CLOZAPINE REMS

FDA Advisory Committee Meeting Clozapine Risk Evaluation and Mitigation Strategy

November 19, 2024

Accord Healthcare, Inc.; Aurobindo Pharma USA, Inc.; Dr. Reddy's Laboratories, Inc.; HLS Therapeutics (USA), Inc.; Mylan Inc., a Viatris Company; Sun Pharmaceutical Industries, Inc.; Tasman Pharma, Inc.; Teva Pharmaceuticals USA, Inc.

CLOZAPINE REMS

Introduction

Jason A. Gross, PharmD

Vice President of Scientific Affairs
HLS Therapeutics (USA), Inc.

Clozapine Product Manufacturers Group (CPMG) Sponsors

accord
We make it better

AUROBINDO
Committed to healthier life!

Dr. Reddy's *

HLS Therapeutics®

SUN PHARMA

Tasman Pharma

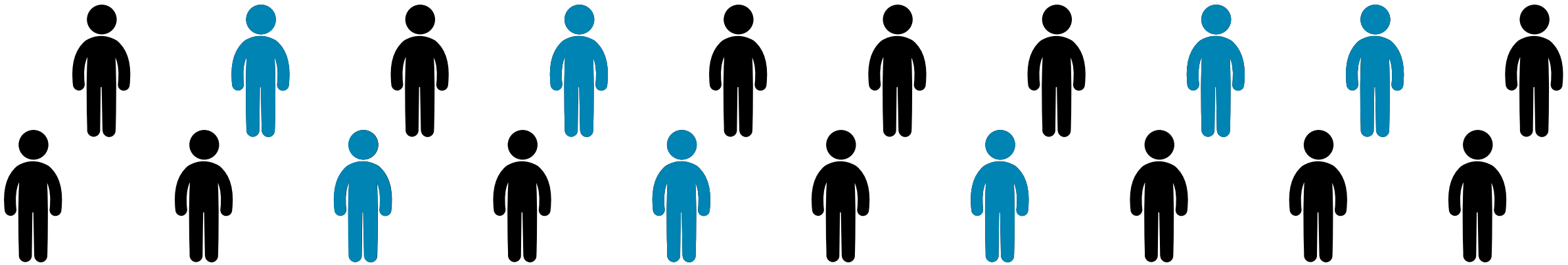
teva

VIATRIS

*Exiting REMS participant.

Treatment-Resistant Schizophrenia

- Schizophrenia affects approximately 1% of people globally[1]



= Individual with TRS

Estimated prevalence of treatment-resistant schizophrenia (TRS): ~22-39.5%[2,3]

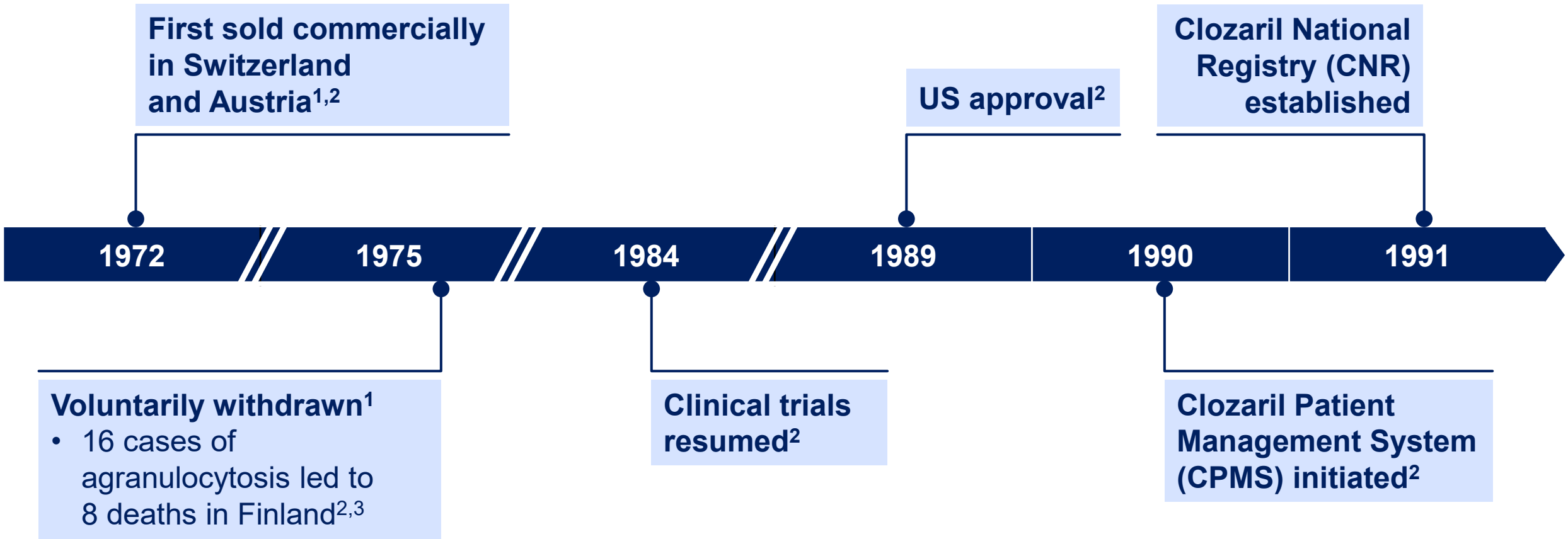
1. Marder SR, Cannon TD. *N Engl J Med*. 2019;381(18):1753-1761; 2. Diniz E, et al. *Braz J Psychiatry*. 2023;45(5):448-458; 3. Mørup MF, et al. *PLoS One*. 2020;15(6):e0234121.

Clozapine: Only Therapy Approved for Patients With TRS

- Serotonin-dopamine antagonist
  - Effective for patients who have not responded to other medicines
- Only treatment to:
  - Reduce suicide risk, improve overall mortality in TRS
  - Reduce persistence of psychosis, risk of relapse, hospitalization, violence, and aggression
  - Improve functioning, reduce burden on families and caregivers
- Treatment disruptions may lead to severe adverse events

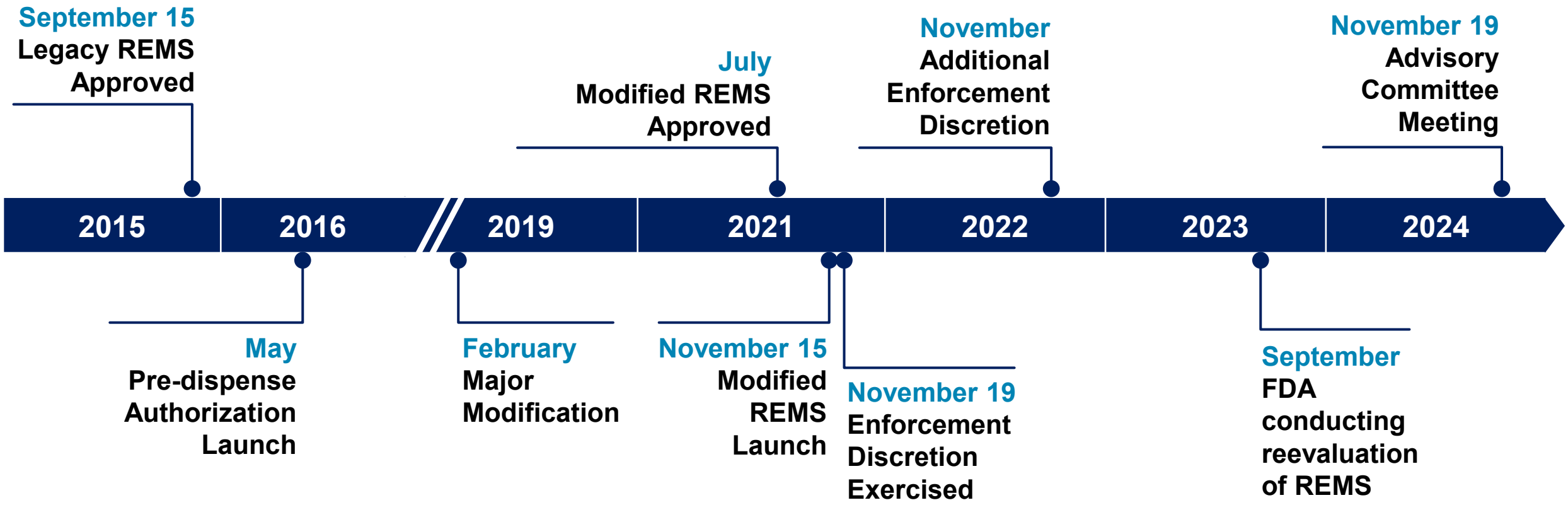
Meltzer HY. *Clin Schizophr Relat Psychoses*. 2012;6(3):134-144; Legge SE, et al. *Schizophr Res*. 2016;174(1-3):113-119.

Early History of Clozapine



1. Turkmani K, et al. *Cochrane Database Syst Rev*. 2019;(1):CD013248; 2. Crilly J. *Hist Psychiatry*. 2007;18(1):39-60; 3. Meltzer HY. *Clin Schizophr Relat Psychoses*. 2012;6(3):134-144.

Regulatory History of Clozapine REMS



What You Will Hear From CPMG Today

- Enrollment/Certification in Modified REMS meets or exceeds prior levels
- When a stakeholder participates in the REMS, the REMS provides a resource to document compliance with monitoring requirements
  - Adherence to monitoring, stakeholder knowledge
  - Enforcement Discretion, REMS design/implementation limit ability to collect data
  - Stakeholder knowledge gaps still exist
- Review of REMS and FAERS data shows no evidence of a change in the clozapine safety profile
- Stakeholders are concerned about obtaining clozapine, maintaining continuity of care
  - REMS programs by their nature have an inherent level of burden
  - Many challenges related to clozapine are independent of the REMS
- CPMG committed to working with FDA and stakeholders to address challenges while maintaining safe use of clozapine

Agenda

Clinical Context of Clozapine

John Kane, MD
The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

- **Role of clozapine in treatment of schizophrenia**

Clinical Implications

Robert O. Cotes, MD
Emory University School of Medicine

- **Clinical perspective on treating patients in clozapine REMS**

REMS Operation and Assessments

James Shamp
Examoto, a UBC Company

- **Review of REMS operation assessment data from 2015 to 2024**

AE Reporting, Stakeholder Feedback, and Opportunities for Improvement

Jason A. Gross, PharmD
Vice President of Scientific Affairs
HLS Therapeutics (USA), Inc.

- **Adverse event reporting and opportunities for improvement to the REMS**

Clozapine REMS Experts

Kelly Coombs
Syneos Health

David Sykes, MD, PhD
Harvard Medical School, Massachusetts General Hospital

CLOZAPINE REMS

Clinical Context of Clozapine

John Kane, MD

The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

Disclosures

- I am a paid consultant to CPMG
- I have received honoraria for lectures from HLS Therapeutics, Inc.
- I am a consultant to Teva Pharmaceuticals USA, Inc.
- I have no financial interest in the outcome of today's meeting

Clozapine Is a Cornerstone in Treatment of Schizophrenia

- Schizophrenia[1]
  - Affects approximately 1% of people globally
  - Lifetime risk of developing schizophrenia ~1%
  - Men more likely to receive diagnosis than women, incidence rate ratio of ~1.7
- Treatment-resistant schizophrenia (TRS)[2,3]
  - Persistence of positive symptoms despite ≥ 2 trials of adequate dose and duration of antipsychotic medication with documented adherence[4]
  - Even among first episode patients, 15-22% are treatment resistant
  - Estimated prevalence increases to as high as 40% with more chronic illness

1. Hany M, et al. Schizophrenia. [Updated 2024 Feb 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539864/;
2. Diniz E, et al. *Braz J Psychiatry*. 2023;45(5):448-458; 3. Mørup MF, et al. *PLoS One*. 2020;15(6):e0234121; 4. Howes OD, et al. *Am J Psychiatry*. 2017;174(3):216-229.

Added Benefits of Clozapine Have Emerged Over Time

- Enormous treatment benefit for patients with TRS
- Patients on clozapine live longer than patients not on clozapine
- Reduced
  - Persistence of psychosis
  - Risk of relapse/hospitalization/suicide
  - Mortality
  - Violence/aggression
  - Family burden
- Improves functioning
- Direct and indirect economic benefits

30 years post-approval, still no other drugs approved for TRS

Meltzer HY. *Clin Schizophr Relat Psychoses*. 2012;6(3):134-144; Legge SE, et al. *Schizophr Res*. 2016;174(1-3):113-119.

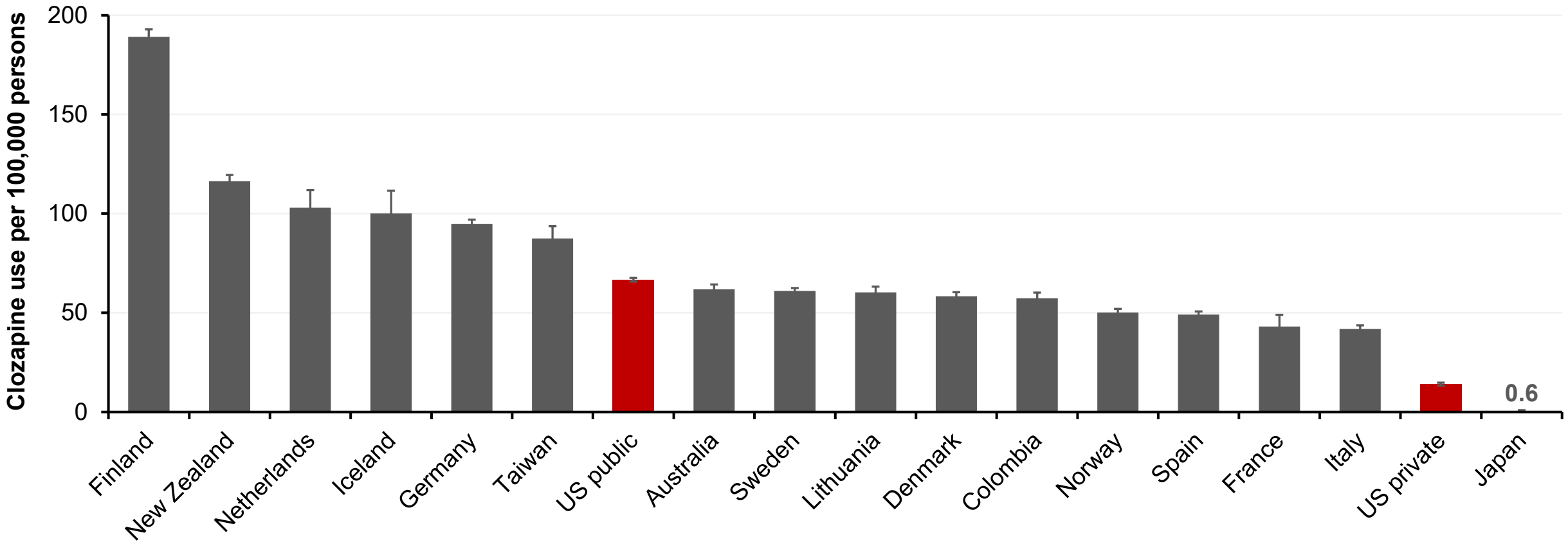
Delays in Prescribing Clozapine Are Common

- Although guidelines recommend starting clozapine after 2 AP treatment failures, its introduction is often delayed by several years[1,2]
- Patients are often exposed to multiple AP medications or combinations before, if ever, receiving a trial of clozapine
- Data suggest that significant delays in its initiation are associated with poorer treatment response to clozapine[3-6]

AP = antipsychotic.

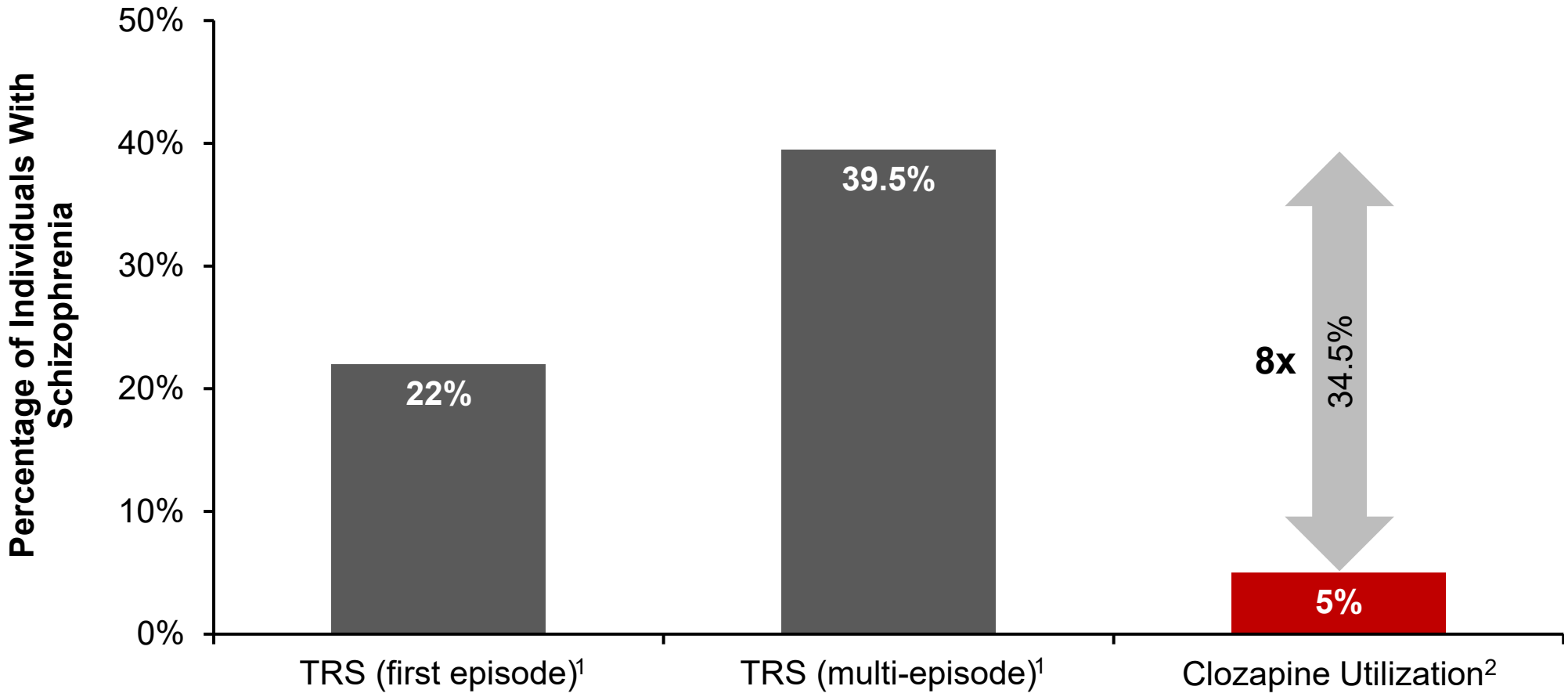
1. Howes OD, et al. *Br J Psychiatry*. 2012;201(6):481-485; 2. Najim H, et al. *Psytchiatry Danub*. 2013;25(suppl 2):165-170; 3. Hatano M, et al. *BMC Psychiatry*. 2023;23(1):673; 4. Shah P, et al. *Psychiatry Res*. 2018;268:114-122; 5. Üçok A, et al. *Int Clin Psychopharmacol*. 2015;30(5):290-295; 6. Yoshimura B, et al. *Psychiatry Res*. 2017;250:65-70.

The US Lags Behind in Clozapine Use



Bachmann CJ, et al. *Acta Psychiatr Scand*. 2017;136(1):37-51
Prevalence of clozapine use in 2014 (or the most recent year available) with the following exceptions: Australia (2005–2013), Colombia (2006–2014), France (2006–2014), Italy (2005–2012), Japan (2009–2014), Spain (2011–2014), Sweden (2006–2014), Taiwan (2005–2013) and publicly insured US cohort (2005–2010).

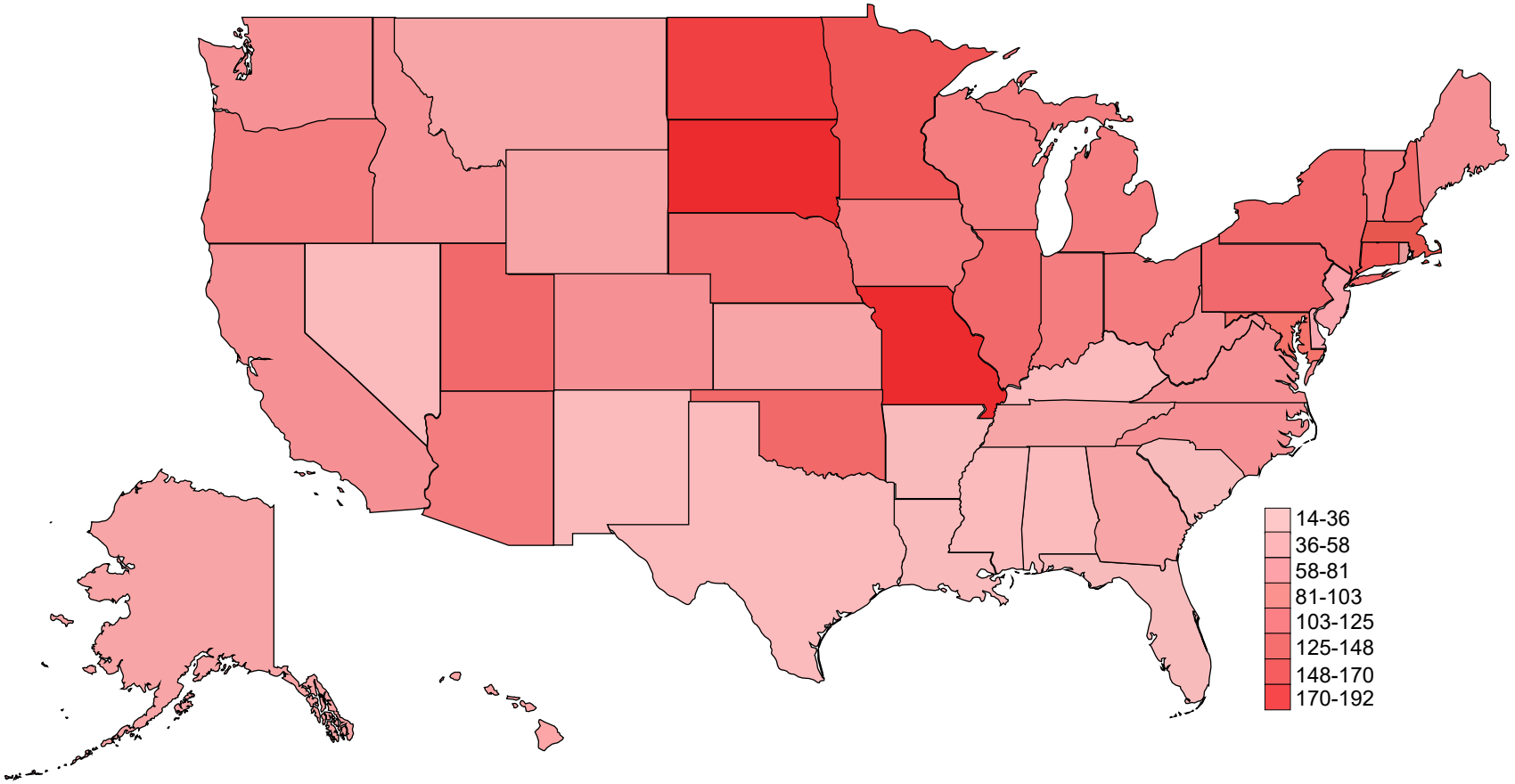
US Clozapine Underutilization Gap



1. Diniz E, et al. *Braz J Psychiatry*. 2023;45(5):448-458; 2. Olfson M, et al. *Psychiatr Serv*. 2016;67(2):152.

Clozapine Use Varies Greatly by Geographic Region

2019 Prescriptions per 100,000 Medicaid Enrollees



Adapted from *Schizophr Res*, 255, Benito RA, et al, Thirteen-fold variation between states in clozapine prescriptions to United States Medicaid patients, 79-81, Copyright 2023, with permission from Elsevier.

Barriers to Using Clozapine in TRS

- Patient/Drug-related barriers:
  - Refusal of blood tests
  - Clozapine tolerability
  - Questionable adherence
- Clinician-related barriers:
  - Reluctant to recommend clozapine
  - Inadequate knowledge/adherence to guidance
  - Benign congenital (ethnic) neutropenia
  - Difficulty in identifying suitable patients and unclear diagnoses
  - Need for intense monitoring
  - Perception that patients may not comply with treatment/monitoring
  - Psychiatrists have stopped hoping that the patient will improve

Farooq S, et al. *BJPsych Bulletin*. 2019;43(1):8-16.

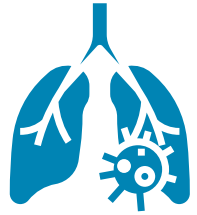
Clinicians Must Manage Clozapine Side Effects

Myocarditis/
Cardiomyopathy

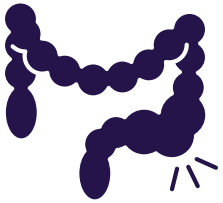
Orthostatic
Hypotension

Bradycardia/
Syncope

Seizures



Pneumonia

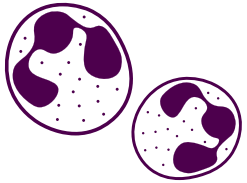


Gastrointestinal
Hypomotility

Hyperlipidemia

Weight Gain/
Metabolic Syndrome

Hypersalivation



Severe
Neutropenia
(Agranulocytosis)

Risk of Clozapine-Induced Neutropenia Decreases Over Time

- Most serious neutropenia leading to clozapine cessation occurs within 18 weeks[1]
  - Incidence negligible after 2 years
- Weekly monitoring after 18 weeks could be safely reduced to every 4 weeks and ceased after 2 years unless clinically indicated[1]
- Clozapine retrial after interruption with 2 cumulative years of unremarkable testing might not require further hematological monitoring[1]
- Long-term risk excess is small compared with advantages of clozapine in outcomes, including life expectancy[2]
- Relaxing long-term monitoring could favor the advantages of clozapine use, without incurring risk of neutropenia[2]

1. Northwood K, et al. *Lancet Psychiatr*. 2024;11:27-35; 2. Rubio JM, et al. *Lancet Psychiatr*. 2024;11:443-450.

Neutropenia-Related Death Is Rare

- Meta-analysis of 36 studies with 260,948 clozapine-treated patients examined prevalence of neutropenia and related death in clozapine-treated patients
- Prevalence of clozapine-associated neutropenia is low
  - Neutropenia caused by clozapine: 0.4%[a]
  - Related death: 0.05%[b]

[a]95% CI: 0.3–0.6%; [b]95% CI: 0.03–0.09%.
Li X-H, et al. *Psychologic Med*. 2020;50(4):583-594.

Stringent ANC Monitoring Can Affect Use

- Frequent monitoring is a factor that can lead both patients and clinicians to underutilize and discontinue clozapine[1,2]
- Previous studies suggested that flexible neutrophil monitoring may contribute to long-term clozapine maintenance[3]

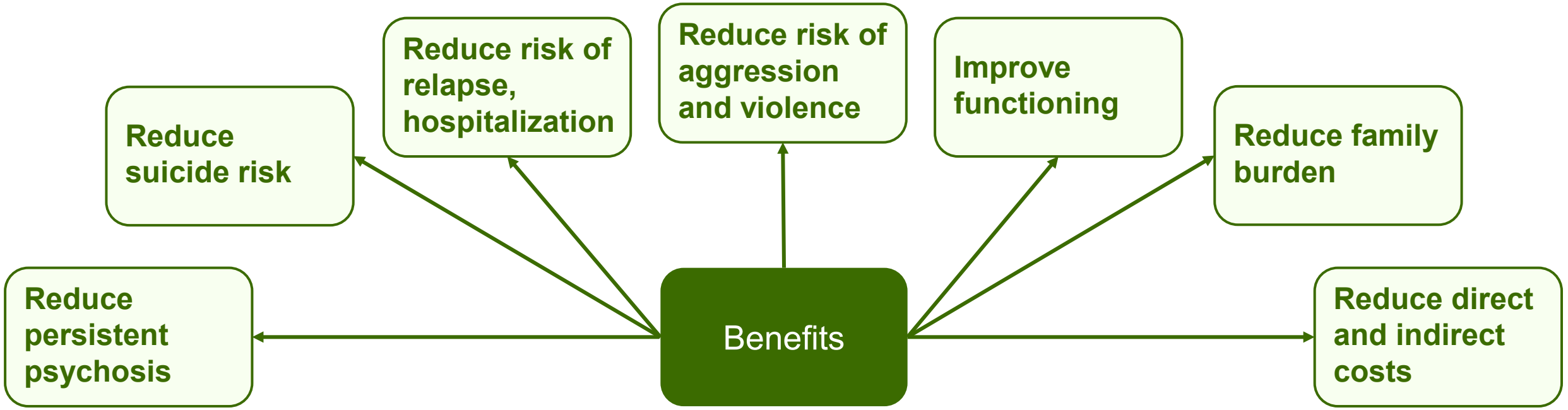
1. Legge SE, et al. *Schizophr Res*. 2016;174(1-3):113-119; 2. Bogers JP, et al. *J Clin Psychopharmacol*. 2016;36(2):109-111; 3. Ingimarsson O, et al. *BMC Psychiatry*. 2016;16(1):441.

Global Monitoring Comparison of Labels

Country	Normal Monitoring
United States[1]	• Monitor weekly for 6 months, then every 2 weeks for months 6-12, then monthly if ANC in "normal range"
Australia,[2] **European Union,**[3] **New Zealand**[4]	• Monitor weekly for 18 weeks, then at least monthly throughout treatment and for 1 month after discontinuation
Canada[5]	• Monitor weekly for 26 weeks, then every 2 weeks for the next 26 weeks, then at least every 4 weeks thereafter

1. CLOZARIL (clozapine tablet) [prescribing information]. HLS Therapeutics (USA), Inc. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=90876802-0e3a-44c9-9ff7-1754dfbe736a;
2. CLOPINE (clozapine) [Australian product information]. Pfizer Australia Pty Ltd. Available at: https://apps.medicines.org.au/files/pfpcloia.pdf;
3. Clozaril [Summary of Product Characteristics]. Mylane Products Ltd. Available at: https://www.medicines.org.uk/emc/product/4411/smpc/print;
4. CLOZARIL [New Zealand data sheet]. Viatris. Available at: https://www.medsafe.govt.nz/profs/datasheet/c/Clozariltab.pdf;
5. PrAA-Clozapine (clozapine tablets) [product monograph]. AA Pharma Inc. Available at: https://pdf.hres.ca/dpd_pm/00070192.PDF.

Clozapine's Potential Role in Improving Patients' Lives



- For some patients, clozapine treatment can be life-changing
- Benefit/Risk assessment individualized; requires therapeutic trial of clozapine

CLOZAPINE REMS

Clinical Implications

Robert O. Cotes, MD

Emory University School of Medicine

Disclosures

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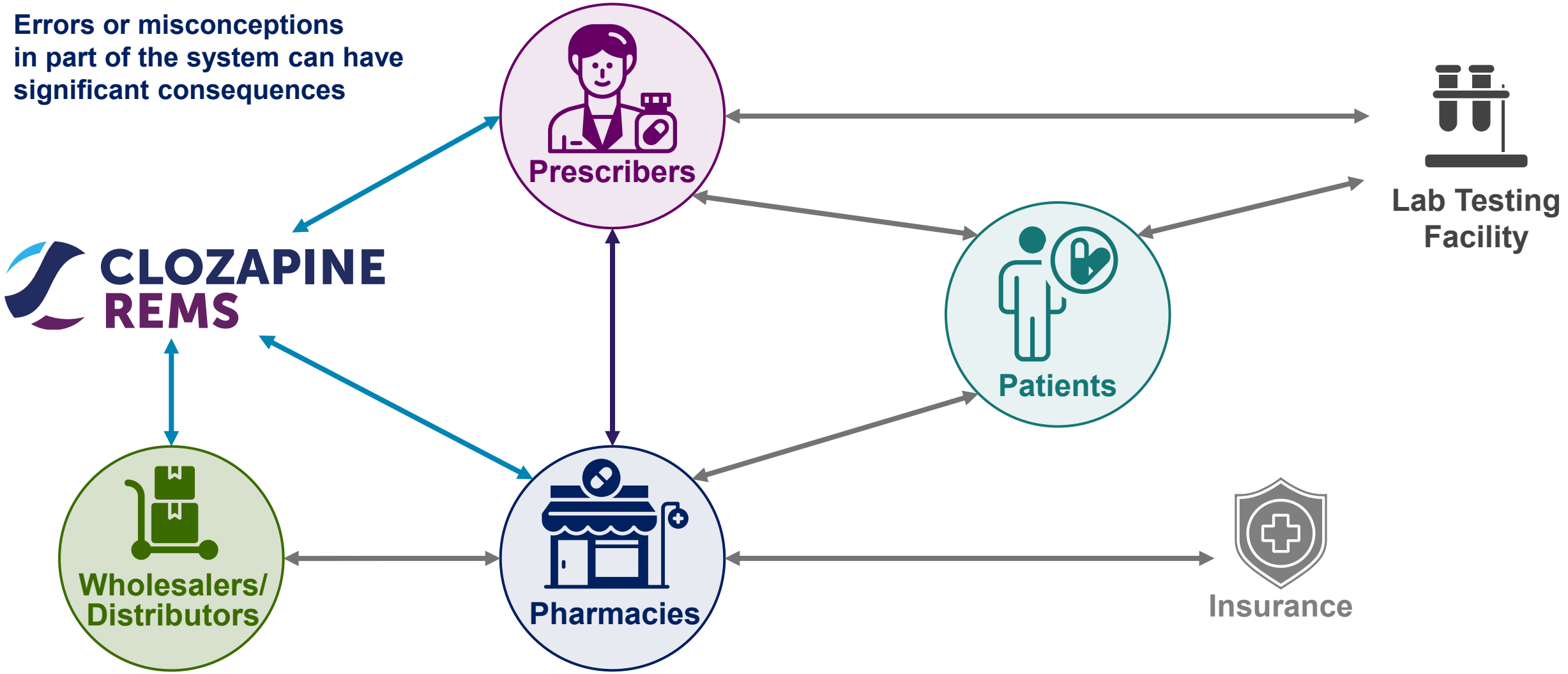
Prescribing Clozapine Occurs in a Delicate System

Errors or misconceptions in part of the system can have significant consequences



Patient and Caregiver Challenges

- Difficulty finding prescribers to start or continue clozapine
- Patients often navigate this process on their own
  - May have executive functioning challenges
  - Transportation can be a barrier
  - May not have caregiver support
- Indefinite monthly hematologic monitoring has unintended consequences

Prescriber Challenges

- Hesitancy to start, troublesome to continue
- Lack of familiarity and knowledge about clozapine
- Perception of patient-related challenges may lead clinicians to choose not to recommend clozapine
- Inpatient clozapine prescribers may not know of outpatient clozapine prescribers
- Lack of time and reimbursement

Cotes RO, et al. *Community Ment Health J*. 2022;58(3):517-525; Verdoux H, et al. *Schizophr Res*. 2018;201:10-19.

Pharmacy Challenges

- Chain pharmacy corporate requirements
  - Even when PSF is completed, prescribers and systems often must fax bloodwork to pharmacy
- Difficulties reaching prescribers
- Opportunities for Dispense Rationale may be missed

Lab Challenges

Lab Testing Facility

- Point-of-care testing helpful but used infrequently
- Appointments needed at labs (rather than walk-ins), and patients must navigate lab hours
- Many labs require order faxed monthly, adding to system burden
- Sometimes the wrong lab test is drawn and ANC not obtained
- Labs exist in a different electronic health record system

Interruption Occurs and Has Consequences

- In one study, 60% of clozapine prescribers (N=196) agreed or strongly agreed with the statement, "The safe use requirements have often caused delay in my patients receiving medication."[1]
- Potential consequences of missed doses include[2]
  - Need for re-titration
  - Psychological distress
  - Physical discomfort/withdrawal
  - Symptom exacerbation (~20%)
  - Hospitalization

1. Sarpatwari A, et al. *Clin Pharmacol Ther*. 2024;115(6):1293-1303; 2. Moncrieff J. *Acta Psychiatr Scand*. 2006;114(1):3-13.

Reality on the Ground: Prescribing Clozapine Is Hard

- Coordinating care across settings is uncommon, transitions in care a vulnerability
- Healthcare system not designed to handle this complexity
- Few specialized clozapine clinics
- Systems needed after-hours to ensure prescriptions are renewed
- Creates a culture of urgency and tending to emergencies

At Grady, a 100% philanthropically supported staff member manages the system for 130 patients on clozapine

Putting Risk/Benefit in Perspective

Risk

- 1 out of 108 patients prescribed clozapine will develop severe neutropenia[1]
- 1 out of 7,700 patients prescribed clozapine will die due to severe neutropenia[1]

Benefit

- 2 out of 5 patients with TRS prescribed clozapine will experience benefit[2]
- On average, treatment of only 12 patients with clozapine rather than olanzapine will show benefit for clozapine to reduce suicidal behavior (InterSePT)[3]

1. Myles N, et al. *Acta Psychiatr Scand*. 2018;138(2):101-109; 2. Siskind D, et al. *Canadian J Psychiatry*. 2017;62(11):772-777; 3. Meltzer HY, et al. *Arch Gen Psychiatry*. 2003;60(1):82-91.

Reality on the Ground: Changes Are Needed

- Modifications to elements of the REMS
- Time limit on centralized ANC reporting
- Prescriber look-up
- Emergency/special circumstances exemptions
- Focus on education, address misconceptions
- Flexibility needed to better manage transitions in care

CLOZAPINE REMS

REMS Operation and Assessments

James Shamp

Examoto, a UBC Company

REMS Operation and Assessment Topics

1. **REMS Design and Operation**

2. **Rationale and Impact of Enforcement Discretion**

3. **Assessment Data**
   - Patient and prescriber background
   - Use of REMS tools
     - Patient Status Form (PSF), REMS Dispense Authorization (RDA), Dispense Rationale, Treatment Rationale
   - Adherence to REMS
   - Stakeholder knowledge

Purpose of Clozapine REMS

Mitigate risk of adverse events related to clozapine-induced severe neutropenia

- Identify low ANC values
- Allow informed decision-making regarding continued use

REMS Logic Model: A Framework to Link Program Design with Assessment, Guidance for Industry, Draft Guidance (May 2024).

Objectives of the Clozapine REMS

1. Educating prescribers and pharmacists about the risk of severe neutropenia and appropriate monitoring requirements

2. Informing patients about the risk of severe neutropenia and appropriate monitoring requirements

3. Ensuring prescribers submit documentation that periodic monitoring of patients is performed to identify severe neutropenia

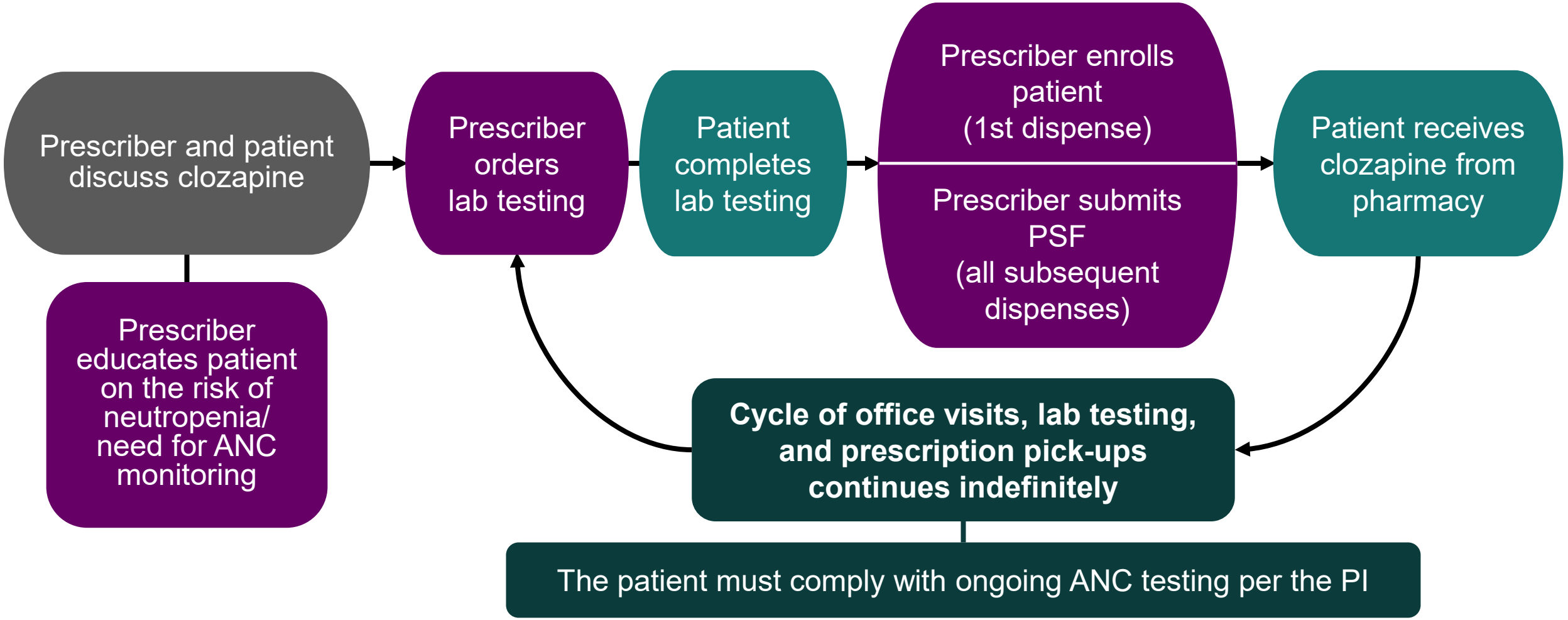
4. Ensuring the prescriber documents a risk-benefit assessment when ANC falls below the acceptable range as described in the Prescribing Information

5. Establishing long-term safety and safe use of clozapine by enrolling all patients who receive clozapine in the registry

Key REMS Requirements for Stakeholders

Prescribers must
• Be certified to prescribe clozapine • Enroll all patients in the REMS (counsel on risks prior to treatment, document/submit ANC) • Submit a patient's ANC results, monitoring frequency, and appropriateness for continuing treatment monthly
Patients must
• Be enrolled by the prescriber • Comply with ANC testing requirements
Pharmacies must
• Be certified • Verify patient is enrolled and authorized to received drug prior to dispensing • Verify a current ANC within acceptable range and document/submit ANC (for patients enrolled but not authorized to receive clozapine) • Report dispensing information
Wholesalers-Distributors must
• Enroll in the REMS to be authorized to distribute clozapine • Establish processes and procedures to ensure the drug is distributed only to certified pharmacies

Patient and Prescriber Journey



PSF = Patient Status Form.

Features Included in Modified REMS to Ensure Continuity of Care

Reason for Missing Lab

Allows dispensing if a lab is missing

Treatment Rationale

Allows treatment despite abnormal ANC values when benefits of continuing care outweigh the risk of neutropenia

Dispense Rationale

Allows treatment in absence of required PSF if current[a] and acceptable[b] ANC value available

Transition Dispense Rationale (intended as temporary feature)

Allows pharmacist to dispense to Legacy REMS patients not enrolled in Modified REMS if a current, acceptable ANC value is available

Robust Reminder System

Informs prescribers about treatment interruptions and assists in maintaining a patient on clozapine

[a]Current: within the last 30 days; [b]Acceptable ANC value: for General Patients >999/μL; for BEN Patients >500/μL.

Robust Reminder System

- Manage patient list
  - Displays reminder when PSF is due or late
- Reminder sent to prescriber 7 days before next PSF is due
- Notification sent to prescriber when pharmacist uses a Dispense Rationale
  - Current PSF not on file
- Notification sent to prescriber when an ANC value moves patient interrupted status
  - Informs prescriber that patient is ineligible for clozapine unless Treatment Rationale is created
- Notification sent to prescriber when pharmacist attempts to obtain RDA for patient in interrupted or discontinued status

RDA = REMS Dispense Authorization.

REMS Operation and Assessment Topics

1. **REMS design and operation**

2. **Rationale and impact of Enforcement Discretion**

3. **Assessment data**
   - Patient and prescriber background
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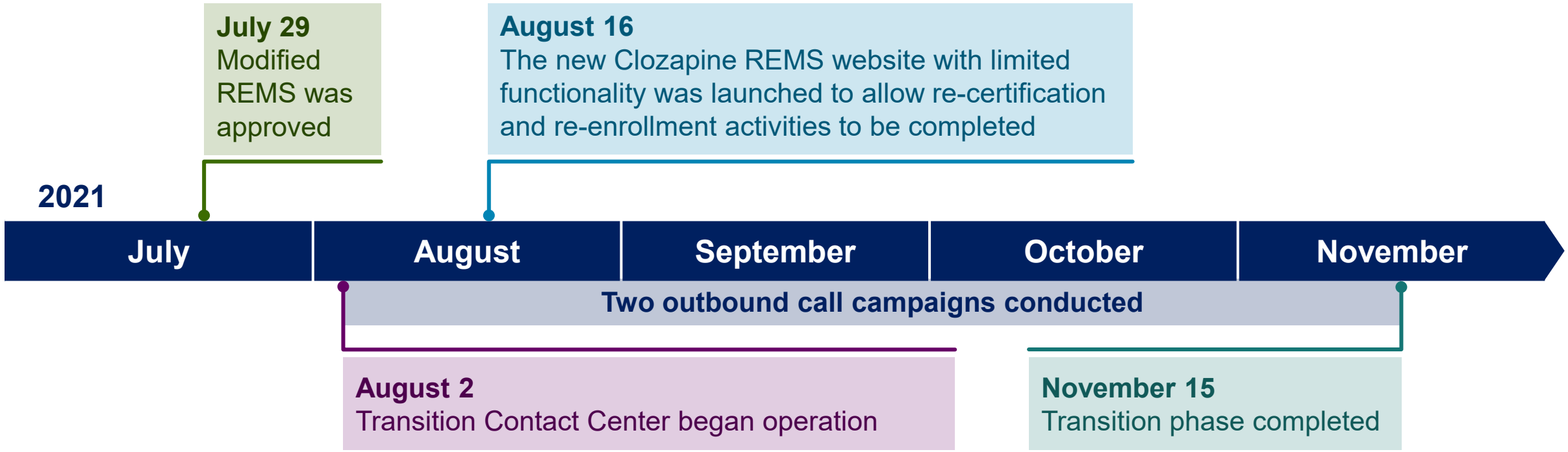
REMS Transition Challenges Led to FDA Enforcement Discretion



Extensive outreach (via email and hardcopy) to prescribers, pharmacies, designees, and wholesalers-distributors was completed prior to the launch of the modified REMS

Participation in Clozapine REMS

November 2021

	Legacy REMS 11/15/2021	End of Transition to Modified REMS 11/15/2021
Certified Prescribers	65,070 35,330 active[a]	20,839
Certified Pharmacies	51,039 10,238 active[b]	35,762
Enrolled Patients	112,059 active[c]	42,943

[a]An active prescriber is a prescriber who submitted an ANC lab value for a patient or was associated with a patient who received at least 1 Pre-dispense Authorization/RDA during the reporting period.
[b]An active pharmacy is a pharmacy with at least 1 Pre-dispense Authorization/RDA during the reporting period.
[c]A patient is considered active if they received at least 1 Pre-dispense Authorization/RDA during the reporting period.

FDA Enforcement Discretion Designed to Ensure Continuity of Care

November 2021

- Pharmacists may dispense without obtaining an RDA
- Wholesalers may ship to uncertified pharmacies

November 2022

- In-patient pharmacy may dispense a quantity of clozapine upon discharge in line with patient's monitoring frequency (eg, weekly monitoring = 7 days' supply, twice-monthly monitoring = 14 days' supply, monthly monitoring = 30 days' supply)

Participation in Modified Clozapine REMS

	Legacy REMS 11/15/2021	End of Transition to Modified REMS 11/15/2021	Modified REMS 5/29/2024
Certified Prescribers	65,070 35,330 active[a]	20,839	58,452 35,195 active[a]
Certified Pharmacies	51,039 10,238 active[b]	35,762	47,604 27,984 active[b]
Enrolled Patients	112,059 active[c]	42,943	115,298 active[c]

[a]An active prescriber is a prescriber who submitted an ANC lab value for a patient or was associated with a patient who received at least 1 Pre-dispense Authorization/RDA during the reporting period.
[b]An active pharmacy is a pharmacy with at least 1 Pre-dispense Authorization/RDA during the reporting period.
[c]A patient is considered active if they received at least 1 Pre-dispense Authorization/RDA during the reporting period.

The Enforcement Discretion Affects Data Collection

- Allows pharmacist to dispense without obtaining an RDA
- Allows wholesalers to ship to uncertified pharmacies
- As a result, key REMS requirements may be bypassed:
  - Pharmacy certification
  - Prescriber certification
  - Patient enrollment
  - PSF submission

REMS Operation and Assessment Topics

1. REMS Design and Operation

2. Rationale and Impact of Enforcement Discretion

3. **Assessment Data**
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Patient Demographics

Modified REMS (Enrolled Patients)

	July 29, 2021 - Nov. 30, 2022		Dec. 1, 2022 - May 29, 2024	
Treatment Status	**Count**	**Percent**	**Count**	**Percent**
Active	122,500	97.81	149,203	96.77
Discontinued	1,707	1.36	3,622	2.35
Interrupted	1,033	0.82	1,353	0.88
Treatment status total	**125,240**	**100**	**154,178**	**100**

- Majority are 20-69 years, with the age group 30-39 years having the largest percentage (21.2%)
- More males (62.0%) than females (37.7%)
- Patients who are not Hispanic or Latino make up >89.6% of enrolled patients
- The 2 most common patient races reported during enrollment are Caucasian (70.0%) and Black or African American (16.3%)

Certified Prescribers, Stratified by Credential

Modified REMS

		July 29, 2021 - Nov. 30, 2022		Dec. 1, 2022 - May 29, 2024	
Status	**Credentials**	**Count**	**Percent**	**Count**	**Percent**
Certified	Physician MD	26,378	55.35	31,872	51.02
	Nurse Practitioner	12,923	27.12	19,216	30.76
	Physician DO	3,069	6.44	4,058	6.50
	Physician Assistant	1,690	3.55	2,348	3.76
	Other	651	1.37	958	1.53
Certified total		**44,711**	**93.82**	**58,452**	**93.57**
Non-certified total		2,944	6.18	4,013	6.42

Certified Prescribers, Stratified by Region

Modified REMS

		July 29, 2021 - Nov. 30, 2022		Dec. 1, 2022 - May 29, 2024	
Status	**Geographic Region[a]**	**Count**	**Percent**	**Count**	**Percent**
Certified	South	12,411	26.04	16,594	26.57
	Northeast	12,399	26.02	16,017	25.64
	West	10,112	21.22	13,080	20.94
	Midwest	9,658	20.27	12,600	20.17
	US Territory	130	0.27	160	0.26
	Military	1	0.00	1	0.00
Certified total		**44,711**	**93.82**	**58,452**	**93.58**
Non-certified total		2,944	6.18	4,013	6.42

[a]As defined by the US Census.

Patient Status Form (PSF)

Primary Tool for Prescribers to Submit Patient Data

Description	July 29, 2021 - Nov. 30, 2022	Dec. 1, 2022 - May 29, 2024
PSFs submitted	**1,089,386**	**1,732,050**
Count of unique patients	110,730	120,943

REMS Dispense Authorizations (RDAs)

Verifies Patient Is Enrolled, Authorized to Receive Clozapine

	July 29, 2021 - Nov. 30, 2022		Dec. 1, 2022 - May 29, 2024		Cumulative July 29, 2021 - May 29, 2024	
RDAs	**Count**	**Percent[a]**	**Count**	**Percent[a]**	**Count**	**Percent[a]**
Authorized	1,195,261	67.09	2,017,864	71.74	3,213,125	69.94
Rejected	543,649	30.52	723,816	25.73	1,267,465	27.59
Reversed	42,622	2.39	70,929	2.52	113,551	2.47
RDA total	**1,781,532**	**100**	**2,812,609**	**100**	**4,594,141**	**100**

[a]May not sum due to rounding.

Dispense Rationales

Allows Dispensing When Current PSF Is Unavailable

	July 29, 2021 - Nov. 30, 2022	Dec. 1, 2022 - May 29, 2024
Number of unique patients receiving a clozapine prescription under a Dispense Rationale	31,745	41,281
Number of Dispense Rationales authorized	97,252	192,552

75.2% patients receiving a Dispense Rationale received it within 7 days of the initial rejection[a]

[a]For the December 1, 2022 - May 29, 2024, reporting period.

Use of the Treatment Rationale

	Time Period	Number of Treatment Rationales Submitted	Number of Patients With Neutropenia[a]
Legacy REMS	July 16, 2016 - July 15, 2017	150	408
	July 16, 2017 - July 15, 2018	191	545
	July 16, 2018 - Dec. 31, 2019		
	July 16, 2018 - Feb. 27, 2019	119	360
	Feb. 28, 2019 - Dec. 31, 2019	177	580
	Jan. 1, 2020 - Dec. 31, 2020	188	796
	Jan. 1, 2021 - Nov. 15, 2021	221	623
Modified REMS	July 29, 2021 - Nov. 30, 2022	619	7,501
	Dec. 1, 2022 - May 29, 2024	282	2,682

Treatment Rationale – for the legacy REMS there were 2 provisions: (1) is a BEN patient, or (2) the benefit outweighs the risk.

[a]ANC <1,000 cells/µL.

REMS Operation and Assessment Topics

1. **REMS Design and Operation**

2. **Rationale and Impact of Enforcement Discretion**

3. **Assessment Data**
   - Patient and prescriber background
   - Use of REMS tools
     - Patient Status Form (PSF), REMS Dispense Authorization (RDA), Dispense Rationale, Treatment Rationale
   - Adherence to REMS
   - Stakeholder knowledge

Limitations of Clozapine REMS Data Collection

Legacy REMS:

- Did not include a metric to measure adherence to monitoring
- Was never fully implemented/enforced
  - Only required to have 1 ANC on file

Modified REMS:

- Never fully enforced

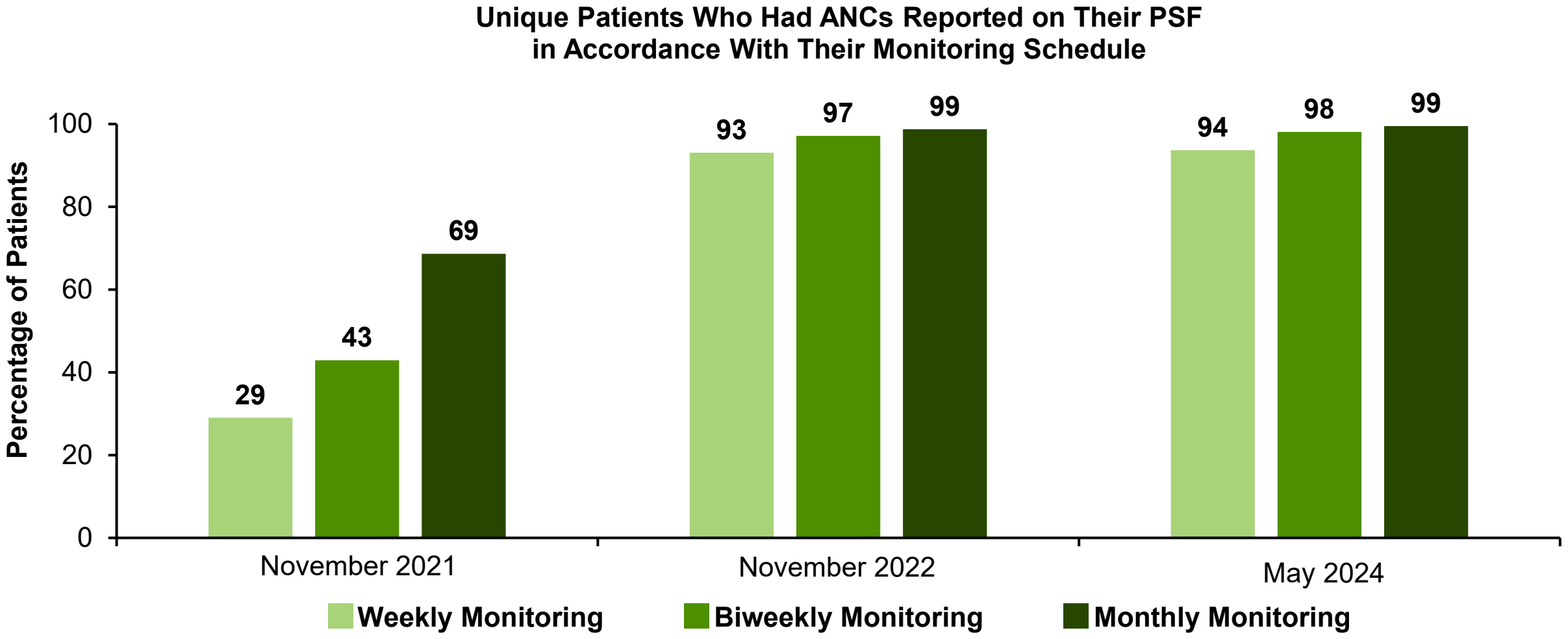
Adherence to the Clozapine REMS

PSFs Not Submitted on Time (Modified REMS)

	Time Period	Number of PSFs Not Received Within 37 Calendar Days After the Date of the Last PSF Submission	Total Number of PSFs Submitted
Modified REMS	July 29, 2021 - Nov. 30, 2022	242,456	1,089,386
	Dec. 1, 2022 - May 29, 2024	501,049	1,732,050

ANCs Reported in Accordance With Monitoring Schedule

Modified REMS



Clozapine REMS Knowledge Surveys

- Measure understanding among prescribers, pharmacists, and patients of:
  - Risk of severe neutropenia associated with clozapine use
  - Appropriate use and monitoring requirements
  - Available only through a restricted program
- Results indicate good understanding overall, but knowledge gaps exist

KRM 1: Understanding Risk of Severe Neutropenia Associated With Use of Clozapine

Modified REMS (Dec. 1, 2022 – May 29, 2024)

	Mean Score of Linked Questions	Low-Scoring Questions
Prescribers	93.0%	No low-scoring question
Pharmacists	88.0%	True/False: Risk of neutropenia appears greater in the first 18 weeks of treatment with clozapine (68% answered correctly)
Patients	37.0%	Most

KRM = Key Risk Message.

KRM 2: Understanding Appropriate Use of Clozapine Including Monitoring Requirements

Modified REMS (Dec. 1, 2022 – May 29, 2024)

	Mean Score of Linked Questions	Low-Scoring Questions
Prescribers	93.0%	No low-scoring question
Pharmacists	86.0%	True/False: Patients with BEN have a separate ANC monitoring algorithm when treated with clozapine (70% answered correctly)
Patients	84.0%	What are the requirements that you [the patient that you care for] must complete to receive Clozapine? If your neutrophils are too low, your doctor may ask you to have blood tests more frequently (66% answered correctly)

KRM = Key Risk Message.

KRM 3: Clozapine Only Available Through a Restricted Program

Modified REMS (Dec. 1, 2022 – May 29, 2024)

	Mean Score of Linked Questions	Low-Scoring Questions
Prescribers	87.0%	True/False: Prescribers must provide a Treatment Rationale (TR) to confirm that the benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia (for patients with moderate or severe neutropenia) (68% answered correctly)
Pharmacists	87.0%	No low-scoring question
Patients	63.0%	Correctly identify the REMS requirement “A patient must review the patient guide: What You Need to Know About Clozapine and Neutropenia” (44% answered correctly)

KRM = Key Risk Message.

REMS Operation and Assessment Conclusions

- Participation in Modified REMS meets or exceeds that of Legacy REMS
- When a stakeholder participates in the modified REMS, it provides a resource to document compliance and adherence to monitoring frequencies
- Overall good understanding among stakeholders of neutropenia risk and REMS requirements
  - Stakeholder knowledge gaps still exist
- Enforcement Discretion and REMS design/implementation limit the ability to collect data

CLOZAPINE REMS

AE Reporting, Stakeholder Feedback, and Opportunities for Improvement

Jason A. Gross, PharmD

Vice President of Scientific Affairs
HLS Therapeutics (USA), Inc.

Adverse Event Reporting Process

REMS Contact Center

- Receives potential adverse event (AE)
- Conducts preliminary outreach
- Provides to responsible Sponsor within 1 business day

REMS Sponsor(s)

- Responsible REMS Sponsor's pharmacovigilance department follows its AE reporting processes
- AEs are reported to the FDA

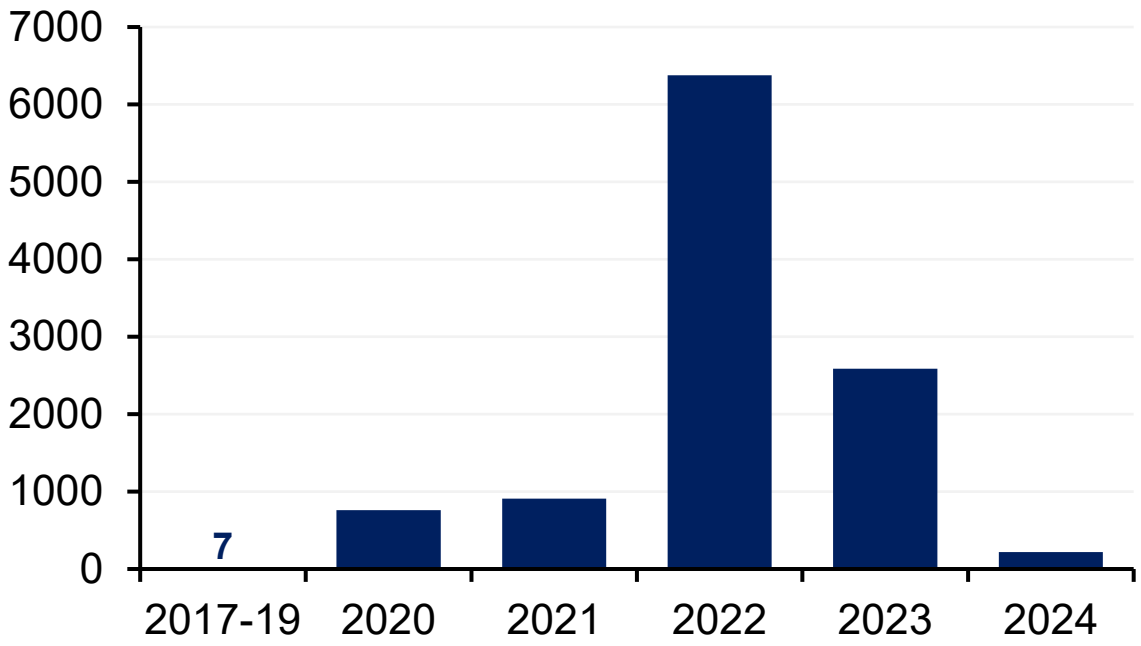
FAERS

- Includes reports submitted directly to the FDA by healthcare professionals and consumers
- Any report accounted for in FAERS annual totals may be counted more than once if a healthcare professional or consumer reports an event directly to the FDA as well as to a manufacturer

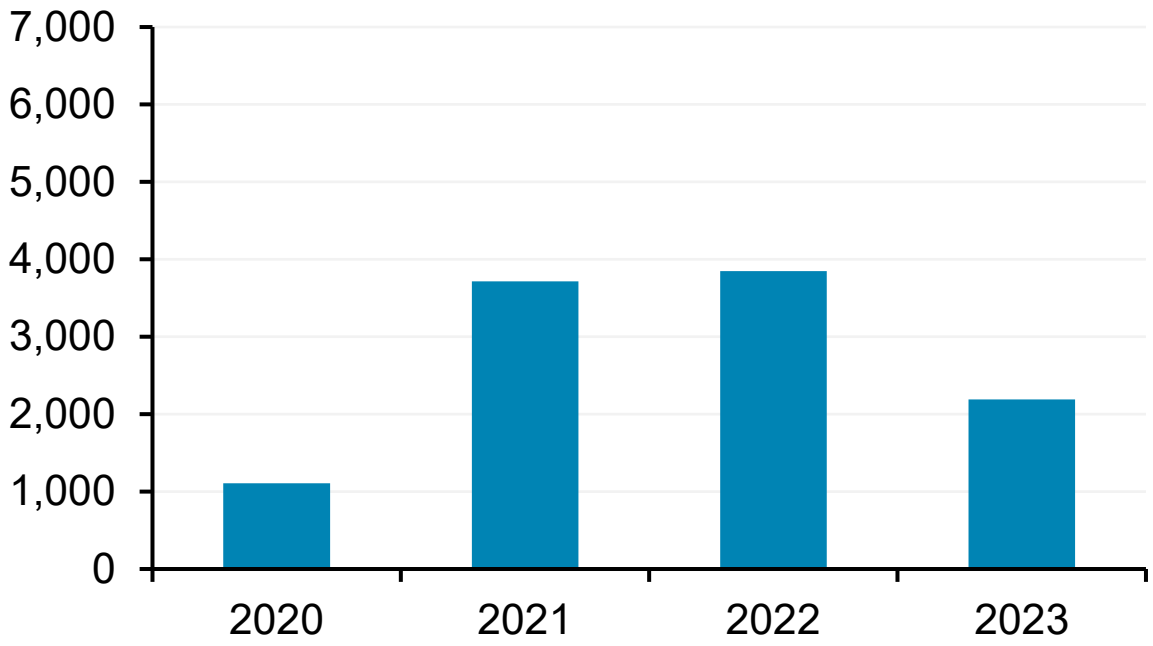
Adverse Event Reporting

FAERS Public Dashboard

Reports of Neutropenia by FDA Receipt Date



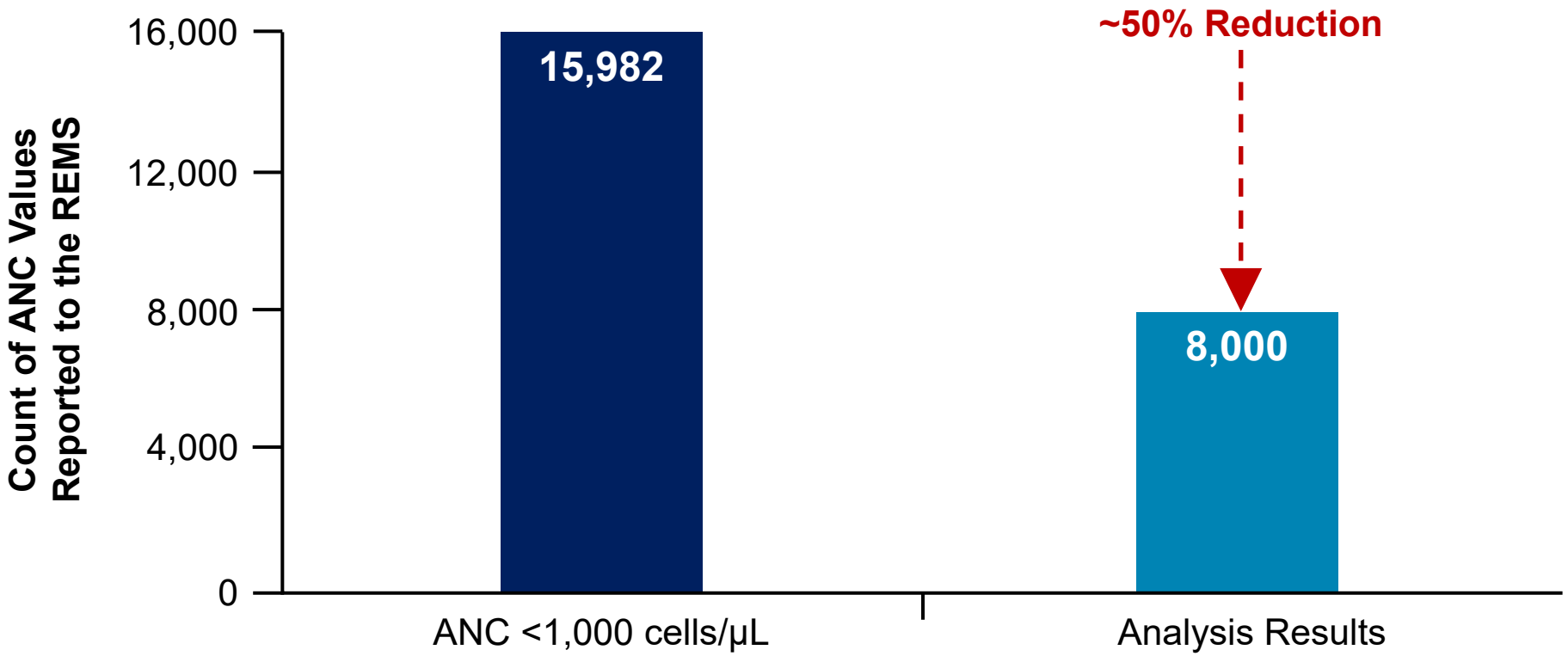
Reports of Neutropenia by Event Date



FAERS = FDA Adverse Event Reporting System.
This clozapine and neutropenia database analysis utilizes the FAERS quarterly data extract (cumulative through 2024 Q2 [April-June]) posted by the FDA on July 30, 2024.

Impact of ANC Values Submitted Using Incorrect Units

Analysis of Low ANC Values Reported to the REMS



Based on the last ANC value entered for the same drawn on date. Data range November 15, 2021 - September 25, 2024.

Mitigation of ANC Values Submitted Using Incorrect Units

System Change

- February 21, 2022: CPMG implemented a system change to mitigate erroneous ANC data provided to the REMS due to misunderstanding of data units
- When an ANC value of <100 cells/μL is entered, the update prompts the user to check the data unit and confirm the value is correct
- Positive impact of system change:
  - Decrease in submission of ANC values <100 cells/μL (from 0.71% to 0.03%)

CPMG is considering additional improvements to mitigate use of incorrect units

FAERS Analysis Methods

- Validated process to remove duplicates (from 2020-2023)
- Assessed events based on date of occurrence
- Converted to MedDRA terms
  - Preferred Term (PT): neutropenia
  - High-level Term (HLT): neutropenia
  - Standardized MedDRA Queries (SMQ): hematopoietic leukopenia
  - Sub-analysis using high-level group terms from SMQ Opportunistic Infections and COVID-19
- Considered the relationship between neutropenia and mortality

Neutropenia
FAERS Analysis

	Cases Reported		
Year	**Neutropenia (PT)**	**Neutropenia (HLT)**	**Hematopoietic Leukopenia (SMQ)**
2020	1,106	1,142	1,472
2021	3,715	3,750	4,044
2022	3,846	4,077	4,486
2023	2,191	2,244	2,766

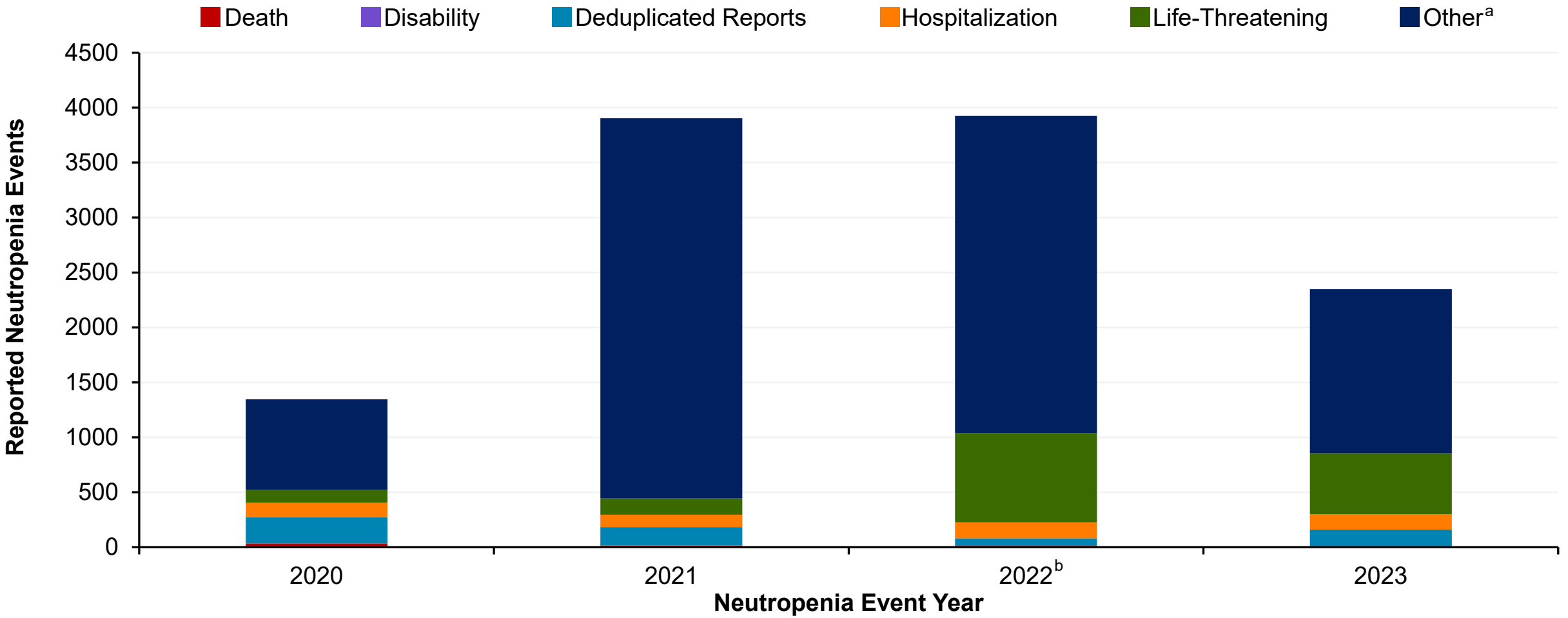
Opportunistic Infections and COVID-19

FAERS Analysis

	Cases Reported	
Year	**Opportunistic Infections (SMQ)**	**COVID-19 (SMQ)**
2020	321	232
2021	234	158
2022	314	241
2023	181	105

2020-2023 Outcomes for Neutropenia

FAERS Analysis



Cases may have more than 1 outcome code and may have been counted in more than 1 category.
[a]FAERS outcome category "Other Serious (Important Medical Event)."
[b]In 2022, 1 additional case appeared in the "Required Intervention" category (not shown).

FAERS Conclusions

- When adjusted for event date versus FDA receipt date, the observed increase in reports appears to be in line with increased data collection under the Modified REMS
- No evidence that the observed increase was associated with a change in the safety profile of clozapine

Number of PSFs That Indicated an AE Due to Clozapine-Induced Neutropenia

Modified REMS

Time Period	Count of Patients With PSF	Count of PSFs Where an AE Is Indicated	Unique Patients With an AE Indicated	Percent of Patients With an AE Indicated
July 29, 2021 - Nov. 30, 2022	110,730	371	319	0.29
Dec. 1, 2022 - May 29, 2024	120,943	439	390	0.32

AE = adverse event; PSF = Patient Status Form.

Adverse Event Investigation Conclusions

- FAERS data are insufficient to characterize the long-term safety of clozapine, but do not suggest a change to the safety profile
- REMS data account for most ANC-related AE reports for neutropenia; only 79 cases reported to FAERS outside the REMS
- REMS data have potential to better inform on the safety profile than spontaneous reporting

Stakeholder Feedback

Listening Sessions: December 2021 - August 2022

- Questioned efficacy of REMS requirements in mitigating patient risks
- Identified increased burden on medical professionals
  - RDA and PSF considered cumbersome
  - Complexity could prevent patients from receiving drug
- Highlighted that long-term care facilities categorized as outpatient centers may delay patient care
- Questioned whether the safety profile changes over time, allowing for reduced restrictions for long-term patients
- Identified challenges with navigating the REMS website

PSF = Patient Status Form; RDA = REMS Dispense Authorization.

Educational Opportunities

Common Misconception	Fact
Only a limited supply of drug can be dispensed (eg, 7, 14, or 28 days)	In an outpatient setting, the REMS does not limit the amount of medication that can be dispensed—only that a PSF or Dispense Rationale must be on file at time of dispense[a]
Cannot dispense without PSF	Pharmacists can dispense using a Dispense Rationale if current ANC is available in the acceptable range
Patients who cannot participate in regular blood/ANC monitoring are denied access	Prescriber may authorize dispensing of medication if patient has missing labs
Lost or missing medications are not allowed to be dispensed per the REMS	Authorization to dispense lost or missing medication or emergency supply is at the discretion of the pharmacy and the insurance company

[a]Inpatient dispensing is limited to 7 days at discharge (not currently enforced under Enforcement Discretion).

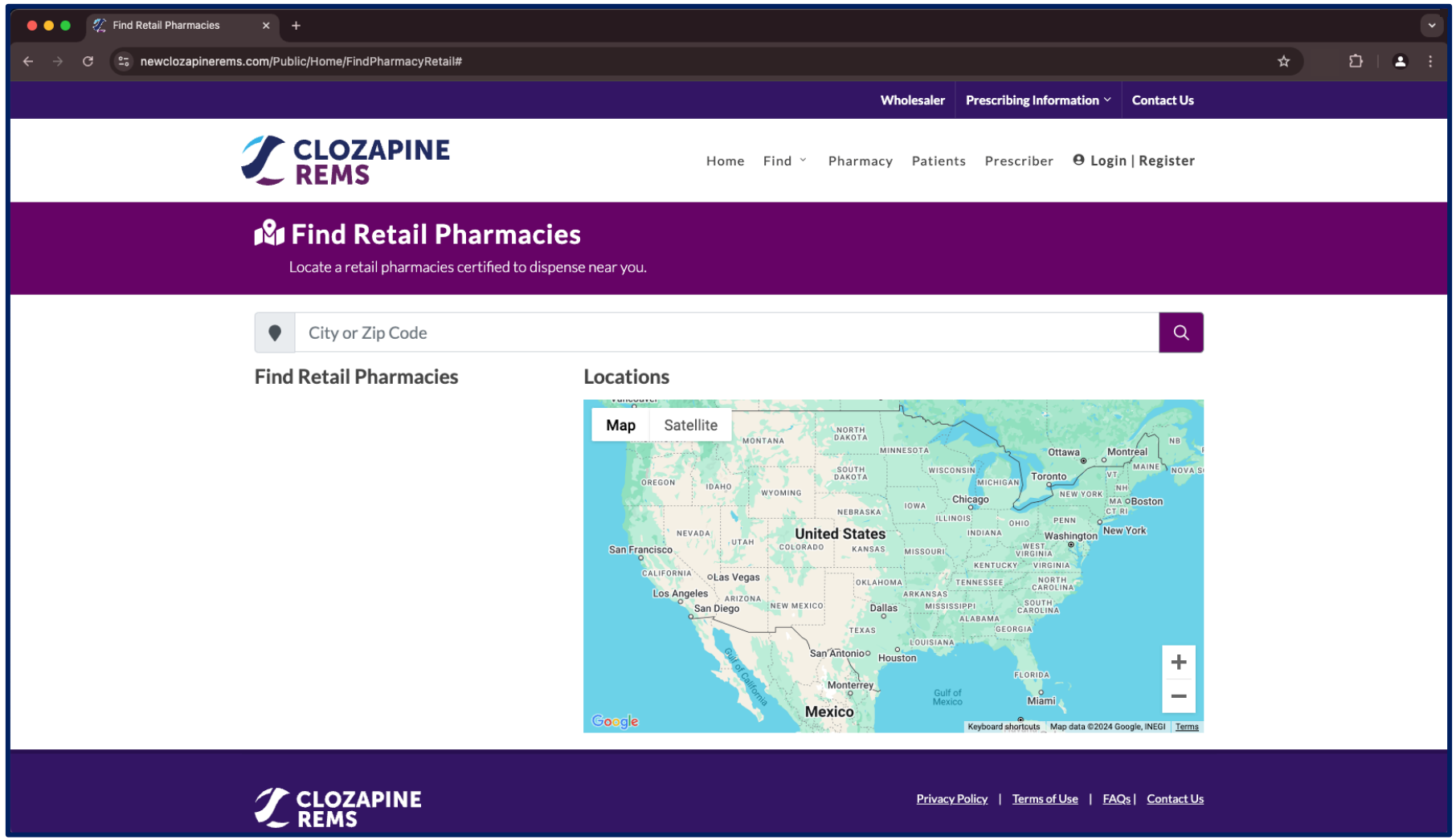
Stakeholders' Input Led to Key System Updates

Clozapine REMS Enhancement	Reduction in Stakeholder Burden
Provided ability to remove incorrect ANC entries	Ensures data accuracy and mitigates potential treatment interruptions
Added ANC and monitoring histories	Provides information pharmacists need to use Dispense Rationale Allows prescribers to review all patient data stored within the REMS, prevents duplicative work, enhances clinical decision making
Changed system to prepopulate current ANC values when submitting the PSF online	Eliminates manual reentry of historical data
Added pop-up warning when ANC <100 cells/μL entered	Confirms proper unit of measurement, mitigates therapy disruptions, and decreases erroneous AE reports

Stakeholders' Input Led to Key System Updates (cont'd)

Clozapine REMS Enhancement	Reduction in Stakeholder Burden
Changed the default sort order of RDAs to make the most recent RDA at the top	Facilitates stakeholder review of most recent authorizations
Streamlined prescriber and designee association process	Alleviates the burden on prescribers to fulfill REMS requirements
Added a checkbox to the portal for verification of pharmacy authorized representative	Allows electronic self-service for verification
Enhanced pharmacy look-up tool	Allows users to find pharmacies by ZIP code

Pharmacy Look-Up



Potential Areas for Improvement

1. **Drive greater awareness and education**
   - Address misconceptions and common questions

2. **Manage transitions in care more effectively**
   - Ensure continued access to treatment during transitions between prescribers and pharmacies and from inpatient to outpatient care

3. **Improve communication across institutional reporting systems**
   - Reduce burden on physicians and pharmacies

4. **Improve AE collection**
   - Obtain more meaningful data on incidence and outcomes of clozapine-induced, neutropenia-related AEs

Summary

AE Reporting, Stakeholder Feedback, Opportunities for Improvement

- FAERS review suggests increase in AE reports likely due to increased data collection
- No evidence of a change in the safety profile of clozapine
- Through stakeholder input, evaluation of assessment data, and ongoing FDA consultation:
  - Identified and clarified misconceptions that may be addressed through awareness and education
  - Implemented improvements to address challenges and streamline stakeholder interaction with the REMS
  - Found opportunities to potentially improve data collection and reduce stakeholder burden while continuing to help ensure patient safety

Overall Conclusions

- Clozapine is a life-saving therapy for individuals with TRS
- The Clozapine REMS
  - Provides a resource to document compliance with monitoring requirements
  - Plays an important role in ensuring safe use and educating stakeholders
    - Stakeholder knowledge gaps remain
- Enforcement Discretion and REMS design/implementation limit the ability to collect data
- CPMG analysis of FAERS data suggests no change in the safety profile of clozapine
- CPMG is committed to collaborating with FDA, CPMG, and stakeholders to address misconceptions and gaps in knowledge, concerns about obtaining clozapine, and maintaining safe use and continuity of care

CPMG Supporting Slides

Time to Authorization Between Rejection and RDA Stratified by Reason for Reject

	Current Reporting Period December 1, 2022 - May 29, 2024	
Reason for Rejection	**Mean**	**Median**
Patient is in a Status of Discontinue Treatment	22.73	4
Dispense Rationale ANC too Low	20.45	2
Patient is in a Status of Interrupt Treatment	19.88	2
Dispense Rationale ANC Not Current	12.52	3
Patient Status Form is Required	10.31	1
The Patient was Not Found	4.26	0
The Pharmacy Personnel was Not Found	2.00	0
Pharmacy is Not Certified	0.54	0
Across all Reasons for Rejection	**10.55**	**1**