clozapine. Authorization is based on the REMS receiving a current patient enrollment or patient status form with a current acceptable ANC value, or if not acceptable, a treatment rationale.

Nearly 4.6 million RDAs have been requested under the Modified REMS. Approximately 28 percent of these were rejected. Most rejections were due to a missing patient status form. Recall that when this happens, the pharmacist may be able to dispense to the patient using a dispense rationale, and under enforcement discretion, the pharmacist may dispense clozapine without obtaining an RDA, so these numbers here may be underreported.

When using a dispense rationale, the ANC value can be obtained from the patient, from the prescriber, or from the ANC history presented to the pharmacist in the clozapine REMS website. We can see here that more than 41,000 patients received more than 192,000 dispense rationales during the most recent reporting period, providing continuity of care to these patients. In fact, of

the patients that received a dispense rationale, 75.2 percent of the patients received it within 7 days of their initial dispense rejection.

The treatment rationale documents that a prescriber believes the risk-benefit favors continued treatment for a patient even in the presence of an abnormal ANC value. The use of the treatment rationale reflects that an informed decision is being made for the patient. Data shows that the treatment rationale has not been widely used to continue treatment when the patient's ANC value indicates neutropenia. In the Modified REMS, we see that more treatment rationales have been used, and this aligns with the increase in reports of neutropenia seen with increased data collection.

We can clearly see a high volume of activity in the REMS, but how do we know if the REMS is actually mitigating the risk of severe neutropenia associated with the use of clozapine? There are several metrics we can consider, including adherence to monitoring, and prescriber, pharmacist, and patient knowledge of the risk of

neutropenia and safe-use conditions.

As we seek to quantify the adherence to monitoring, it's important to note some limitations in our ability to collect pertinent data. First, the Legacy REMS did not include a metric to measure adherence to monitoring. This is due, in part, to the fact that the Legacy REMS was never fully enforced. In fact, only one ANC level from any time point was required to dispense clozapine. And now, as we move forward in the Modified REMS, which has never been fully enforced, enforcement discretion allows dispensing without obtaining a REMS dispense authorization.

So now, when we focus on the Modified REMS and look at submission of patient status forms, we see that the number of patients status forms submitted after the due date doubled from the first to the second reporting period under the Modified REMS. By looking at the number of unique patients who had ANC values reported on their patient status form in accordance with their monitoring schedule, we see that the Modified REMS has been successful

in ensuring that patients have timely ANC values documented.

In the first month of the Modified REMS, which was November of 2021, you can see that the percentage of patients who had all of the required ANC labs submitted on the patient status form was low across all three monitoring frequencies. This was likely due to prescribers getting accustomed to the new patient status form requirements, but as we can see, these numbers improved quickly. By the end of the two Modified REMS reporting periods in November of 2022 and May of 2024, most patients had their ANC labs submitted according to their monitoring frequencies.

Another important measure of the REMS effectiveness is whether it's meeting its objective of educating stakeholders. To assess this, we conduct periodic knowledge surveys that measure understanding of the risk of severe neutropenia associated with the use of clozapine; understanding of appropriate use of clozapine and its monitoring requirements; and recognition that clozapine is

only available through a restricted program. When reviewing these data, we look at a set of questions linked to each measure and calculate a mean score for the questions in that set. We also note any questions in which a low score detracts from the mean.

A more detailed reporting of the historical results is available in your briefing document starting on page 68, but for this presentation, we'll focus on the most recent results, which indicate that there are gaps in stakeholder knowledge that can be addressed.

For key risk message 1, the mean score for prescribers and pharmacists was 93 percent and 88 percent, respectively, suggesting the risk was generally understood. For patients, the mean score was 37 percent, suggesting a low level of understanding of the risk. Seventy-five percent of patients surveyed were aware that clozapine can cause white blood cells to drop in number, which is neutropenia; however, patients often answered incorrectly when asked to identify the signs and

symptoms of neutropenia.

Now, for key risk message 2, prescribers and pharmacists again had a good understanding with a mean score of 93 percent and 86 percent, respectively. For patients, the mean score was 84 percent, which suggests this key risk message was better understood than in prior surveys. And finally, for key risk message 3, the mean score of linked questions for both prescriber and pharmacists was 87 percent, suggesting that key measure 3 was generally understood. For patients, the score was 63 percent, suggesting key risk measure 3 was poorly understood. In general, most questions were low scoring for patients.

Now, to summarize our assessment of the clozapine REMS, participation in the Modified REMS now meets or exceeds that of the Legacy REMS. Given the high adherence to patients monitoring schedules and generally high level of understanding of the Modified REMS requirements, when a stakeholder participates in the REMS, the REMS provides a resource to document compliance. Data

from the knowledge survey suggests that some gaps in understanding exist and can be addressed; however, we recognize that enforcement discretion and other REMS design and implementation factors limit our ability to collect data.

And now, I'd like to turn it back to Dr. Gross, who will discuss the sponsor's adverse event reporting and assessment of FAERS data, and potential opportunities for improvement in the REMS.

Dr. Gross?

Industry Presentation - Jason Gross

DR. GROSS: Thank you, Mr. Shamp.

In this last presentation, I will discuss what we've learned from the adverse event reports capturing the REMS and by sponsors and provide our assessment of the observed increase in adverse event reports seen in the FDA FAERS database; then we will review stakeholder feedback and consider opportunities to address burden while continue to ensure patient safety. Based on stakeholder feedback, we've already implemented some changes,

and while our objectives are not to present proposed modifications today, we will share additional areas that could be considered for improvement. Let's start by looking at the adverse event reporting.

Pharmaceutical companies must submit postmarketing safety surveillance data to the FDA. The REMS, however, does not directly submit adverse events data to the FDA. When an adverse event report is submitted to the REMS contact center, they gather the basic information and forward the report to the specific sponsor. The specific sponsor then is responsible for the drug product.

During the reporting period from December 1, 2022 through May 29, 2024, 26,968 potential adverse event reports were reported to the sponsors by the contact center. These included all reports whether they were related to neutropenia or not. Events received from the REMS, as well as other sources, are in turn reviewed by each sponsor, who in turn investigates and reports their adverse events to the FDA. This process may vary slightly by

organization, but all sponsors must follow the federal regulations for postmarketing regulations.

The FDA then reviews, aggregates, and makes reported potential adverse events available for the public consumption in the FAERS reporting system. It is important to recognize that anyone can report an adverse event directly to the FDA, and all these reports are also counted in the FAERS totals. After implementation of the Modified REMS, the agency observed a spike in the FAERS reporting of low ANC values. Here on the left, we see the spike as reflected by reports of neutropenia to the FDA FAERS system by receipt date.

In analyzing these data, we see three causes for this increase in reports. First, the Modified REMS captures more ANC data on each patient than the Legacy REMS did. It stands to reason that an increase in serial ANC collection would have a corresponding increase in adverse events. Second, in 2022, there was a delay between the actual report date and the FDA received date. On the right, we now see these same report counts based on

the date of the event rather than the date of the FAERS receipt. The event rate does not show the same singular spike initially observed in 2022. And finally, the third cause was that many ANC values had been entered with an incorrect unit of measurement, which led to erroneous AE reports that inflated the totals.

To clarify, the REMS collects ANC values in a unit that's referred to as cells per microliter, which was defined in the product label. As the agency noted in their briefing document, if a patient had a value of 8,000 cells per microliter, but provider entered the value as 8, corresponding to an equal but different unit of measure being 1,000 cells per microliter, the system records the value as 8 cells per microliter, triggering what would be a low ANC value. Many times when this occurs, the system will trigger a low ANC value, the healthcare provider is notified, and many times when this happens, we often see a corrected or higher ANC value being entered for the same drawn-on date.

To evaluate the magnitude of this error in the unit of measure, an internal review was conducted. Here, we see a summary of total data entered into the system as a low ANC value in the Modified REMS from launch through September 2024, including those that appear to have a report that was the result of a wrong unit of measure. When we correct for these entry errors, we see a reduction of nearly 50 percent with respect to the ANCs entered as less than 1,000 cells per microliter.

To address this issue of erroneous units of measure, the CPMG implemented a system change which prompts the user to check the data unit and confirm if the correct value has been entered as ANC less than 100 cells. Following this change, we observed a change in the reports of ANCs with less than 100 cells per microliter, from 0.71 percent of ANCs submitted to 0.03 percent, representing a 95 percent reduction of events. We think this will continue to improve; however, we're continuing to monitor this change to determine if additional action may be required.

Turning now to our review of data from the FAERS database, we began by using a validated process to remove duplicates from the years 2020 to 2023. We then assessed events based on the date the event occurred rather than the date the FDA received the report. We converted reports to MedDRA terms, which is standard practice using the preferred term and high-level term such as "neutropenia," along with the standard MedDRA queries for hematopoietic and leukopenia. We then conducted further subanalysis using the high-level group terms from the System Organ Class Infections and Infestations; and finally, we considered the relationship between neutropenia and mortality.

When we analyzed the data by report date, the events normalized. We don't see the kind of spike that was originally observed in the FAERS data. This is true for the preferred term and high-level term neutropenia, as well as the standard MedDRA queries of hematopoietic and leukopenia.

To further consider if there could be a

safety signal related to agency reporting, we looked at reports of opportunistic infections in COVID-19. An increase in opportunistic infection occurs in 2022, which we believe was driven by the surge in COVID-19 occurrences in the same year. As noted, COVID-19 is a viral infection which on its own can cause neutropenia.

In 2022, there was a significant increase in the reported outcomes of life-threatening events associated with clozapine use and neutropenia events compared to the preceding 2 years. Interestingly, fewer fatalities were reported and fewer duplicate reports were identified and removed for the same year, in 2022. Reported outcomes of hospitalization and disability remain stable across all 4 years.

In conclusion, based on the FAERS analysis, the increase in reports appears to be a function of increased data collection required under the Modified REMS. In reviewing the data, we agreed with the FDA that the reports of neutropenia, infections and infestations, and mortality do not

suggest any change in the safety profile of clozapine.

Turning now to adverse reports within the REMS, when a prescriber submits a patient status form, they can indicate if the patient experienced an adverse event due to clozapine-induced neutropenia. During the first reporting period for the Modified REMS, 371 patient status forms were submitted for 319 patients related to clozapine-induced neutropenia. This means an adverse event or outcome such as hospitalization or illness that was a result of a developing neutropenia.

During the most recent reporting period, 439 patient status forms noting an adverse event were submitted for 390 patients. This represents a significant number of patients that are being identified and ensuring that informed decisions are being made regarding their care.

We agree with the FDA that the data within the FAERS system is insufficient to characterize the long-term safety of clozapine but does not

suggest a significant change to the safety profile. It's important to also note that the REMS is responsible for the vast majority of ANC reporting adverse events reported to the FAERS. The FDA noted in their briefing document that there were only 79 adverse events reported from other sources between January 2017 through September 2024. While postmarking reporting is not perfect, the REMS process has a better potential of informing ANC-related events of clozapine than spontaneous reporting.

Today's meeting is to consider changes to the CPMG while maintaining safe use of clozapine. We have clearly heard from stakeholders who sometimes struggle to obtain clozapine and maintain continuity of care. Following the launch of the Modified REMS, we held five listening sessions with stakeholders. Comments from these stakeholders are included here. They had such things as questions regarding the efficacy of the REMS and mitigating patient risk. They noted they found the REMS dispense authorization, patient status forms, and

reminders cumbersome, and said this complexity could prevent patients from receiving the drug.

Representatives from long-term care facilities, including psychiatric hospitals and prisons, said their classification as an outpatient rather than inpatient facility may delay patient care, and stakeholders expressed their belief that the risk of neutropenia may be reduced after the first year of treatment, which could follow reduced restrictions for long-term patients. Some stakeholders also highlighted challenges of navigating the REMS website.

Based on this feedback, we have made some updates that I will highlight in a moment, and we look forward to discussing other ideas with you today. These discussions also reveal a number of misconceptions and knowledge gaps that have led to the treatment challenges. These examples include that only a limited supply of drug can be dispensed.

The current REMS has a limitation of a 30-day supply which is correlated with the

requirement to submit a patient status form every 30 days; however, if a request to provide an additional supply is made prior to the end of the 30 days, REMS does not prevent this additional refill; that a pharmacist cannot dispense without a patient status form, however, a pharmacist can bypass this restriction using a dispense rationale if a current acceptable ANC is available; that patients who cannot participate in regular blood ANC monitoring are denied access, and in actuality, the prescriber can bypass this using a treatment rationale if a patient has missing labs; and finally, that lost, missing, or emergency supply of medications are not allowed to be dispensed per the REMS, and in actuality, the REMS does not restrict redispensing if medication is lost or if emergency supply is required.

These and other misconceptions are important, very important, as they have led to unnecessary delays or disruptions in treatment, and there is an opportunity to alleviate these concerns through greater awareness and education.

Based on stakeholder feedback, we've implemented a number of changes, some of which are highlighted here today: providing the ability to remove incorrect ANC entries; adding the ability for pharmacists, prescribers, and designees to review all ANCs and monitoring frequencies; changing the system to prepopulate current ANC values when submitting the patient status forms online; and adding a pop-up warning when ANC values of less than 100 microliters per liter are entered. We also moved the most recent dispense authorization to the top of the display; allowed a designee to initiate the association with the prescriber; and added a checkbox to the portal for authorized representative verification.

We have also heard critical feedback from patients and caregivers that it can be difficult to find pharmacies that dispense and physicians who prescribe clozapine, so we enhanced our pharmacy look-up tool to allow users to find pharmacies by zip code, and we've also had discussions with the FDA on how to establish a physician look-up tool

within the registry.

Beyond the changes we've already made, there are other opportunities we've identified for potential improvement. First is to drive greater awareness and education regarding the REMS to address the misconceptions and common questions. Second is to manage transitions in care more effectively to help ensure that patients have continued access to treatment during transitions to new prescribers, new pharmacies, or from inpatient to outpatient pharm care.

Third, is to explore improving CPMG data interfaces with large institutional reporting systems to replace manual or duplicative ANC reporting practices and reduce burden on physicians and pharmacists, and finally is to improve adverse event collection to obtain more meaningful data on incidence and outcomes of clozapine-induced neutropenia related to adverse events.

In summary, a review of the available adverse event data suggests the increase in event reports in FAERS following the Modified REMS launch

was likely due to increased reporting and erroneous units of measurement rather than a change in the clozapine safety profile. Through stakeholder input, evaluation of assessment data, and ongoing FDA consultation, we have identified and clarified misconceptions that may be addressed through awareness and education. We also believe more work can be done to alleviate misconceptions, which are, for the most part, external to the REMS program, and we have implemented improvements to address challenges and streamline the use of the REMS as part of good governance. We are committed to continue to implement improvements as necessary. In addition, we found opportunities to potentially improve data collection and reduce stakeholder burden while continuing to ensure patient safety.

Now, to conclude the CPMG presentation, we know that clozapine is a life-saving therapy for those living with treatment-resistant schizophrenia. When a stakeholder participates in the REMS, the REMS provides a reassurance to document compliance with monitoring requirements

defined by the label. The REMS plays an important role ensuring the safe use and educating stakeholders, although some knowledge gaps remain.

That said, we recognize enforcement discretion and elements of the REMS design and implementation limit ability to collect data. The Modified REMS has continued to evolve and has been integrated into clinical practice. All stakeholders can and should collaborate to reduce burdens and ensure continuity of care. CPMG is committed to working with the FDA and our stakeholders to address challenges while maintaining the safe use of clozapine. Thank you. We look forward to your discussions and questions today.

Clarifying Questions

DR. FLOYD: Thank you for those presentations.

We're now going to take clarifying questions from the panel to CPMG. When acknowledged, please state your name for the record, and feel free to direct your question to a specific speaker. You

can also reference a specific slide, which we can put up. So go ahead and raise your hand if you want to ask questions.

Dr. Salvas?

DR. SALVAS: Brian Salvas. My question is for Mr. Shamp, slide CA-26. Your data shows increasing participation and compliance on the program, particularly for the most recent time period. I believe Dr. Farchione on slide 45 showed that about a third of patients are operating outside of the REMS. Is that a fair conclusion, that folks that are operating within the REMS are compliant to the monitoring, but there's still a third of the patients that are not operating within the REMS?

MR. SHAMP: Jim Shamp with UBC. First of all, is this the slide you were referring to?

DR. SALVAS: Yes.

MR. SHAMP: Okay. So as I stated, you'll recall in my presentation that this is the compliance when a stakeholder participates. And we do agree with the the numbers from the agency on

the number of patients that are not participating. We estimate probably about 42,000 patients are not participating in the REMS.

DR. SALVAS: Got it. Okay. Thank you.

DR. FLOYD: Dr. Ballon?

DR. BALLON: Jake Ballon. This is a general question, although maybe for Mr. Shamp in particular. What data has been collected on the amount of time that is spent, on average, when one is using the REMS system? I wonder about 150,000 patients times 12 REMS entries per year, and what the burden is on the healthcare system for that in terms of the amount of time lost for other patient care.

MR. SHAMP: If I can just clarify your question, you're asking if we've measured and have data on the amount of time spent performing the administrative entries in the burden, or in the REMS; is that correct?

(No audible response.)

MR. SHAMP: Yes. So we do not have any data collected that measures that, but what we do have

is data that suggest how many forms have been submitted. And you'll recall in my presentation, I did present numbers on the number of patient status forms that have been submitted, so you could extrapolate from that.

DR. FLOYD: Dr. Dunn?

DR. DUNN: Hi. Walter Dunn, and also a question for Mr. Shamp. It sounds like there's going to be potentially a spectrum of recommendations as far how the REMS could be modified or changed to make this closely being easier to access and to prescribe. In the briefing document, they talked about how the REMS was a closed-loop system with all these components -- the prescribers, patients, the pharmacies -- and if you remove one of the requirements, it kind of falls apart.

So I'm wondering if there's a scenario where we say there's a REMS required for the first 18 weeks, and maybe after the first year, there's no longer a REMS requirement. Would that be able to work? If you have these pharmacies that are not

registered, if you have wholesalers that are not registered, does that first 18 weeks even work? Can you imagine a scenario where it's required in the first 18, but then it's optional or not required thereafter?

MR. SHAMP: Yes. Can I presume with your question that enforcement discretion is removed and the REMS is fully enforced?

DR. DUNN: Correct; so fully enforced in the first 18 weeks, and then nothing there afterwards.

MR. SHAMP: Yes. Once it's fully enforced, a pharmacy could not obtain clozapine from a wholesaler without being certified. So it is absolutely a closed loop. I do think it could work because what you're suggesting is that perhaps after 18 months, you don't need to have the patient status form submitted anymore. Is that accurate?

(No audible response.)

MR. SHAMP: So all you would do is if the patient that is enrolled has met that milestone, then they are just always authorized to receive drug.

DR. DUNN: But they'd still be restricted to, I guess, the pharmacy's dispense. They would still have to be registered at some level. So unregistered pharmacies even past 18 weeks would not have access to the drug.

MR. SHAMP: That is correct.

DR. DUNN: Thank you.

DR. FLOYD: Dr. Stegmann?

DR. STEGMANN: Jens Stegmann. First of all, thanks to the CPMG for bringing in the historic/global perspective. I do think this could be very useful later on when we are talking about alternatives, how the REMS can be modified in that regard. But my question refers more to Dr. Gross for the AE reporting, being a pharmacovigilance expert on that one, and refers to CM-2.

Dr. Gross, the briefing book describes how adverse event reporting functions. The REMS call center can be called, and given, for example, an ANC is being reported, this will, in stream, be forwarded, or the sponsor, PV department, will be contacted. And if that is not accessible, then it

will be followed up later, which brings further complexity into that, what ultimately is spontaneous reporting.

Is my understanding correct that the way this is organized with respect to sponsor companies that differ, we might have some who are using call centers, some in-house? What is the level of granularity, so we are aware of that?

MR. SHAMP: I'd like to have Dr. Gross respond, please.

Dr. Gross?

DR. GROSS: Jason Gross with HLS Therapeutics. I believe, Dr. Stegmann, you're referring to the flow of adverse events, the reporting flow, and how that is perceived, and how that could be optimized. In the current process, it follows a pretty standard process within the pharmaceutical industry in that the call center is an extension of the CPMG. They are the forward-reaching contact point for healthcare providers and patients, if they do call.

Because it's a contact center, we have

spontaneous reporting and we have non-spontaneous reporting. So it's a non-spontaneous reporting program in the sense that these are being solicited at times because the adverse event is -- as an example, the difference is, a non-solicited adverse event is something that just comes in spontaneously, that somebody might have fallen off a ladder, had a car accident, had nausea and vomiting. Solicited is something that the call center's reached out to.

As I said in my presentation, the adverse event that is listed -- as an example, a neutropenia that occurs -- we call up to identify that or have a case report form generated so we understand what has happened. That call center is responsible for recording a certain amount of information, and then process it to the drug company, who has a more in-depth pharmacovigilance team to then further process that. There may be some opportunity identified between that report and getting to the pharmacovigilance teams at our respective companies to improve that process and

refine that data, and we'd be open to having further discussions in looking at that.

DR. FLOYD: Dr. Dublin?

DR. DUBLIN: Thank you. Dr. Sascha Dublin from Kaiser Permanente, Washington. I have a comment, and then a question. The comment refers to the idea that perhaps there could be a REMS restricted to the first -- I don't know if it was 18 weeks or 18 months. I guess my question would be, how does that work when some patient may have their therapy disrupted for a while and be restarting? We should think about any complexity that might involve, if people have more than one of those first initiations, but I think it's a creative and innovative idea.

My question is more prosaic. It's about the slides -- I think it's to Mr. Shamp -- CA-28 to 30, about when you do a knowledge survey of providers. I'm interested in hearing about how those are selected and from what universe. Are those only providers who are enrolled in the REMS, or do you reach out to a larger universe of psychiatrists who

may be prescribing either outside of the REMS or even people who aren't prescribing yet?

MR. SHAMP: Yes. So for prescribers and pharmacists, the outreach is done just to prescribers and pharmacists that are certified in the REMS.

DR. DUBLIN: Are there any barriers or obstacles to redefining the survey sample in the future so you could hear from people who may identify to you that they're prescribers, if you did a wider survey and wider outreach, so we could learn about people prescribing outside the REMS as well?

MR. SHAMP: That is certainly something that we can take under consideration, and we look forward to working with FDA on future surveys and the possibility of expanding that.

DR. DUBLIN: Thank you.

DR. FLOYD: Dr. Perkins?

DR. PERKINS: Yes. Thank you. Jeremy Perkins. I'm a hematologist, not a psychiatrist, and I prescribe a lot of medications that are high

risk and have narrow therapeutic index. This question is really more perhaps for Dr. Kane or Dr. Cotes. On one of the slides, you indicated that the estimate on risk of death from febrile neutropenia was like 1 in 7700 with the use of clozapine, and there was also an indication that there are many patients with treatment-resistant schizophrenia that are not receiving clozapine for various different reasons.

Is there a, a rate or a risk -- and forgive my ignorance -- just a risk of completed suicide for untreated or undertreated schizophrenia, to put it in context? Thank you.

MR. SHAMP: I'll ask Dr. Kane to respond to the question.

Dr. Kane?

DR. KANE: John Kane, Zucker School of Medicine at Hofstra/Northwell. The estimates are that about 5 percent of people with schizophrenia die as a result of suicide. In the VA database, there were about 4,000 veterans who made suicide attempts. Only 9 percent of them were receiving

clozapine, so we have a considerable underutilization. It's hard to come up with exact benefit-risk ratios, as you're sort of implying, but I think when we look at some of the data following clozapine-treated patients for years, for example, in Finland, we see a significant reduction in mortality rates for patients receiving clozapine despite the risk of severe neutropenia.

So it does appear when you look at all the potential benefits of clozapine, and you weigh that against the risk of fatality due to severe neutropenia, I think the benefits outweigh the risks.

DR. FLOYD: I'm going to --

DR. KANE: Rob Cotes also wants to comment. Sorry.

DR. COTES: Hi. Rob Cotes, Emory University School of Medicine. I would say this is an area that there's a tremendous lack of education around, and we could do a much better job as a field promoting clozapine's other FDA-approved indication. In my clozapine practice over the

years, receiving 600-700 referrals, only about 3 percent of those are related to the reduction in suicidal behavior; the rest are treatment-resistant schizophrenia.

DR. FLOYD: I'm going to jump in with two quick follow-up questions to Dr. Kane and Dr. Cotes. I like the question about trying to estimate the treatment benefits. The statistic about 5 percent lifetime risk of completed suicide, or death-related schizophrenia, or suicide attempt, do we have an estimate on the treatment effect of clozapine? For example, I think he showed some findings that in the pivotal trial, there was a reduction in the incidence of suicide attempt, and maybe it was a relative risk of like 0.8 or something like that.

Do you have some type of treatment effect that we can try to impute how many deaths could be prevented by clozapine?

MR. SHAMP: Dr. Cotes will respond.

Dr. Cotes?

DR. COTES: Slide 1 up, please. Rob Cotes,

Emory University School of Medicine. I think that some of the best data really comes from the InterSePT study, and the InterSePT study was looking at people who were treated with clozapine versus people who were treated with olanzapine. Only treatment of 12 patients with clozapine, rather than olanzapine, would show benefit for clozapine to reduce suicidal behavior.

DR. FLOYD: Yes, go ahead, Dr. Vyas.

DR. VYAS: Thank you so much. I just want to highlight a point here that we're kind of talking around, and that is that in the InterSePT study, just 26.8 percent of the folks were treatment resistant, and that that didn't have an impact on their ability to respond to clozapine as a benefit. It's just worth highlighting that point, that when we're talking about suicide, it is entirely independent of whether or not they're defined as treatment resistant. That's all. Thanks.

DR. FLOYD: And one follow-up question for Dr. Cotes. Thank you for sharing details about

your clozapine program. One question I have is because the REMS is not enforced currently, do you still participate and submit all the forms and requests authorizations in your program currently?

MR. SHAMP: Dr. Cotes?

DR. COTES: Yes. Rob Cotes, Emory University School of Medicine. Obviously, this is a clinic size N of 1, but there doesn't appear in my practice to be much in the way that I see of enforcement discretion. All the systems that I have worked with, we are participating in the REMS, the 30 pharmacies that we work with. When I saw 25 to 35 percent of people are receiving clozapine outside the REMS, I was a little surprised by that number because I don't really feel enforcement discretion in my practice.

DR. FLOYD: And one more follow-up. As an example of a very, well functioning, top-of-the-line program for treatment-resistant schizophrenia, if the REMS were to go away, would you change any of the monitoring that you do in looking for severe neutropenia?

DR. COTES: I think it's important that we, again, differentiate reporting of monitoring versus monitoring itself. My practice would be to monitor as per the package insert. I think that the FDA could consider relaxing monitoring after 2 years, or whatever, as decided, but in my practice, I would continue to monitor.

DR. FLOYD: Dr. Ballon had a follow-up on this point.

DR. BALLON: Jake Ballon, Stanford. This is for Dr. Cotes. I just want him actually to expand a bit on the enforcement discretion. We've heard a lot about the use of that term today. I find that term to be troubling. In my experience, enforcement discretion has actually been mischaracterized and misunderstood, and therefore actually not considered to be discretion. And I was hoping you might expand a bit on your experience with enforcement discretion, and specifically times where clozapine has been disrupted because of misunderstandings of that term, and to perhaps expand a little bit on the

ramifications symptomatically for people, both in terms of having to retitrate clozapine and/or potential psychosis relapse because of misunderstandings of enforcement discretion.

MR. SHAMP: I'm sorry. Was that question directed at Dr. Cotes?

DR. BALLON: Dr. Cotes.

MR. SHAMP: Okay. Dr. Cotes, please.

DR. COTES: So again, at least from where I sit, we are adherent with the REMS reporting, and we do the monitoring as per the package insert. In my experience, I have not really seen enforcement discretion utilized. There have been times where there's additional requirements, like the pharmacy requiring the fax of the ANC despite the patient has an active PSF, and that is not a part of the REMS. But sometimes that fax doesn't go through, and there can be disruptions in care.

In our prescriptions, we typically put our information so the pharmacy can reach out to us easily. We put the REMS ID number so people can find that easily. I don't even know how to go

about working outside the enforcement discretion system, and there are times I think I probably wish I could.

The ramifications of missed doses can be pretty significant, and in my experience, some patients are extremely sensitive to a missed dose, and other patients, it may take a few days or longer. It's very difficult to know, but it's a system that really can require -- it needs to have zero error. And typically, the risk of people missing doses, in my slides, I showed a 20 percent risk of symptom exacerbation, and it's sort of hard to know when that happens. And again, some people are quite vulnerable to it, and other people, it might just take a few more days.

The retitration process is also quite complex, and there's some new guidance in the package insert around retitration. Retitration really requires calling somebody and developing an individualized retitration plan if they miss more than 2 doses. Sometimes people miss doses of their medication due to a variety of reasons, but there

are sometimes delays where people can't get medication for a couple days, and we need to figure out how to safely retitrate them.

The challenge with that is, on one hand, you want to retitrate people quickly so they're not risking a symptom exacerbation; but on the other hand, if you do it too quickly, you're worried about tolerability issues, and sedation, and other types of problems. So it puts us in a pretty difficult bind, and there's not a lot of, really, clear literature about how to do these retitrations successfully.

DR. FLOYD: Dr. Ehret, is your question a follow-up to this issue?

(No audible response.)

DR. FLOYD: Okay. Please go ahead.

DR. EHRET: Dr. Cotes, if you could provide us with maybe an estimate of how much time your clinic spends implementing things into the REMS and documenting within the REMS system. It might give us an idea to Dr. Ballon's question about how much time goes into the REMS if you had an estimate.

MR. SHAMP: Dr. Cotes?

DR. COTES: So completing the PSF itself is relatively a straightforward process. The problem is everything else, the complexity of everything else. There was a study that I referred to earlier by Sarpatwari and colleagues that compared eight different REMS programs, and in that study, 41 percent of physicians said that they were primarily responsible for helping patients to complete the administrative requirements; the rest has someone else helping out with that. And up until 2022, I used to do that myself, and it really required daily attention. So every day, having my morning coffee, I'd wake up, look at the REMS, look at the labs, and put everything.

One of the other major missions of our clinic is to train psychiatry residents and other trainees on how to use clozapine because education is really, really quite paramount here. The residents are really wonderful, but there was a concern that inputting the PSF and faxing the labs veered outside the -- it was seen as more service

rather than education, and the residents were concerned about that, and that then led us to get a philanthropically supportive person to actually manage the system.

So I talked to our person, who's a 40-hour-a-week person, and she spends about 30 hours per week coordinating. Part of it is updating the REMS; part of it's faxing the labs; part of it's reminding people to get the blood work, so it's a pretty significant time period. She's an efficient person and has a system to really do this most efficiently, but it does require significant effort.

DR. FLOYD: Dr. Rebo?

DR. REBO: I have a question around wholesaler shipping. Do we have any data at all about how often or to understand how many times they are shipping to non-certified pharmacies?

MR. SHAMP: We do have data that we collect. I'm not sure if we have it available at this time. If not, it's something we can ask our backroom to try to obtain.

DR. REBO: Okay.

MR. SHAMP: So we do collect data monthly on which wholesalers have shipped, and specifically trying to identify if they're shipping to a non-certified pharmacy so that we can do that outreach to the pharmacy and try to get them to certify.

DR. REBO: Thank you.

DR. FLOYD: Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi. I had a question for Dr. Gross. In your presentation, you put up a map where you could find a clozapine provider or pharmacy. I just was wondering if we had any information, as we're rethinking this REMS, if there are clozapine deserts, if you will. For example, is the pharmacy requirement overly prohibitive in that, in some rural areas, it may take 45 minutes to an hour to get to a pharmacy, and then if we don't have a pharmacy that's a clozapine pharmacy nearby, how that would limit patient access? So a little bit of geographical awareness I think would be helpful for us so we

could get a better sense of the true burden for patients. Thank you.

MR. SHAMP: Yes. There are likely healthcare deserts. It's very challenging at this time to determine that, primarily because the enforcement discretion, as we've pointed out, doesn't require prescribers to be certified at this time. But when we looked at data from the NPI registry, and particularly the individuals who had a primary taxonomy of psychiatry, and compared that against the prescribers that we do have certified, we have just slightly less than 50 percent of those with that primary taxonomy of psychiatry certified today. But that doesn't mean that there aren't prescribers out there that are prescribing; they just may not be certified. So it's very difficult to determine that.

DR. AMIRSHAHI: One thing I was particularly considering was the pharmacy as well, because a lot of healthcare insurances require you to go to a particular pharmacy. So perhaps also considering an assessment with regard to insurance coverage and

also distance to clozapine pharmacies because the provider is one aspect, but the pharmacy is another aspect for us to consider.

MR. SHAMP: Yes. So the same limitations exist with the pharmacies, but I can tell you that we do have probably the majority of the large chain pharmacies that are certified just because that is their process. Whether or not they are actually participating by obtaining the authorization every time, that is difficult to determine, but yes, that's my answer.

So as a follow-up to that question, we'll have Dr. Dublin, and then Dr. Rebo, and then we'll move back into the queue.

DR. DUBLIN: Hi. I'm Sascha Dublin from Kaiser Permanente Washington. My follow-up question is about the involvement of mail-order pharmacies to address some of these geographic deserts. Can you speak to the number or the participation of mail-order pharmacies and whether you're aware of any challenges with insurance coverage of the mail-order pharmacies?

MR. SHAMP: I'm not aware of any challenges with insurance from mail-order pharmacies. We do allow mail-order pharmacies to participate in the REMS. I'm not sure if we have data prepared today that shows the breakdown of those but, again, that's something we can ask our backroom to try to obtain. It may be slightly challenging because the way the pharmacies enroll, they do not have to identify themselves as a specific type of pharmacy. So that is a little challenging to do, but we'll see if we can obtain any data.

DR. REBO: Hey. Liz Rebo, Kaiser Permanente. This is less of a question and more of a statement, piggybacking on what was said earlier from Maryann. I think we also have to think about the changing climate with our pharmacies in the U.S. It's very well documented in the news that major chains are reducing stores. That's really going to increase our pharmacy deserts that exist. So I think as we are considering this topic today, we need to think about the changing landscape of our brick and mortar pharmacies.

DR. FLOYD: Dr. Dejos?

DR. DEJOS: Mike Dejos, system medication safety officer for Methodist Le Bonheur Healthcare. This question's for Mr. Shamp. Thank you so much for sharing the dispense rationale data with us and that there's an increase. I do recognize in your slide that 75.2 percent of patients receiving a dispense rationale received it within 7 days of the initial rejection. What were some of the main causes for that initial rejection? I know we're talking about access to care, but if we are seeing those initial rejections, how soon would they get it if it's outside those 7 days?

MR. SHAMP: Can I have slide 2 up, please? You'll see on slide 2, these are the reasons for rejections. And as you'll recall in my presentation, I did say that the primary and the largest majority of reasons for rejection is because of a missing patient status form. But what we see here is the mean and median days between a rejection for this specific reason and a subsequent authorization. So you can see, overall, the mean

is just about 10 and a half days and the median is 1. Looking specifically at that patient status form reason, you do have 10.3 as the mean and 1, again, as the median.

DR. FLOYD: We'll take four more questions from who have been waiting patiently before we break, starting with Dr. Dunn, then Dr. Vyas, Dr. Narendran, and then Dr. Hertig.

DR. DUNN: Hi. Walter Dunn. This is a question for Dr. Cotes, two quick related questions. I want to hear a little bit more about your perspective as far as the reasons why patients discontinue off clozapine and the delays you talked about. I work in a clozapine clinic that works primarily with insured patients, and you mentioned most of yours are uninsured.

So the first question is, you talked about the role of the REMS in potentially causing missed doses or delays. What percentage of that occurs within the first 18 weeks versus the one year afterwards when they're consistently taking clozapine in a maintenance phase?

MR. SHAMP: Dr. Cotes?

DR. COTES: Yes. Hi. Rob Cotes, Emory University School of Medicine. I don't have data that can really help to parse that out. I think that most of the time, people will discontinue clozapine early during the clozapine initiation. In my experience, it's been that maybe at a year, half of people will discontinue clozapine, maybe even more, due to a number of factors. Sometimes it's tolerability issues. Sometimes it's not being able to keep up with the monitoring, et cetera. The most common reason for discontinuation is typically sedation.

I think in my experience, however long someone is a part of the process, they're always at risk for missed doses because the process continues indefinitely, and there are things that happen that are outside of people's control that come up that can sometimes result in missed doses. I do think that there are probably more issues earlier in the titration, as people are getting into a rhythm and getting into a routine, but I do feel people are

vulnerable throughout the time that they're taking clozapine to really make sure that all the requirements are satisfied.

DR. DUNN: As a quick follow-up, you mentioned that even if the REMS were changed but the label did not, that you would continue to follow the label. Let's say the monthly monitoring was still recommended, do you have a sense of how many potential long-term clozapine patients would not continue on it even though the REMS would no longer be in place, but you'd still require them to do a monthly blood draw? In our clinic, I don't think I've actually come across a patient who's discontinued off of clozapine because of pass that one year mark. It's primarily because of the other side effects.

So I'm curious. In your clinic, would you foresee some patients -- even though there's no longer a REMS requirement per se but you still following the label, would still want them to get regular blood draws?

DR. COTES: Yes. I would encourage the FDA

to consider whether or not monitoring is required after 2 years, but as the package insert is right now, I would probably continue to monitor. I also would encourage us to take in mind the patient's voice here and what level of risk they'd be willing to tolerate. If I had the opportunity to, I would want to be able to decide what that monitoring frequency was at some point, maybe 2 years or so, based on that patient's individualized risk.

DR. FLOYD: Dr. Vyas?

DR. VYAS: Thank you so much. I just wanted to make a quick comment, and then I had a question. Our group has published a case series of patients that have died from suicide after a clozapine discontinuation. The one example that was most egregious was someone that died 4 years out based on a single ANC value that resulted in abrupt discontinuation. This has been in the literature, but there are examples, and that is monthly monitoring 4 years out.

The other comment I had was that the 7 days before the dispense authorization was reinstated,

just to put it plainly, is a catastrophic amount of time. That is a high degree of human suffering, 7 days.

(Applause.)

DR. VYAS: I just wanted to say that.

The enforcement discretion, I think many of us are reacting to that term. I don't know; it's certainly bringing up emotions. But the question I have is, a number of the common misconceptions and the facts to counter those, any ideas of how we would go about, or how CPMG would go about, educating interested parties, people that should be in the know about that?

Generally, in my experience, as Dr. Cotes mentioned, I've had patients go to the pharmacy with a PSF submitted, and the pharmacy still requests the ANC. And I just very, sort of kindly say, "I know you want that, but I can't give it to you. Please call the higher ups in corporate or whoever," with excessive kindness, and they've always called back saying, "You're right." But how are we going to fix that knowledge gap? Any ideas?

Because right now, the enforcement discretion ends up oftentimes resulting in people behaving in legally safer ways as opposed to in patient interest.

MR. SHAMP: I'll ask Dr. Gross to respond to the question.

DR. GROSS: Thank you. Jason Gross with HLS Therapeutics. This is a topic that is ultimately of significant concern, and it's something that needs to be addressed. One is, there's a significant amount of misconceptions that are happening and are occurring in patients delayed in getting their medication; and as you said, 7 days is a very egregious amount of time to go without medication. It's the responsibility of everybody in this room. It's the possibility of all the healthcare providers. And there is an aspect that people revert back into, an aspect of maybe legalese or concern to protect themselves within the pharmacy environment when they don't need to.

The guidelines are there, the REMS program is there, but as a physician or as a

pharmacist -- I'm a pharmacist by training -- you have an aspect of a degree of discretion. You have a patient in front of you that's saying I'm out of medication. I need my medication. As a pharmacist, you can say, "Do you have a fever? How are you feeling? When was your last ANC? Okay," and then there's a right of discretion for that.

This all does come back to a little bit of a labeling aspect also. I date myself. I said I was here at the FDA many years ago, so I'm able to see the aspect of the clozapine labeling change over the years. Actually, old labeling actually did have a paragraph that suggested that emergency supply should be dispensed. That kind of went away, and then we stayed very strictly to 7, 14, and 30 days.

So there's an aspect of further education. How that education will transform and how we should do that is something that we need to evolve and we need to talk to. It's a very large discussion topic, but we are open to having further suggestions on who we should outreach to and how we

would do that.

DR. FLOYD: Dr. Narendran?

DR. NARENDRAN: Raj Narendran, UPMC. I'm curious in the underutilization of clozapine. What percentage of prescribers are affiliated with a major academic institution, or some sort of VA, or a highly specialized clozapine clinic like Dr. Cotes? Because, to me, it seems like most of them are, and those are the people being reported into the REMS. Can you separate from your REMS what percentage is community psychiatrists versus a machine in place, like a well-oiled machine?

MR. SHAMP: The REMS does not collect affiliation with any center for prescribers, so we're not able to do that. But I'm looking to see if we have any data that we could discuss.

DR. NARENDRAN: A K database, or Medicare, health insurance. It would be helpful if you could. Thanks.

MR. SHAMP: Yes. It is possible that some of the external prescription databases could provide that information, but we do not have that

today.

DR. NARENDRAN: Thank you.

MR. SHAMP: Dr. Cotes would like to respond as well.

Dr. Cotes?

DR. FLOYD: Sure. Go ahead.

DR. COTES: I appreciate this point. I would also say that even in academic medical centers, you can't necessarily guarantee that people have had training in clozapine. And I really think that we have to make collaborative efforts and work with the ACGME to make clozapine a mandatory part of psychiatry residency training.

(Applause.)

DR. FLOYD: Dr. Hertig?

DR. HERTIG: John Hertig, Butler University. First a statement, and then a question. I know we're all aware, but education is certainly effective. And coming from an academic, I feel this is a little funny, but also it's the least sustainable strategy that we have. Education fades, so certainly there needs to be education,

but also some hard-wired safety mechanisms in place to ensure safe and effective use.

My question is really geared either towards the agency or CPMG, and I know this information is likely difficult to ascertain. But we see lots and lots, and increasing examples, of patients who are accessing medicines outside of a typical supply chain, either because of REMS or regulation, or even shortage, so they'll go online. If they can't access something, and they know they need it or it's been discontinued, they'll find other sources of that medication.

Does either the agency or CPMG have any evidence or data, or estimations, of how many patients may be accessing these medicines beyond our traditional supply chain? Thank you.

MR. SHAMP: I don't believe the CPMG has any data to provide for that.

DR. LaCIVITA: Hi. This is Cynthia LaCivita at the FDA. I'm not aware of any data, but we can look and see during the break if we can find any.

DR. HERTIG: Thank you.

DR. FLOYD: Does anyone else from FDA want to respond?

(No response.)

DR. FLOYD: Okay.

So, right now, I have that it's 11:02. We're going to break until 11:15. For panel members, please don't discuss any of the meeting topics during the break. Thank you.

(Whereupon, at 11:02 a.m., a recess was taken, and meeting resumed at 11:17 a.m.)

DR. FLOYD: Before we get started, I'd like to make a kind request to our audience members. There are a lot of people in attendance today, and if you have discussions, I'm going to kindly ask that you keep it to a whisper because other members of the audience are having a hard time listening. Thank you.

Our break is over now, and we're going to proceed with the FDA's presentations, starting with Dr. LaCivita.

FDA Presentation - Cynthia LaCivita

DR. LaCIVITA: Good morning. My name is

Cynthia LaCivita, and I'm the Director of the Division of Risk Management. I wanted to answer the first question that was asked in the previous session regarding outside use.

DR. FLOYD: Please go ahead. Do you have a slide you're waiting for?

DR. LaCIVITA: No. Hold on to this one for a second. The question was about use beyond the REMS or use outside of the U.S. population and the normal ways of obtaining clozapine. The agency does not have any information on that, so thank you.

Again, my name is Cynthia LaCivita. I'm the Director for the Division of Risk Management, and I'll be presenting the collective work of my colleagues on the studies conducted to re-evaluate the clozapine REMS. It should be noted that while none of the studies we conducted were able to answer all of our questions, collectively they provide data and help us better understand the risk of severe neutropenia and adherence to monitoring with clozapine.

This is an overview of my presentation. I will first provide our rationale for conducting the additional studies, and then provide the findings of the studies that assess the risk of severe neutropenia, adherence to monitoring, and prescriber experience with the clozapine REMS. For the purposes of my presentation, the terms "agranulocytosis" and "severe neutropenia" may be used interchangeably since "agranulocytosis" was the previous term used to describe severe neutropenia in the literature and approved labeling.

As you've heard from my colleagues, the Clozapine REMS Program has never been fully implemented since its approval, and furthermore, in the 6th and the 7th assessment reports, the CPMG noted issues with data entry and processing. And since the implementation of the 2021 REMS modification, the CPMG has been unable to confirm reports of severe neutropenia.

Thus, the CPMG's REMS assessment reports have been insufficient to inform us about the risk

of severe neutropenia, the outcomes associated with the risk, and adherence to the ANC monitoring with clozapine; therefore, we conducted additional studies to better understand if the risk of clozapine-induced severe neutropenia has changed since 1989; the types and the incidence of serious outcomes, including death associated with severe neutropenia; and if patients are being monitored as described in labeling.

The data indicate that clozapine can cause severe neutropenia, though the estimates of the frequency vary. Perhaps because of this variability, there are conflicting perceptions about the risk of neutropenia with clozapine. Some perceive the severe risk of neutropenia as low and believe that it aligns with the risk of severe neutropenia observed with other drugs that are approved without REMS and that the risk of neutropenia is unlikely to result in fatal outcomes.

A better understanding of the risk of severe neutropenia with clozapine was an important

component of our re-evaluation of the REMS; therefore, we conducted a review of the biomedical literature, as well as three pharmacoepidemiological studies in collaboration with researchers from Brigham and Women's Hospital, or BWH, FDA's Sentinel system -- I'll refer to that as Sentinel -- and the Department of Veterans Affairs or the VA.

Collectively, these studies provide approximately 20 years of data and capture different settings of patient care and different types of healthcare systems and insurance. In the next few slides, I'll present an overview of the methodologies and the findings of each of the studies. I'll start with a literature review.

Using PubMed, we performed two systematic literature reviews of articles published through June 25th of 2024. We identified 230 articles addressing the incidence of neutropenia with clozapine use. Fourteen of these studies provided quantitative estimates of the incidence of severe neutropenia among clozapine users. Of the

14 studies, we identified one study looking at the risk of severe neutropenia without hematologic monitoring. This was a Finnish study published in 1977, and it was conducted prior to widespread adoption of clozapine monitoring. This study examined 16 cases of agranulocytosis and identified that 7 of the 16 cases, or 44 percent, were fatal. Based on inpatient data, the authors estimated a agranulocytosis rate of 2.6 per hundred patient-years over the first 6 months without monitoring.

The remaining 13 studies investigated the risk of severe neutropenia with hematologic monitoring where patients treated with clozapine had their neutrophil counts monitored regularly. Collectively, these 13 studies support that most cases of agranulocytosis occur in about the first 18 weeks of treatment, approximately 1 percent of patients develop agranulocytosis over the course of treatment, and the fatality rates with severe neutropenia range from approximately 0 to 6 percent across the studies; however, the data on the risk

beyond one year of use were sparse.

I'd like to focus on one of the 13 studies that I just discussed that had more complete data and included weekly hematologic monitoring, and was conducted in the U.S. This is Alvir's 1993 study. This study used the manufacturer's surveillance database to estimate the cumulative incidence of agranulocytosis based on patients treated with clozapine between February of 1990 and April of 1991. The study found the cumulative incidence of agranulocytosis at one year was 0.8 percent and at 1.5 years was 0.9 percent. In the graph, the steepest part of the slope indicates the risk of agranulocytosis is greatest during the first 100 days of treatment; however, the curve never completely flattens.

I will now discuss the first of three different studies that we conducted with BWH. The first study is relevant to our evaluation of the risk of severe neutropenia. The other two studies will be described later and look at the adherence to monitoring and the prescriber experience with

the clozapine REMS.

The first BWH study assessed neutropenia-related hospitalization among clozapine initiators compared to olanzapine initiators. The objective of this retrospective study was to evaluate the risk of neutropenia observed in claims data following treatment initiation with clozapine versus olanzapine in a hospital setting. The study included new users of clozapine and those on the oral formulation of olanzapine. New use was defined as having no dispensing of clozapine or any formulation of olanzapine in the prior 6 months.

Initiators were required to be at least 18 years old and to have continuous insurance plan enrollment, a recorded diagnosis of schizophrenia or schizoaffective disorder, and at least one dispensing of a different antipsychotic that was not clozapine or olanzapine in the prior 6 months. Patients with cancer or HIV were excluded.

Outcome measures included all inpatient hospitalization with a discharge diagnosis code for neutropenia occurring in any position, which is

less stringent, or in the primary position, which is more stringent. Kaplan-Meier survival analyses were used to assess the cumulative incidence over time. BWH performed a 1 to 1 propensity score matching on 101 baseline covariates. This was a well-matched cohort that consisted of over 16,000 patients in each group.

Looking at hospitalization with a discharge diagnosis code for neutropenia in their primary position, the incidence rate of neutropenia-associated hospitalization per 1,000 person-years was about 2 for clozapine and 0.2 for olanzapine. The incidence rate ratio was about 12 at 6 months in using as an as-treated analysis. At 1 year, 2 year, and 3 years, the incidence rates of neutropenia-associated hospitalization per 1,000 person-years was 1.3, 0.9, and 0.7, respectively, for clozapine. The incidence rates for olanzapine did not change.

A significant limitation of this study was that the ANC test results were not available to confirm the diagnosis code of neutropenia, and

without ANC values, we are unable to distinguish between mild, moderate, and severe neutropenia. A second limitation was that the median follow-up time was 6 months. In summary, the study found that the risk of neutropenia-related hospitalization was significantly higher with clozapine as compared to olanzapine. Although the absolute risk of neutropenia-related hospitalization was low, the risk was greatest in the first 6 months of treatment.

I will now discuss three studies that used Sentinel to assess the risk of neutropenia. Sentinel study number 1 is a descriptive query that describes and compares demographic, clinical, and healthcare utilization characteristics among the clozapine user population captured in Sentinel with and without ANC test results between January of 2010 and July of 2024. The study included new users of clozapine at least 12 years of age with no dispensing of clozapine in the prior 183 days.

Among all the data partners, we identified over 164,000 episodes of new clozapine use among

over 105,000 unique patients. Of note, ANC values were not available for patients who were not publicly insured; therefore, the subset of users with ANC test results were primarily privately insured patients. Among these, we were able to identify over 10,000 episodes of new clozapine use among 6,700 unique patients. Of the 10,000 episodes, 2,223 had complete ANC test information that could be used to confirm the neutropenia diagnosis and classify severity. We found that clozapine user population with complete ANC test results had fewer schizophrenic diagnosis recorded in their claims, fewer ambulatory visits, and were dispensed fewer prescriptions.

Sentinel study number 2 was a patient episode profile retrieval. It was conducted in a subset of clozapine users with complete ANC test results. A patient episode profile retrieval is a line by line review of all health administrative claims and a select period prior and subsequent to the event of interest. The objective was to estimate neutropenic risk during the first 6 months

of treatment and describe the frequency and timing of the ANC monitoring.

This was a retrospective cohort study. A new clozapine episode was defined as a clozapine dispensing with no dispensing of clozapine in the prior 30 days. The outcomes of interest were how ANC monitoring was performed, whether it was weekly, biweekly, or monthly, and the severity of the neutropenia.

From the 2,223 clozapine episodes, we identified 53 cases of neutropenia that had an ICD-10 claim code for agranulocytosis and/or an ANC test result. Of these, 32 were mild, 6 were moderate, and 15 were severe neutropenic cases. Of the 15 severe neutropenic cases, only six had ANC test results that confirmed the severe neutropenia. Severe neutropenia that confirmed ANC test results had an event rate of 8 per 1,000 person-years at risk. The study found that mild neutropenic clozapine episodes were about twice as likely as severe neutropenic clozapine episodes to have an ANC screening in the 30 days prior to the day of

the neutropenic event.

Sentinel study number 3 has a medical chart review to describe ANC monitoring, neutropenia-related outcomes, and clozapine discontinuation in the first 6 months of clozapine treatment among Medicare and Medicaid insured patients. A broad claims-based definition for neutropenia was used to identify potential neutropenic cases and the dates for medical record extraction.

The medical records of ANC test results were then extracted for review 7 days prior and 7 days after the events. The study focused on new clozapine episodes, defined as episodes with no dispensing of clozapine in the past 30 days. Standardized extraction sheets were created a priori to accurately capture information about neutropenia, ANC monitoring, indications, and additional information about clozapine use.

2,525 clozapine episodes were identified. There were 39 neutropenic events within 180 days of starting clozapine among Medicare and Medicaid

beneficiaries, with some record of a Massachusetts General Brigham affiliated facility. After excluding cases with no recent medical records and no mention of neutropenia in structured or unstructured medical records, or ANC test results, there were 6 cases of neutropenia for in-depth electronic health records review. Clozapine was recorded as a suspected cause of neutropenia in all 6 cases. All 6 episodes recorded clozapine discontinuation following neutropenia, and the management strategies for neutropenia included prophylactic antibiotics and/or filgrastim treatment. One out of the six episodes of clozapine was recorded to have led to a serious infection requiring inpatient management. No deaths were recorded. Of note, we found no mention of monitoring plans, no records of adherence to the guidelines for ANC testing in the structured or unstructured medical records.

The next study was performed in collaboration with the VA. This study was designed to examine the risk of neutropenia among clozapine

users in the VA. The objective was to evaluate the risk of neutropenia and agranulocytosis following the initiation of clozapine use and over time. This was a retrospective cohort study performed in the VA healthcare database, covering the period from 1999 to 2023. The study captured new users of clozapine as defined as no clozapine prescription in the prior 12 months among patient 18 years and older.

The outcomes of interest were mild, moderate, and severe neutropenia defined by ANC values, as well as deaths attributed to neutropenia. The statistical methods we used to analyze the data were descriptive, and we looked at the cumulative incidence of neutropenia by duration of clozapine exposure using a life table analysis of the data and a Kaplan-Meier plot.

The study sample included approximately 6,500 clozapine users that met the inclusion/ exclusion criteria. The mean age was 50 years and the majority were male. The study population had a high psychiatric comorbidity burden, and there were

approximately 200 to 300 new users each year, and the follow-up was up to 23 years.

The findings regarding adherence to monitoring in the VA were that approximately 70 percent of the patients had at least 21 tests performed in the first 6 months of treatment. With perfect monitoring, which would be once a week, we would expect to see 26 tests. Thirty-two cases of severe neutropenia were identified, which occurred during the first episode of treatment. A cumulative 12-month incidence of severe neutropenia was 0.4 percent. Approximately one-fifth of the severe neutropenic cases occurred after the patient was on treatment more than 2 years and some of which involved recent dose increases. Two deaths including severe neutropenia were identified. One death was definitely related to severe neutropenia, and the patient was on treatment for 23 days, and one was possibly, and the patient was on treatment for 5 years.

This life table includes the analysis as of November 6 of 2024. We recently became aware of

five additional patients with severe neutropenia that were not included in the briefing document. These are currently being analyzed; however, we note that these additional cases could impact this table and may increase the cumulative incidence of severe neutropenia seen at 5, 8, and 13 years. On the left side of this table, you see treatment intervals by month, and the row displays the number of severe neutropenia events during the course of clozapine treatment. The top of the table includes the total number of events and each of the three different analyses that we performed. The published literature does not describe the extent to which the cases they included were evaluated; however, in this study, we describe how the cases were evaluated.

The first analysis identified 32 events as severe neutropenia based only on outpatient prescription data; the second censored for treatment with cancer chemotherapy and reduced the number to 28 events; and the third analysis took the 28 cases and performed a medical chart review.

After review, these three cases were removed from the analysis because severe neutropenia was probably due to laboratory error in 2 cases, and a third due to an underlying diagnosis of lymphoma. The reduced number of cases of severe neutropenia went to 25.

In the area of the table that is boxed in red, we are focusing on the treatment in the first nine months. Across the three analyses, the risk is similar, ranging from 9.6 to 8.9 per thousand person-years for the first 3 months following initiation of clozapine, and represents the period of greatest risk. The risk is somewhat lower through 9 months, and it appears to level off to approximately 1 to 2 cases per thousand person-years through 8 years of use.

Please direct your attention to the section of the table boxed in red. After 96 months, or 8 years, we're unable to determine the risk level. Beyond 96 months, the data are too sparse, and therefore there is less statistical power to assess the risk.

This is a Kaplan-Meier plot of the cumulative incidence of severe neutropenia based on the life table data that I just discussed. The dotted red line represents the 32 patients with severe neutropenia during the first episode of treatment; the blue line represents the 28 patients after censoring for treatment with cancer chemotherapy; and the black dotted line represents the 25 patients after censoring for cancer chemotherapy and conducting a medical record review. The steepest part of the slope for all three lines indicates that the risk is greatest between 0 to 9 months, although cases of severe neutropenia continue beyond that time.

The strengths of the VA study include the completeness of the ANC test results; the comprehensive clinical, pharmacy, and laboratory data; the long-term follow-up; and the chart reviews of the neutropenic cases; however, there are several limitations. The data on inpatient clozapine use was not included; however, there is an ongoing analysis to look at this, and the

pharmacy records do not show brief interruptions in clozapine therapy; for example, if a patient has a brief interruption in treatment or even a week, this would not be detected.

The findings from the VA study may not be generalizable to other less structured healthcare delivery systems. The adherence to monitoring in this population was fairly good, and it may not be seen in other settings. Also, the data are sparse on longer durations of treatment, and this is an older male population, which, again, impacts the generalizability of the findings.

This concludes our review of the studies assessing the risk of severe neutropenia. I will now turn to the studies that were conducted to assess adherence to monitoring.

In this study, Sentinel was used to assess adherence to ANC monitoring requirements. Sentinel includes four national commercial health insurers, Medicare fee-for-service, and Medicaid. Clozapine episodes of use were identified based on dispensed prescription dates and days' supply. New clozapine

episodes had no clozapine use in the past 30 days; however, we performed a secondary analysis, and we look at new clozapine episodes that had no clozapine use in the past 180 days.

ANC testing was assessed during individual episodes of clozapine use for three different episode periods, months 0 through 6; months 7 through 12; and months 13 through 24. We assessed adherence in two different ways. We looked at the number of ANCs that were performed per month, or the rate, and secondly, we looked at the gap or the time between the ANC values for the claims.

Over all three periods, we found that 63 to 69 percent of the clozapine episodes had greater than or equal to 1 ANC laboratory value in the 30 days prior to clozapine initiation. Across the study periods, approximately 16 to 22 percent of the clozapine episodes had no observed ANCs during the first 6 months of treatment. For the first 6 months of treatment in patients with no clozapine use in the prior 30 days, the median number of ANC

test results per month ranged from 2.3 to 1.6; however, these median values excludes patients with no ANC tests.

With weekly monitoring, we would expect to see 4 tests per month. If the definition of a new user is changed to a patient with no clozapine use in the prior 180 days, which was the secondary analysis, the median number of tests per month increased for each time period and ranged from 3.8 to 3.1. For patients who continued clozapine beyond 6 months, in general, the median number of tests results is closer to the expected number of test results for the monitoring frequency.

To better understand the timing of monitoring, we also assessed the time between the ANC claims. During months 0 to 6 of treatment, we expect the length of time or the gaps between the ANC tests to be 7 days. This would be perfect adherence; however, for the purpose of this analysis, we used something less than that. It was less than or equal to 10 days.

For the first 6 months of treatment among

patients who had no clozapine use in the prior 180 days, the percentage of patients who had 10 days or less between all of their ANC tests, or nearly perfect adherence, ranged from approximately 17 to 12 percent across the three periods. Note that if the patient had one gap between the ANC tests that exceeded 10 days, they would not be considered adherent. This is a very strict definition of adherence.

If we were to expand the allowable gap to less than or equal to 33 days instead of 10 days between the ANC tests for the first 6 months of treatment, the proportion of clozapine episodes that were adherent increases, and ranges from 41 to 46 percent across the time periods. Looking at both the number of ANC tests that patients receive per month and the time or the gap between the ANC tests help us better understand and assess adherence to ANC monitoring. For example, the number of tests per month may not reflect weekly monitoring, as ANC testing could occur over a few days, then weekly throughout the month.

A similar study was performed with BWH with the objective of assessing the prevalence and the frequency of ANC monitoring in patients starting clozapine. Clozapine initiators with at least 6 months of enrollment and no prior clozapine use were included. Among the 62,000 clozapine initiators, 63 percent were preceded by ANC testing within 31 days.

During the first 6 months of treatment when a patient is supposed to have weekly testing, the median testing rate was 2.1 tests for 30 days. During months 7 through 12, when a patient was supposed to have biweekly testing, the median testing rate is 1.6 tests for 30 days. And during the second year of treatment, when a patient is supposed to have monthly ANC tests, the median testing rate was 1.1 tests for 30 days. Similar to the Sentinel study, adherence to testing increased when the frequency for testing declined.

This concludes the review of the studies assessing adherence to monitoring. The next study I'll be discussing was conducted in collaboration

with BWH to gather information on the prescriber's experience with the clozapine REMS. The objective of this study was to understand how the Clozapine REMS Program has impacted clinical practice. The survey had 7 closed-field study questions, and 750 physicians were randomly selected using IQVIA; 196 physicians returned their survey, yielding a response rate of 26 percent. In terms of the demographics of the respondents, 86 percent of the physicians were psychiatrists; 84 percent were in practice for more than 15 years; 80 percent spent more than 80 percent of their time in direct patient care; and 53 percent prescribed clozapine to 11 or more patients in the past 3 years.

Regarding questions about the physician's perspective of REMS activities, 66 percent of the survey respondents agreed that it is reasonable that clozapine has prescriber certification, and approximately 75 percent of the survey respondents agreed that certification provided useful information, and that testing is clinically necessary. Slightly more than 50 percent of the

respondents agreed that the paperwork facilitates discussion, and 88 percent of the respondents indicated that they always, or almost always, discuss the risk of severe neutropenia with patients starting clozapine.

When asked about the burden with the safe-use requirements, 71 percent of the survey respondents agreed that the safe-use requirements were burdensome for most patients; however, the study did not tease out burden associated with the clinical management versus the burden of the REMS. Forty-four percent of survey respondents reported it's hard to complete ANC testing, and 60 percent of survey respondents agreed that the safe-use requirements have often caused a delay in patients receiving clozapine.

Again, we're unable to tease out the burden associated with clinical management versus the burden of the REMS. Thirty-one percent of survey respondents reported that insurance is more burdensome than the safe-use requirements.

That concludes my summaries of the studies.

I just wanted to give you the key findings here. I presented a lot of information. To summarize, regarding the risk of severe neutropenia, collectively the literature and the studies indicate that the risk of severe neutropenia with clozapine is greatest in the first several months of treatment. In the BWH study, the risk of neutropenia-associated hospitalization was higher with the clozapine initiators compared to olanzapine initiators.

In the Sentinel studies, the severe neutropenia event rate was 8 per 1,000 person-years at risk. Among the six severe neutropenic cases that were identified, interventions included stopping clozapine, the use of prophylactic antibiotics, and/or the use of filgrastim.

In the VA study, the cumulative 12-month incidence of severe neutropenia was 0.4 percent in a population with reasonably good adherence to monitoring, and approximately one-fifth of severe neutropenic cases occurred after the patient was on treatment for more than 2 years, and that the risk

persists through at least 8 years of treatment.

Regarding adherence to monitoring, in the Sentinel and the BWH studies, we found that for the first 6 months of treatment, patients are monitored but less frequently than what is described in labeling, and adherence to monitoring increases as the monitoring frequency decreases. Not specifically conducted for the purpose of assessing adherence to monitoring, in the VA study, we saw that approximately 70 percent of the patients had 21 tests performed in the first 6 months of treatment.

Adherence to monitoring in the VA patients may not be generalizable to other settings. And regarding the physician experience with the clozapine REMS, in the BWH study, most responding physicians thought that certain aspects of the REMS were useful, but also noted there was burden with the requirements and that they delayed treatment. Thank you, and this concludes my presentation. I'd like to introduce the next speaker, which is Dr. Carolyn Tieu.

FDA Presentation - Carolyn Tieu

DR. TIEU: Good morning. My name is Carolyn Tieu, and I am a team leader in the Division of Risk Management at FDA. You've heard a lot just now about the studies and analyses we conducted. For this presentation, I will present a summary of FDA's approach in re-evaluating the clozapine REMS and our conclusions.

I will start with a brief introduction, and then I'll go into FDA's updated assessment of the risk of severe neutropenia and healthcare gaps that are currently being addressed by the clozapine REMS. Lastly, I will touch on some REMS considerations as you're considering whether the REMS is still needed to educate or to ensure ANC monitoring is performed.

In order to understand how the clozapine REMS can be modified, it's important to understand what care gaps the REMS are addressing. Recall that clozapine was first approved in the United States in 1989. At the time of approval, clozapine was the first antipsychotic approved with a boxed

warning for severe neutropenia and with a need for weekly monitoring of white blood cells.

At the time of approval, there were minimal resources and a general lack of knowledge about the risk of severe neutropenia or the need for regular ANC monitoring with clozapine. Also, monitoring for neutropenia and its management wouldn't have typically been performed by psychiatrists at the time. Thus, these two care gaps were identified and needed risk mitigation beyond labeling. Risk mitigation focused on two strategies: educating healthcare providers and ensuring that ANC monitoring was performed. These care gaps and strategies continue to be the basis for the clozapine REMS today.

To re-evaluate the clozapine REMS, FDA undertook two assessments. The first assessment was to characterize the risk of severe neutropenia, and the second assessment was to assess whether the two care gaps that I mentioned in the previous slide still exist today. This was done by analyzing the extent to which practitioners

understand the risk of severe neutropenia and the appropriate actions that need to occur if neutropenia is detected, and by analyzing the extent to which ANC monitoring for the approved labeling is being performed in today's healthcare landscape.

Now, I'll provide a summary of FDA's updated assessment of the risk of severe neutropenia with clozapine. There are two key takeaways from our updated assessment of the risk of severe neutropenia. First is that severe neutropenia remains a serious risk of clozapine. Based on the studies and analyses we've conducted, we saw that what we knew about the risk of severe neutropenia since 1989 still applies today. Severe neutropenia is occurring with clozapine, and there is a greater risk of severe neutropenia for clozapine than for other antipsychotics.

The time course for severe neutropenia is also similar to what we knew based on the findings of the VA study, where the risk of severe neutropenia was highest during the first 3 months

of clozapine, subsequently declined but was still seen beyond 8 years. Finally, fatal outcomes are still associated with clozapine.

The second key takeaway from our updated assessment is that ANC monitoring remains necessary with clozapine. We know that before widespread monitoring, the estimated agranulocytosis risk was 2.6 cases per 100 patient-years of clozapine treatment for the first 6 months, based on the Finnish article that was previously reviewed in the last presentation.

Without monitoring, the proportion of fatal cases range from 35 to 44 percent for those with clozapine-induced severe neutropenia. In our updated assessment, we found that with monitoring, the cumulative incidence at one year for severe neutropenia ranged from 0.4 to 1.3 percent. Additionally, with monitoring, the proportion of fatal cases decreased significantly to a range of 6 percent or less among those with severe neutropenia. This supports that frequent ANC monitoring can mitigate severe neutropenia and

related death.

Now, I'd like to move on to our updated healthcare gap assessment. As I mentioned in my previous slides, we identified two healthcare gaps in 1989 that required risk mitigation beyond labeling. The first was that knowledge and available resources about the risk of severe neutropenia and the need for frequent ANC monitoring was lacking in the prescribing population.

Currently, an objective of the clozapine REMS is to educate healthcare providers on the risk of severe neutropenia and the need for frequent ANC monitoring. To assess whether this knowledge gap still exists today, we analyzed the current knowledge, training, and resources available to healthcare providers. The next several slides provide a brief overview of this assessment and our conclusion as to whether there is still a gap in knowledge.

We have survey data from REMS assessments showing that prescribers and pharmacists certified

in the REMS are knowledgeable about the risk and the need for ANC monitoring. The surveys were conducted 4 times, between 2017 and 2024. In each survey, respondents demonstrated understanding of the risk and the need for monitoring. This tells us that not only are they aware of the risk, but also that knowledge is sustained over the years. Notably, respondents across all surveys reported that they used other resources outside of the REMS.

While assessment survey data gives us insight into the knowledge for healthcare providers participating in the REMS, because the REMS has not been fully implemented, prescribers don't have to participate in the REMS. Thus, we look at other data sources to try to assess knowledge among prescribers who may or may not participate in the REMS to get a better picture of what knowledge looks like holistically across U.S. prescribers. Specifically, we look at the studies from BWH, VA, and Sentinel.

In the BWH study on physicians' experience with prescribing clozapine, about 75 percent of

respondents found REMS certification provided useful information, and 88 percent of respondents indicated that they almost, or always, discussed the risk of severe neutropenia with patients starting clozapine. In order to counsel on the risk, presumably prescribers would have to be first knowledgeable about the risk themselves.

In the VA study and the Sentinel medical chart review, we saw evidence that some providers were actively managing patients based on ANC monitoring such as discontinuing clozapine when ANC dropped. This suggests that prescribers' understanding of the risk and management is supported by the actions that they are taking in a patient who has developed neutropenia.

To see what training is available outside of the REMS, we reached out to several professional organizations to assess the extent that monitoring for neutropenia is incorporated into psychiatric medical training and board certification examinations. Both the American Board of Psychiatry and Neurology and the American College

of Psychiatry confirmed that there are questions about clozapine in the question bank for their respective exams. It may be reasonable to assume that, then, psychiatrists studying for the physician in training and board exams likely are studying about clozapine and its risk, and the need for ANC monitoring.

For the Accreditation Council for Graduate Medical Education, we were unable to determine the extent managing clozapine is incorporated across residency or fellowship programs, but we were informed that residents and fellows are required to attend 70 percent of regularly scheduled didactic sessions that are coordinated with their concurrent clinical experiences. Thus, we believe that residents and fellows may be trained or exposed to clozapine during the didactic session of the residency or fellowship programs.

We also looked at published studies of surveys conducted among psychiatrists and psychiatry residents, and found that the surveys were mixed, with some surveys indicating limited

experience and inadequate training with clozapine use, while one survey indicated there were adequate training and education in clozapine management.

When clozapine was first approved in 1989, there were no published guidelines about clozapine or ANC monitoring for neutropenia. Guidelines started emerging in the 1990s, with the first guideline from the American Psychiatric Association in 1997. Since then, this practice guideline for the treatment of schizophrenia has been updated twice, in 2004 and 2020. All three editions include information about the risk of neutropenia, as well as monitoring recommendations. The current edition has about 3 pages dedicated to clozapine, and it also mentions agranulocytosis and ANC monitoring.

The American Academy of Child and Adolescent Psychiatry last updated their practice parameter for the assessment and treatment of children and adolescents with schizophrenia in 2013. This also includes information on using clozapine and monitoring recommendations. There are also books,

such as the Clozapine Handbook, and Maudsley's Prescribing Guidelines in Psychiatry, that include extensive information about the management of patients on clozapine.

Furthermore, information on the safety of clozapine has been incorporated in several common electronic resources such as Uptodate, Micromedex, Medscape, and Dynamed. Respondents from the BWH survey and REMS assessment surveys reported using these electronic resources outside of the REMS. Respondents from the BWH survey also noted that clinical decision support tools like Uptodate were most useful in contributing to their understanding of the risk of neutropenia.

In summary, we concluded that the knowledge gap has likely narrowed since approval of clozapine in 1989, in part, due to the availability of resources beyond the educational materials in the REMS. Our updated assessment found that information and training on clozapine and its safe use is more widely incorporated into medical training, guidelines, electronic decision support

and drug information resources, and healthcare systems. Therefore, in general, we believe that prescribers have greater knowledge about the risk of severe neutropenia and the need for ANC monitoring today compared to 1989, though it's important to note that having greater knowledge alone doesn't necessarily equate to safe-use behavior.

Next, we will move on to the second healthcare gap that the clozapine REMS is addressing, which is to ensure that ANC monitoring is performed. In this updated assessment, we wanted to understand to what extent is ANC monitoring being performed according to labeling and whether there is still a gap in the safe-use behavior.

We analyzed data and information from REMS assessment reports, literature review, FAERS, BWH study, Sentinel studies, and the VA study. Keep in mind that each of these studies we conducted has limitations, and none could answer the question of whether the REMS itself is impacting the safe-use

behavior. Also, we are unable to determine whether these studies or analyses included providers who were or were not actively participating in the clozapine REMS.

Now, I will discuss key findings from each data source in the next several slides. Data from REMS assessment reports showed that among the stakeholders participating in the REMS, there appears to be high compliance with label ANC monitoring across all monitoring schedules. We couldn't sufficiently assess the appropriateness of monitoring using data from FAERS and the literature because of a lack of documentation in these reports; however, a small subset of 27 reports indicated that providers typically follow clozapine labeling recommendations.

This data may not be generalizable, as most of these cases involve clozapine management in complex scenarios like concurrent cancer treatments, and providers may not publish or report when they aren't following recommended monitoring. Furthermore, these cases don't describe monitoring

in large populations where data on monitoring is rigorously and systematically captured.

When looking at data from BWH and Sentinel studies on ANC monitoring, the studies show that about 20 percent of patients had no ANC monitoring during the first 6 months of treatment. For the first 6 months of treatment, where we would expect 4 ANC tests in a month for new clozapine users, we observed a median of 2.1 ANC tests per month in the BWH study and 3.1 ANC tests per month in the Sentinel analysis. Note that in the BWH analysis, the rate of 2.1 was calculated among all episodes, while the rate of 3.1 in the Sentinel analysis was calculated among episodes with at least 1 ANC.

It should be noted that looking at the number of tests done per month does not inform us whether these tests are occurring weekly for the first 6 months; thus, we also look at the time elapsed or gaps between ANC tests in Sentinel. About 12 percent of clozapine episodes had gaps of 10 days or less in between ANC tests during the first 6 months of treatment, reflecting nearly

perfect adherence to monitoring. When loosening the definition of adherence to allow for gaps of up to 33 days, the proportion of those considered adherent increased to 41 percent.

After 6 months of treatment, where the monitoring frequency is reduced, adherence to ANC monitoring is improved. Collectively, what this tells us is that ANC monitoring is being performed, but not as described in labeling, particularly for the first 6 months of treatment where weekly monitoring is required, and also when the risk for severe neutropenia is greatest.

We also looked at ANC monitoring from the VA study, which was fairly complete. Within the VA study, approximately 70 percent of patients appeared to have weekly testing most of the time through the first 6 months of use. The median number of ANC tests obtained during the first 6 months was 25. Although monitoring was extensive, it is still not as described in product labeling.

In summary, we concluded that ANC monitoring

is occurring but not as described in labeling. Adherence to monitoring is worse when the recommended monitoring frequency is weekly. Although each data source has limitations, these findings are consistent across the studies we conducted. Because the REMS have not been fully implemented, it isn't clear how much the REMS contributes to ensuring ANC monitoring is performed, and therefore mitigating the risk of severe neutropenia. The data suggests that some ANC monitoring is occurring even in the absence of participation in the REMS. We also note that in population-based studies where monitoring was high, the incidence of severe neutropenia and clozapine-related mortality was substantially lower than in the pre-monitoring era.

This slide provides a recap of our updated assessment of the risk of severe neutropenia and the care gaps that are addressed in the clozapine REMS. Importantly, during our assessment of the risk, we found that what we know about the risk of severe neutropenia today is consistent with what

we've known since 1989. Severe neutropenia remains a serious risk of clozapine. It is greatest in the first several months; and it never goes to zero. ANC monitoring continues to be an effective intervention to identify neutropenia early so that appropriate actions can occur.

For the care gaps that are being addressed by the clozapine REMS, we found that knowledge of the risk and the need for ANC monitoring appears to be more broadly understood today compared to when we approved clozapine in 1989. There are training guidelines and resources for clozapine outside of the REMS. There is evidence of ANC monitoring, but it is less than what is recommended in the labeling for the first 6 months. After the first 6 months, adherence is more consistent with labeling as monitoring frequency is reduced.

That wraps up our re-evaluation of the clozapine REMS. I will now discuss some REMS considerations for you to keep in mind for the discussions and voting questions later today. First is burden and access. REMS burden includes

additional steps beyond routine care that the participants in the REMS must take in order to use clozapine, such as the burden associated with additional training, certification, and documentation.

Fully implementing the REMS as designed may result in more burden than what we are currently seeing. Keep in mind that patients with schizophrenia may have circumstances that contribute to healthcare disparity, so full implementation of the REMS may further impede access to clozapine for some patients.

Another consideration is the length of time that has elapsed since approval. We know that often there is a lack of science to practice. Research suggests that new research evidence takes an average of 17 years to be adopted into clinical practice. Clozapine has been approved for more than 35 years, and we believe that the knowledge gap has narrowed since approval. We generally expect that routine ANC monitoring is more integrated into clinical care today compared to

35 years ago.

Another consideration is that there are other healthcare gaps that are outside of the REMS that likely play a significant role in burden and access to clozapine. Our literature searches have identified several of these gaps, including providers' comfort and familiarity around prescribing; patient difficulty in accessing psychiatric care; and fragmentation of services that should be coordinated. These healthcare gaps will not be resolved by modifying the REMS to reduce burden or eliminating the REMS. There will still potentially be providers who don't prescribe clozapine for other reasons, and there will still exist healthcare system-wide challenges that can negatively impact patient care for patients with schizophrenia.

Another important consideration is the interconnectedness of REMS requirements. REMS requirements are often not mutually exclusive, and in combination can form a closed system of checks and balances to achieve the REMS goals.

Modifications to the clozapine REMS may include removing specific requirements. In the next several slides, I will walk through examples of how REMS requirements may be connected to each other under the clozapine REMS.

As a reminder, these are REMS requirements in the clozapine REMS. The requirements include prescriber certification; pharmacy certification; patient enrollment; documentation of ANC monitoring; and patient registry. If the REMS is modified to remove documentation of ANC, no ANC tests would be collected in the REMS. This would mean that the REMS requirements for patient enrollment, documentation of ANC monitoring, and patient registry would be removed.

If the REMS is modified to retain prescriber education, a closed system is still necessary to ensure clozapine prescribers will be educated prior to dispensing. To keep it as a closed system, pharmacy certification must also be maintained to link prescriber certification to the dispense of the drug. The last consideration I want to note is

that modification or elimination of the REMS does not change the prescribing information for clozapine. The boxed warning for severe neutropenia and the need for ANC monitoring will still be a part of the approved labeling. Prescribers will still have to monitor patients' ANC for safety.

I would like to acknowledge the key review teams at the FDA. Re-evaluating the clozapine REMS was a huge effort and the culmination of years of work with OSE and OND. This concludes my presentation. Thank you.

Clarifying Questions

DR. FLOYD: Thank you for those presentations.

Now, we're going to take about half an hour before lunch to ask clarifying questions to our FDA presenters. Please be sure to state your name for the record, and if you raise your hand, we'll start the queue up.

Go ahead, Dr. Amirshahi.

DR. AMIRSHAHI: Hello. Maryann Amirshahi.

My question is for Dr. LaCivita. Thank you for your presentation. I'm not a psychiatrist, I'm a medical toxicologist, so I always think in terms of the dose making the poison. When you presented data with regard to the development of severe neutropenia, you did a great job of demonstrating that it was associated with time. But perhaps if we want to ease the burden on patients and not miss cases of severe neutropenia, perhaps we could focus our recommendations for screening.

Did we do a look and stratify the patients that developed neutropenia with regard to dose? I know you alluded that one case was associated with a dose increase, and it does seem to be that there is a wide range of dosing. Is that something that we have or could explore to help streamline the screening recommendations? Thank you.

DR. LaCIVITA: Hi. Cynthia LaCivita from the FDA.

Dr. Marc Stone?

DR. STONE: Yes. To the best of our knowledge, it's not a direct toxic effect of

dosage. It is more of an idiosyncratic reaction.

DR. AMIRSHAHI: Yes. I was just wondering because there was the one case that they specifically mentioned that it was associated with a dose increase, so perhaps if there was a signal, at some point that maybe we could identify patients that might be more vulnerable or may need more intensive screening because they may not necessarily all be the same, just to refine and think about the burden of illness.

DR. STONE: Right. But you when you have an N of 1, you can't really generalize about anything.

DR. FLOYD: Dr. Dunn?

DR. DUNN: Walter Dunn. This is a question for the agency in general. As was brought up previously and what was mentioned in Dr. LaCivita's presentation, the question between the effect of the REMS and clinical management in terms of a patient burden and access, is there a consideration, or can there be consideration, that if we do make modifications to the REMS, that there can also be an accompanying label change?

I'm thinking about this mostly from closed medical systems such as the VA, which is where I work, and possibly also maybe something like Kaiser, where a REMS may change, labeling does not, but these internal systems still keep the same mechanisms in place to require patient monitoring and so forth.

DR. FARCHIONE: This is Tiffany Farchione, Director of the Division of Psychiatry. The information that we have in the label about the need for monitoring is unlikely to change because we still think that that's the frequency of monitoring that's needed in order to make sure that patient safety is maintained. The difference would just be in the additional administrative checks and balances to ensure that that monitoring is happening.

DR. FLOYD: Dr. Vyas?

DR. VYAS: Thank you. I have a follow-up to that point. It seems as though the risk diminishes -- the question is to the agency and to presenters, that the risk dramatically diminishes

with time but never goes to zero, but the monitoring at a reduced frequency, I've always wondered about that. So finding an event further on in the time course would be more rare if we're monitoring with increasingly rare frequency. So we're looking with less frequency to find less frequent events, which makes it harder and harder. For the Higgs boson, it's a really rare event. They had to do like 800 trillion collisions before they found something.

DR. STONE: Marc Stone, Deputy Director for Safety and Psychiatry. It's a bit of a paradox to be sure, but the other thing you have to consider is there's a bit of an illusion. You start off with a very high risk, and then risk is greatly reduced, but that doesn't mean that the residual risk is negligible. It might be easier to see the risk wasn't as high in the beginning, and then declined less, and would seem less anomalous, and we'd be less concerned with the frequency of monitoring.

I guess the best way to look at it is like

the results that we saw from the VA, where we were seeing cases of neutropenia years out, but that the incidence of fatal or cases requiring significant intervention like hospitalization were pretty rare. So it might suggest it does a pretty good job of catching people that have mild or moderate neutropenia, and stopping the drug before it becomes severe.

DR. VYAS: To follow up, I was wondering -- a question for Dr. LaCivita -- if you'd looked at the work of David Taylor at the Maudsley. One of the papers that he put out in the last couple years was this recognition -- so in that, they had 3500 samples, 3500 patients that they follow at this clozapine clinic in South London and Maudsley, in there, over 14 years, and they're exclusively using clozapine.

Among the 3500 patients, they found 23 individuals with severe neutropenia, and then they used a set of criteria, which they now call the Taylor criteria, and I'd be happy to mention those. But they specifically narrow down those

23 cases to 9 individuals, 9 instances, of which one patient represented 2 cases because they had re-challenged the person, and a hundred percent of those occurred in the first 18 weeks. I was wondering if you'd looked at that and the Taylor criteria in particular for this.

DR. LaCIVITA: Hi. This is Cynthia LaCivita from the FDA. I think I'd like to ask Dr. Graham to speak to that, only because what you're explaining sounds like similar findings that we saw in the VA study. I don't have the criteria that you're mentioning. Would that help at all, or is that not helping you?

DR. VYAS: I don't know. I'm just wondering if you've included that or considered that because I really find the Maudsley work to be really compelling.

DR. LaCIVITA: I'd have to say we did not look at that. Thank you.

DR. VYAS: Okay.

DR. FLOYD: Let me interject. Are you talking about some type of causality assessment?

Are you saying that a big chunk of the neutropenia was unrelated, and then they use criteria to --

DR. VYAS: Exactly.

DR. FLOYD: Okay.

DR. VYAS: So the paper I'm looking at is A Distinctive Pattern of Neutrophil Count Change and Clozapine-Associated LTA, Life-Threatening Agranulocytosis. And in that, they come up with this set of criteria to screen these events. So the LTA, the inclusion criteria, that they came up with was a recorded neutrophil count of less than 500 in patients who stopped clozapine because of the low count; and then signs of infection such as raised temperature or elevated CRP; and/or admitted to a general hospital for the treatment of infection; and/or prescribed antibiotics; and/or given filgrastim, and that ended up being one of the best means of finding actual events that we're concerned about, and they did fall in the first 18 weeks. But that's a big body of literature to look at.

DR. STONE: Marc Stone again. You are

describing cases with unsatisfactory outcomes; that they had infection, they were hospitalized, so the question is, really, what can be done to prevent those outcomes, and how much does monitoring prevent those outcomes? Also, because these are very rare events, the statistical uncertainty about frequency, of course, is huge. So that's only one case. That might be a bit of publication bias or you want to look for replication of the findings, but it is certainly something to be considered.

DR. VYAS: Yes.

DR. FARCHIONE: This is Tiffany Farchione. If I could just follow up. I think it's helpful to hear about additional literature that we may have missed, that maybe wasn't included. It sounds like what our colleagues are saying over here, this was a relatively recent publication.

DR. VYAS: 2022.

DR. FARCHIONE: Oh, okay. So it's not -- but I think that, ultimately, in terms of what we might do with the labeling versus what we might do with the REMS, we want to really focus on

what your recommendations are for the REMS. So if there is something, a take-home message that you got from that particular study you're looking at that you would like us to consider, that would be important for us to hear.

DR. VYAS: I brought it up only because we're talking about different studies that were being looked at. Thank you.

DR. FLOYD: Mr. Brisbin?

MR. BRISBIN: Hi. I'm Michael Brisbin. I'm the clozapine patient representative. I have a question for whoever wants to answer. Did the FDA conduct any studies on patient experience or impact of REMS restrictions from a patient or caregiver perspective, in addition to all the studies on the rates of neutropenia conducted?

(Applause.)

MR. BRISBIN: If not, why not?

DR. LaCIVITA: Hi. This is Cynthia LaCivita from the FDA. So we actually did work with the BWH on a study from a patient's perspective. It was focus groups that they did. We didn't present

those study findings yet because it's still under analysis. But some of the things that they were advocating for during that time period was loosening the monitoring requirements. They advocated for not limiting the supply. They had concerns about lack of coordination of care, and also, they wanted more information from their prescriber upfront, as what needed to be done in terms of managing those patients, and there were a few that also had a disbelief about the risk of neutropenia. So we're still analyzing that data, but we did do that. Thank you for asking that question.

MR. BRISBIN: Thank you.

DR. FLOYD: Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. I just wanted to make a brief comment. On slide 88, there's mention about the risk without monitoring, and that's based on one study. I just want to make sure that the group is aware. This was a finished study in 1977 by Albert de la Chapelle and colleagues. They really made a heroic effort to try to estimate

risk, and they were also exploring genetic hypotheses, but their denominator about exposure was based on surveys to hospitals; and therefore, their estimates about their patient-years of exposure was survey based. And to the extent that they might have undercaptured those receiving the medications, the risk could be overestimated.

So I just want to make sure people are aware of the methods that were used there, since a fair amount of conclusions are being drawn from that one study. Thank you.

(Applause.)

DR. FLOYD: I just want to say that's a very helpful comment because those findings are completely inconsistent with the literature later, so I think the different methods of attributing person time on treatment, that makes a lot more sense now.

Next we have Dr. Dublin.

DR. DUBLIN: I'm Sascha Dublin from Kaiser Permanente. I first want to thank the FDA for a really wonderful body of work of the studies, and I

think it's super helpful to have the data. I have a couple of questions about specific studies. For the VA study, which I thought was so impressive, I'm wondering if you are considering or have started to look at suicide or suicide attempts as an outcome because I think having those two outcomes side by side in a well-defined population would be very illuminating --

(Applause.)

DR. DUBLIN: -- recognizing that it's a non-representative population and may be people who are more engaged in care and have access to care.

DR. LaCIVITA: This is Cynthia LaCivita from the FDA. I'm going to ask Dr. Graham to take that question. Thank you.

DR. GRAHAM: David Graham, FDA. We've discussed whether we might be able to look at suicide. There are a lot of difficulties with identifying suicide, suicide attempts, completed suicides, but it's something that we're thinking about doing. It's a really complicated issue because you've got these various time-varying

risks, and so you've got this period of incredible risk early in use, like the first 3 to 9 months where the risks for neutropenia are high, and what are the risks of suicide, which can be indefinite, sort of over an entire time period, and then identifying what those events are.

But the short answer to your question is we haven't looked at it. We're thinking about ways that we might be able to look at it. What we'd like to do right now, first, is to integrate the hospital prescription data into the outpatient prescription data so that we can link all the episodes and get a best estimate for what the profile of risk is in the cohort; and then once we have that, to drill down on those to look at what are the different patterns of dose cessation versus continuation.

Some of the episodes of neutropenia in our cohort were pretty short, 5 days. Somebody had severe neutropenia for some time. The clozapine was stopped over 5 days or a week, and the neutropenia resolved. In others, clozapine was

continued, and the neutropenia resolved; so trying to sort out what is serious severe neutropenia from what is maybe transient neutropenia that is related to something that's not clozapine, we'd like to try to understand that better, and then to tackle the the big one, which is suicide, and identifying that, recognizing that we don't have a comparator group, so we'd only be able to look at what's happening in the clozapine cohort.

When we thought about could we study olanzapine or quetiapine as a comparator group, we don't think that we're going to be able to get rid of the selection bias of patients that go on clozapine versus patients who don't; so we don't think we'd ever be able to fully trust that analysis. So we can look at suicide, but it may not answer all of our questions, but it may show you what the profile of the risk is for suicide among clozapine users.

DR. FLOYD: Dr. Stone, go ahead.

DR. STONE: Marc Stone, Deputy Director for Safety. When you're trying to compare the risk of

suicide, or the reduction of risk of suicide, from using clozapine to the risk of using clozapine, you can't just look at neutropenia. There are many other very serious adverse reactions. Probably more people die from intestinal infarction, for example, from clozapine than die from neutropenia; and, of course, there are all the elements of unstable pharmacokinetics and toxicity from that. You have myocarditis, which is sometimes fatal; liver failure; all these other things. So you just can't weigh one against the other.

DR. DUBLIN: Sure. And I think that's, to me, even more appealing about the VA cohort, that you have such rich data, people who are often getting their primary care, their psychiatric care, and their inpatient care in a relatively closed system with access to imaging reports and labs. It just seems like a pretty amazing data resource.

The other question I had is about the BWH provider survey. Maybe I missed it, but could you speak a little more about how those providers were selected? Those are all within the BWH system, or

when you say they were randomly selected, like across all specialties? I was a little confused about who those providers were.

DR. LaCIVITA: Cynthia LaCivita, FDA. The BWH study that looked at the prescriber perception of the REMS; is that the study you're asking about?

DR. DUBLIN: Yes.

DR. LaCIVITA: So that study that they selected, they used IQVIA to select 750 prescribers, and then out of that, there were 196 that responded to the survey. So we don't know whether those prescribers were certified in the REMS or not.

DR. DUBLIN: So it's called the BWH survey. Was it a national sample of providers or was it within BWH? I'm sorry. I'm finding this confusing.

DR. LaCIVITA: BWH did the survey. Dr. Toyserkani can give you more information.

DR. TOYSERKANI: Hi. Gita Toyserkani from FDA. So yes, it was a national survey that was conducted. They identified prescribers that

prescribe clozapine through the IQVIA data, so it was not within Brigham and Women's hospital group.

DR. DUBLIN: Thank you.

DR. FLOYD: Dr. Ehret?

DR. EHRET: Meghan Ehret. I had a question about that survey because it's listed here that it's physicians, but when we look at the REMS, we're seeing that half of the providers are not physicians. So did that include nurse practitioners, PAs, psychiatric pharmacists, anyone else who might be prescribing clozapine, to learn about their knowledge of it as well?

DR. TOYSERKANI: Gita Toyserkani from FDA. So these were randomly selected prescribers through IQVIA data. I'm sorry. Can you repeat your question again?

DR. EHRET: I was just looking, it says "physician experience survey."

DR. TOYSERKANI: Yes. They were --

DR. EHRET: So was it just physicians or did it include other prescribers?

DR. TOYSERKANI: Just physicians.

DR. EHRET: Okay, just trying to clarify because there are half of those people prescribing clozapine who are not physicians, according to the REMS certification.

DR. FLOYD: Mr. Brisbin?

MR. BRISBIN: Michael Brisbin. This is to whoever wants to answer it again. How many blood for drug REMS does the FDA have in place, including clozapine? And of those programs, how many require actual blood test results to be reported to the REMS to dispense the treatment?

DR. LaCIVITA: This is Cynthia LaCivita from the FDA. I don't have the exact numbers, but if I can get that for you on break, I'd be happy to do that. There aren't specific blood draws, but there are other REMS that require tests that use the blood, not for ANC. Thank you.

DR. FLOYD: Dr. Ballon?

DR. BALLON: Jacob Ballon, Stanford. I think one of the challenges that has been brought up throughout all of this is that the REMS system reflects our fragmentation of our healthcare system

overall, and difficulties in obtaining labs and things like that. I'm wondering what thought has been put into using also the consolidation we have of medical records through Epic, and Cerner, and other companies like that, or large systems for obtaining blood draws, and being able to help integrate some of these large data sets into something like the REMS that would at least help reduce some of that fragmentation perhaps on the provider level.

DR. CHAN: Irene Chan, FDA. Yes. The FDA is exploring, in cooperation with MITRE, opportunities for better REMS integration into pharmacists and provider workflows. We do recognize that fragmentation of care is a broader issue here, and certainly accessing the data in a way that can decrease some of that burden is something that the FDA has a great interest in.

DR. FLOYD: Dr. Dunn?

DR. DUNN: Walter Dunn. My question is regarding the policy, regulatory requirements, for the REMS. Obviously, the tenor of this

conversation has been to potentially ratchet down the REMS, but as was mentioned, if it was fully implemented and enforced, obviously, creating a lot more burden. Is there a requirement that it move toward that if the recommendation is, let's say, not to make any changes, or can it potentially exist status quo with all these waivers and treatment to dispense rationales in place?

DR. LaCIVITA: Hi. This is Cynthia LaCivita from the FDA. I think we have maintained the enforcement discretion knowing that we were going to have this advisory committee, so I think we'd like to move forward with something that doesn't involve enforcement discretion.

DR. DUNN: And that's considered a temporary measure.

DR. LaCIVITA: Yes. Thank you.

DR. FLOYD: Is this a follow-up?

DR. AMIRSHAHI: [Inaudible - off mic 4:39:24]

DR. FLOYD: Okay.

Dr. Stegmann?

DR. STEGMANN: Jens Stegmann. Dr. Tieu, you very nicely outlined that in the beginning when the REMS were being set up, there were two care gaps being addressed. We talked about knowledge already previously, but is my understanding correct, that by seeing all the evidence and all the studies which have been performed, including the BWH study we previously discussed, that this is a knowledge assessment within the REMS system, so to say?

Do we have an understanding about what is the knowledge about clozapine and ANCs for psychiatrists outside that, hesitating and not having prescribing because of the burden or limited understanding of ANC?

DR. LaCIVITA: Hi. This is Cynthia LaCivita from the FDA. I'm going to ask Dr. Tieu to summarize our findings again, because we know what is occurring within the system in terms of the training that they need to complete, but for prescribers that are functioning outside of the REMS system, that's what we explored in terms of what the residency programs and others support.

DR. STEGMANN: Okay. You're referring to what Dr. Tieu already summarized --

DR. LaCIVITA: Yes.

DR. STEGMANN: -- and the various association, which might or might not provide an understanding about clozapine. So we have not in the U.S., as it being mandatory, which has been discussed earlier this morning, being implemented. So we are guessing it's being addressed?

DR. FARCHIONE: This is Tiffany Farchione, Division of Psychiatry. I think the comment earlier about ACGME requirements and physician training -- and I think it would extend even beyond just physicians to other prescribers as well, nurse practitioners, and so on -- that is not a mandatory part of training. A, we don't have any jurisdiction over that, which makes it a difficult thing for us to consider; B, I think that that could potentially be a point for patient advocacy or for industry advocacy in order to try to expand that knowledge base.

DR. STEGMANN: No, I certainly understand,

and this was not what I'm asking for. I just wanted to highlight that closing an existing knowledge gap might be outside the remnant [indiscernible - 4:42:13] of FDA and in REMS. So I just wanted to clarify that.

DR. FLOYD: I have a question for the FDA. We saw earlier that maybe a quarter to a third or so of the clozapine prescribing is happening outside of the enforced REMS component. If we eliminated the documentation of ANC monitoring, and we went to just the physician registry with required training, pharmacy verification, do we feel like it's feasible to make that work?

I understand there have been so many barriers, and it's been impossible to get the REMS to function the way it was intended. But if we limit it to just the physician registry, do we think that, actually, we could do that close to a hundred percent?

DR. LaCIVITA: Cynthia LaCivita from the FDA. I think that is one of the reasons why we're at the advisory committee today, to get the

feedback from the committee in terms of if certain REMS requirements were lifted, would we feel comfortable and ensure that those monitoring requirements were still followed.

DR. FLOYD: Yes. So the question isn't about does the FDA feel like that's adequate; it's if the advisory committee recommends that, do we have confidence that the REMS infrastructure could actually make that happen without paperwork snafus or patients -- do you know what I'm saying? All the reasons why we're even having this meeting because of the ANC documentation, if we went to just a physician registry, do we think we could eliminate those barriers; that this would just kind of run seamlessly?

DR. LaCIVITA: Cynthia LaCivita from the FDA. Regarding prescriber certification and pharmacy certification, that would ensure that the prescribers had completed the training or the education; and, of course, the component of documenting the ANCs to the REMS is another layer that's added to ensure that monitoring is done. We

do have other programs that have certification of prescribers and pharmacies, and they are implemented successfully.

Is that what you were asking?

DR. FLOYD: Yes, that's very helpful. That's exactly what I was asking. Thank you.

Mr. Brisbin?

MR. BRISBIN: Hi. Just to follow up on my last question, I was asking about the blood for drug and how many medications have those programs. I believe the answer should be two, clozapine and tolvaptan. And the answer to how many actually require blood tests to dispense the treatment is only clozapine.

(Applause.)

DR. LaCIVITA: This is Cynthia LaCivita with FDA. I know there are other products that are not checking for ANCs, but they have tests to check liver function, which requires a blood draw, and that's necessary for dispensing. So let me get back to you after the break, and we can give you the exact numbers. Thank you.

DR. FLOYD: So we're going to finish with two more questions before we break for lunch.

Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi. This is for whoever wants to answer it. I was thinking that we alluded to this, that there are other products that require certain testing, and one of the things that I was thinking, back to when I practiced as a pharmacist many years ago, were things like Accutane, where you had to document a negative pregnancy test, for example, and you do have to have it within a healthcare setting, and with medications like Accutane, you don't have to go to a specialty pharmacy.

So is there something that we have done to review other REMS programs that require monitoring for things such as pregnancy tests that have worked well and lessons learned that we can apply to streamline the process for clozapine?

DR. LaCIVITA: Cynthia LaCivita with FDA. For the programs that require the documentation of the monitoring or the testing, typically those

programs require that the prescriber is certified, the pharmacy is certified. So in the iPLEDGE REMS, those pharmacies are certified, then the requirement would be something; that the pharmacy would need to have some type of authorization prior to dispensing. There are multiple programs that close that loop like that.

DR. AMIRSHAHI: I guess my question is, is there anything from any of these programs -- for example, I know that most pharmacies will dispense Accutane as opposed to clozapine. So is there a difference in pharmacy access, or have we taken any lessons from programs? I don't know which ones have run particularly well, but is there anything that we can learn and take away from that? That would be helpful information.

DR. LaCIVITA: Cynthia LaCivita, FDA. That's a good question. We can go back and look at that, certainly. Thank you.

DR. FLOYD: Dr. Salvas?

DR. SALVAS: Thank you for the presentations. They were phenomenal for helping me

understand. I am unclear on one thing, and it's related to your question, Dr. Floyd. Are we trying to bring the third of patients that are outside the program in, or are we trying to expand the underserved population in this program by 2, 3, 4, 5x, for example? I feel like the solutions we're going to have to consider are going to be different, depending on which of those goals we actually have.

DR. FARCHIONE: This is Tiffany Farchione, Division of Psychiatry. I think what we're ultimately trying to do is to figure out what's necessary in order to ensure that the benefits of clozapine outweigh the risks. And in this case, the fact is that we know the drug is being underutilized, and we have to examine what -- there's benefit that is not occurring, so we need to be able to examine are there things that we can do to improve the benefit side of that equation so that it's not overly burdensome, whether it's the REMS, or a lack of a REMS, or whatever. Whatever is needed to make sure that you

can use the drug, use it safely, and help the patients who need it, that's the bar that we're trying to hit.

DR. FLOYD: Before we excuse for lunch, I want to make one comment that's been on my mind that we'll get into more during discussion, which is that, right now, we have a population that is getting rigorous monitoring. I suspect most of it's happening in mature programs and well-resourced centers, and it's not being used enough. If you relax some of these elements to assure safe use and it becomes more widely available, we have to consider not just the risk-benefit to existing patients, but to all the new patients who are going to be prescribed by maybe their GP in a very rural area, or a PA who doesn't have support and is in a mobile clinic or something.

So I think those are the counterfactuals and the considerations that we really need to dive into during the discussion period.

Sorry. I'm supposed to give the time. We

are a little bit behind schedule, but we want to stay on pace for the open public hearing, so I'd ask that you please be back at 1:35. Thank you.

(Whereupon, at 12:51 p.m., a lunch recess was taken, and meeting resumed at 1:38 p.m.)

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

(1:38 p.m.)

Open Public Hearing

DR. FLOYD: We're going to go ahead and resume now. We'll now begin the open public hearing session.

Both the FDA and the public believe in a transparent process. To ensure this transparency, the FDA believes that it is important to understand the context of each presentation. For this reason, at the beginning of your written or oral statement, please advise the committee of any financial relationships you may have with the industry group. For example, this might be payment for travel, lodging, or other expenses. Likewise, the FDA encourages you at the beginning of your statement to state if you have no financial relationships. And if you don't do this, it's not going to prevent you from speaking.

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

and this committee consider the issues before us. That said, in many instances and for many topics, there'll be many opinions. One of our goals is for this open public hearing to be conducted in a fair and open way, where everyone is listened to carefully and treated with dignity and respect.

For those of you presenting virtually, please remember to unmute and turn your camera on when your OPH number is called. And for those of you presenting in person, please step up to the podium, just like that, when your number is called. And also, please only speak when you're called on by the chair. Thank you.

So with that, we'll start with speaker number 1. Please say your name and any organization you're with, and you have 3 minutes.

AUDIENCE MEMBER: In the interest of public disclosure, might I, as one of the great unwashed, beg you to modestly turn up the volume, please, because some of the rest of us back here can't hear it.

DR. FLOYD: Sure. We'll do our best.

AUDIENCE MEMBER: Thank you.

MS. WALLACE: Good afternoon. Thank you for giving me the opportunity to speak to you today. My name is Kerry Wallace. My son, Nathan Wallace, was diagnosed with schizophrenia. He passed away June 12, 2023 at the age of 23. Nathan's schizophrenia was treatment resistant. We were unable to ascertain if clozapine would have provided Nathan with relief from his agonizing and debilitating symptoms, due to factors directly related to the Clozapine REMS Program, which, in my family's experience, rendered that therapeutic approach unattainable.

The first hurdle was finding a clinician who would agree to administer the program requirements. This was not available in the resort mountain town in Colorado where we lived. There were no testing sites available. And most importantly, from my experience, was the challenge of getting a person who suffers from paranoid schizophrenia to jump through the myriad of hoops necessary just to receive a much needed medication. Lack of

medication adherence is a hallmark of schizophrenia. Anosognosia, the belief that you are not ill and do not require treatment, is prevalent in many individuals who suffer from schizophrenia, and that included my son.

Strict adherence to a blood work program not readily accessible was an impassable roadblock not only for providers, but for my son who believed that each time his blood was drawn, it drained his life force. It would likely be challenging for a person not suffering from a serious mental illness to adhere to the Clozapine REMS Program in a rural community, let alone someone who suffers from paranoid hallucinations, delusions, and executive functioning challenges.

The Clozapine REMS Program creates a classic catch-22. Clozapine is intended to help schizophrenics overcome debilitating symptoms, but due to the severe REMS program requirements, those symptoms block access to the drug. Consequently, the only way for a person to receive clozapine for treatment of schizophrenia symptoms is for that

person to do the very things that the illness symptoms prevent.

I will never know if clozapine would have saved my son's life and given him the opportunity to experience a reality that was not terrifying and othering. It is time to ease the restrictions upon clozapine in order to provide access to this critical therapeutic intervention that can provide a lifeline to wonderful people like my son.

I have been a practicing attorney for 33 years. The tragic loss of my son via the profoundly dehumanizing experience of a lack of continuity of care, access to care, and community support for what is one of the most debilitating illnesses led me to seek a certificate in U.S. health law at Georgetown University Law Center. This country is experiencing a mental health crisis. Access to treatment is critical. It is time to ease the restrictions that block access to a key therapeutic drug that can change and save lives.

In my studies so far, related to food and

drug law, there is more than ample basis and evidence over the past three decades to support easing the restrictions on access to clozapine. Please provide access to those in our communities who so desperately need the help. Thank you.

DR. FLOYD: Thank you, speaker number 1.

Speaker number 2, if you could please come to the podium.

(No response.)

DR. FLOYD: Is speaker number 2 here? Okay. Speaker number 2 is online. Please go ahead.

DR. BARNETT: Good afternoon. My name is Brian Barnett. I'm a psychiatrist and the Director of the Psychiatric Treatment Resistance Program at Cleveland Clinic. I'm also one of the minority of psychiatrists in the United States who regularly prescribe clozapine. I have no financial relationships with any manufacturer of clozapine. Today, I'm speaking on behalf of myself and my patients to call for a critical reassessment of the clozapine REMS.

The clozapine REMS has created significant

barriers to care, contributing to the underutilization of a life-saving medication. The neutrophil monitoring requirements, while well intentioned, have become a logistical nightmare for clinicians, pharmacists, and, most importantly, patients. Many pharmacies simply refuse to dispense clozapine, likely due to the administrative burden and lack of financial incentives. Others still insist on outdated practices, like requiring faxed lab results even when I've already submitted the patient status form electronically.

These behaviors directly harm patients by discouraging clinicians from prescribing clozapine and patients from starting or continuing it. Some of the most distressing calls I received as a clinician are from patients at the pharmacy, where a pharmacist is unwilling to fill their clozapine.

One of the most dangerous features of the current REMS system is its inflexibility, driven by the so-called no blood/no drug ethos, which has been baked into the minds of America's pharmacists.

Pharmacists often refuse to fill prescriptions if there are delays in lab reporting, even for patients who have been stable on clozapine for years. I've observed multiple cases of clozapine withdrawal, psychosis, delirium, and catatonia in long-stable patients due to this rigid myopic approach, which jeopardizes patients' lives and livelihoods. These tragedies were entirely preventable, but many pharmacists are either unwilling or unable to cooperate, even when the FDA has granted flexibility in dispensing, as it did during the COVID-19 pandemic.

Given the decreasing risk of clozapine-induced agranulocytosis over time, and the fact that 97 percent of affected patients survive it, the risk of death from agranulocytosis after being on clozapine for 6 months is similar to that of general life mortality risks, including traffic and occupational accidents; and yet, long-term patients remain subject to only slightly less frequent neutrophil monitoring requirements as newer users despite the lack of evidence supporting

this approach.

It is unreasonable and unethical to single out individuals with serious mental illness for burdensome monitoring that is not imposed on other medications with elevated risks of neutropenia, such as the anticonvulsive carbamazepine and the antithyroid drugs methimazole and propylthiouracil. In China, clinicians are entrusted with the responsibility of monitoring clozapine patients without a REMS type program. This approach has successfully expanded access to clozapine and has likely saved many more lives through averted suicide than those lost due to clozapine-induced agranulocytosis.

I urge the FDA to follow suit by abolishing the clozapine REMS entirely, or at the very least, eliminating ANC monitoring requirements for patients after 6 months. If the FDA insists on maintaining the clozapine REMS, I call for equitable treatment. Patients taking medications with similar neutropenia risks and providers prescribing them should be subject to REMS programs

as well.

Clozapine is the most effective treatment we have for schizophrenia; yet only a small fraction of --

DR. FLOYD: Sorry to interrupt you, but you're over time. If you could please wrap up.

DR. BARNETT: The REMS program as it stands is a major reason why. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker number 2.

Speaker number 3, please come up to the podium.

DR. ZUCKERMAN: Hello. I'm Dr. Diana Zuckerman. I'm President of the National Center for Health Research, and our center is a nonprofit public health research center that works directly with patients and providers. We scrutinize the safety and effectiveness of medical products, and we don't accept funding from companies or entities that have a financial interest in those products, so we have no conflicts of interest.

Thank you for the opportunity to speak

today, and thank you for the important work that these committees are doing, and the FDA. Prior to my current position, I was a post doc in psychiatric epidemiology and public health at the Yale Medical School, and was a faculty member and PI at Yale and Harvard. I also conducted hearings on FDA safety issues and standards while working in the U.S. Congress and the White House. I'm a founding board member of the Alliance for a Stronger FDA, which lobbies to make sure that there's enough appropriations for the important work of the FDA.

REMS are very important, but they're not always very effective, and you've heard a lot, and you will hear more, I'm sure, about the barriers that REMS can present. They are burdensome, and in this case, there are a lot of hurdles, and we have to consider which ones are really essential and which ones aren't. But as has been noted, if you relax some of these barriers, you increase other risks.

I've worked with a lot of patients and

patient advocates who have been harmed by psychotropic drugs, so I want to remind us that there's a reason for these REMS, and there's a reason for these labels, and there's a reason for monitoring. Although reducing barriers is very important, safety is also essential.

Even though enforcement deterrence is seen as a temporary matter, and even though it sounds like it's not effective, it does make a difference. We can't assume that just because fewer people are being harmed with this enforcement weakening that it doesn't have an effect because as we know, many physicians do not read labels, and they don't read them carefully even if they do read them, and they don't necessarily remember what's in them.

So I think that REMS really is important, in addition to labeling. And the important issue for you today is to figure out which are the ones that really are helping patients and which are the ones that are too burdensome. And to consider that, I hope you'll think about the fact that when there are REMS, even if they're not enforced, it still

has an impact, and you've heard that this morning. You've heard about universities that continue to act as if the REMS are in place whether they're enforced or not. Thank you very much.

DR. FLOYD: Thank you, speaker number 3.

I realize that our speakers can't see the clock that I can see, so what I'm going to do, so I don't interrupt as much, I'm going to raise my arm and point at my watch when you have about 20 seconds left. If you'd please respect that and try to wrap up your comments, I won't have to interrupt. Thank you.

Speaker number 4?

MR. LAITMAN: Team Daniel, Rob Laitman, Dr. Rob Laitman, and I have no financial interests to disclose. I understand that you think you know the data. I know you want to do the right thing, but the underutilization of clozapine is the single biggest failure of American medicine. So how can we fix the problem?

The first thing is to eliminate any barrier to clozapine's appropriate use. It has been

demonstrated that the current elements to assure safe use in the current REMS have contributed to clozapine never being used or being given as a drug of last resort, often many years after unbearable, persisting suffering. Any clozapine REMS mandatory monitoring needs to be eliminated. The site needs to be changed to a purely educational site.

Prescribing this medicine should be like any other antipsychotic. Physicians, family, and patient hesitancy must be eliminated if we are ever going to see this medication used appropriately. The following measures are a few examples that will help in the safe and effective use of clozapine. I recommend monitoring the ANC weekly for the first 18 weeks; implement the EASE model of clozapine use. E is for early use, A is assertive monitoring and management, S is a slow titration, E is ensure engagement.

Pneumonia risk is a real concern, so controlling sialorrhea and the awareness that any inflammatory state will decrease clozapine metabolism is critical. With symptomatic

pneumonia, clinicians need to decrease clozapine dosing from their patient's usual dose, and monitor and adjust. Constipation is a physiologic certainty and needs to be managed using stool charts, laxatives, and stimulants. Cardiac issues from myocarditis to cardiomyopathy can be avoided, and cardiac side effects from tachycardia to hypotension can be managed by a slow initial titration and the use of beta blockers. Weight gain and metabolic issues are quite manageable with diet, exercise, metformin, SGLT2s, GLPs, or even fluoride.

All of this is deeply personal. I've spent the last 18 years managing, first, my son's illness, and later my wife and I have transformed our medical practice to care for hundreds of patients on clozapine. We formed a charity, Team Daniel. That's now grown to over 5,000 active Facebook users. In 2017, my family with Lew Opler co-authored Meaningful Recovery from Schizophrenia and Serious Mental Illness with Clozapine; 2024, a documentary Into the Light: Meaningful Recovery

detailed our approach. We've teamed up with Angry Moms, Myogenes, and more recently, I've started Doro Mind to bring our approach to others.

As for Daniel, our son, he graduated from college, and for the last nine years has lived independently and works as a stand-up comic. For the last year, he has also a steady girlfriend, a job, and a relationship. He is living a meaningful life. Help us give everyone else this opportunity. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker number 4.

Our next speaker, speaker number 5, is virtual. Please go ahead and begin.

DR. LAWSON: Hi. I'm Dr. William Lawson. I'm a board certified psychiatrist in multiple states, and just wanted to emphasize not just the REMS issue in relation to clozapine, but also a failure to recognize the importance of racial and ethnic issues and taking those into account in terms of making decisions about access to medication.

First slide? It didn't show, so I'll just state that it has been demonstrated repeatedly that there are racial and ethnic differences in terms of access to medication.

DR. FLOYD: I'm sorry to interrupt. Is there a slide that the speaker has shared that he's referring to?

(No audible response.)

DR. FLOYD: Oh, we don't have any. Please go ahead.

DR. LAWSON: Okay. Then I'll just state it. Again, it's been well-demonstrated repeatedly, racial and ethnic differences and access to medications, but also that there are racial and ethnic differences in terms of the metabolism of medications and how they are made available. What we've seen with clozapine is there is a phenomenon called benign leukopenia, and this is that white blood counts of African Americans in some groups tend to run lower. If you just monitor it every day, you see it will drop below the range, which REMS says that the medication can be given. What

happens? African Americans do not get this medication.

Well, we can improve the REMS, do better monitoring, and so forth, but the reality is that many folks do not have access to high-tech or careful monitoring, or lab tests that are available, especially in rural communities and in many of our inner city communities. So the problem is that it's a failure to look at the availability or access to key important medications because of a failure to take into account disparities that exist in our healthcare delivery system.

I was in psychiatry because I had a great uncle who had spent years in the mental hospital, got released because he was involved with this agent called Thorazine, and now I am involved in terms of the development of clozapine, although I don't have any financial relationship with it, and was thinking that this will be a new direction to psychiatry.

It's been my great disappointment that despite our technology, despite our efforts, that

we still have done very little in terms of focusing on the access to medication --

DR. FLOYD: Twenty seconds left.

DR. LAWSON: -- rather than saving [indiscernible - 5:57:26] saving. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker number 5. I realize that my visual warnings aren't really working, so I'm just going to say 20 seconds when there's 20 seconds left.

Speaker number 6 is also virtual. Please go ahead and begin.

DR. DE FONTNOUVELLE: Hello. I'm Dr. Christina de Fontnouvelle, a psychiatry resident at the University of Virginia. We have no financial disclosures or relationships.

Thank you for the opportunity to speak today. We are here to strongly advocate for reducing the restrictiveness of the Clozapine REMS Program, as we believe the current requirements do more harm than good and deny patients access to a life-changing medication.

Clozapine remains the gold standard medication for treatment-resistant schizophrenia and schizoaffective disorders. The literature consistently demonstrates the superior efficacy, and I have personally witnessed many cases where clozapine has transformed patients' lives from frequent hospitalizations and debilitating psychosis to largely symptom-free, high-functioning individuals pursuing careers and interests. No other medication approaches clozapine's effectiveness for treatment-resistant cases; however, the current REMS restrictions cause significant barriers.

After two years of treatment, the risk of neutropenia with clozapine decreases to levels comparable to other antipsychotics like olanzapine, which have no such monitoring requirements. A seminal study has found that agranulocytosis developed in only 0.8 percent of clozapine-treated patients; yet all patients face lifelong frequent blood draws, which for many is burdensome or even impossible to adhere to long term.

DR. JABR: I'm Dr. Amir Jabr. I'm a colleague of Dr. de Font's. Clozapine treatment interruptions due to logistical issues with faxing lab results or pharmacy certifications can lead to severe patient decompensation. Outpatient providers are using clozapine less than indicated to avoid frequent lab checks, depriving patients of our most effective option.

The risk of missing doses due to REMS-related issues, which can lead to serious adverse effects like inflammation of the heart or decreasing blood pressure to the point where patients can faint, far outweigh the benefits of such frequent monitoring, especially after the initial months of treatment. As providers, we spend large amounts of time navigating REMS logistics rather than providing excellent patient care.

DR. ZELIG: And my name is Dr. Matthew Zelig. I'm a colleague of Dr. Fontnouvelle and Dr. Jabr. We conducted a study on clozapine utilization at the University of Virginia and

presented our findings to the Psychiatric Service of Virginia. Our results show disparities in clozapine initiation, especially with black patients and women under 35. Our patients had tried 4.3 antipsychotics before starting clozapine, with an average delay of 10.8 years from initial diagnosis to starting, and we found that it is effective. Once they're on clozapine, hospitalizations drop significantly, from 0.72 to 0.13 per year.

The overarching theme of this is that this REMS represent a tax on our time, on the time of patients, on the time of their families, on the time of pharmacists, and on our healthcare system as a whole, and that tax leads to lower clozapine utilization, and especially lower clozapine utilization in our vulnerable populations. Thank you for your time. We really, sincerely hope that we can reduce our REMS burdensome criteria.

(Applause.)

DR. FLOYD: Thank you, speaker number 6.

Speaker number 7, if you're at the podium,

please go ahead and begin.

MS. STREIFF: My name is Rachel Streiff from Tempe, Arizona. I am here on behalf of the Angry Moms. Our recommendations to end the clozapine REMS and update the product label were submitted to the FDA with 4,000 signatures.

My loved one's clozapine was interrupted because someone entered an ANC of 3.7 instead of 3,700 following the Modified REMS conversion in 2021. Her case was one of the thousands of adverse events falsely reported to the FDA as neutropenia instead of a REMS-related interruption. It was the Angry Moms website that exposed this chronic problem in October of 2023.

Clozapine is the safest antipsychotic in the world. This refers not to the short-term management of clozapine's adverse effects, but in long-term epidemiological data showing patients live significantly longer than those treated with other medicines. The fatal risks of clozapine are minuscule in relation to the lives saved.

Today, we received extensive studies about

neutropenia in 150,000 current clozapine patients, but nothing about more than a million treatment-resistant and suicidal patients who didn't get clozapine. What were their outcomes? The largest category of patients harmed by the clozapine REMS have never taken a single dose of clozapine. Today, we confirmed the REMS blocks thousands of refills by mistake, often taking days to resolve. Thousands are discontinued for alleged neutropenia with relatively few continuing treatment.

Did anyone investigate those outcomes? Are they dead, jailed, institutionalized? How many completed suicide? CPMG reports low rates of adherence to the Modified REMS with no evaluation of patients who are out of compliance with the REMS. This is a blood for drug program. Hardly any pharmacies are using enforcement discretion. Were their refills delayed? Did they deteriorate? Did they experience a black box event from titrating too quickly?

The FDA has previously argued that there are

not enough studies to suggest clozapine interruptions are indeed catastrophic. Instead of answering this vital question, the FDA spent their resources on more neutropenia studies, giving us no new information. What a profoundly missed opportunity. Knowledge assessments asked hundreds of doctors and pharmacists questions about clozapine-induced neutropenia --

DR. FLOYD: I'm sorry. Your time is up. If you could please wrap up.

MS. STREIFF: -- but not one question on the risk of interrupting treatment or not using clozapine at all; even worse, no one assessed a single non-clozapine prescriber. This is a conceptual error when the wrong conclusion is drawn because the wrong question is asked. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker 7.

(Applause.)

DR. FLOYD: So before we move on, I appreciate the enthusiasm and applause, but I can tell you that we're going to run out of time and

not be able to have everyone speak unless we keep to a really tight schedule. So out of respect for all the future speakers, brief applause, if anything, better if there's none, and speaker 8, please go ahead.

MS. CASTELLANOS: Buenas tardes. Good afternoon. I am with the Arizona Mad Moms, and my name is Lisa Maria Castellanos. I lived in Northern California with my children prior to 2023. I am here to share my son Daniel's story, which is painful for me, in hopes that it would also give a voice to the stories of the over 400,000 incarcerated individuals with SMI in the United States.

Daniel experienced his first psychotic episode in 2008, shortly after his 18th birthday. He was never offered clozapine, but he was given ineffective medicines, which he quickly stopped taking. His illness progressed. He became aggressive and violent. I begged for help, but was told he had to harm himself or someone else.

In 2012, he did just that. While in a

psychotic state, he was arrested for assault in Sacramento County. Instead of seeing him thrive in college, I visited him for 4 years while he sat in pretrial detention. With each visit, I saw him behind plexiglass lose his mind and his physical health. Daniel was ultimately found incompetent to stand trial. He was ordered to be restored to trial competency at Napa State Hospital. That's when I saw a miraculous recovery. Unbeknownst to me, Daniel received his first ever trial of clozapine. Of course, it was too little too late. He was found guilty but insane. Nevertheless, he accepted a plea to serve 20 years at the California Department of Corrections and Rehabilitation.

What a cruel, unjust, and disordered system would require harm to self or others to get help, but then puts up barriers in the form of the REMS to access clozapine? It is unfathomable that we aggressively use clozapine in forensic settings to restore individuals to trial competency, only to discontinue clozapine once they are transferred to prison.

This is what happened to my Daniel. Since his time in CDCR's custody, he has relapsed several times. Without clozapine, his violent and aggressive behaviors returned. His 10-year parole date has come and gone, and he may be facing a lifetime of incarceration.

DR. FLOYD: I'm sorry. Your time is up. If you could please wrap up.

MS. CASTELLANOS: How many of the 400,000 currently incarcerated people with SMI were, like my Daniel, restored to trial competency with clozapine only to have it later discontinued? What is behind this failure to carry clozapine in prison formularies? Is clozapine just too inconvenient? Like my fellow mothers, I am angry.

(Applause.)

DR. FLOYD: Thank you, speaker 8.

Speaker 9, please go ahead.

MS. SUNAR: Hello. My name is Neesa Suncheuri Sunar. I've taken clozapine for treatment-resistant schizophrenia since 2012. Clozapine is a miracle. I cannot live without it.

It is the only drug that puts my schizophrenia in remission. It allows me to work as a social worker. I'm a therapist. I'm also a grant writer. The experience of not taking clozapine makes life a nightmare. It is a death sentence.

In psychosis, my body becomes very overheated, my blood feels like it's boiling, and every second, I feel I will burst into flames. I scream because I'm scared of what my mind is saying to me, and only clozapine can make this stop. I developed psychosis first when I was 21 years old. I was hospitalized, put on Zyprexa, and sent home. I had to drop out of a master's program for music at the time. For five years, I was put on other drugs that did not work -- Abilify, Stelazine, Latuda, and so forth -- and it was a pattern.

Medications stopped working, I relapsed, and I went to the hospital, then I was put on something else. Due to repeated hospitalizations, I lost jobs and had to go on disability. I started clozapine in 2012, and I slowly rehabilitated, worked, and got full time employment. I went to

graduate school, and now I'm a therapist myself.

In 2023, I was commissioned to write a book, and I decided to travel at the time. I remained in treatment and met with psychiatric professionals in Germany, Spain, Andorra, and India. In these countries, clozapine is like any other drug. There is no blood work required for a routine prescription. In these countries, it appears that the average psychiatrist can prescribe clozapine, and they are expected to know how to prescribe it. The psychiatrist I spoke to said immediately, "Clozapine puts schizophrenia a hundred percent in remission."

When I returned to the United States, I contacted my previous psychiatrist to resume treatment. She refused to see me because I was too high risk. For Medicaid clients, we only have a choice of a few clinics. The clozapine REMS causes a system of psychiatric segregation not found in other countries. I am segregated in my treatment because the vast majority of U.S. psychiatrists refuse to work with me. I recently consulted with

one of my European psychiatrists and told her about the clozapine REMS and this meeting, and she said she already knew about these blockages that we face.

After receiving expert psychiatric care in my clozapine management in four other countries in a kind manner --

DR. FLOYD: Twenty seconds.

MS. SUNAR: -- I am now skeptical of the expertise of any U.S. psychiatrist who remains blindly faithful to the clozapine REMS in its current form. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker 9.

Speaker 10, please go ahead.

MS. WHITE: Hello. My name is Christen White from Phoenix, Arizona. My brother, Matthew Quinn, was a brilliant airplane mechanic who loved life. At 28 years old, he was diagnosed with schizophrenia, joining the 1 percent of people whose lives are profoundly impacted by this disease. He was often hospitalized and suicidal.

His psychiatrist tried eight different antipsychotics: Abilify; Invega; Risperdal; Latuda; Vraylar; Caplyta; Geodon; and Zyprexa. When those failed, the doctor started using them in different combinations.

On July 7, 2023, just shy of his 39th birthday, we found my brother dead by suicide. There were sticky notes placed all over his apartment that said, "Don't listen to the voices." On his tenure journey with schizophrenia, none of his doctors ever mentioned clozapine; not one. We recently asked a psychiatrist why she never tried clozapine, and she did not have a good answer. The clozapine REMS did not directly cause my brother's death; ignorance did, but the clozapine REMS has contributed to fear, ignorance, and systematic failures.

Today, we are hearing the FDA review a half-dozen extremely thorough studies of neutropenia in clozapine patients, some of them going line by line reviewing chart notes. Yes, there will be a few hundred cases of severe

neutropenia and perhaps a handful of fatalities among the 150,000 patients currently taking clozapine, but what about the 1 million patients in the U.S. who need clozapine but don't get it; patients like my brother? Who is documenting those outcomes line by line, reviewing chart notes? With the 1 million treatment-resistant patients in the U.S. that don't have access to clozapine, 50,000 will die by suicide that could have been prevented by clozapine treatment; 100,000 will die prematurely from inadequate treatment.

The FDA has surveyed hundreds of clozapine providers, looking for knowledge gaps in their understanding of clozapine-induced neutropenia. Not one knowledge gap assessed whether doctors understood the risks of not using clozapine. Not one knowledge gap assessment surveyed a prescriber who doesn't use clozapine to find out why. The greatest risk of clozapine is not getting clozapine. Thank you for your time.

(Applause.)

DR. FLOYD: Thank you, speaker 10.

Speaker 11, please go ahead.

MS. TAGGART: I do have slides. My name is Patty Taggart. I'm here from Lake Tahoe, California, and I'm here to tell my story about why delays in clozapine almost cost my daughter her life, and to share the reasons why the delays.

At the age of 19, while in a Division 1 volleyball scholarship, my daughter developed severe bipolar disorder, and subsequently schizoaffective disorder. Sarah has struggled with her mental health for years but somehow managed to graduate from college. She's been treated at some of the best facilities by some of the best clinicians and therapists; yet no one at any of these facilities ever offered her clozapine.

Her suicidality started in 2011. Each day felt like we were treading water, trying to keep her from sinking. It was a daily struggle with suicidality that we couldn't seem to manage, no matter how many treatments we tried. None of the medications on this slide helped, but when it became clear that clozapine could offer her a

lifeline, we hit an unexpected barrier. No one would prescribe it.

Two hours after this photo was taken, my daughter tried to end her life. In 2020, while massively depressed and on her prescribed medication, my daughter drove her car into a tree, sustaining multiple fractures, a punctured lung, broken ribs, and a concussion. She was hospitalized for over a month, but no one offered her clozapine.

Finally, this July, while depressed and psychotic but on her meds, my daughter drove her car off the side of a mountain. The car traveled nearly 600 feet. She was ejected through the windshield and thrown 100 feet. She sustained multiple fractures, cuts and bruises, and somehow survived. She was hospitalized, and no one suggested clozapine. I begged the inpatient psychiatrist to use it, and they refused.

Over the past few years, I have literally begged for clozapine, but no one would agree to prescribe it, and the reasons given all centered

around the REMS, the arduous reporting requirements, the difficulty encountered while trying to fill the prescriptions, and it was just too difficult for the pharmacist. Finally, in August of this year, after contacting over 30 residential facilities, I was able to find a facility that offered her clozapine. The difference was almost immediate.

DR. FLOYD: Twenty seconds.

MS. TAGGART: It was as if a weight had been lifted off her shoulders. She wasn't cured, but the darkness that consumed her lifted. It gave us hope that in the future, she might have a life.

As a parent and a family who has lived through 14 years of hell, I'm asking you to reduce the REMS requirements and make it easier to get this life-saving drug to families. And with regard to the REMS discretionary use that we've heard of today, as a parent, let me tell you, that does not exist. In the 3 months since my daughter's been on clozapine, we've had to fight the pharmacy over 3 times. The first time because the pharmacist

required a piece of paper with her lab results.

DR. FLOYD: I'm sorry. We're over time now.

MS. TAGGART: Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker 11.

Speaker 12, please go ahead.

MS. MUSGROVE: Hi. My name is Francis Musgrove. I'm from Tempe, Arizona. My son, Justin, developed psychosis in his late teens.

Can I have slide 1?

DR. FLOYD: I'm sorry, but I was informed we didn't receive any slides for your presentation, so please proceed without them as best you can.

MS. MUSGROVE: Okay.

He is now 42. He's been hospitalized more than 70 times. Doctors tried many different psychotics over the years. When I brought up clozapine, the doctor said to me, "That causes death." She looked at my son and asked him if he wanted death.

Justin has cycled in and out of homelessness. I could not get him help. The best

I could do was to deliver him food at his home under the freeway overpass. His illness made him disoriented. I worried constantly that he would get hit by cars. I had a right to worry. Justin nearly died 3 years ago when he wandered into the street and was hit head on by a car. Two decades of poorly treated psychosis left my son with brain atrophy in his frontal lobe. Many psychiatrists told me, "Your son can't have clozapine because he won't be able to participate in the REMS requirements." It wasn't the side effects that they were worried about; it was Justin's ability to adhere to the REMS. He's very delusional. He thinks the blood tests are lethal injections.

Three years ago, a hospital started Justin on clozapine. He was able to continue because his outpatient clinic had a finger stick device, but very few clinics at our hospitals have these devices. My son's clozapine has been interrupted several times during hospitalizations and delays in getting outpatient refills. Justin's new clinic doesn't have the fingerstick device, and I live in

fear that he won't be able to do the blood draws anymore. I've asked why they don't have the device. Apparently, Medicaid doesn't pay for it. This is severe discrimination against mental illness.

Justin's doing better. He doesn't mind clozapine, and he's no longer on the streets, but he is not doing well. He is permanently disabled. He should have had clozapine 20 years ago, but he couldn't participate in the REMS. Clozapine is the safest antipsychotic in the world. The greatest risk of clozapine is not getting clozapine. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker 12.

Speaker 13, please go ahead.

DR. CHOU: Hi. I have slides. My name is Margaret Chou. I'm an associate professor at the University of Pennsylvania School of Medicine and Children's Hospital Philadelphia, but I'm not here today as a representative of those institutes. I'm here to represent the clozapine online community,

which has over 6,000 members, as indicated here.

As a biomedical researcher, I think I would really appreciate all the research that the panel has shown today, all the data, all the analyses, all the numbers. I'm here to tell you that you're asking the wrong question. You're looking at the wrong thing because REMS, even though the attempt was great, and I appreciate everything that you guys have done -- and enforced discretion, it's not used. It's useless. So listen to the families and the caregivers. REMS is failing families and patients.

There is no reason why clozapine cannot be treated just like any other potentially immunosuppressive drug. Take methotrexate, for example, which has higher rates of neutropenia and agranulocytosis, higher than clozapine, and yet there is no REMS, no FDA oversight. It is administered by doctors who work with patients and inform them of the risks. They don't need this. They can work on it together and decide whether the risks are worth the benefits.

Let's talk about the benefits. One thing that has not been touched upon I'm going to talk about is inhumane rationing. So we're not only talking about weekly blood draws, but getting exactly the amount of medication that you need for that short period of time. You're given a dose to the very last day. You would never do something like this to somebody with insulin, which is the equivalent. It's a life-saving medication. It's treated like it's a blood pressure medication. Missing several doses -- clozapine is not the same thing as blood pressure medication.

I want to give you an example. My son at the peak of his psychosis thought that I was trying to murder him, and he tried to act accordingly, and thank God he didn't. But my family lives in constant fear that we are 3 days of missed doses away. My daughter fears of losing her mother. My husband lives in fear of losing his wife and having his son imprisoned for murdering his mother. That is our reality because of this ridiculous REMS oversight.

So I ask you, I implore that the panel step back 30,000 feet, stop fixating on ANCs, and think about the larger picture. Anybody who's on clozapine will tell you, the benefits far outweigh this myopic fixation on ANCs.

(Applause.)

DR. FLOYD: Fifteen seconds.

DR. CHOU: Trust physicians and patients to manage their own care and decide what is best for them. We do not need to be micromanaged. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker 13.

Speaker 14, please go ahead.

MS. CHASE: Hi. My name is Analisa Chase, and I'm from Tacoma, Washington. I'm here to tell my story and represent myself. At the age of 24, I was diagnosed with schizoaffective disorder. My illness causes severe hallucinations. The worst part is that when symptoms occur, I cannot function or even recognize that I am sick. It is a very dangerous illness. Most people with this illness

are not like me. Most are too disabled to travel across the country, stand before an audience, and speak about their condition. I hope to give these suffering people a voice today.

Before clozapine, I was forced to use seven different antipsychotics, each of them having severe side effects. I suffered for years until my mother fought for me to get clozapine. Clozapine was a miracle drug, but then I missed a blood draw, and my clozapine refill was denied. Within 3 days, I became severely ill with terrible hallucinations. I became delirious and confused. It took months to recover. I was institutionalized for 5 weeks just because I didn't get a blood test in time.

I now live in fear that a logistical problem or misinformed pharmacist will block my clozapine prescription. The options to waive missing labs are not being used. It is impossible to even start clozapine without a blood test. The FDA's announcement of enforcement discretion is not being followed. Pharmacists are interpreting the policy the opposite of what it means because enforcement

discretion sounds like don't dispense this regulated drug or you will be fired. You cannot simply re-educate an entire nation of doctors and pharmacists. These professionals fear for their jobs. Doctors, pharmacists, and drug manufacturers care more about liability than about what happens to me.

I have experienced years of unnecessary suffering, unnecessary testing, and severe discrimination. I should have autonomy over my body and my brain. I should have a right to life-saving treatment. I should have a right to waive the REMS requirements. I should have a right to live without terrible hallucinations and torment that none of you can possibly imagine.

The clozapine REMS is discrimination against a disabled person's rights to reasonable treatment services. Clozapine is the safest antipsychotic in the world. The greatest risk of clozapine is not getting clozapine.

(Applause.)

DR. FLOYD: Thank you, speaker 14.

Speaker 15 is virtual. Please go ahead.

MR. BLOCK: Hello. My name is Max Block, and I live in Orange County, California. I'm thankful for this opportunity to speak about my personal negative experience with the clozapine REMS. For a decade, I've been dealing with serious mental illness, including periods of psychosis warranting involuntary and voluntary hospitalization.

Clozapine ultimately works the best for me; however, in September 2023, the lab I used for my REMS refills failed to report my results in a timely manner due to a technical computer glitch and shut down. We tried everything to get a refill. We begged for help to get my prescription. After 2 and a half days, my father and I obtained a refill, but it was too late. I suffered from rebound psychosis after just 2 and a half days without clozapine. I was manic and suicidal [indiscernible - 6:26:53] this could happen to me again.

While I was in full psychosis, I drove alone

in my car away from my home in the middle of the night. I left home with only my wallet, not my phone and belongings. As I was driving in the darkness, I drove into a fence on the side of the road to the interstate highway. A fire started in my car. Luckily, I was pulled from my car by a man who lived nearby. He contacted law enforcement, who took me to a local hospital emergency room. I was placed on a 72-hour hold. My family had no way of reaching me.

The emergency room failed to adequately administer my medications, and my psychosis deepened. I was so confused at discharge, my mother, a psychiatric social worker, drove me directly to an inpatient psychiatric facility. I was again placed on successive holds due to my psychosis. It was a long journey to fight my way back to health.

Because I was on successive holds, I could not obtain the correct medical care for my Crohn's disease. I suffered severe internal bleeding requiring blood transfusions. I still have poor

health from this incident. I was in hospital residential treatment for 4 months and hospitalized for severe symptoms of Crohn's disease for weeks. All this came at great cost to me and my parents, both emotionally and economically. Before this incident, I was stable, attending college, and healthy. One single glitch with the clozapine REMS nearly cost me my life while severely degrading my overall health. Please remove this hazardous program. It is only causing problems and risking lives. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker 15.

Speaker 16, please go ahead.

DR. KELLY: I'm Deanna Kelly. I'm a professor at the University of Maryland School of Medicine. I'm here today to present additional data for your consideration. I do clinical trials, and have been working with clozapine for over 27 years. Recently, we have completed a randomized-controlled trial of a validated, telementoring clozapine education program in the

entire state of Maryland versus treatment as usual. There were over 265 prescribers. These are physicians, nurse practitioners, and PAs that participated. This was an NIMH-funded study. They participated in 26 weeks of 1 and a half hours weekly of didactic and case presentations, and it represented a diverse prescriber population.

What we were able to show is that in terms of general competency ratings for all of the prescribers at baseline, among 26 competencies, monitoring for neutropenia is the top-rated competency among all competencies rated, and in fact, it's as high as diagnosing and characterizing treatment-resistant schizophrenia.

What we looked at in terms of people's ratings of competencies around the REMS program, on a scale of 0 to 100 at baseline, prescribers rated their competency using the program at about 61 of a score of 0 to 100, and after a year-long educational program, that increases to about 73. But despite having education for a year, weekly, 1 and a half hours, going over this and talking

about the REMS each week with these providers in the ECHO system, we cannot change their perceptions of this barrier and their unwillingness to use the REMS system. In fact, if you look at the blue lines, it's a total group, those assigned to the education, those assigned to treatment as usual.

At baseline we asked to rate the REMS if it was a significant barrier, and about 25 percent of people rated this as a significant barrier. At endpoint, the red lines actually represent the most significant barrier of all barriers that people could rate. In fact, you can still see that after a year-long education of the program, prescribers -- these are people prescribing and not prescribing -- they still say that this is the number one barrier 25 percent of the time. We have a clozapine consultation line. The majority of calls come in are asking for help with the REMS system.

I wanted to touch upon that Dr. Lawson on the screen mentioned a few minutes ago that while we know severe neutropenia is rare, he mentioned

about neutropenia being common among black patients. We know that people who have the ACKR-1 genotype, the Duffy null genotype, have naturally occurring low white blood cell count, so neutropenia happens. In fact, two studies that we haven't talked about today include a black population, a study that was published last week by Johns Hopkins University. Almost 1,000 patients over a 10-year period, zero cases of severe neutropenia; 40 percent of these patients were black.

DR. FLOYD: I'm sorry. Your time is over. If you could please wrap up.

DR. KELLY: Yes. We conducted the largest randomized clinical trial to date in black patients. Thirty-three percent will have neutropenia, only 1 patient -- I just want to say that severe neutropenia will happen, but no data is available that the clozapine REMS program prevents deaths. Around the world, we are changing guidelines all the time. We're involved with the International Clozapine Delphi Consensus

Guidelines. We will be changing and monitoring after a few years. This is changing all around the globe.

DR. FLOYD: I'm sorry. I have to cut you off. Thank you so much.

DR. KELLY: In conclusion, the risks outweigh the benefits [sic] right now.

(Applause.)

DR. FLOYD: Thank you.

Speaker 17, please go ahead.

MR. PASTORIZA: Hello. My name is Javan Pastoriza, and I live in Staten Island, New York. If we can, I'd like to just take a moment to share a glimpse of my experience of paranoid schizophrenia.

Things typically start off with a total erasure of the barrier between my mind and the world. Every thought, emotion, and experience I have is suddenly broadcasted everywhere. I get messages from everything and everyone. Every person is replaced by what I call the entity, and this entity lives through people like puppets, a

single being controlling all humans whose only intent is to torment me.

People around me are merely part of the hive mind, life becomes a living hell, and there is no one to help. Everyone is the entity, life is torture, and day by day, the thought of enduring this agony for the simple sake of enduring more tomorrow becomes less and less reasonable. This is not just the result of runaway thoughts. With the same clarity that you sense, you are seated in this very room listening to me right now, my reality becomes this nightmare. The only reprieve, the only real way back to life, is my medication, Clozaril.

I am subjected to a REMS system because Clozaril patients might develop neutropenia, but that risk is statistically negligible. And what about the other medications regulated by the FDA with a high risk of neutropenia that don't require REMS? There is fundamental discrimination within the Clozaril dispensing system, subjecting individuals like myself to risks of relapse.

Surely, we should be more concerned with actual active psychosis than the comparatively minuscule risk of neutropenia.

The REMS system is also riddled with dangerous complications. Doctors and pharmacies often get mixed up, distribution becomes inflexible, needles scare off patients, and the co-pays are mandatory and expensive; constant commutes, frequent malpractice, and the list goes on. Additionally, diabetics are allowed emergency insulin surplus, so what explains the discrepancy with Clozaril? More stigma, perpetuated error, or simple inaction?

We live in constant fear of our medication being cut short, of falling back into insanity. This is more than being confined to some nightmare. With schizophrenia, we can quickly become violent and suicidal. When your mind is warped by disease to believe any number of delusions, even the most unsuspecting people can easily commit such acts. I'm lucky to have escaped unscathed.

The FDA's own mission statement is to ensure

the safety, efficacy, and security of human drugs. Are the conditions here safe, effective, or secure?

DR. FLOYD: Twenty seconds.

MR. PASTORIZA: We come to the FDA with a simple plea, to make the logical and compassionate choice, end the discrimination, and to end the clozapine REMS system once and for all, especially since clozapine is the safest antipsychotic in the world. The greatest risk of clozapine is not getting clozapine. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker 17.

Speaker 18, please go ahead.

MS. TARBELL: I'm Phyllis Tarbell, and I am here on behalf of my daughter, Joni Martin, who asked me to speak for her because she's in the hospital again. This is her story.

"In December 2021, due to the REMS, I was not able to fill my monthly prescribed clozapine, which I had been on successfully for over 20 years. Due to this 5-day interruption in clozapine, I developed severe psychosis and subsequently lost my

apartment, my job, my independence, and my peace of mind.

"I grew up in a small Vermont town, developed psychosis in 2001 at the end of my senior year in high school. I spent months in a psychiatric hospital and was diagnosed with schizoaffective disorder, treated with a succession of antipsychotics, Risperdal, Seroquel, Geodon, lithium, and others I can't recall, none of which were effective. And finally, I was prescribed clozapine, which was effective and gradually helped me to achieve a productive and meaningful life for 20 years.

"Because of clozapine, I graduated high school, and subsequently college with an associate's degree in massage therapy and body work, and began to work on my bachelor's degree. I achieved national certification in massage therapy. I worked at high-end spas in Vermont and started my own successful massage therapy business.

"I was stable and successful for two decades, and finally became financially

self-supporting and got off of Social Security Disability and SSI. But in December of 2021, suddenly I was unable to refill my clozapine at the pharmacy, and was told to contact my psychiatrist. He was no help, and told me it was because of the FDA, and there was a paperwork problem affecting thousands of people nationwide. I'd always complied with the lab testing and never failed a blood test, but something in the paperwork had gone wrong. He did not get me my refill, and only offered me trazodone as a substitute, which was useless.

"As the days passed, I was totally unable to sleep. The voices in my head became unbearable, harassing, disgusting. They were constant and tortured me 24/7 with horrible messages I cannot repeat. After 5 days of no clozapine and no sleep, my breathing became difficult, and I felt my heart would stop beating. I believed I was going to die.

"I called 911 to go to the emergency department at Dartmouth Hitchcock Medical Center. They tried to give me other meds, but I refused. I

explained I needed clozapine. I'd been well on it for over 20 years. They offered me one dose and planned to send me home. I asked how that was going to help me the rest of my life. One dose was not the answer. I was struggling to advocate for myself and not sink into psychosis. I was fighting for my life and my sanity. Finally, I was admitted to their psych unit and restarted on a titration of clozapine.

"After 2 to 3 weeks there, I remained very fragile and needed to go to a rehab therapeutic program. I was there for two more years, where I made very slow progress -- "

DR. FLOYD: Twenty seconds.

MS. TARBELL: "-- and continued with paranoia and psychosis. I've not yet achieved my previous level of function for after almost 3 years. I must take more than twice as much clozapine as before. I cannot live alone or work due to anxiety, paranoia, the voices which never go away. I've had three hospitalizations this year alone, and I'm back on Social Security Disability

and SSI. For two decades, I was well, and now I've lost all of that. Please stop the REMS bureaucracy. One 5-day loss of clozapine has ruined my life. Thank you."

(Applause.)

DR. FLOYD: Thank you, speaker 18.

Speaker 19 is virtual. Please go ahead.

MS. ROTARU: Hello. My name is Janina Rotaru. I'm a psychiatric nurse practitioner, and I have no financial interest to disclose. I have been treating my patients for 14 years. I practice at one of Arizona's largest community outpatient SMI clinics. I have seen thousands of patients representing the full spectrum of illness severity. I'm currently the provider for a community treatment team, providing care to patients with schizophrenia, particularly TRS, acting surrogate with [indiscernible - 6:39:24] intensive care unit of psychiatry.

Many of my patients have failed numerous trials of medications and treatment settings, and on the acting, we are trying to provide them with

consistency of psychopharmacological and psychotherapeutic interventions. The importance of medication supply cannot be overemphasized, and it can make the difference between life and death. I have many patients for whom clozapine is the only option. Without this life-saving medication, they will end up in the hospital, jail, on the street, or worse, dead. They have no other choice. The journey towards clozapine is a story in itself for all my patients.

The FDA Clozapine REMS Program ironically represents a hazard. The main issue of REMS is the huge barrier that is presented in providing medication consistency for patients. While the value of safety monitoring under REMS guidelines is not questioned, the implementation, rigidity, scrutiny, and required lab draws can present serious challenges.

Clozapine is approved for treatment-resistant schizophrenia, and most often than not, patients do not have the insight and judgment to understand the ramifications of blood draws.

Furthermore, there are unexpected events that can lead patients to not be able to complete the lab draws required, leading to treatment interruptions, hospitalizations, rebound psychosis, severely ill with no room for early intervention or prevention. This is contradictory to what REMS stands for, safety, monitoring, and consistency.

Due to stringent REMS guidelines, inpatient facilities decide to stray away from the use of clozapine. This is pure and simple not providing adequate treatment to this severely ill population. While REMS has a waiver for missing tests, that's a utopian concept. The reality is that other entities can deny the prescription.

As a provider, I have the ethical duty to do no harm, to act in the best interest of my patients, and the FDA's Clozapine REMS Program prevents me from doing this. As part of the medical community, I can say for certain that REMS needs serious changes, if not to be abolished completely. The clinical guidelines are still to be followed. I'm not asking for leniency from that

perspective. What I'm here to ask is to make this medication available to patients, remove the barrier that REMS poses, and provide adequate treatment to the sickest patients that have no other option besides clozapine. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker 19.

Speaker 20, please go ahead.

MS. JEPSON: My name is Jane Jepson, and I am an Arizona Mad Mom and also a NAMI volunteer. Barriers, they've been my overwhelming preoccupation since my son was diagnosed with treatment-resistant schizophrenia. Clozapine is the only medication that works for him. Unfortunately, when my son encounters barriers, I encounter barriers, and these are my barriers.

Clozapine is a life-saving medication, and sometimes the lives that are saved are those of dads and moms like me. My son suffers from a really severe delusion called the Capgras delusion. When not on clozapine, my son thinks I'm an impostor, and he refuses to call me Mom.

Dangerously, he believes I have harmed his real mother.

During an episode of uncontrolled psychosis, my son did the unthinkable. He assaulted me and put me in an almost lethal chokehold that resulted in unconsciousness and criminal charges. Clozapine effectively treats his persistent psychosis and delusions. Sustained treatment on clozapine restores his humanity and his ability to call me Mom. Interrupted treatment unleashes a monster.

My son's access to clozapine is a life and death matter to him, and to me. We experience interruptions to treatment because of the clozapine REMS. As a result to barriers to treatment, I spend most of my time behind the physical barriers of my safe room. Despite proven effectiveness, my my son frequently experiences disruptions in the continuity of care with clozapine treatment. This happens all the time, during hospitalizations because of lab errors; refill delays; rationing of pills; and the physical confiscation of any excess pills that we have in the house by his ACT team.

Each interruption in care results in protracted bouts of psychosis and increased caretaker risk.

DR. FLOYD: Twenty seconds.

MS. JEPSON: Each bout of psychosis results in damage to the brain and poor expectations.

I want you to imagine for a minute what your life would be locked in a safe room because your loved one couldn't get life-saving medication. Clozapine is the safest antipsychotic for my son. The greatest risk for him is not getting his clozapine. Please act now to remove the REMS required for clozapine administration, and help this mom live barrier free.

(Applause.)

DR. FLOYD: Thank you, speaker 20.

Speaker 21, please go ahead.

MR. JONNALA: My name is Basava Jonnala, and I'm here on behalf of the healthcare technology company Athelas. Our request to the FDA is to enable the CPMG's clozapine REMS funding to cover our fingerstick device and patient care services

for every clozapine patient.

My company makes a device that detects neutropenia with only a fingerstick drop of blood. We offer a nationwide pharmacy care program through Golden Gate Pharmacy that proactively monitors patients' ANC results and dispenses mail-order clozapine directly to the patients and clinics. Our fingerstick device was FDA approved in 2019. Dr. Deanna Kelly, who also testified here today, led the pilot study that advanced our technology. Today, more than 375,000 ANC measurements have been performed for more than 15,000 patients.

I have been the Athelas deployment specialist for 5 years, and I have gotten to know our customers and their families. Insurance plans do not cover our device, and families must pay out of pocket. It has been heartbreaking to turn away patients that cannot afford our device and supplies. A few hospitals and clinics have our devices, but it must be purchased using clinical budgets without federal funds. The total cost of our device, with enough test strips to cover the

entire first year of clozapine treatment, cost less than the single month of injectable antipsychotic.

Clozapine saves lives and reduces costs. Expanding clozapine utilization prevents hospitalization and relapse. In the U.S., only 3 percent of clozapine patients have access to our technology. This is unacceptable and inconsistent with the Mental Health Parity Act. Every clozapine patient should have our device, period. Just like the diabetics are given glucose meters to effectively combat neutropenia, the tens of millions of dollars spent by the FDA each year on the clozapine REMS should include a fingerstick device for each patient.

Patients with Athelas' home device are spared significant burdens REMS poses for clozapine users. The report significantly increased satisfaction with the REMS program than clozapine users without a device. Imagine if every patient had an at-home alternative to a blood draw. It would transform the REMS experience, particularly patients in rural areas for those without

transportation.

I urge the FDA to extend patient care options to private sector and to use the REMS agency funds to cover our fingerstick ANC devices and patient care services for every clozapine patient. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker 21.

Speaker 22, could you please come to the podium?

MS. CUTRELL: Good afternoon. I'm Linda Cutrell from Marblehead, Massachusetts. I will speak about familial suicide and treatment-resistant schizophrenia with my son and our 18-year wait to access clozapine treatment. I will show you documented public costs also. Since Basava showed you what the cost of medications were, I'll show you what the cost of one year of hospital treatment is when someone is on a sub-effective medication.

I've had three immediate family members commit suicide. It was my father whose death

really established the fact that we had a family history of suicide. My closest sibling, George, suffered from depression and suicidal ideation. He sought treatment, therapy, medication, hospitalizations for decades. He described his emotional state as just an intolerable way to live, and completed his suicide in 2013. His son, Craig, committed suicide in 2020, wanting to be with his father and not wanting to go through the same devastating and unfathomable depression that his dad had gone through. He was never offered clozapine even though both of them went to many clinicians. He leaves behind two sons, which makes me very nervous for that fourth generation.

My second part of my story is about my son, David, who waited 18 years. You see pictures of him here. You can see the two states he's in. It's easy to see the before and after of an effective medication. For 18 years, he was treated with sub-effective medications, six of the alternative antipsychotics, both oral, long-acting injectables, combinations.

I sent him to private care. I've had four PAC teams, 16 hospitalizations, but only this year -- he's in his fifth month of trying clozapine -- immediately I saw an improvement within the first week, cognitive improvement, energy improvement.

His outpatient team really balked at the idea of putting him on clozapine because of the difficulty in trying to manage a patient with schizophrenia through the blood draws, taking him to labs, and the medication management, but we pushed, and we had the trial, and within days, we saw gradual but consistent increases.

Why is clozapine the last resort when this seems to be the best line of defense? We suffered 18 years of horrible --

DR. FLOYD: Twenty seconds.

MS. CUTRELL: -- life.

This is just quickly one year of what the public costs were just for hospitalizations. You can see at the bottom, out of a year of 365 days, he spent 314 in hospital, and you see Medicare

cost A and Medicare cost B. That's $440,000, and it was ineffective treatment.

We saw in the opening remarks that 150,000 patients in the U.S. are using clozapine. I'm offering that those 150 are probably the only ones that have really intense family advocates and some angry moms.

(Applause.)

DR. FLOYD: Thank you, speaker 22.

Speaker 23 is virtual. Please go ahead.

DR. ERICKSON-RIDOUT: Good afternoon. My name is Kathryn Ridout, and I'm a psychiatrist representing the American Psychiatric Association. I'm a current member of the APA Council on Quality Care. Outside of my work with the APA, I'm a physician, researcher, and staff psychiatrist. I prescribe clozapine regularly as a community inpatient psychiatrist in an integrated healthcare delivery system. I'm involved in quality measurement and research related to clozapine use. I have no disclosures.

It is an honor to speak to you today and

share the impact clozapine and REMS have on patients and access to this life-saving treatment. I've been treating patients with treatment-resistant schizophrenia for 12 years. I've seen the life transforming benefit of this medication, controlling otherwise treatment-resistant psychotic symptoms, resolving suicidality, and providing cognitive clarity.

The REMS program does create a barrier to prescribers and patients using clozapine. Disorganized behaviors, paranoia, and social difficulties such as social withdrawal lead to patients not being able to attend regularly scheduled blood draws and appointments or other REMS-related criteria. I have many patients who have had transformative responses to clozapine just to return inpatient due to discontinuation from REMS-related barriers.

Speaking as a researcher and prescriber, in 12 years, I have come across no cases of agranulocytosis in my patients. This tracks with the numerous studies that indicate there is less

risk of agranulocytosis than was thought when the drug was approved. The studies further indicate that an elevated risk may be time limited and that indefinite monitoring is not required. Psychiatrists are capable and confident to appropriately monitor a patient's hematologic status and intervene without central reporting.

While the FDA REMS briefing document includes a survey of physicians prescribing clozapine, surveys by organizations, including NAMI and the APA, report REMS as a barrier to clozapine prescribing. APA conducted a needs assessment in 2023 to understand the impact of access to clozapine due to the changes to the REMS system granted during the COVID-19 public health emergency.

Of the 60 prescribers who treated 1 to 300 patients each with clozapine, 57 percent of respondents reported problems getting clozapine prescriptions due to REMS; a third of respondents said that more than 10 percent of their patients refused to start clozapine due to monitoring

requirements; less than half of prescribers reported reduced monitoring; and a minority reported adverse outcomes with loosened regulations. Most respondents reported that the barriers of the clozapine REMS system outweigh its benefits.

DR. FLOYD: Twenty seconds.

DR. ERICKSON-RIDOUT: Modification to the clozapine REMS could balance better monitoring the risk of neutropenia versus administrative system burden. Finally, the REMS seems to impact minority communities disproportionately. While 4.4 to 4.8 percent of individuals in the U.S. are on clozapine, that number is even lower for black patients, even after adjustment for care, access, and social determinants of health.

Thank you to this committee for taking the time to listen and reflect on the testimony today, and I hope you will consider the underutilization of a life-saving drug that has already been shown to be safe and effective by the FDA, and consider reducing the scope of the current clozapine REMS

program to focus on education only.

(Applause.)

DR. FLOYD: Thank you, speaker 23.

Speaker 24, please go ahead.

MS. BRISBIN: Hello. My name is Angela Brisbin from Odessa, Missouri. I'm a caregiver, advocate, and assistant producer for the film, Into the Light: Meaningful Recovery from Psychosis. I am studying to become a psychiatric nurse practitioner. My father and father-in-law both had schizophrenia but never had access to clozapine. My father-in-law is part of the 5 percent who died by suicide, and my father lived a lonely, painful life, unable to get the help he needed.

But for my son Michael, the story is different. Diagnosed with schizophrenia at 19, he tried 13 antipsychotics that did not work, but clozapine saved his life. In a few weeks, he will graduate with a degree in social work, and he is here today as an FDA panelist. Clozapine is what made this possible.

For seven years, Michael has never had a low

ANC; yet he has spent entire days missing school and work, traveling between one lab and another, and even to emergency rooms just to get a simple blood draw. This isn't just inconvenient, it's dangerous. The risk of dying from not receiving clozapine is far greater than the risk of neutropenia.

The FDA's own data shows that the risk of severe neutropenia is minimal; yet in 2023, only 148,000 of the 1.2 million eligible treatment-resistant people received clozapine. Let me say that again. Only 148,000 prescriptions were written. REMS requirements are a key reason for this underutilization. Even in hospitals, patients can't start clozapine without a blood test. Many with psychosis cannot leave their homes due to fear and delusions, and in rural areas, labs and finding a certified pharmacy is almost impossible. We drive an hour to go to the lab and to get a prescription filled. What about people that don't have transportation? There are no rural public transportation systems.

Doctors are very reluctant to prescribe clozapine, not because of neutropenia risk or side effects, but because of the logistical difficulties of REMS compliance. My son's psychiatrist, Dr. Casey Prough of Kansas City, is one of many doctors who have stopped accepting new clozapine patients because of these roadblocks.

Now consider this. Cancer drugs with much higher risks of severe neutropenia don't have these restrictive programs because we understand their life-saving importance. Chemotherapy, methotrexate for rheumatoid arthritis, HIV antivirals, and organ transplant drugs all carry greater risks than clozapine; yet we trust those doctors to monitor patients responsibly without these burdensome programs.

DR. FLOYD: Twenty seconds.

MS. BRISBIN: Clozapine for treatment-resistant schizophrenia and suicidality, why is it the only one held to a different standard? This discrimination and disparity in care is unacceptable. Serious mental illness

deserves the same respect and urgency as other life-threatening conditions. These individuals deserve the chance to live stable, fulfilling lives just like my son. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker 24.

Speaker 25, please go ahead.

DR. LOVE: Thank you. My name is Raymond Love. I've worked with clozapine since before the drug was approved in 1989. I directed Maryland's clozapine program until my 2023 retirement. The clozapine REMS is complex and confusing. It negatively impacts patients, providers, and systems. In order to address issues presented today, my slides may not exactly match my remarks, but I'll keep trying.

There were 47 slides presented today to show changing clozapine requirements, and we wonder why enforcement discretions are inadequate. As one example, FDA and CPMG say there are no limits on the amount of clozapine that can be dispensed; yet the briefing document for today's meeting states

that the REMS includes an entry limit of 30 days supply on each pharmacy dispense. And the REMS pharmacist guide, which is supposedly what instructs us about how to use clozapine, says, quote, "The amount of clozapine that can be dispensed depends on when the patient's next blood draw is scheduled to occur," end quote. That would be 7, 14, or 28 days.

The process to prescribe an antipsychotic should be fairly straightforward, but the REMS complicates the process. Even reimbursement is affected. Pharmacies can be audited and penalized by payers for not complying with the letter of REMS requirements, even if that requirement's in an enforcement discretion or it's only published in a guide. The REMS is an administrative minefield that consumes limited pharmacy resources, makes it difficult to comply with standards, and may interfere with reimbursement.

These are a few of the many potential points of failure where the REMS can break down. When the current REMS was implemented, the complexity caused

the FDA to issue an immediate enforcement discretion. We're still in that enforcement discretion. While pharmacists have many concerns about the REMS, most of them relate to the RDA, the PSF, and dispensing quantities; however, our biggest concern is our inability to help patients when we're caught in the middle between a confusing REMS, prescribers, insurers, and PBMs.

The REMS is like an iceberg. Its unanticipated consequences are hidden below the surface and extend far beyond the FDA's jurisdiction --

DR. FLOYD: Twenty seconds.

DR. LOVE: -- or recognition. It can harm patients, burden providers, and restrict access to a potentially life-saving medication. It's time to get rid of the PSF, and the RDA, and all of the restrictive REMS provisions. Simplify the process, update the labeling, and help us educate the healthcare workforce on how to safely and effectively use clozapine. Please help us reduce the stigma on clozapine use. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker 25.

Speaker 26, please go ahead.

MS. FOX: My name is Crystal Fox. I am from Goodyear, Arizona, and I'm here on behalf of Arizona Mad Moms. I am an inpatient psychiatric nurse. I spent three decades at the Arizona State Hospital with the most acute psychiatric patients. I was there when clozapine came out during the 1990s. It was a miracle drug. I saw hundreds of violently ill and gravely disabled patients walk away from the state hospital, freed from their afflictions. I haven't seen a single death caused by clozapine. I have seen deaths from lithium, Depakote, and insulin. These medications carry high risk, but none of them have a REMS, and none of these medications, including clozapine, carry higher risks than the illnesses that they treat.

Several of my patients died. One woman jumped off a table and broke her neck; one man was violently assaulted by another; one patient swallowed several CD discs; and another

intentionally choked himself on an apple core. I have heard little mention of the assault against healthcare workers by aggressive patients. Sadly, this is a reality. In my job, I have been punched, assaulted, and bitten. I have many scars.

Serious mental illnesses are devastating, and I have been personally affected. My son Joshua developed severe schizophrenia in 2020. He hallucinated Morse code signals from a car engine that told him to kill his father. This led to the death of his father, John Fox, in 2021, leaving his six children fatherless.

In jail, Joshua jumped off the balcony twice. He suffered auditory hallucinations from the devil that told him if he jumped, he would resurrect an innocent girl from hell. He crushed his back, both heels, and one heel went through his ankle. He suffered paraplegia, causing him to have to catheterize himself for months. Joshua eventually died by suicide just 11 months ago in 2023. He was 23 years old. He was transferred from jail to prison, and 30 hours later, he hung

himself on a bunk bed.

Joshua should have had clozapine at the first sign of suicidal and violent behavior, no questions asked. Instead, jails and hospitals gave him a weaker antipsychotic all because of the impossible barriers to clozapine. Joshua never had that same chance at the recovery that I had witnessed for hundreds of patients during my time as a psychiatric nurse at the Arizona State Hospital.

The FDA has turned a blind eye to the dangerousness of psychosis and suicidal disorders. This is discriminatory. We don't withhold or interrupt life-saving medications for any other serious medical conditions. We should not withhold clozapine for an individual that is not just at risk for the death of themselves, but also the death of family members. Clozapine is the safest antipsychotic in the world, and the greatest risk of clozapine for my son was not getting clozapine.

(Applause.)

DR. FLOYD: Thank you, speaker 26.

Our next speaker, speaker 27, is virtual. Please go ahead.

DR. BHATT: Dear esteemed members of this committee, I'm Dr. Apurva Bhatt, a child psychiatrist at Stanford and Director of the Child INSPIRE Early Psychosis Clinic, where I prescribe clozapine to young people living with schizophrenia spectrum illness. I also treat children with cancer, experiencing psychosis secondary to chemotherapeutic drugs and steroids, and have often wondered why my oncologic colleagues do not face the REMS as I do. I have no financial disclosures or relationships with ineligible companies.

I'm here speaking on behalf of the American Academy of Child and Adolescent Psychiatry, which represents over 11,000 child and adolescent psychiatrists, fellows, residents, and medical students. Many of our members and the individuals we serve are negatively impacted by the overly stringent REMS program.

Studies have shown that 12 percent of adult individuals diagnosed with schizophrenia spectrum

illness developed this before the age of 18, and 3 percent before the age of 14. When accessed in a timely fashion, clozapine can meaningfully improve the developmental trajectory of young individuals living with psychosis, such that they're able to achieve meaningful recovery that's highly personal to them, including pursuing their goals and what matters most to them.

Despite its efficacy, the clozapine REMS program imposes substantial barriers that disproportionately affect young people, particularly those from marginalized or underserved communities. Key challenges include the burden of frequent blood draws, which is really not feasible for most families, regardless of socioeconomic status. This requirement disproportionately impacts those individuals and families who cannot easily take off time from work or school, who lack consistent access to transportation, or those who don't have a lab nearby.

Many pharmacies opt out of carrying clozapine due to REMS requirements, and then those

that do, face procedural delays leading to missed doses. The complexity of coordinating prescribers, labs, and pharmacies creates barriers for families, especially those with language barriers or healthcare literacy challenges. And then there's the impact of climate change and weather disruptions. Extreme weather such as heat waves, blizzards, wildfires, can make it difficult for individuals to leave their homes, brave the elements to complete required clozapine REMS monitoring, especially if they have to use public transportation. Natural disasters, hurricanes, wildfires can cause difficulty in accessing pharmacies, exacerbating treatment gaps.

Finally, the administrative burden of the REMS has deterred prescribers, reducing access to clozapine for young people and limiting training opportunities for our future workforce. To address these issues, AACAP urges the following: make all REMS-related data de-identified and publicly available for studies to be conducted on the appropriateness of the current lab draw

requirements and safety of reduced blood draw monitoring, especially in pediatric population --

DR. FLOYD: Twenty seconds.

DR. BHATT: -- remove restrictions requiring pharmacies to enroll, or check REMS, or require all of them to enroll; support clinical trials for at-home fingerstick blood draw for ANC monitoring in pediatric populations; allow covering prescribers to temporarily provide prescriptions for clozapine without requiring REMS enrollment; provide individuals, parents, legal guardians with REMS access so that they can navigate these system challenges.

By reducing these barriers for vulnerable populations, we can improve access to a life-saving medication for youth living with psychosis. Thank you for the opportunity to comment on this critical issue.

(Applause.)

DR. FLOYD: Thank you, speaker 27.

Speaker 28, please go ahead.

DR. DUCKWORTH: Hello. I'm Ken Duckworth.

I'm a psychiatrist, the Chief Medical Officer for the National Alliance on Mental Illness. I'm a big fan of clozapine. I worked on John Kane's study. I worked on the InterSePT study. I have treated hundreds of patients with clozapine. There is no other compound like it in the treatment of schizophrenia.

I was treating a man in my clozapine clinic at the Massachusetts Mental Health Center, and I was going through all the risks of this complicated medicine; there are risks. And he looked at me and he said, "Doc, there's dignity in taking risks." This is a critical thing that I think has been relatively underplayed today.

NAMI believes that people should be able to make their own decisions, integrating risk of, say, agranulocytosis, like with myocarditis, like with ileus, like with other problems that come with clozapine, and make their own decisions. We believe it should happen at the pharmacy; that a pharmacist should not be able to say you can't get 3 days of meds. The patient should be able to say,

"I've weighed the risks and benefits. This is my life, actually. This is my risk."

NAMI does not believe that REMS should be mandatory after the 18-week risk period. We think people should be allowed to opt out. I allow there's going to be a handful of people that really, really don't want this particular risk, but we at NAMI believe that people should be in charge of their own decision-making, integrate their own sense of risk. They're taking risks every day, and this is just another one of them. We would then say if a large percentage of people opt out of REMS after 18 weeks, I think you could re-evaluate what REMS means to them for the first 18 weeks. I want to thank you for this hearing, very important to help people have the dignity of taking their own risks. Thank you.

(Applause.)

DR. FLOYD: Thank you, speaker 28.

Speaker 29 is virtual. Please go ahead.

DR. GRAHAM: Hello. My name is Regina Graham, and I'm a child, adolescent, and adult

psychiatrist at the University of California, Davis, where I serve as Medical Director of our Early Psychosis program. I'm here speaking for myself, and I have nothing to disclose.

As a practicing psychiatrist for nearly the past 20 years, I've seen firsthand how the clozapine REMS requirements prevent individuals in dire need of this life-saving drug from benefiting from it. There are significant racial and ethnic disparities in clozapine utilization patterns. Specifically, black patients with treatment-resistant schizophrenia have a lower likelihood of being prescribed clozapine than white patients.

One likely contributor is that those from African and Mediterranean backgrounds may have lower white blood cell count at baseline, which is now recognized that this could be due to a variant range of neutrophil count known as benign ethnic neutropenia, BEN; however, most clinicians are unaware that BEN exists, and they do not know how to diagnose it.

The REMS neutrophil monitoring may lead individuals from minoritized backgrounds who have BEN to be prematurely excluded from clozapine treatment. I worked with an African American patient whose clozapine was discontinued after about 3 weeks due to his relatively low neutrophil counts, and subsequently his psychosis symptoms worsened to the point that he became involved in non-violent criminal activity and was deemed incompetence to stand trial due to his mental illness. He was then sentenced to confinement to a state mental hospital and lost many valuable years of his youth.

Five years later, when I met this young man, I discovered he had BEN and was able to restart clozapine, which greatly improved his functioning; however, over the past 5 years, he's had to face criminal charges, housing instability, and lose educational and vocational opportunities due to his undertreated schizophrenia. Due to all the administrative burdens with clozapine monitoring, some providers assume that individuals from

minoritized and underserved communities will be non-adherent with these requirements and often do not attempt to prescribe them to them.

Clinicians, patients, and families have outsized beliefs about the inherent dangers of clozapine due to the frequent blood monitoring requirements. I've had families express their emotional distress and fearfulness of negative health consequences if their loved ones were subjected to these repeated blood draws over the long term. The availability of labs to do blood monitoring frequently is difficult in low resource communities, and individuals living in these communities may not have accessible transportation options to take them to these laboratories.

The burden imposed by clozapine REMS does not affect all communities equitably due to differential access to number one, pharmacies registered with REMS in low income neighborhoods; number two --

DR. FLOYD: Ten seconds.

DR. GRAHAM: -- laboratories being staffed

with speakers in one's native language; and number three, providers knowledgeable of describing clozapine are unequally distributed during geographically. All these barriers disproportionately impact underserved and minoritized communities' abilities to reap the benefits of clozapine. Thank you.

(Applause.)

Clarifying Questions (continued)

DR. FLOYD: Thank you, speaker 29.

This concludes the open public hearing portion of the meeting. I want to thank all the people who took time out of their lives to come talk to us about their, sometimes, deeply personal stories or those of their loved ones.

Now, we have about an hour and 45 minutes left, and we need to preserve most of that for the discussion. We also will have a quick break, and I understand FDA and CPMG are eager to provide responses to some of the questions that panelists had. So what I'd like to do is very briefly start with CPMG, and I'd like you to go ahead and share

the information that was requested.

MR. SHAMP: There were two questions, and then one clarification I'd like to make. The question about the mail-order pharmacies, I said we'd try to determine if we can get that data. We are not. As I stated before, we do not collect on the enrollment form whether a pharmacy is a mail-order pharmacy or not, so we're not able to provide that.

Secondly, we do collect data on wholesalers that are shipping to uncertified pharmacies. We have had 7 wholesalers indicate that they do ship to uncertified pharmacies. And just to give you an example, in October, last month, there were 42 uncertified pharmacies that received shipments.

Then the clarification, can we bring that slide up? This is just one clarification. I believe, Dr. Dunn, just before the lunch break, you had asked a question to the agency about the enforcement discretion. Their response was that they are looking to remove it at some point. I just wanted to make sure I understood from your

question that perhaps you thought the treatment rationale and dispense rationale were part of that enforcement discretion; they are not.

As you can see from the slide from my presentation, the only thing on here that would potentially go away at some point is this transition dispense rationale. It was always intended for the enforcement discretion to be a temporary tool to use, so everything else would remain even after the enforcement discretion is removed.

DR. FLOYD: Thank you for sharing that.

And FDA, did you have some materials you'd like to share in response to earlier questions?

DR. LaCIVITA: Yes. Thank you so much. This is Cynthia LaCivita, FDA. Mr. Brisbin, you had a question about ANC monitoring. I did go back and check, and there are other products that require blood monitoring. They're not for ANC. One is for thrombocytopenia for or to assess liver injury, but clozapine is the only one that requires weekly monitoring. Thank you.

We had one other. I think Dr. Vyas had a question about the study, and I'm going to ask Dr. Mosholder to speak to that a little bit. Thank you.

DR. MOSHOLDER: Andy Mosholder, Division of Epidemiology 1. Thanks for the reference. We identified what we think is the Taylor et al. 2022 publication. I describe it as essentially an in-depth case series of 23 cases of agranulocytosis. The authors are arguing that really worrisome agranulocytosis cases can be distinguished by the trajectory of the ANC counts leading up to the event. It's worth looking at, but we'd have to realize this is based on just those 23 cases, so it's kind of in the realm of hypothesis-generating perhaps.

DR. VYAS: [Inaudible - off mic 7:18:20]

DR. MOSHOLDER: It was from their site.

DR. VYAS: Yes, from their pool of 3500.

DR. MOSHOLDER: Right, but they only had 23 cases to work with, so we have to bear that in mind.

DR. FLOYD: I'd like to take a break now. It's 3:19. We'll come back and start promptly at 3:30. Thank you.

(Whereupon, at 3:20 p.m., a recess was taken, and meeting resumed at 3:31 p.m.)

Questions to the Committee and Discussion

DR. FLOYD: Now, this is the part of the meeting where we address the task at hand, the consideration of all the data that we've been presented, focusing on two discussion questions and two voting questions. People in the audience, if we could have you wrap up your conversations and sit down, please. We really need to get moving.

I want to proceed with our first question, which is a discussion question, if we could please have that up on the screen. This question is, how reassured or concerned are you that current and potential clozapine healthcare providers have sufficient knowledge and access to resources about the risk of neutropenia and the need for monitoring?

Jessica, if you don't mind taking down who

wants to talk, I'm going to start with a few comments of my own.

I think that these questions are written and designed in a certain way, but I find it a little difficult to consider these specific components of clozapine or the REMS in isolation without thinking about risk and benefit. I think one thing I want to put on the table up front is we're not considering labeling changes right now, so for all the discussion, I want you to assume that the label for clozapine is what it is.

Now, it's possible that could change someday. I don't know if FDA is considering or is not considering that, but for now, given what the label is, our task is really to discuss what elements of the REMS, or if any REMS at all, are needed to ensure safe use.

So as I mentioned, I like thinking about risk and benefit, but everything the FDA does is in terms of risk and benefit. It differs based on a patient, based on a population, based on the counterfactual you're considering. And what I've

heard today, overwhelmingly from our psychiatry experts who would treat these patients day in and day out, our pharmacists who deal with a lot of the headaches of implementing the elements of the REMS, and even myself -- I'm a general internist but I've practiced my entire career at a safety-net hospital, where we serve the most severe mental illness in the entire region, so I'm very familiar with the types of patients that my psychiatry colleagues are treating. And it's also very clear to me that the best evidence of the impact of clozapine comes from the RCT, and the evidence of benefit is substantial.

I don't think we can encapsulate it with preventing suicide deaths, which you never can measure in a trial, but it's clear that in terms of reducing the symptoms and preventing all the downstream health effects from that, short of and including death, there are tremendous treatment benefits.

There are also well-characterized risks of which neutropenia is just one. Our knowledge of

neutropenia is not going to change 5, 10, 15 years from now. We know pretty much what there is to know about neutropenia from this drug. So when we think about questions of is there a safety issue, do we know enough about the neutropenia monitoring, I think you always have to ask how does that compare with the benefits if you expand this to a new population. And what I see now is that the operational details of the REMS as it stands are not tenable, so we're charged with thinking about different options.

Two options came to mind, and other panel members may think of other ones that we want to discuss. One is to keep REMS with elements to assure safe use, but remove all the documentation requirements for monitoring, and simply leave it as a physician and a pharmacy registry. So to say, if you're a physician and you want to prescribe clozapine, you have to register, do some CME, and make an attestation, and then you're an official clozapine prescriber. Then, if you write a prescription, a pharmacy that wants to fill that

also has to be registered and simply confirms that the prescriber is on that list. So that's one version of REMS with elements to assure safe use. That would be different than what exists now.

Another very discreet option is to dismantle all of the elements to assure safe-use provisions. So that would mean not requiring that physicians register and that pharmacies check on it, but simply to allow anybody to prescribe clozapine. That doesn't change the label, doesn't change what the recommendations are, but that's a different reality.

So those are two discrete options, and based on what I've seen, the first one seems like a winner. It seems like there's so much untreated treatment-resistant schizophrenia simply because of barriers, and some of those barriers are because of REMS and some are external to REMS. As far as the second option I presented, I actually don't have enough information about that, but I'm hoping that my colleagues here on this panel can consider that option and see what they think about it.

We only have two people who raised their hands so far, so we'll start with them, but I hope others will raise their hands and join the discussion. Now, the official question is, are you concerned that healthcare providers don't know how to do ANC monitoring? So that's the narrow question, but as I mentioned, feel free to expand on other aspects of this.

So we'll start with Dr. Vyas, and then we'll go to Dr. Ballon, and then Dr. Narendran.

DR. VYAS: Thank you. I think it's clear from what we've heard today that the knowledge regarding neutropenia is certainly present, perhaps even excessive to the point that it's blinding. We haven't heard about this fully, but I think people that are familiar with clozapine would say that there are other aspects of clozapine that are more important than neutropenia. The focus on neutropenia and dispensing based on these very hard numbers is impairing learning of other components of safe prescribing.

So I think the idea of having a purely

educational REMS, or at least a component that's very educational, that isn't restricted, neutropenia would be something that's worth considering. But I think that there's a lot of knowledge, and -- I'm sorry. I'm sort of losing my thought, but thank you.

DR. FLOYD: It's ok. There's going to be opportunities to weigh in multiple times during this discussion.

Next, we have Dr. Ballon.

DR. BALLON: Jacob Ballon from Stanford. I think that it's very clear that, in fact, we have overtaught on this issue, and having a REMS has actually so focused people on understanding that there is some kind of neutrophil something that they have to know, that if you've asked almost anybody what is the first thing you think of with clozapine, you think neutrophils.

We're talking about 0.4 percent of patients that are having severe neutropenia, much less, how many of those patients are actually having severe consequences from that. It's de minimis almost;

and yet, because we have focused so much on ANC, we have lost sight of actually the more debilitating daily problems that people have when they're on clozapine that we need to be monitoring for, like constipation, like metabolic syndrome, like sialorrhea that can cause pneumonias and things like that.

If you ask most residents about that, you're not going to get a detailed explanation, but you will get that they will know that they have to monitor the labs, and that's a problem. And that somehow makes it more difficult than what they do. "I don't do blood, so I don't really know. What am I supposed to do with that if I do find it?" They don't know about using filgrastim and things like that.

So there are so many ways that we make trade-offs, and we have overcompensated on this issue, and it's a silent issue. If somebody walks into my office and they have a low ANC, I can't see that. It's not a symptom. There's not a question that I can ask them, necessarily, unless they have

a fever or some other way that they are identifying themselves as being at severe risk, so it does bear some consideration.

I would expect that as people know about this, and as the labeling maintains that this is there, we monitor for other black box warnings all the time. There's no REMS that makes it so that we have to check liver enzymes for people on Depakote. We do that because we know we have to do that. We know that we have to check cholesterol levels and things like that for people who are on antipsychotics, in general, because of side effects.

Psychiatrists can monitor side effects. And while not every psychiatrist or every person who's going to prescribe is going to actually follow every single thing, we do know that, by and large, people are going to be able to follow that, and they're going to be held to a standard, frankly, because they could get sued if they don't follow that, and pay attention to it, and have a bad outcome. So it's in their best interest to keep

track of actually what is known.

Having a REMS system doesn't really assure any of that, frankly, and it's unclear to me from the discussion today whether the REMS system even catches a neutropenia in time to make a big difference anyway. So I think that it's, to me, very clear that this is an overabundance of focus on neutropenia as a specific singular entity, when, in fact, there are so many other things, irrespective before we even get to the potential benefits of clozapine that people need to know about. So I'll leave it with that.

DR. FLOYD: Dr. Narendran?

DR. NARENDRAN: Hi. This is Raj Narendran from Pittsburgh. Yes, I do kind of agree with my colleagues. I think everybody who's went through psychiatry residency, when they hear clozapine, they think 1.3 percent are going to have neutropenia and agranulocytosis. I think everyone is aware, and the REMS made sense 30 years ago, but at this point, people are monitoring; like Depakote, you're monitoring liver function, you're

doing metabolic syndrome, you're doing hemoglobin A1C. I think people could read the package insert and do it, and that would get the drug out to more people.

I strongly feel that the REMS at this point is just a hindrance. It's only being prescribed by these specialty clinics like the big universities, and VA, and these well-oiled machines. Community psychiatrists who probably should be treating patients if they fail multiple antipsychotics can't put them on because they don't want to deal with the REMS.

Personally, I do have to say, working in a crisis clinic, where I've done that for decades, at least half a dozen times I encounter patients on clozapine who can't get the script renewed. Their psychiatrist is on vacation or they're out of county, and they show up here. I'm not registered on the REMS to do it. I don't have a pharmacy that can do it. I call around to my colleagues and say, "Hey, this person's from New York. He needs clozapine," and they're like, "Well, we can't do

anything. We can't do it. Does the ER have a doctor? We can't do anything." I don't know what to tell you. I call the Clozaril clinic, and they're like, "Hey, we're really backed up. We can't do it." And I'm like, I don't know what to tell you. You can go to the hospital and get admitted.

I know you have to get the neutrophil count, give them blood work, send them to Quest, get the blood work. I didn't even know about this dispense that they can do, and it's not being enforced. I'm kind of ashamed to admit that, but I don't think any of my colleagues knew it when I called around either. No one even brought that up that, "Hey, you can just do a blood count and fill this script at the pharmacy." So I think it's a concern, so I think you should get rid of the REMS, is where I would land.

(Applause.)

DR. FLOYD: If we could please hold applause and comments from the audience. Thank you.

Dr. Dunn?

DR. DUNN: Walter Dunn, UCLA VA. I agree with my colleague, Dr. Ballon, that ANC monitoring is probably the least concerning thing about prescribing clozapine. And I would say that even our medical students are quite aware of this. I teach a psychopharm course, and that's the one question they always get right.

The other things, however, are more important, such as the bowel regimen, myocarditis. So to your point, Dr. Floyd, about the winner being just the educational component, I think that's a consideration, in addition to ANC, adding those other complications of clozapine as part of that educational aspect.

I would like to maybe add a third potential option -- this hasn't been discussed -- where we may have a Modified REMS during the first 18 weeks, or maybe first 6 months, when the risk is the highest for neutropenia, and then afterwards make participation in the REMS either voluntary or not even have a REMS after that.

The other component, I would say that if we

go down that route where we still have some type of required ANC monitoring, even during the initiation phase, is the treatment rationale and the dispense rationale. I like the fact that you're giving providers and patients options or different treatment pathways so that if they run into some barriers or friction points, that there's a way around it.

Now clearly, from the testimony of the audience, these treatment dispense rationales are not working for a variety of reasons, and perhaps wording them in a different light, perhaps different treatment options, different treatment pathways so that it doesn't look like a waiver. I think the term "waiver" conjures up potential liabilities from the pharmacies. So if it's a normalized pathway, perhaps people would be more willing to accept and pursue these options when the medications aren't able to be obtained through the straightforward pathway. But again, another consideration for the agency if they're looking to step down a REMS program rather than completely

abolish it. Thank you.

DR. FLOYD: Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi. Thank you. I had some thoughts regarding the knowledge base that we talked about. I work in a busy urban emergency department, and I see patients with schizophrenia every day, and often at their worst. I have a good relationship with our psychiatry staff, and they seem to be very familiar with how to use clozapine. And most people that are treatment resistant generally do see a specialist that is very comfortable doing so and initiating treatment.

My comment is I think that is adequate for most individuals. My question is, other groups -- for example, psychiatric nurse practitioners or physician assistants -- I don't have enough backdrop to say do they have an adequate knowledge base because I interact mostly with physicians. Secondarily, I agree with limiting perhaps to maybe the 18 weeks, and then perhaps doing additional studies where we look at

perhaps the late patients that develop severe neutropenia; that maybe we can do some risk assessment to see -- I know it's mostly idiosyncratic -- is there a dose component? Is there an escalation? Are there genetic or other factors?

Then finally, as part of improving access, one of the things that I took away from the public hearing was that gaps in getting patients medication can be extremely detrimental. So perhaps we could work into our policy something that myself as an ER doctor -- I can't tell you how many times I see somebody that comes and says, "I ran out of my medication, and I need my blood pressure pills. I need my insulin." And I give it to them readily, and I'm not able to help people in this scenario, even with a few days. Those are just a few initial thoughts. Thank you.

DR. FLOYD: Yes. I want to restate what I heard from you because I think it's important. You reflected that we had a lot of information for physician prescribers, especially psychiatrists.

They know the hematology issues with clozapine. What we know less about are the other prescribers who make up a large proportion of the individuals who are prescribing this drug. But then I also weigh it against the harm from not getting treatment for treatment-resistant schizophrenia.

So I think it's a legitimate open question that maybe we didn't get the results to here today, but when I pose that against all the harm done from having uncontrolled schizophrenia, it seems like the risk-benefit favors one direction.

Yes, go ahead.

DR. VYAS: Our education program -- Deanna Kelly is in the audience still I think -- really takes allcomers. We've taken PAs, nurse practitioners, people in practice for a long time, going over the A to Z of clozapine. And thankfully, clozapine monitoring is different in different countries and different healthcare systems. Clozapine, the drug itself is the same.

So those training programs we are putting together, as one example. I know, Dr. Cotes, the

website that you guys do, SMI -- exactly, thank you -- they have a number of resources that they have put together as well, a number of cases, sort of crash sheets where if you have a patient with this, what do you do next, and consultation.

Additionally, we've tried to include in our education non-prescribers because sometimes those are the best advocates for people to have on their side. They may be the ones to recommend to a reluctant prescriber. Our social workers, psychologists, non-prescribers are some of the best advocates we have to improve our utilization. So I'm not worried about the education component.

I think that with regards to the dispense rationales and discretion, anytime there's any of that wording, like Dr. Dunn said, that sparked in me the worry that there is some type of monitoring or some type of consequence to that. And that has been the biggest enemy of clozapine utilization, is what happens if we don't do this? The FDA doesn't have an armed division, nobody else is coming for you, and there is no immediate consequence, but it

conjures up any number of fears in people that I will lose my license. I will no longer be able to practice. There is a lot that happens.

The one thing that's really important and really has to be highlighted is the intensity of suffering that people go through prior to getting to clozapine, and then staying on it. I think the public speakers today highlighted that and was very moving, and I think we have to listen to that. The amount of benefit that can come from clozapine is so great that any mandatory monitoring for any amount of time I feel would be dangerous to the patient.

(Applause.)

DR. FLOYD: Please, no applause.

Dr. Ballon, is your comment directly related to that?

DR. BALLON: Yes, just a brief follow-up. I mentioned this earlier, but I do think that the term "enforcement discretion" has actual consequences, which is that for me as a physician, I sit across the room from the patients and the

families, and I know how long it took for them to get to see me. And I know that maybe my license is on the line if there's some kind of enforcement discretion, but I would much rather answer the question about why did I give somebody a prescription for clozapine, than why did they die by suicide. But I can't expect that necessarily from the pharmacies and the people who are further downstream who don't feel as empowered, who maybe don't have the level of training specifically in schizophrenia and specifically in using clozapine like I have.

So while I might feel like I can click that button on the REMS, the clinician discretion or whatever, I find that it is really hard to get the entire system to do that. And I think that, actually, the word "enforcement" is a big part of that barrier because it does conjure up the idea that somebody's going to come take you away in handcuffs, or do something to your license, or to your business that is going to be of dire consequence. So it ends the conversation when I'm

trying to just talk about it with somebody who's standing in the pharmacy waiting to get their medication, or they didn't get their lab, and I'm on vacation, and I'm calling on the phone trying to get it all organized. It doesn't work.

So I really do think that the concept of enforcement discretion is great, but it's not actually being communicated the way it needs to be as well. So I would certainly want to make sure that we're -- again, I think that at this point, we have overemphasized the neutrophils in this conversation anyway, and would step back from this level of enforcement of any kind. But in particular, if we're going to maintain some kind of middle ground, I would really, really ask that we change that term from "enforcement discretion" to "options" or some other pathway.

(Applause.)

DR. FLOYD: Dr. Rebo, go ahead.

DR. REBO: Yes, I just wanted to comment on that from a pharmacy perspective. I will say I do not work in a retail pharmacy. I do not work in a

hospital pharmacy. I'm in an administrative role, but knowing how pharmacists think, I had no idea, until I got the materials for this meeting, that that was even a thing, the enforcement discretion. All that I have been told in my organization is that this is mandatory. We must do it. We have built clinical decisions support into our EMR. That is the way we are doing all of this.

So I think to everyone's point, if we are not going to eliminate the REMS for this completely, we have to do something where the pharmacy piece is left out because, otherwise, I think we're going to run into the exact scenario of what we're talking about, where the pharmacies are going to be the gateholders with this, and that's going to result in patients not getting what they need.

(Applause.)

DR. FLOYD: Go ahead, Dr. Salvas.

DR. SALVAS: Brian Salvas, CVS Health. Guys, let me put this in perspective for everybody. There are some 30,000 approved products that get

dispensed at retail pharmacies, probably 3 to 5 billion scripts a year. We're talking about a couple 100,000 maybe that are pumping through maybe 27,000 enrolled pharmacies across the country. The reality is that these are very infrequent encounters for your typical pharmacy provider.

So when you look at the information asymmetry for someone, it's a Friday night, and one of the children of the speakers, or one of the folks comes in with their prescription and they don't have the labs. You're asking for enforcement discretion, or you're asking for some sort of professional judgment, and what information do they have to draw upon? They do not have the rich information that any of the physicians that treat these people on a daily basis have, and they're operating in a context where 99.9 percent of the encounters they have are for other much simpler conditions.

So I think it's a really important context when we're thinking about our pharmacy providers,

but I want to connect that to education because I think one of the other takeaways from this is that provider education is something that's going to be very important to us. We think there's value in it. What are the right mechanisms, though? I'm not sure that enrollment of a provider, particularly a pharmacy provider, is getting us what we actually want in terms of people who truly understand the program.

When we think about some of the failures that we've had -- I'll loan some of these because I'm a pharmacy operator that operates in all 50 of the states across this country -- you have a program that has evolved stepwise over a 20-30 year period, and then has incomplete implementations each time along the way. So my ask would be, as we look to simplify this, let's touch it once, and then we can get the word out to everyone.

DR. FLOYD: I want to move on to Dr. Stegmann in our queue, but very quickly in response to that, I want to draw on some context from other therapies and other REMS. We've spent

years discussing REMS for opioids, for example, and specifically around this issue of what's the best way to educate. The evidence was pretty clear, if you just put some CME out there, it doesn't get very far; it just doesn't. So if you really feel like it's essential that new providers learn how to do clozapine and all the adverse effects, the physician registration, an element to assure safe use may be the best way. I don't know for sure, but I think we should be honest about how far non-mandatory CME goes.

Dr. Stegmann?

DR. STEGMANN: Yes, Jens Stegmann. I think the FDA purposely put forward two questions, that they described two care gaps, initially. One is about knowledge, the other one is about behavior, and I do think we're already in the middle of a mixed conversation about both, knowledge and behavior. I'm trying to come back to the question being asked and in front of me because in all openness, I do see 4 or 5 different questions here being asked.

Certainly very quickly, about those healthcare providers already in the REMS system, clozapine users or the prescribers, I think that's been said multiple times, and I think the knowledge is there. I think at one point, it was mentioned as being overly focused about that, so there is more concern. It's even a concern that it's a bit too overemphasized.

The question or where I cannot make an assessment is about potential clozapine healthcare providers or prescribers who would be able to help patients to access clozapine, but with limited knowledge, or bias, or misunderstanding, or not granting access to that. This is why I asked the question earlier about if we have any data about those potential prescribers not being too exposed to clozapine until now, and what kind of knowledge is for them. And certainly, FDA made me rightfully aware that this is not something a REMS can provide because you have to run the REMS in order to do so, nor can the FDA be charged in order to make sure that this knowledge does exist.

I think we do have to take here particular prescribers, physicians, psychiatrists, or whoever, by their responsive accountability. Does it mean that we do need education here in the REMS? I don't know. I doubt that in all openness, but I think this is a group we have to somehow make sure that this knowledge is there, and in particular, Dr. Floyd, as you rightfully mentioned, less talking about the risk and being very clear about the benefit of that product because I don't know whether this has been widely known, et cetera, in that regard.

We heard very clear messages from those people, either themselves or the caretakers of patients, who benefit enormously from clozapine, and I think this is a population we have to focus on, not about those who already have an exposure to clozapine.

DR. FLOYD: Thank you.

So we have three in the queue, Dr. Ehret, Dublin, and Fiedorowicz. I think with the last comments, we're kind of shifting towards discussion

of item 2. I don't think there's a lot of debate on item 1. If those three people don't mind shifting to question 2, you'd be first up.

Do you want to stay on question 1?

(No audible response.)

DR. FLOYD: Let me read out discussion question 2, and then we'll go down the list starting with those three. Discussion question 2 is, how reassured or concerned are you that current and potential -- based on any changes to REMS -- clozapine providers will perform ANC monitoring without the requirements of REMS?

So next up is Dr. Ehret.

DR. EHRET: Thank you. Meghan Ehret, University of Maryland. I want to thank the pharmacy colleagues across the aisle for talking about pharmacies. I think we're well educated on neutropenia -- probably too much -- on being nervous to dispense, but we miss the lack of knowledge probably on the REMS. I don't have concerns that healthcare providers will perform the ANC testing. I think pharmacists need less

restrictions to be able to give this medication.

I've given many 3-day supplies of clozapine when I've stood in a community pharmacy. If we go with an 18-week ANC monitoring, pharmacies need to not be involved because they'll be too many retitrations, too many missteps, too many opportunities for every pharmacy to make their own policies, which is how things are running now, and it's not working for our patients. So I'm in favor of option 1. I have no problem trusting providers to do what they're being asked in a package label.

(Applause.)

DR. FLOYD: Dr. Dublin?

DR. DUBLIN: Thank you. I'm going to start with the education questions, and then talk about the monitoring questions. I think with the education, what came through to me really loud and clear, both from the original presentations and from the discussion around the table, is that there's a lot of knowledge and fear out there about neutropenia, and there's a huge knowledge gap about both the potential benefits, the missed

opportunities, and the other day-to-day side effects you need to monitor to allow people to be able to succeed in adhering. And I don't think that having people register for a REMS is going to help get the word out about positive aspects of prescribing clozapine.

So I think we have a dilemma here that a REMS doesn't really solve, so I'm a little less excited about maintaining an education requirement because I think what you get is people who are enthusiastic and they're highly motivated to prescribe will register and do the REMS because we're not going to force every psychiatrist in the country to do the REMS. So I think there's an important education gap, I don't think it's about neutropenia, and I'm not confident a REMS fixes it.

But I also want to point out that, to me, a big-picture learning was that I really appreciate the work that's been done, but I feel like we've been looking for knowledge in the wrong places, and I think this should be a lesson for all future REMS that when you want to know do providers know what

they need to know, you can't only start with the people who chose to enroll in the REMS, and you can't only only start with people who choose to prescribe the med, and you can't only focus on physicians.

So we really need to say that when we need it about knowledge, you can't just look under the light where the light happens to be for the key you've lost. You need to look in a more systematic way at people you either wish would prescribe it who aren't and at non-physician prescribers. So I think we have an opportunity to learn how to do this better.

(Applause.)

DR. DUBLIN: In terms of doing the monitoring, I worry a little that if there isn't a REMS forcing people to do it, it may slide, but I'm also much more concerned that what we're talking about here with the REMS is not about lifting a monitoring recommendation; we're just talking about lifting a reporting recommendation.

The heartbreak of people falling through the

cracks because the right data doesn't transmit between computers and misunderstandings to me is a couple of orders of magnitude of much bigger harm than my fear of less monitoring. And I would just say coming from a system like Kaiser, where we just try to build things in and make it easy to do the right thing, we need to learn how to make Epic, and Cerner, and these other platforms help support us in doing the right monitoring, and not create an entire separate computer system that doesn't interact with Epic to make it so burdensome that people choose not to be in the REMS and not prescribe. So I'm not a hundred percent reassured, but I think the harms we could inflict are worse than the benefit we would get.

(Applause.)

DR. FLOYD: Before we move on to Dr. Fiedorowicz, I wanted to follow up on something Dr. Dublin said. You're not persuaded that just having a physician registry is going to educate the people we need to prescribe it, and I think that's correct, too; I agree. I think about three

different pools of providers. There are the ones currently suffering through the REMS who are dedicated. They work at clozapine clinics. There are a handful of people who do that. Then there's the small bucket of psychiatrists who know enough how to do it but just don't want to deal with the paperwork, or are afraid of going to jail or losing their DEA; that's another chunk who might sign up for a mandatory CME, but it's maybe not big. And it's really the bigger pool who are working in rural communities. Maybe it's a psychiatric NP, maybe it's a family practitioner who is the only doctor in a 100-mile radius, and those people are never going to do that REMS.

So unless you remove that requirement, there are different populations served based on what the REMS are, and I tend to agree with Dr. Dublin that a physician registry may not expand the prescriber population to address this really underprescribing of a severe life-threatening illness.

So now I'd like to move to Dr. Fiedorowicz.

DR. FIEDOROWICZ: Thank you so much.

Several speakers today highlighted the importance of asking the right questions. Speaker 13, Dr. Chou, further emphasized it's important looking at the big picture here rather than the myopic focus on ANC. But even within the context of our focus discussion of REMS for ANC, I find these discussion questions to be very focused in the midst of that big picture of balancing of the risks and benefits that you and others have spoke of. So I'm going to use question 2 as a springboard to talk more broadly here, as others already have set precedent there.

I really appreciate this meeting to re-evaluate the Clozapine REMS Program and some of the studies that were done to provide more information. We have a good sense of the absolute risk of neutropenia, and as others have said, that's not likely to change. I think we can be really less confident, though, about whether and to what extent the REMS reduces this risk, and for that matter, what frequency of monitoring is needed to mitigate the risk. It seems like the frequency

is all focused on what is the prevalence at this time point, but not if it were to develop at some point in time, how soon do you have to catch it.

So it's quite difficult, I think, still, after all these decades of research, to inform monitoring. But regardless of recommended monitoring, there's a very valid concern about the harms of REMS that might outweigh its unclear benefits; and therefore, I support the removal of the REMS. While REMS was intended to protect, the barrier imposed by it, which isn't applied to other medications with comparable risk profiles, discriminates against the vulnerable population's ability to receive an effective treatment. And in treating those with serious and persistent illness, we really have to do a complex risk-benefit assessment collaboratively between prescribers, patients, and families.

So I would say that it's time to retire the clozapine REMS. Weighing this all in, I'll save my discussion for later --

(Applause.)

DR. FIEDOROWICZ: -- since I think I've already given my responses for questions 2 and 3.

DR. FLOYD: Dr. Stegmann?

DR. STEGMANN: I would like to build enormously on what Dr. Dublin has already described as the situation. Again, I'm coming back to the accountability of the prescribing physician and knowing about the risk, the identified risk, of ANC as going to happen. Is it something which by various certifications, the program needs to be controlled? I doubt that because a prescribing physician, in general, should know about the benefit but also the risk, and adequately mitigate the risk by making, as stated by the label, the blood draws in order to check for ANC in that regard.

A similar thing, as we previously discussed, for the education, I think this does require further education, certainly. Dr. Floyd, you mentioned the various different groups, and some of them might benefit from this education. But this is not something a REMS can do or should do in that

regard. I think this is also a call for my colleagues in industry because we can also provide educational material once we have some distributing product, and then we have other examples where this is working.

As a personal reflection, in all openness -- and it was also mentioned in one of the public statements here -- before going to medical school in Germany, I'd done a training as a male nurse in a psychiatric hospital. The first day I entered the ward and was told you have to dispense the medication clozapine. This was 1989, and was immediately being told that you need to be aware that those patients on clozapine need to be regularly getting blood draws in order to check for the neutrophils. This was in Germany where something like a REMS doesn't exist. Germany had various iterations of control access in the '60s from my understanding, but not in the '90s when I made my education as a male nurse.

So it's proof for me we can get the message across. We don't need a restrictive measure like a

REMS. And I would simply say it comes down to benefit-risk when it comes to whether or not the ANC monitoring is performed. This needs to remain the accountability of the treating physician in that regard, so I would not further restrict it via a REMS for these measures to be taken.

(Applause.)

DR. FLOYD: Mr. Brisbin?

MR. BRISBIN: Hi. Michael Brisbin. On discussion question 2, how reassured are you the healthcare providers will perform ANC monitoring without the requirement of REMS? I feel comfortable that the healthcare providers can do this because they manage drugs with rare serious side effects such as cancer treatments and Alzheimer's drugs without REMS, indicating their ability to perform ANC monitoring responsibly without regulatory mandates. As a patient that is also on clozapine, I'd say that I have increased barriers to obtain my medication, and that's a big deal. Thank you.

(Applause.)

DR. FLOYD: Thank you for sharing your personal experience. It's helpful context for the panel.

I'm going to move on to Dr. Dejos.

DR. DEJOS: Mike Dejos, Methodist Le Bonheur Healthcare. I also do feel reassured that current and potential clozapine healthcare providers will perform ANC monitoring. I think there was a wonderful presentation by our FDA friends that stated something like after 17 years of implementing some sort of best practice, some sort of knowledge or evidence, that's really put into practice. And Clozapine's been used for several decades now. I think many folks do know that ANC is something that we monitor whenever we're ordering, preparing, or administering this medication.

Also, as I'm sitting here absorbing all the different discussions, I know we're looking at risk versus benefit, which is very important, but also looking at risk versus risk. What is the risk of keeping the current status of our REMS program, and

then also what's the risk of perhaps lifting off some of those current requirements? So I'm sitting here and trying to think of what are the three variables that medication safety leaders will use. It's severity, frequency, and detection.

So if we go down one rail, what is the severity or impact if we were to stay with our REMS program? We've already heard a number of stories and situations that have led to various unfortunate outcomes as a result of not having greater access to clozapine. So that's something to consider. Then if we do remove the required status of REMS, what is the risk for that? The risk would be perhaps different cases of neutropenia. But when we look at that, actually, we've had very mild and infrequent cases of neutropenia, as we see overall throughout our data sets.

Then we also look in terms of detectability, in terms of another variable from a med safety perspective, because I do believe that we have the capability and the commitment to do ANC monitoring, and I do think that our providers will be able to

catch that from a detectability perspective. So, for me, I am reassured that we will be doing this monitoring appropriately, so I'm also in favor of lifting a number of the requirements with our current REMS program.

(Applause.)

DR. FLOYD: Dr. Ballon?

DR. BALLON: Jake Ballon, Stanford. I do want to say that I think that the people who will prescribe clozapine are capable of monitoring as needed. I do want to say I don't think that the REMS is the only reason that people don't prescribe clozapine in the community, and in some cases that's actually probably for a good reason. I built an early psychosis program at Stanford, which is a full team with psychologists, social workers, and others, peer specialists, and that is often what is, actually, best practice for treating psychosis. And many people in the community, solo practitioners, may just not be equipped always to do that.

That said, I don't want the REMS to be the

reason that they don't do that. I don't mind if they call me and say I have somebody who would like to get into your program who would benefit from having more comprehensive and wrap-around services than what I can provide in just my office. But also, we have to go a long way to recognize the impact of stigma, both within the profession, within individuals who are experiencing psychosis, and what they think they can or can't do, and to be able to recognize how to really drive people to feel like they have a positive future for them.

I call my clinic the INSPIRE Clinic for good reason, which is that we want people to feel inspired. We draw inspiration from people, and we want them to feel inspired. But the fact is that many people don't have that, so we have a long way to go as a field and as a society to really understand mental illness and understand psychosis in particular, and to make sure that people aren't discriminating against folks with psychosis. Unfortunately, I do think that the REMS program does serve to reinforce some of that stigmatization

by making things more difficult.

I also will say I think that people do need to get monitored, and if and when we can move on from the REMS program, I will still monitor many of my patients. But I have also been in that scenario, whether it's with the patients themselves, with family members, or with just my colleagues, where we've had to say this person would be perfect for clozapine, but you know what? They're not going to get the blood draws. They are unhoused, and they're unstable in where they go. There's no way that we're going to be able to actually adequately pull this one off. The system is getting too fragmented.

I would prefer to take that chance that that person can get on clozapine, and actually maybe then be able to fit into a fragmented system, and to be more likely able to do some of the things we heard from the stories, or from Michael, and to be able to reclaim their life in such a positive way that, in fact, maybe we could get out of some of that cycle and not have to make that decision for

themselves.

I think it was Dr. Duckworth who said that there's dignity in the choice and dignity in being able to take that risk. I would like to be able to present that to people, again, with all of this knowledge that we have, to say that, "Okay. You know what? I would like for you to get a blood draw every week for the next 18 weeks. I think that is going to help us make things safer." But I don't want to have to spend an hour explaining exactly how the REMS works, and it's 6 months, and then 6 months, and it's the rest of your life. I'm trying to get this person to think about the next couple of weeks, or even how about the first dose?

So to me, I think that there is going to be a patient who's not going to get blood draws. And you know what? Most likely that patient is going to do better because they were on clozapine. If they happen to be the really unfortunate person who does develop a problem, that is, again, part of the discussion. And actually, I feel like by not having a REMS, it empowers me to have a more

productive and reasonable conversation about the risk of agranulocytosis or neutropenia because I'm actually presenting it to them as something that I'm concerned about as a potential side effect and not as a regulatory requirement.

(Applause.)

DR. FLOYD: I'd like to briefly comment on something that you said. I think currently with the REMS, there is no possibility of a risk-benefit discussion and saying the benefits are overwhelming compared to the risks from not monitoring. As someone has brought up, it is actually uncertain what the benefits are of monitoring in terms of preventing mild neutropenia, to go into symptomatic, and sepsis, or something like that, so I agree with you.

We have about 40 minutes left in the meeting, and that's about how long it takes for a whole panel to get through two voting questions and have plenty of time to explain their rationale. We have Dr. Narendran and Dr. Canuso. I'd like them to go.

Is there anyone else who wants to make comments in an open-ended way before we get to the voting questions, where you'll once again get a chance to explain your thinking?

Okay, go ahead, Dr. Vyas.

DR. VYAS: Thank you. Really quick, just to continue on Dr. Ballon. The number of people that wouldn't even consider clozapine -- because right now we can't register for REMS unless you have that initial ANC. You have to get at least one, and there are many people that I will -- we run a unit where most everybody is on clozapine, but when we have folks come over, as soon as I get a CBC -- if it's infrequent, sometimes they will not have had a CBC from when they were first admitted, and this is a long-term kind of forensic setting.

The second I get a CBC, I'll just register them just in case they change their mind and agree to try it later. They're at least registered. And that's the thing, that if somebody is so sick, they won't even agree to one, but they'll take the pill, but you're not coming at me with that needle.

(Applause.)

DR. FLOYD: Dr. Narendran?

DR. NARENDRAN: I'll keep this short. I just want to echo my colleague, Dr. Ballon. I think most psychiatrists are going to do it. They're going to do the ANC; I do feel confident. Will there be a patient who maybe doesn't want to do it and then miss a week when they should be taking it weekly? It may happen. But again, that's a conversation they can have between the provider and the patient, and the risk-benefit could be weighed against it. So I think there could be a slightly increased risk, but don't even know; that with the REMS, they didn't seem like they got it weekly. A lot of people were getting it less because of all these dispense authorizations and stuff, which most people like me didn't even know about.

So I wouldn't really burden them more with education, and registration, and stuff. It's a little bit like we had with the Suboxone X-waiver problem. When we had the X-waiver, a lot of people

had it but they weren't prescribing it, and when you removed the X-waiver, that burden is gone, and now people are getting it. It's more access. People can bridge people, so it's not just the people in internal medicine. So I think you'll get a lot more providers who would provide this option for patients. So that's my take.

(Applause.)

DR. FLOYD: Dr. Canuso?

DR. CANUSO: Yes. I'd like to echo the sentiments of colleagues as well, and I think that physicians will monitor as required by the label. But whether we abolish the REMS or whether we minimize the burden of the REMS, I think it's going to take a wholesale educational campaign and that there's an opportunity with this change in this meeting, with the community coming together, to make that effort.

I think there are a lot of barriers besides the REMS, and all the testimony of the drug being the last resort and the resistance. I was very reassured to hear from the APA, especially the

young psychiatrist, the trainees, with I think some renewed interest in really bringing this life-saving treatment to patients after 40 years. But I think we as a community together really need to move the needle, and it's not just going to be with the blood draws.

(Applause.)

DR. FLOYD: Okay. So we're moving now to the voting part.

I'm supposed to summarize the discussion. I feel like there have been so many great points. I feel like there's broad agreement, and people have brought up numerous issues about how the current implementation of the REMS, while well-intentioned, has presented numerous obstacles. And it seems overwhelming that the benefits outweigh the risks for the vast majority of patients who might be considered for clozapine who have treatment-resistant schizophrenia, and also for the vast majority of providers who right now don't consider it an option and aren't willing to enroll in a registry or something like that.

I have to be honest, I'm not going to remember all the detailed issues but, fortunately, we have a transcript of all these great comments if the FDA wants to listen. But I do want to move along to the questions and the votes.

The question here is, are the requirements for the prescriber to document ANC results and the pharmacy to verify these results necessary to ensure safe use; yes or no? So this question is specifically talking about the documentation aspect of REMS, not whether physicians will do monitoring or whether the labeling will change, but just is it necessary to have that documentation requirement.

We'll be using an electronic voting system. Once we begin the vote, the buttons will start flashing, and will flash even after you enter your vote. Press the button firmly that corresponds to your vote. If you're unsure or you want to change your vote, you may press the corresponding button until the vote is closed.

After everyone votes, the vote will be locked. It'll then be displayed on the screen.

The DFO will read the vote from the screen into the record; then we'll go around the room, and each individual who voted will state their name and vote into the record. You can also explain your reason, if you want. If you've already kind of explained your reasoning in previous comments, there's there's no requirement that you do that.

I also want to bring up a little bit of nuance just to get the FDA as much granular feedback as we can give them. Others have brought up an option for a shorter period of documentation of ANC monitoring, 18 weeks as an option. So if that's something that you support, you can vote yes and explain that detail. If you don't think there should be any documentation requirements, you simply would vote no, just to make that clear.

DR. SEO: Sorry, Dr. Floyd. If we could just take a moment and confirm if anyone on the panel has any questions related to the wording of the question; if not, I'll hand it back to Dr. Floyd.

(No response.)

DR. FLOYD: Please vote.

(Voting.)

DR. FLOYD: Has everyone voted?

DR. SEO: This is Jessica, DFO. The results are as follows. For the record, 1 yes, 14 noes, and 0 abstentions.

Dr. Floyd?

DR. FLOYD: Now that the vote is complete, we'll go around the table and have you record your vote into the record. State your name and your vote, and if you want, you can share your reasoning. We'll start with Dr. Perkins.

DR. PERKINS: Jeremy Perkins, hematologist/oncologist. The reason why I voted no is there are many other medications with risk for immunosuppression that do not require REMS and require conversations between patients and their providers. And this is, in my mind, no different than many other medications that we use, and we shouldn't have to do REMS for this.

(Applause.)

DR. EHRET: Meghan Ehret. I also voted no.

Prescribers should be monitoring per the label without the need for submission. The benefits of clozapine far outweigh the risks. In a patient-centered approach, a patient and provider should be creating this plan, and I believe the REMS has created an undue burden on patients and the healthcare providers.

(Applause.)

DR. DUBLIN: I'm Sascha Dublin. My vote was no, and I very much mirror my colleagues who've spoken; that I do believe in monitoring in the ideal situation, particularly in the first 18 weeks, but I do not believe that the REMS approach to documenting and enforcing that is serving the health of the patients, the needs of the community, or the well-being of providers. I hope we can find better ways to support appropriate monitoring that don't have a punitive and technocratic approach that are a burden.

(Applause.)

DR. FLOYD: James Floyd. I voted no for reasons I've shared already.

MR. BRISBIN: Michael Brisbin. I voted no. The logistical challenges caused by REMS discourages prescribers from using clozapine, reducing access to medication that saves lives. This excessive caution has harmed more patients by restricting treatment than rare cases of neutropenia.

(Applause.)

DR. NARENDRAN: Raj Narendran. I voted no for reasons already I explained.

DR. DUNN: Walter Dunn. I voted yes, but let me explain. I was about to vote no, but then when Dr. Floyd mentioned the 18-week scenario, I just want to give an opportunity to kind of explain the rationale there. I think certainly during that first 18 weeks where there's an increased risk, there can be a role for a REMS to require monitoring; however, I would still advocate the creation of a more streamlined care option, where providers, patients, and pharmacies can easily avoid the necessity for a documented ANC. So basically, if it's clear that that's going to be an

absolute barrier to care or that's going to make it difficult for the patient, we should make it as easy as possible to remove that requirement.

Again, what my colleagues mentioned earlier about calling it a waiver, calling it a dispense rationale, that clearly is not working. So I think all the options should be on the table, and they should be equally accepted by pharmacies because that seems to be one of the friction points. So whether it's A, B, or C, no ANC, ANC, or no half of ANCs. It should be equally accepted by the pharmacy. So it's a yes; however, it's not an absolute requirement that the ANC be there.

DR. VYAS: Hi. I'm Gopal Vyas from University of Maryland. I voted no. Believe it or not, I changed my mind. I mean, I'm still for no, but I would have said yes initially for 18 weeks, and I'm very much a clozapine zealot. But being in touch with the testimony from loved ones, caregivers, individuals living with the illness, it is very moving, and certainly has moved me. One of the things that's important is reducing every

barrier, and the only way to do that I think now is elimination of this. Thank you.

(Applause.)

DR. BALLON: Jake Ballon from Stanford. I have fantasized for years about abolishing clozapine REMS --

(Laughter.)

DR. BALLON: -- so I very enthusiastically voted no in this case. That said, like Dr. Vyas just mentioned, I was also persuaded in thinking about whether or not actually having a partial monitoring program or something like that would make sense, and very strongly persuaded not to do it.

Recognizing that I live and work in a suburban environment with abundant resources makes it kind of a choice about whether or not to get labs and things like that; that many people do not have those kinds of access. I work with a population that's, by and large, well resourced, privately insured. They have the ability to get that; many people really do not have that and

shouldn't be withheld from clozapine for that. So I really appreciate the opportunity to be able to give my views and to be able to express that in this meeting.

(Applause.)

DR. SALVAS: Brian Salvas. I voted no. Simply put, it should be up to the prescriber and their professional judgment to follow the FDA labeling. Creating barriers at the pharmacy counter does not serve the goals of clozapine therapy.

(Applause.)

DR. DEJOS: Mike Dejos. I voted no for reasons already stated.

(Applause.)

DR. REBO: Elizabeth Rebo. I voted no as well, for reasons already stated.

(Applause.)

DR. AMIRSHAHI: Maryann Amirshahi. I voted no. I just wanted to add that I think that it is important that prescribers do check the ANC and monitor patients appropriately, but it doesn't need

to be verified by a pharmacist because that is an extra step that isn't always integrated into the EMR and creates an unnecessary barrier. I also feel that clozapine should be available at any and every pharmacy, and shouldn't be restricted to specific pharmacies. Also, we can maybe use this as a dialogue to help allow for bridging prescriptions as well. Thank you.

(Applause.)

DR. SEO: Dr. Floyd, before you summarize, could we recognize our virtual participants to read their vote into the record?

DR. FLOYD: Oh, my apologies. Yes, please. Could we start with Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. Hello. Jess Fiedorowicz. I voted no, and previously discussed reasons why we should retire the REMS.

(Applause.)

DR. FLOYD: And Dr. Hertig?

DR. HERTIG: John Hertig, Butler University. I also voted no. The nice thing about going near the end is it's been well articulated, but I will

say I use the brand model, so we're looking at benefit, and clear benefit exists here much more than the risks. But also, what are the available alternatives? And those available alternatives are really insufficient. They're really insufficient. And then the end is doing nothing and, really, I think we heard from public testimony and the data that doing nothing is clearly not an option here. We have to reduce the barriers. We see a lot of the barriers in the pharmacy. Really, we need to enhance the access to this important therapy. Thank you.

(Applause.)

DR. FLOYD: Thank you. I'll summarize now. I think we heard an overwhelming majority who voted that a documentation requirement of ANC results is not necessary to ensure safe use, with some caveats. I think many of us acknowledge the substantial benefits of this treatment, a life-threatening condition, highly effective, no alternative. So any discussion of safety or benefits of REMS for preventing neutropenia has to

consider the evidence of benefit.

There was recognition that, of course, monitoring should be done. The label recommends it. Current guidance does. All the providers who are engaged in clozapine prescribing continue to do that, although there are some circumstances where the benefits outweigh the risks even in the absence of monitoring, and putting that in the hands of the providers or the physicians was also part of the rationale for some of the no votes.

There was a yes vote, and more than one person commented that if we could relieve some of the friction and have a system of monitoring and documenting results that work better somehow, that it's plausible there could be some benefit in ensuring safety. So that was an opinion that we heard, and I think that's it for the summary.

I'm going to move on to the second voting question. This question states, is the requirement to educate healthcare providers through REMS about the risk of severe neutropenia and the need for ANC monitoring necessary to ensure safe use; yes or no?

And to clarify, this is not asking should we invest resources in CME so that providers can go on a website and learn. This is specifically asking about elements to assure safe use. So this means a physician completes some training and becomes a registered provider, and this goes hand in hand with pharmacies also having to do that to verify a physician/prescriber status, just to make that very clear.

Does anyone have any questions or want additional clarification from the FDA on this question?

DR. DEJOS: Mike Dejos. I have a clarifying question. If we did want to perhaps separate out where prescriber certification be performed and that pharmacy certification be waived, I imagine we would do something similar where we vote yes and state our clarification?

(No audible response.)

DR. DEJOS: Thank you.

DR. FLOYD: That's right, although I think some of the information we got from FDA was to

consider those linked. Is this acceptable if we explain this option?

DR. LaCIVITA: Hi. This is Cynthia LaCivita, FDA. If the education is mandatory and you want to ensure that all the prescribers have received that training, you would have to link it to pharmacy certification because you would want to make sure that those prescriptions were written by a certified pharmacist -- I mean, certified prescriber. Sorry. I misspoke. Thank you.

DR. FLOYD: Okay. If there are no further questions, we'll begin the voting process. Press the button next to your microphone that corresponds to your vote. You have 20 seconds. Press it firmly. After you make your selection, a light may flash. If you're unsure of your vote, just press the button again.

(Voting.)

DR. SEO: This is Jessica Seo, DFO. For question 4, the results are as follows: 1 yes, 14 no, and 0 abstentions.

Dr. Floyd?

DR. FLOYD: Thank you. Dr. Dunn has to leave to catch a flight, so we're going to start with you. Go ahead and read your record into the vote, and provide an explanation if you like, and then we'll start from that side of the room.

DR. DUNN: Thank you. Walter Dunn. I voted yes. The scenario I envisioned is what you mentioned before about only having an educational component. Certainly, as my colleagues have elucidated today, this drug, no doubt this is a life-saving drug. This is pretty much our only option for treatment-resistant schizophrenia. Nobody's contesting that, but clearly, it has more management issues than some of our other antipsychotics.

So just thinking about other medications in our psychiatric armamentarium that require an educational component, esketamine comes to mind, where there does need to be registration by the provider, and then the pharmacy. So I think that probably, at the minimum, is what I think we can tolerate at this point.

I will use this opportunity to talk about the labeling. I know that's not really something that the agency was looking to today, but at the end of the day, I think the goal is two things: number one, reduce the number of missed doses, delayed doses. I think, clearly, the REMS requirement, plays a huge part in that. So if the REMS was modified or removed, I think all those refused prescriptions or doses can be alleviated.

The question for me is, what can we do to increase the number of providers who are willing to prescribe clozapine and what can we do to increase the number of patients willing to take clozapine. And getting rid of the REMS, modifying the REMS, that's not entirely clear to me it's going to achieve that goal. As Dr. Ballon mentioned before, there are a whole host of other issues associated with clozapine other than ANC that are more concerning.

So even if we got rid of the REMS but the label stayed the same, I think that would still be a major friction point, because even though there

wouldn't be a regulatory requirement to fulfill all this paperwork, prescribers would still be reading and go, "Well, but this is the standard of care for clozapine management, and if I can't or I'm not willing to do that, then I'm not willing to prescribe clozapine." So that will be your prescriber out in the community. For those of us in the closed medical system such as the VA or Kaiser, if that label stands, I think we will still have internal controls that will require us to do ANC, and we may not capture more patients even though the REMS is out.

So something for the agency to think about, and again, maybe a stepwise process where we first modify the REMS, and then if we don't see a huge spike in adverse events, then we consider something for the label; but maybe softening the label a little bit so that it gives prescribers latitude to not do the monitoring if it's clear in their clinical judgment that the benefits outweigh the risks.

I know that as clinicians, we're always able

to prescribe off label, so if we deviate from the current label, we could make our justification. But I think giving us a little bit more leeway and space to maneuver, I think, again, will help achieve that goal of getting more patients and getting more prescribers to prescribe clozapine.

(Applause.)

DR. FLOYD: Okay, and now we'll start from this side.

Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi. I voted no. The one thing I will comment on is that I think requiring certification of a pharmacy or a physician to prescribe this medication does present an additional barrier, particularly when we talk about patients running out of their medication and perhaps needing an emergency supply. So I think this would be just one less barrier to prevent people from falling through the cracks and decompensating. Thank you.

(Applause.)

DR. REBO: Elizabeth Rebo. I voted no for

all the reasons that Maryann just stated.

(Applause.)

DR. DEJOS: Mike Dejos, Methodist Le Bonheur Healthcare. I ended up voting no because of the link situation. I think it would actually muddy up the waters a little bit more. So again, I voted no.

(Applause.)

DR. SALVAS: Brian Salvas, CVS. I voted no. The neutropenia risk, particularly during therapy initiation and titration, is real. That said, alternative mechanisms to drive provider awareness and compliance to the labeling should be considered, including alternatives to prescriber and pharmacy enrollment. All of that said, we did not have a conversation today focused on unlocking the care gap for the providers that are not currently engaged in clozapine.

DR. BALLON: Jake Ballon, Stanford. I voted no. I did actually come to this meeting thinking that I was probably going to vote yes on this but am persuaded by the potential for really

overcomplicating things by mandating a particular and specific training. I think about a scenario recently where I was asked to prescribe a medication by one of my patients to target a side effect with weight gain, and the original prescriber of that medication did not want to continue prescribing it because of a rare side effect. And it was incumbent upon me to educate myself, and to reach out to other affiliated prescribers to understand the risk and benefit of doing that, and I chose to prescribe that medication, in that context.

I feel like we can expect psychiatrists and we can expect physicians to educate themselves on important medications, and if they're going to take on a medicine that they don't typically prescribe, it is incumbent upon their responsibility, their oath, their education, and their training to educate themselves enough to be able to write a prescription, and to understand what they need to do to follow that up, and to engage with other providers when it is outside of their expertise.

I'm an academic. I want to teach. I want to educate. I believe there are an abundant number of resources that are even free for people to learn about clozapine. I would encourage that we push our efforts to make sure people are taking advantage of those resources.

(Applause.)

DR. VYAS: Gopal Vyas, University of Maryland. We heard a lot of reference today to well-oiled machines, maybe here and there, some reference to well-oiled machines, and that in academia this is being done, and it's being done smoothly. But there are folks here from Pitt, and UCLA, and Maryland, and Stanford, and Emory. I don't think anybody would say that despite being in an ivory tower and having a well-oiled machine, that any of this goes smoothly.

I think to do our best job to provide the people that we're charged to care for, REMS is like pouring a little bit of gravel into that well-oiled machine, and I don't think it'll run very well with that. Thank you.

(Applause.)

DR. NARENDRAN: This is Raj Narendran, and I voted no. Having sat on the PDAC for almost a decade, I tell everyone, "Don't prescribe anything without reading the package insert. These people put a lot of work into it." So I think all you need to know about how to prescribe is in the package insert, so I think the package insert, the black box, should be sufficient for people to do it. And if they don't, they're exposing themselves to liability. So I think a good physician in this country should read the package insert, and that's sufficient.

(Applause.)

MR. BRISBIN: Hi. Michael Brisbin. I voted no. My rationale was the FDA's data confirms that prescribers and pharmacists already have high levels of knowledge about the risks of clozapine-induced neutropenia and the need for ANC monitoring. This education is already widely integrated into standard medical training, professional guidelines, and continuing education

programs, rendering the REMS education redundant.

(Applause.)

DR. FLOYD: James Floyd. I voted no. I actually came into this meeting, after reading the briefing materials, thinking that this might be a yes because I've seen physician registration, pharmacy registration, as a much less onerous obstacle than documentation. But after understanding the magnitude of untreated, treatment-resistant schizophrenia, it became clear to me that even this barrier was not worth the harm done.

I also want to be clear that we're not talking about dismantling REMS; we're talking about these specific elements to assure safe use. Most REMS don't involve any of these. REMS can be a black box warning, a Dear Doctor letter, and also postmarket safety studies. Whatever changes the FDA might make, I'd imagine you'd want to study the impact in the VA, or a Kaiser, or something like that. So those are useful aspects of the REMS that I hope would continue.

(Dr. Farchione gestures no.)

DR. FLOYD: They're not?

DR. FARCHIONE: They're there. That's part of labeling and pharmacovigilance, but they're not REMS. But that's ok. The sentiment is understood.

(Applause.)

DR. DUBLIN: I'm Sascha Dublin from Kaiser Permanente Washington, and I voted no. So many wonderful rationales have been given. I think, to me, this isn't the right avenue to educate providers. It's not the right mechanism, it's not the right providers we'd be educating, and it's not the right topic. So I think it's doing more harm than good, and we need to add more oil to the machines, not less.

(Applause.)

DR. EHRET: Meghan Ehret. I voted no. I realized after today that providers are not learning about the risks and benefits of clozapine from the REMS itself. They know this material prior to taking that assessment. No study that was presented here, to me, today demonstrated that the

knowledge learned through the REMS prevented any severe neutropenia, and the studies presented here today looked at those of physicians, where half of prescribers are not physicians.

(Applause.)

DR. PERKINS: Jeremy Perkins. I voted no. I feel like the REMS requirement to educate healthcare providers about the risk of neutropenia is excessive, and the package insert for monitoring by providers should be sufficient without that additional REMS requirement.

(Applause.)

DR. FLOYD: Dr. Fiedorowicz?

DR. FIEDOROWICZ: I voted no as well. I want to thank everyone for convening this meeting, and I also want to thank the participants who presented and made it clear that for some patients, the greatest risk of clozapine is not getting clozapine. That was, I think, heard loud and clear by the committee, and I think it's important --

(Applause.)

DR. FIEDOROWICZ: -- for us to remove REMS.

(Applause.)

DR. FLOYD: Dr. Hertig?

DR. HERTIG: John Hertig. I voted no. I trust our physicians. I trust our physician extenders and our pharmacists to take care of their patients. They have the ability and skills to do that outside of a REMS program. This REMS program clearly isn't working as intended, and we need to enhance access to really vital mental health services, including clozapine. Thank you.

(Applause.)

DR. FLOYD: So to summarize briefly, I think we heard an overwhelming majority express the sentiment that the big issue is untreated treatment-resistant schizophrenia and less so deficiencies and monitoring, and registering physicians and pharmacies still presents a barrier that would result in treatment gaps. We also did hear that even with the REMS gone, there are some healthcare systems that might not change monitoring and documentation requirements, so that's a possibility.

With that, I think that we are about ready to adjourn, but first I should ask, are there any comments from the FDA?

DR. LaCIVITA: Hi. Cynthia LaCivita from the FDA. I want to thank the committee, and I want to thank those of you that spoke at the public hearing today. We appreciated all your comments, and we thought this was a very worthwhile meeting. Thank you.

(Applause.)

DR. FARCHIONE: This is Tiffany Farchione. I want to echo those sentiments as well, thanking the committee for your thoughtful discussion, and especially thanking the folks who actually spoke during the open public hearing. I want you to know that we hear you. We're here today because of you and your loved ones, and your stories are important, and your experience is important. And what you've shared today will have an impact on regulatory decision-making. So I want you to know that and hear it straight from me that we do appreciate you.

(Applause.)

Adjournment

DR. FLOYD: And the panel would like to thank all of you for coming and sharing your stories, too. So with that, we'll adjourn the meeting on time. Thank you, everyone.

(Whereupon, at 4:53 p.m., the meeting was adjourned.)