Disclaimer

The following report(s) provides findings from an FDA-initiated query using Sentinel. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand Sentinel capabilities.

Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Request ID: cder_mpl1r_wp278

Request Description: In this report, we identified incident users of clozapine in the pre-Risk Evaluation and Mitigation Strategies (REMS) (January 1, 2010 - September 30, 2015), post-REMS (October 1, 2015 - December 31, 2019), and COVID-REMS (January 1, 2020 - September 30, 2023) time periods in the Sentinel Distributed Database (SDD). Among these new use episodes, we present information on absolute neutrophil count (ANC) procedures and laboratory results as well as diagnoses of neutropenia. This is report two of two, wherein we include data from all Data Partners (DPs) in the SDD regardless of whether the DP includes ANC laboratory results in the Laboratory Results table within their Sentinel Common Data Model.

Sentinel Routine Querying Module: Cohort Identification and Descriptive Analysis (CIDA) module, version 13.1.0, with the Multiple Events Module

Data Source: We distributed this query to 13 Sentinel DPs on March 11, 2024. Data from Medicare patients having both fee-for-service medical coverage and Part D drug coverage are included. The study period included data from January 1, 2010 through a maximum of March 31, 2024. Please see Appendix A for a list of minimum and maximum dates of available data for each DP (maximum of all DPs is September 30, 2023).

Study Design: We identified individuals with incident use of clozapine and evaluated the occurrence of ANC procedures, ANC laboratory results in various ranges, and neutropenia diagnoses during exposure episodes, among a cohort who were at least 12 years of age. This is a Type Two analysis with the Multiple Events add-on module in the Query Request Package (QRP) documentation.

Exposure of Interest: We defined the exposure of interest, clozapine, using outpatient dispensing data and National Drug Codes (NDCs). We defined incident exposure as no prior evidence of clozapine dispensed in the 30 days prior to the first qualifying (index) exposure. Each qualifying dispensing of clozapine (index) was included in the cohort; cohort re-entry was allowed. Please see Appendix B for a list of generic and brand names of medical products used to define exposures in this request.

Outcomes of Interest: We identified the following outcomes of interest:
  1) ANC procedure codes in Procedure Table
  2) ANC procedure codes in Laboratory Table
  3) ANC procedure codes in Procedure and/or Laboratory Table
  4) ANC laboratory result
    4.1) "Clean" ANC laboratory result (0 - 7.8 K/uL)
      4.1.1) "Non-neutropenic" ANC laboratory result (1.5 - 7.8 K/uL)
      4.1.2) "Neutropenic" ANC laboratory Result (0 - 1.499 K/uL)
      4.1.3) "Mildly-neutropenic" ANC laboratory result (1.0 - 1.499 K/uL)
      4.1.4) "Moderately-neutropenic" ANC laboratory result (0.5 - 0.999 K/uL)
      4.1.5) "Severely-neutropenic" ANC laboratory result (<0.5 K/uL)
  5) Neutropenia diagnoses in any care setting except for those in the "other ambulatory" setting.

Please see Appendix C for a list of Current Procedural Terminology, Fourth Edition (CPT-4), Healthcare Common Procedure Coding System, Level II (HCPCS), and Revenue (RE) procedure codes, and Logical Observation Identifiers Names and Codes (LOINC) and Sentinel Operations Center (SOC) defined lab codes used to define outcomes in this request.

Cohort Eligibility Criteria: We required members to be continuously enrolled in health plans with medical and drug coverage in the 30 days prior to their index date in order to be included in the cohort; when bridging enrollment spans, a gap in coverage of up to 45 days was allowed and treated as continuous enrollment. The following age groups were included in the cohort: 12-18, 19-35, 36-50, 51-64, 65-74, and 75+ years. We excluded index exposure episodes if there was evidence of clozapine in the 30 days prior to the exposure of interest.

Follow-Up Time: We created exposure episodes based on the number of days of product supplied per dispensing in the outpatient pharmacy dispensing data. We bridged together exposure episodes with gaps of up to 30 days. These "as treated" episodes are the time during which we assessed outcomes. Follow-up for all outcomes began on the day of the index dispensing and continued until the first occurrence of any of the following: 1) disenrollment; 2) death; 3) the end of the data provided by each DP; 4) the end of the query period; 5) end of the exposure episode. When reporting occurrence of neutropenia diagnoses (outcome #5 above), we additionally censor after the occurrence of the first qualifying outcome. We additionally report ANC procedure and laboratory result occurrence during follow-up time with an additional censoring criteria of six months treatment duration.

Baseline Characteristics: We assessed the following characteristics on the index date: age, year, sex, race, and ethnicity.

Please see Appendices D and E for the specifications defining parameters and the design diagrams for this request.

Limitations: Algorithms used to define primary events, secondary events, and baseline characteristics are imperfect; thus, it is possible that there may be misclassification. Therefore, data should be interpreted with this limitation in mind.

Notes: Please contact the Sentinel Operations Center (info@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document. For more information on Sentinel's routine querying modules, please refer to the documentation (https://dev.sentinelsystem.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse).

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Glossary of Terms for Analyses Using
Cohort Identification and Descriptive Analysis (CIDA) Tool*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing.

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency Department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). The Care Setting, along with the Principal Diagnosis Indicator (PDX), forms the Care Setting/PDX parameter.

>   **Ambulatory Visit (AV) -** includes visits at outpatient clinics, same-day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes emergency department encounters.
>   **Emergency Department (ED) -** includes ED encounters that become inpatient stays (in which case inpatient stays would be a separate encounter). Excludes urgent care visits.
>   **Inpatient Hospital Stay (IP) -** includes all inpatient stays, same-day hospital discharges, hospital transfers, and acute hospital care where the discharge is after the admission date.
>   **Non-Acute Institutional Stay (IS) -** includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays.
>   **Other Ambulatory Visit (OA) -** includes other non overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: 01: Cohort includes only the first valid treatment episode during the query period; 02: Cohort includes all valid treatment episodes during the query period; 03: Cohort includes all valid treatment episodes during the query period until an event occurs.

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Eligible Members - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a "continuously enrolled" sequence.

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensings

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment episode.

Evaluation Period - number of days relative to index wherein a member is required to have evidence of a condition (diagnosis/procedure/drug dispensing).

Event Deduplication - specifies how events are counted by the Modular Program (MP) algorithm: 0: Counts all occurrences of a health outcome of interest (HOI) during an exposure episode; 1: de-duplicates occurrences of the same HOI code and code type on the same day; 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode. Extensions are added after any episode gaps have been bridged.

Maximum Episode Duration - truncates exposure episodes after a requester-specified number of exposed days. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Member-Years - sum of all days of enrollment with medical and drug coverage in the query period preceded by an exposure washout period all divided by 365.25.

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered.

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Monitoring Period - used to define time periods of interest for both sequential analysis and simple cohort characterization requests.

Principal Diagnosis (PDX) - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting values, forms the Caresetting/PDX parameter.

Query Period - period in which the modular program looks for exposures and outcomes of interest.

Treatment Episode Truncation Indicator - indicates whether the exposure episode will be truncated at the occurrence of a requester-specified code.

Washout Period (drug/exposure) - number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) - number of days before exposure episode that a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

*All terms may not be used in this report

Table 1a. Characteristics of New Clozapine Episodes in the Sentinel Distributed Database (SDD) from January 1, 2010 to September 30, 2015

Patient Characteristics[1]	Number	Percent
Unique patients	51,766	N/A
Episodes	73,984	100.0%
Demographic Characteristics	**Mean**	**Standard Deviation**
Age (years)	47.9	14.7
	Number	**Percent**
Age		
12-18 years	784	1.1%
19-35 years	17,897	24.2%
36-50 years	23,607	31.9%
51-64 years	21,606	29.2%
65-74 years	6,899	9.3%
≥ 75 years	3,191	4.3%
Sex		
Female	21,413	41.4%
Male	30,353	58.6%
Race[2]		
American Indian or Alaska Native	504	1.0%
Asian	1,065	2.1%
Black or African American	7,041	13.6%
Multi-racial	56	0.1%
Islander	30	0.1%
Unknown	6,553	12.7%
White	36,517	70.5%
Hispanic origin		
Yes	2,145	4.1%
No	44,888	86.7%
Unknown	4,733	9.1%
Year		
2010	14,628	19.8%
2011	12,349	16.7%
2012	11,761	15.9%
2013	11,682	15.8%
2014	12,770	17.3%
2015	10,794	14.6%

[1]All metrics are based on total number of episodes per group, except for sex, race, and Hispanic origin which are based on total number of unique patients.

[2]Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

N/A means not applicable.

Table 1b. Characteristics of New Clozapine Episodes in the Sentinel Distributed Databased (SDD) from October 1, 2015 to December 31, 2019

Patient Characteristics[1]	Number	Percent
Unique patients	54,857	N/A
Episodes	74,499	100.0%
Demographic Characteristics	**Mean**	**Standard Deviation**
Age (years)	43.0	14.7
	Number	**Percent**
Age		
12-18 years	3,216	4.3%
19-35 years	26,591	35.7%
36-50 years	19,310	25.9%
51-64 years	17,799	23.9%
65-74 years	5,602	7.5%
≥ 75 years	1,981	2.7%
Sex		
Female	22,036	40.2%
Male	32,821	59.8%
Race[2]		
American Indian or Alaska Native	738	1.3%
Asian	1,731	3.2%
Black or African American	8,563	15.6%
Multi-racial	127	0.2%
Native Hawaiian or Other Pacific Islander	104	0.2%
Unknown	11,283	20.6%
White	32,311	58.9%
Hispanic origin		
Yes	4,154	7.6%
No	43,127	78.6%
Unknown	7,576	13.8%
Year		
2015	3,347	4.5%
2016	17,801	23.9%
2017	17,831	23.9%
2018	17,289	23.2%
2019	18,231	24.5%

[1]All metrics are based on total number of episodes per group, except for sex, race, and Hispanic origin which are based on total number of unique patients.

[2]Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

N/A means not applicable.

Table 1c. Characteristics of New Clozapine Episodes in the Sentinel Distributed Database (SDD) from January 1, 2020 to September 30, 2023

Patient Characteristics[1]	Number	Percent
Unique patients	29,865	N/A
Episodes	39,623	100.0%
Demographic Characteristics	**Mean**	**Standard Deviation**
Age (years)	46.6	15.4
	Number	**Percent**
Age		
12-18 years	826	2.1%
19-35 years	12,095	30.5%
36-50 years	10,392	26.2%
51-64 years	9,626	24.3%
65-74 years	5,028	12.7%
≥ 75 years	1,656	4.2%
Sex		
Female	12,070	40.4%
Male	17,795	59.6%
Race[2]		
American Indian or Alaska Native	366	1.2%
Asian	893	3.0%
Black or African American	4,174	14.0%
Multi-racial	97	0.3%
Native Hawaiian or Other Pacific Islander	60	0.2%
Unknown	6,361	21.3%
White	17,914	60.0%
Hispanic origin		
Yes	1,703	5.7%
No	22,649	75.8%
Unknown	5,513	18.5%
Year		
2020	17,429	44.0%
2021	9,138	23.1%
2022	8,695	21.9%
2023	4,361	11.0%

[1]All metrics are based on total number of episodes per group, except for sex, race, and Hispanic origin which are based on total number of unique patients.

[2]Race data may not be completely populated at all Data Partners; therefore, data about race may be incomplete.

N/A means not applicable.

Table 2. Summary of New Clozapine Episodes and Absolute Neutrophil Count (ANC) Laboratory Results in the Sentinel Distributed Database (SDD) from January 1, 2010 to September 30, 2023

	Number of Patients	Number of Exposure Episodes	Total Days at Risk	Total Days Supply During Exposure Episodes	Mean Days Supply per Exposure Episode	Total Number of Secondary Events	Episodes with Any Secondary Event	Episodes with No Secondary Event
Secondary Events[1] in First Six Months of Clozapine Episode								
Pre-Risk Evaluation Mitigation Strategies (REMS) Incident Clozapine from January 1, 2010 to September 30, 2015	**51,766**	**73,984**	**9,304,537**	**8,638,418**	**166.87**	**--**	**--**	**--**
ANC Procedure Codes in Procedure Table	--	--	--	--	--	729,669	63,345	10,639
ANC Procedure Codes in Laboratory Table	--	--	--	--	--	6,569	767	73,217
ANC Procedure Codes in Procedure and/or Laboratory Table	--	--	--	--	--	730,415	63,371	10,613
ANC Laboratory Result	--	--	--	--	--	15,036	1,771	72,213
"Clean" ANC Laboratory Result (0 - 7.8 K/uL)	--	--	--	--	--	11,623	1,449	72,535
"Non-neutropenic" ANC Laboratory Result (1.5 - 7.8 K/uL)	--	--	--	--	--	11,587	1,449	72,535
"Neutropenic" ANC Laboratory Result (0 - 1.499 K/uL)	--	--	--	--	--	37	24	73,960
"Mildly-neutropenic" ANC Laboratory Result (1.0 - 1.499 K/uL)	--	--	--	--	--	26	20	73,964
"Moderately-neutropenic" ANC Laboratory Result (0.5 - 0.999 K/uL)	--	--	--	--	--	*****	*****	73,979
"Severely-neutropenic" ANC Laboratory Result (<0.5 K/uL)						*****	*****	73,981
Post-REMS Incident Clozapine from October 1, 2015 to December 31, 2019	**54,857**	**74,499**	**9,051,607**	**8,465,280**	**154.32**	**--**	**--**	**--**
ANC Procedure Codes in Procedure Table	--	--	--	--	--	653,311	60,434	14,065
ANC Procedure Codes in Laboratory Table	--	--	--	--	--	8,717	1,019	73,480
ANC Procedure Codes in Procedure and/or Laboratory Table	--	--	--	--	--	654,437	60,467	14,032
ANC Laboratory Result	--	--	--	--	--	17,009	2,027	72,472
"Clean" ANC Laboratory Result (0 - 7.8 K/uL)	--	--	--	--	--	12,954	1,643	72,856
"Non-neutropenic" ANC Laboratory Result (1.5 - 7.8 K/uL)	--	--	--	--	--	12,856	1,643	72,856
"Neutropenic" ANC Laboratory Result (0 - 1.499 K/uL)	--	--	--	--	--	98	31	74,468
"Mildly-neutropenic" ANC Laboratory Result (1.0 - 1.499 K/uL)	--	--	--	--	--	69	24	74,475

	Number of Patients	Number of Exposure Episodes	Total Days at Risk	Total Days Supply During Exposure Episodes	Mean Days Supply per Exposure Episode	Total Number of Secondary Events	Episodes with Any Secondary Event	Episodes with No Secondary Event
"Moderately-neutropenic" ANC Laboratory Result (0.5 - 0.999 K/uL)	--	--	--	--	--	21	*****	74,493
"Severely-neutropenic" ANC Laboratory Result (<0.5 K/uL)						*****	*****	74,494
COVID-REMS Incident Clozapine from January 1, 2020 to September 30, 2023	**29,865**	**39,623**	**4,526,113**	**4,221,088**	**141.34**	**--**	**--**	**--**
ANC Procedure Codes in Procedure Table	--	--	--	--	--	284,259	31,484	8,139
ANC Procedure Codes in Laboratory Table	--	--	--	--	--	6,495	967	38,656
ANC Procedure Codes in Procedure and/or Laboratory Table	--	--	--	--	--	285,225	31,505	8,118
ANC Laboratory Result	--	--	--	--	--	15,516	2,334	37,289
"Clean" ANC Laboratory Result (0 - 7.8 K/uL)	--	--	--	--	--	12,174	1,976	37,647
"Non-neutropenic" ANC Laboratory Result (1.5 - 7.8 K/uL)	--	--	--	--	--	12,100	1,972	37,651
"Neutropenic" ANC Laboratory Result (0 - 1.499 K/uL)	--	--	--	--	--	75	37	39,586
"Mildly-neutropenic" ANC Laboratory Result (1.0 - 1.499 K/uL)	--	--	--	--	--	38	23	39,600
"Moderately-neutropenic" ANC Laboratory Result (0.5 - 0.999 K/uL)	--	--	--	--	--	13	*****	39,613
"Severely-neutropenic" ANC Laboratory Result (<0.5 K/uL)						24	*****	39,616
Secondary Events in Entire Clozapine Episode								
Pre-REMS Incident Clozapine from January 1, 2010 to September 30, 2015	**51,766**	**73,984**	**33,614,576**	**32,221,256**	**622.44**	**--**	**--**	**--**
ANC Procedure Codes in Procedure Table	--	--	--	--	--	2,003,012	64,452	9,532
ANC Procedure Codes in Laboratory Table	--	--	--	--	--	14,152	888	73,096
ANC Procedure Codes in Procedure and/or Laboratory Table	--	--	--	--	--	2,004,465	64,476	9,508
ANC Laboratory Result	--	--	--	--	--	31,025	1,943	72,041
"Clean" ANC Laboratory Result (0 - 7.8 K/uL)	--	--	--	--	--	23,936	1,567	72,417
"Non-neutropenic" ANC Laboratory Result (1.5 - 7.8 K/uL)	--	--	--	--	--	23,877	1,566	72,418

Table 2. Summary of New Clozapine Episodes and Absolute Neutrophil Count (ANC) Laboratory Results in the Sentinel Distributed Database (SDD) from January 1, 2010 to September 30, 2023

	Number of Patients	Number of Exposure Episodes	Total Days at Risk	Total Days Supply During Exposure Episodes	Mean Days Supply per Exposure Episode	Total Number of Secondary Events	Episodes with Any Secondary Event	Episodes with No Secondary Event
"Neutropenic" ANC Laboratory Result (0 - 1.499 K/uL)	--	--	--	--	--	73	33	73,951
"Mildly-neutropenic" ANC Laboratory Result (1.0 - 1.499 K/uL)	--	--	--	--	--	43	27	73,957
"Moderately-neutropenic" ANC Laboratory Result (0.5 - 0.999 K/uL)	--	--	--	--	--	*****	*****	73,977
"Severely-neutropenic" ANC Laboratory Result (<0.5 K/uL)	--	--	--	--	--	23	*****	73,980
Post-REMS Incident Clozapine from October 1, 2015 to December 31, 2019	**54,857**	**74,499**	**25,301,584**	**24,268,859**	**442.40**	**--**	**--**	**--**
ANC Procedure Codes in Procedure Table	--	--	--	--	--	1,393,749	61,890	12,609
ANC Procedure Codes in Laboratory Table	--	--	--	--	--	16,111	1,094	73,405
ANC Procedure Codes in Procedure and/or Laboratory Table	--	--	--	--	--	1,395,683	61,919	12,580
ANC Laboratory Result	--	--	--	--	--	30,771	2,193	72,306
"Clean" ANC Laboratory Result (0 - 7.8 K/uL)	--	--	--	--	--	23,580	1,781	72,718
"Non-neutropenic" ANC Laboratory Result (1.5 - 7.8 K/uL)	--	--	--	--	--	23,418	1,779	72,720
"Neutropenic" ANC Laboratory Result (0 - 1.499 K/uL)	--	--	--	--	--	169	46	74,453
"Mildly-neutropenic" ANC Laboratory Result (1.0 - 1.499 K/uL)	--	--	--	--	--	121	36	74,463
"Moderately-neutropenic" ANC Laboratory Result (0.5 - 0.999 K/uL)	--	--	--	--	--	28	*****	74,490
"Severely-neutropenic" ANC Laboratory Result (<0.5 K/uL)	--	--	--	--	--	20	*****	74,491
COVID-REMS Incident Clozapine from January 1, 2020 to September 30, 2023	**29,865**	**39,623**	**10,014,856**	**9,537,203**	**319.34**	**--**	**--**	**--**
ANC Procedure Codes in Procedure Table	--	--	--	--	--	522,140	32,062	7,561
ANC Procedure Codes in Laboratory Table	--	--	--	--	--	11,376	1,037	38,586
ANC Procedure Codes in Procedure and/or Laboratory Table	--	--	--	--	--	523,638	32,081	7,542
ANC Laboratory Result	--	--	--	--	--	27,491	2,501	37,122
"Clean" ANC Laboratory Result (0 - 7.8 K/uL)	--	--	--	--	--	21,782	2,138	37,485

Table 2. Summary of New Clozapine Episodes and Absolute Neutrophil Count (ANC) Laboratory Results in the Sentinel Distributed Database (SDD) from January 1, 2010 to September 30, 2023

	Number of Patients	Number of Exposure Episodes	Total Days at Risk	Total Days Supply During Exposure Episodes	Mean Days Supply per Exposure Episode	Total Number of Secondary Events	Episodes with Any Secondary Event	Episodes with No Secondary Event
"Non-neutropenic" ANC Laboratory Result (1.5 - 7.8 K/uL)	--	--	--	--	--	21,651	2,134	37,489
"Neutropenic" ANC Laboratory Result (0 - 1.499 K/uL)	--	--	--	--	--	132	55	39,568
"Mildly-neutropenic" ANC Laboratory Result (1.0 - 1.499 K/uL)	--	--	--	--	--	77	39	39,584
"Moderately-neutropenic" ANC Laboratory Result (0.5 - 0.999 K/uL)	--	--	--	--	--	20	13	39,610
"Severely-neutropenic" ANC Laboratory Result (<0.5 K/uL)	--	--	--	--	--	35	*****	39,616

*****Data are not presented in these cells due to a small sample size or to assure a small cell cannot be recalculated through the cells presented.

Data presented by two dashes (--) indicate the column is not relevant for the row.

[1]Secondary events are listed in each row, where the primary event was clozapine treatment episode initiation.

Table 3. Summary of Neutropenia Diagnoses in the Sentinel Distributed Database (SDD) from January 1, 2010 to September 30, 2023

	Number of Patients	Number of Exposure Episodes	Number of Exposure Episodes with an Event	Total Days at Risk	Total Years at Risk	Event Rate per 1,000 Patient-Years at Risk (95% Confidence Interval)
Neutropenia Diagnoses in Clozapine Episode						
Pre-Risk Evaluation Mitigation Strategies (REMS) Incident Clozapine from January 1, 2010 to September 30, 2015	51,766	73,984	1,078	33,126,285	90,694.8	11.89 (11.19, 12.62)
Post-REMS Incident Clozapine from October 1, 2015 to December 31, 2019	54,857	74,499	931	25,009,456	68,472.2	13.60 (12.75, 14.49)
COVID-REMS Incident Clozapine from January 1, 2020 to September 30, 2023	29,865	39,623	538	9,865,695	27,010.8	19.92 (18.30, 21.67)

Table 4. Neutropenia Diagnosis Code Distribution Among New Clozapine Episodes in the Sentinel Distributed Database (SDD) from January 1, 2010 to September 30, 2023

Code	Code Description	Code Category	Code Type	Overall Counts	Encounter Care Setting
Pre-Risk Evaluation Mitigation Strategies (REMS) Incident Clozapine from January 1, 2010 to September 30, 2015					
288.00	Neutropenia, Unspecified	Diagnosis	ICD-9-CM	684	Ambulatory
288.00	Neutropenia, Unspecified	Diagnosis	ICD-9-CM	79	Acute inpatient, position not classified
288.00	Neutropenia, Unspecified	Diagnosis	ICD-9-CM	47	Acute inpatient, secondary position
288.00	Neutropenia, Unspecified	Diagnosis	ICD-9-CM	39	Non-acute institutional, secondary position
288.00	Neutropenia, Unspecified	Diagnosis	ICD-9-CM	*****	Emergency Department
288.00	Neutropenia, Unspecified	Diagnosis	ICD-9-CM	*****	Acute inpatient, principal position
288.09	Other Neutropenia	Diagnosis	ICD-9-CM	184	Ambulatory
288.09	Other Neutropenia	Diagnosis	ICD-9-CM	*****	Acute inpatient, position not classified
288.09	Other Neutropenia	Diagnosis	ICD-9-CM	*****	Acute inpatient, secondary position
288.09	Other Neutropenia	Diagnosis	ICD-9-CM	*****	Non-acute institutional, secondary position
288.09	Other Neutropenia	Diagnosis	ICD-9-CM	*****	Emergency Department
288.09	Other Neutropenia	Diagnosis	ICD-9-CM	*****	Acute inpatient, principal position
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-9-CM	*****	Non-acute institutional, secondary position
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-9-CM	*****	Non-acute institutional, secondary position
Post-REMS Incident Clozapine from October 1, 2015 to December 31, 2019					
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM	265	Ambulatory
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM	29	Acute inpatient, secondary position
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM	14	Non-acute institutional, secondary position
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM	12	Acute inpatient, position not classified
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM	*****	Emergency Department
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM	*****	Acute inpatient, principal position
D70.8	Other Neutropenia	Diagnosis	ICD-10-CM	43	Ambulatory
D70.8	Other Neutropenia	Diagnosis	ICD-10-CM	*****	Acute inpatient, position not classified
D70.8	Other Neutropenia	Diagnosis	ICD-10-CM	*****	Acute inpatient, secondary position
D70.8	Other Neutropenia	Diagnosis	ICD-10-CM	*****	Non-acute institutional, secondary position
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM	415	Ambulatory
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM	47	Acute inpatient, position not classified
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM	45	Acute inpatient, secondary position
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM	32	Non-acute institutional, secondary position
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM	*****	Emergency Department
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM	*****	Acute inpatient, principal position

Table 4. Neutropenia Diagnosis Code Distribution Among New Clozapine Episodes in the Sentinel Distributed Database (SDD) from January 1, 2010 to September 30, 2023

Code	Code Description	Code Category	Code Type	Overall Counts	Encounter Care Setting
COVID-REMS Incident Clozapine from January 1, 2020 to September 30, 2023					
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM	182	Ambulatory
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM	13	Acute inpatient, secondary position
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM	*****	Acute inpatient, position not classified
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM	*****	Emergency Department
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM	*****	Non-acute institutional, secondary position
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM	*****	Acute inpatient, principal position
D70.8	Other Neutropenia	Diagnosis	ICD-10-CM	31	Ambulatory
D70.8	Other Neutropenia	Diagnosis	ICD-10-CM	*****	Non-acute institutional, secondary position
D70.8	Other Neutropenia	Diagnosis	ICD-10-CM	*****	Acute inpatient, secondary position
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM	229	Ambulatory
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM	25	Acute inpatient, secondary position
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM	19	Acute inpatient, position not classified
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM	14	Non-acute institutional, secondary position
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM	*****	Emergency Department
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM	*****	Acute inpatient, principal position

*****Data are not presented in these cells due to a small sample size or to assure a small cell cannot be recalculated through the cells presented.

Table 5. Summary of Episode-Level[1] Cohort Attrition in the Sentinel Distributed Database (SDD) from January 1, 2010 to September 30, 2023

	Pre-Risk Evaluation and Mitigation Strategies (REMS) Incident Clozapine from January 1, 2010 to September 30, 2015		Post-REMS Incident Clozapine from October 1, 2015 to December 31, 2019		COVID-REMS Incident Clozapine from January 1, 2020 to September 30, 2023	
	Remaining	Excluded	Remaining	Excluded	Remaining	Excluded
Members meeting enrollment and demographic requirements						
Enrolled at any point during the query period	240,944,825	N/A[2]	295,094,638	N/A	244,099,571	N/A
Had required coverage type (medical and/or drug coverage)	165,239,318	75,705,507	221,263,953	73,830,685	179,829,749	64,269,822
Enrolled during specified age range	141,034,519	24,204,799	184,265,236	36,998,717	150,948,282	28,881,467
Met demographic requirements (sex, race, and Hispanic origin)	140,959,501	75,018	184,228,893	36,343	150,900,241	48,041
Members with a valid index event						
Had any cohort-defining claim during the query period	104,298	140,855,203	125,889	184,103,004	104,368	150,795,873
Cohort episodes with a valid index date						
Total number of claims with cohort-identifying codes during the query period	4,437,853	N/A	4,114,416	N/A	2,370,053	N/A
Claim recorded during specified age range	4,436,907	946	4,111,310	3,106	2,369,880	173
Episode defining index claim recorded during the query period	140,242	4,296,665	103,784	4,007,526	53,362	2,316,518
Cohort episodes with required pre-index history						
Had sufficient pre-index continuous enrollment	73,984	66,258	74,499	29,285	39,623	13,739
Final cohort						
Number of members	51,766	N/A	54,857	N/A	29,865	N/A
Number of episodes	73,984	N/A	74,499	N/A	39,623	N/A

[1]Cohorts are formed by first evaluating enrollment and demographic requirements as well as index events among members, then evaluating index dates, pre-index history, and post-index follow-up among episodes. Because of this, the number remaining often increases from the member- to episode-level steps.
[2]N/A means not applicable.

Appendix A. Dates of Available Data for Each Data Partner (DP) as of Request Distribution Date (March 11, 2024)

Masked DP ID	DP Start Date	DP End Date[1]
DP01	01/01/2000	05/31/2023
DP02	01/01/2000	08/31/2022
DP03	01/01/2004	07/31/2023
DP04	01/01/2006	06/30/2023
DP05	01/01/2005	07/31/2022
DP06	01/01/2007	06/30/2023
DP07	01/01/2000	10/31/2022
DP08	01/01/2000	08/31/2022
DP09	01/01/2000	04/30/2023
DP10	01/01/2008	04/30/2023
DP11	01/01/2014	12/31/2020
DP12	01/01/2010	06/30/2023
DP13	01/01/2008	09/30/2023

[1]End Date represents the earliest of: (1) query end date, or (2) last day of the most recent month for which all of a Data Partner's data tables (enrollment, dispensing, etc.) have at least 80% of the record count relative to the prior month.

Appendix B. List of Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
Clozapine	
clozapine	Clozapine
clozapine	Clozapine
clozapine	Clozaril
clozapine	FazaClo
clozapine	FazaClo
clozapine	Versacloz
clozapine	Clozaril
clozapine	FazaClo
clozapine	Versacloz
clozapine	Clozapine

Appendix C: List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes, Current Procedural Terminology, Fourth Edition (CPT-4), Healthcare Common Procedure Coding System, Level II (HCPCS), and Revenue (RE) Procedure Codes, and Logical Observation Identifiers Names and Codes (LOINC) and Sentinel Operations Center (SOC) Defined Lab Codes Used to Define Outcomes in this Request

Code	Description	Code Category	Code Type
	Neutropenia		
288.00	Neutropenia, Unspecified	Diagnosis	ICD-9-CM
288.09	Other Neutropenia	Diagnosis	ICD-9-CM
D70.2	Other Drug-Induced Agranulocytosis	Diagnosis	ICD-10-CM
D70.8	Other Neutropenia	Diagnosis	ICD-10-CM
D70.9	Neutropenia, Unspecified	Diagnosis	ICD-10-CM
	Absolute Neutrophil Count (ANC)		
0305	Laboratory-Hematology	Procedure	Revenue
80050	General health panel This panel must include the following: Comprehensive metabolic panel (80053) Blood count, complete (CBC), automated and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Thyroid stimulating hormone (TSH) (84443)	Procedure	CPT-4
80055	Obstetric panel This panel must include the following: Blood count, complete (CBC), automated and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Hepatitis B surface antigen (HBsAg) (87340) Antibody, rubella (86762) Syphilis test, non-treponemal antibody; qualitative (eg, VDRL, RPR, ART) (86592) Antibody screen, RBC, each serum technique (86850) Blood typing, ABO (86900) AND Blood typing, Rh (D) (86901)	Procedure	CPT-4
85004	Blood count; automated differential WBC count	Procedure	CPT-4
85007	Blood count; blood smear, microscopic examination with manual differential WBC count	Procedure	CPT-4
85008	Blood count; blood smear, microscopic examination without manual differential WBC count	Procedure	CPT-4
85009	Blood count; manual differential WBC count, buffy coat	Procedure	CPT-4
85025	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count) and automated differential WBC count	Procedure	CPT-4
85027	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count)	Procedure	CPT-4
85032	Blood count; manual cell count (erythrocyte, leukocyte, or platelet) each	Procedure	CPT-4
85048	Blood count; leukocyte (WBC), automated	Procedure	CPT-4
G0306	Complete CBC, automated (HgB, HCT, RBC, WBC, without platelet count) and automated WBC differential count	Procedure	HCPCS
G0307	Complete CBC, automated (HgB, HCT, RBC, WBC; without platelet count)	Procedure	HCPCS
752-6	Deprecated Neutrophils [#/volume] in Blood by Automated count	Laboratory	LOINC
26499-4	Neutrophils [#/volume] in Blood	Laboratory	LOINC
751-8	Neutrophils [#/volume] in Blood by Automated count	Laboratory	LOINC

Appendix C: List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes, Current Procedural Terminology, Fourth Edition (CPT-4), Healthcare Common Procedure Coding System, Level II (HCPCS), and Revenue (RE) Procedure Codes, and Logical Observation Identifiers Names and Codes (LOINC) and Sentinel Operations Center (SOC) Defined Lab Codes Used to Define Outcomes in this Request

Code	Description	Code Category	Code Type
753-4	Neutrophils [#/volume] in Blood by Manual count	Laboratory	LOINC
L0032013010104	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, specimen source not populated, "Emergency Department" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013010204	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, specimen source not populated, "Home" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013010304	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, specimen source not populated , "Inpatient" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013010404	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, specimen source not populated, "Outpatient" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013010504	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, specimen source not specified, "Unknown or null" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013020104	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, "Blood" specimen source, "Emergency Department" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013020204	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, "Blood" specimen source, "Home" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013020304	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, "Blood" specimen source, "Inpatient" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013020404	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, "Blood" specimen source, "Outpatient" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013020504	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, "Blood" specimen source, "Unknown or null" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013070104	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, "Unknown" specimen source, "Emergency Department" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013070204	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, "Unknown" specimen source, "Home" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013070304	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, "Unknown" specimen source, "Inpatient" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013070404	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, "Unknown" specimen source, "Outpatient" patient location, and "K/UL" result unit	Laboratory	SOC
L0032013070504	Lab records in SOC-defined "Absolute Neutrophil Count" laboratory concept, "Unknown" specimen source, "Unknown or null" patient location, and "K/UL" result unit	Laboratory	SOC

Appendix D: Specifications Defining Parameters for this Request

An execution of the Cohort Identification and Descriptive Analysis (CIDA) module, version 13.1.0 to estimate number of Absolute Neutrophil Count (ANC) screenings according to different definitions among clozapine users in the Sentinel Distributed Database (SDD) was requested.

Query period:	Multiple Query Periods, specified per scenario. See below.
Coverage requirement:	Medical & Drug Coverage
Enrollment gap:	45
Age groups:	12-18, 19-35, 36-50, 51-64, 65-74, 75+
Stratifications:	Year-quarter, Follow-up duration categories (FOLLOWUP_CAT), Number of secondary events (EPI_COUNT) {note: not outputting latter two in report, just for info}
Restrictions:	No
Envelope macro:	Reclassify encounters during inpatient stay as inpatient
Distribution of index-defining codes:	Yes, Health Outcomes of Interest (HOIs)
Never-exposed cohort:	No
Freeze data:	Yes

			Exposure					
Query Period	**Cohort Group**	**Episode Type**	**Pre-Index Enroll. Req.**	**Index Exposure**	**Cohort Definition**	**Incidence Washout Period**	**Incident w/ respect to:**	**If Incidence Should Search for Date Only (Instead of also an Interval)**
01/01/10 - 09/30/15, 10/1/15 - 12/31/19, 1/1/20 - 3/31/24	First Six Months of Incident Clozapine Treatment Episodes	Primary	30	Clozapine	All valid exposure episodes during query period	30	Clozapine	No
""	Neutropenia Diagnoses During First Six Months of Incident Clozapine Treatment Episodes	Primary	30	Clozapine	All valid exposure episodes during query period	30	Clozapine	No
01/01/10 - 09/30/15, 10/1/15 - 12/31/19, 1/1/20 - 3/31/24	Neutropenia Diagnoses During Incident Clozapine Treatment Episodes	Primary	30	Clozapine	All valid exposure episodes during query period	30	Clozapine	No

Appendix D: Specifications Defining Parameters for this Request

| Query Period | Cohort Group | Exposure | | | | | | | | | Censor Treatment Episode at Evidence of: | Create Baseline Table? Y/N |
		Point Exposure?	Treatment Episode Gap	Exposure Episode Extension	Minimum Exposure Episode Duration	Minimum Days Supplied	Maximum Exposure Episode Duration	Care Setting	Principal diagnosis position	Forced Supply to Attach to Dispensings		
01/01/10 - 09/30/15, 10/1/15 - 12/31/19, 1/1/20 - 3/31/24	First Six Months of Incident Clozapine Treatment Episodes	No	30 days	0 days	1 day	N/A	183	N/A	N/A	N/A	Disenrollment, death, Data Partner (DP) end date, query end date, episode end	No
""	Neutropenia Diagnoses During First Six Months of Incident Clozapine Treatment Episodes	No	30 days	0 days	1 day	N/A	None	N/A	N/A	N/A	Disenrollment, death, DP end date, query end date, episode end	No
01/01/10 - 09/30/15, 10/1/15 - 12/31/19, 1/1/20 - 3/31/24	Neutropenia Diagnoses During Incident Clozapine Treatment Episodes	No	30 days	0 days	1 day	N/A	None	N/A	N/A	N/A	Disenrollment, death, DP end date, query end date, episode end	No

Query Period	Cohort Group	Episode Type	Pre-Index Enroll. Requirements	Index Exposure	Cohort Definition	Secondary Events			
						Incidence Washout Period	Incident w/ Respect to:	If Incidence Should Search for Date Only (Instead of also an	Point Exposure?
01/01/10 - 09/30/15, 10/1/15 - 12/31/19, 1/1/20 - 3/31/24	ANC Procedure Codes in Procedure Table	Secondary	30	ANC screening (procedure code in procedure table)	All valid exposure episodes during query period	0	N/A	N/A	Yes
""	ANC Procedure Codes in Laboratory Table	Secondary	30	ANC screening (procedure code in lab table)	All valid exposure episodes during query period	0	N/A	N/A	Yes
""	ANC Procedure Codes in Procedure or Laboratory Table	Secondary	30	ANC screening (procedure code in procedure or lab table)	All valid exposure episodes during query period	0	N/A	N/A	Yes
""	ANC Laboratory Result	Secondary	30	ANC lab result	All valid exposure episodes during query period	0	N/A	N/A	Yes
""	"Clean" ANC Laboratory Result (0 - 7.8 K/uL)	Secondary	30	ANC lab result (lab result 0-7.8 K/uL)	All valid exposure episodes during query period	0	N/A	N/A	Yes
""	"Non-neutropenic" ANC Laboratory Result (1.5 - 7.8 K/uL)	Secondary	30	Non-neutropenic ANC lab result (lab result 1.5-7.8 K/uL)	All valid exposure episodes during query period	0	N/A	N/A	Yes
""	"Neutropenic" ANC Laboratory Result (0 - 1.499 K/uL)	Secondary	30	Any-neutropenic ANC lab result (lab result <1.5 K/uL)	All valid exposure episodes during query period	0	N/A	N/A	Yes
""	"Mildly-neutropenic" ANC Laboratory Result (1.0 - 1.499 K/uL)	Secondary	30	Mildly-neutropenic ANC lab result (lab result 1-1.4999 K/uL)	All valid exposure episodes during query period	0	N/A	N/A	Yes
""	"Moderately-neutropenic" ANC Laboratory Result (0.5 - 0.999 K/uL)	Secondary	30	Moderately-neutropenic ANC lab result (lab result 0.5-0.9999 K/uL)	All valid exposure episodes during query period	0	N/A	N/A	Yes
""	"Severely-neutropenic" ANC Laboratory Result (<0.5 K/uL)	Secondary	30	Severely-neutropenic ANC lab result (lab result <0.5 K/uL)	All valid exposure episodes during query period	0	N/A	N/A	Yes

Query Period	Cohort Group	Secondary Events									Create Baseline Table? Y/N
		Treatment Episode Gap	Exposure Episode Extension	Minimum Exposure Episode Duration	Minimum Days Supplied	Maximum Exposure Episode Duration	Care Setting	Principal Diagnosis Position	Forced Supply to Attach to Dispensings	Censor Treatment Episode at Evidence of:	
01/01/10 - 09/30/15, 10/1/15 - 12/31/19, 1/1/20 - 3/31/24	ANC Procedure Codes in Procedure Table	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	Disenrollment, death, DP end date, query end date	No
""	ANC Procedure Codes in Laboratory Table	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	Disenrollment, death, DP end date, query end date	No
""	ANC Procedure Codes in Procedure or Laboratory Table	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	Disenrollment, death, DP end date, query end date	No
""	ANC Laboratory Result	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	Disenrollment, death, DP end date, query end date	No
""	"Clean" ANC Laboratory Result (0 - 7.8 K/uL)	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	Disenrollment, death, DP end date, query end date	No
""	"Non-neutropenic" ANC Laboratory Result (1.5 - 7.8 K/uL)	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	Disenrollment, death, DP end date, query end date	No
""	"Neutropenic" ANC Laboratory Result (0 - 1.499 K/uL)	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	Disenrollment, death, DP end date, query end date	No
""	"Mildly-neutropenic" ANC Laboratory Result (1.0 - 1.499 K/uL)	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	Disenrollment, death, DP end date, query end date	No
""	"Moderately-neutropenic" ANC Laboratory Result (0.5 - 0.999 K/uL)	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	Disenrollment, death, DP end date, query end date	No
""	"Severely-neutropenic" ANC Laboratory Result (<0.5 K/uL)	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	Disenrollment, death, DP end date, query end date	No

		Primary Event Criteria								
Query Period	**Cohort Group**	**Event (See Tab for Definition)**	**Incident Event Washout Period**	**Care Setting**	**Principal Diagnosis Position**	**If Should Search for Date Only (Instead of also an Interval)**	**Event De-Duplication**	**Forced Supply to Attach to Dispensings**	**Blackout Period**	**Risk Window Interval Start**
01/01/10 - 09/30/15, 10/1/15 - 12/31/19, 1/1/20 - 3/31/24	First Six Months of Incident Clozapine Treatment Episodes	Non-cancer neutropenic diagnosis	0	Any care setting *except* Other Ambulatory (OA) visits	N/A	No	De-duplicates occurrences of the same event group on the same day	N/A	N/A	0
01/01/10 - 09/30/15, 10/1/15 - 12/31/19, 1/1/20 - 3/31/24	Neutropenia Diagnoses During Incident Clozapine Treatment Episodes	Non-cancer neutropenic diagnosis	0	Any care setting *except* OA	N/A	No	De-duplicates occurrences of the same event group on the same day	N/A	N/A	0

Appendix D: Specifications Defining Parameters for this Request

Query Period	Analysis Group	Primary Episode	Secondary Episode	Observation From Anchor	Observation From:	Observation To Anchor	Observation To:	Secondary Ep to Use for Time to Secondary Ep Output	Minimum Cutoff to be Considered Adherent	Scale for Minimum Cutoff	Primary Episode Duration Categories	Create Baseline Table for this Primary-Secondary Episode Pair (AKA Analysis Group)
						Secondary Event Criteria						
01/01/10 - 09/30/15, 10/1/15 - 12/31/19, 1/1/20 - 3/31/24	ANC Procedure Codes in Procedure Table During First Six Months of Incident Clozapine Treatment Episodes	First Six Months of Incident Clozapine Treatment Episodes	ANC Procedure Codes in Procedure Table	Index	0	EpisodeEnd	0	1	1	Count	1-7, 8-14, 15-21, 22-28, 29-35, 36-42, 43-49, 50-56, 57-63, 64-70, 71-77, 78-84, 85-91, 92-98, 99-105, 106-112, 113-119, 120-126, 127-133, 134-140, 141-147, 148-154, 155-161, 162-168, 169-175, 176-182, 183+	Yes
""	ANC Procedure Codes in Laboratory Table During First Six Months of Incident Clozapine Treatment Episodes	""	ANC Procedure Codes in Laboratory Table	Index	0	EpisodeEnd	0	1	1	Count	""	No

Appendix D: Specifications Defining Parameters for this Request

				Secondary Event Criteria								
Query Period	Analysis Group	Primary Episode	Secondary Episode	Observation From Anchor	Observation From:	Observation To Anchor	Observation To:	Secondary Ep to Use for Time to Secondary Ep Output	Minimum Cutoff to be Considered Adherent	Scale for Minimum Cutoff	Primary Episode Duration Categories	Create Baseline Table for this Primary-Secondary Episode Pair (AKA Analysis Group)
""	ANC Procedure Codes in Procedure or Laboratory Table During First Six Months of Incident Clozapine Treatment Episodes	""	ANC Procedure Codes in Procedure or Laboratory Table	Index	0	EpisodeEnd	0	1	1	Count	""	No
""	ANC Laboratory Result During First Six Months of Incident Clozapine Treatment Episodes	""	ANC Laboratory Result	Index	0	EpisodeEnd	0	1	1	Count	""	No
""	"Clean" ANC Laboratory Result (0 - 7.8 K/uL) During First Six Months of Incident Clozapine Treatment Episodes	""	"Clean" ANC Laboratory Result (0 - 7.8 K/uL)	Index	0	EpisodeEnd	0	1	1	Count	""	No
""	"Non-neutropenic" ANC Laboratory Result (1.5 - 7.8 K/uL) During First Six Months of Incident Clozapine Treatment Episodes	""	"Non-neutropenic" ANC Laboratory Result (1.5 - 7.8 K/uL)	Index	0	EpisodeEnd	0	1	1	Count	""	No

| Query Period | Analysis Group | Primary Episode | Secondary Event Criteria | | | | | | | | Primary Episode Duration Categories | Create Baseline Table for this Primary-Secondary Episode Pair (AKA Analysis Group) |
			Secondary Episode	Observation From Anchor	Observation From:	Observation To Anchor	Observation To:	Secondary Ep to Use for Time to Secondary Ep Output	Minimum Cutoff to be Considered Adherent	Scale for Minimum Cutoff		
""	"Neutropenic" ANC Laboratory Result (0 - 1.499 K/uL) During First Six Months of Incident Clozapine Treatment Episodes	""	"Neutropenic" ANC Laboratory Result (0 - 1.499 K/uL)	Index	0	EpisodeEnd	0	1	1	Count	""	No
""	"Mildly-neutropenic" ANC Laboratory Result (1.0 - 1.499 K/uL) During First Six Months of Incident Clozapine Treatment Episodes	""	"Mildly-neutropenic" ANC Laboratory Result (1.0 - 1.499 K/uL)	Index	0	EpisodeEnd	0	1	1	Count	""	No
""	"Moderately-neutropenic" ANC Laboratory Result (0.5 - 0.999 K/uL) During First Six Months of Incident Clozapine Treatment Episodes	""	"Moderately-neutropenic" ANC Laboratory Result (0.5 - 0.999 K/uL)	Index	0	EpisodeEnd	0	1	1	Count	""	No

Appendix D: Specifications Defining Parameters for this Request

			Secondary Event Criteria									
Query Period	Analysis Group	Primary Episode	Secondary Episode	Observation From Anchor	Observation From:	Observation To Anchor	Observation To:	Secondary Ep to Use for Time to Secondary Ep Output	Minimum Cutoff to be Considered Adherent	Scale for Minimum Cutoff	Primary Episode Duration Categories	Create Baseline Table for this Primary-Secondary Episode Pair (AKA Analysis Group)
""	"Severely-neutropenic" ANC Laboratory Result (<0.5 K/uL) During First Six Months of Incident Clozapine Treatment Episodes	""	"Severely-neutropenic" ANC Laboratory Result (<0.5 K/uL)	Index	0	EpisodeEnd	0	1	1	Count	""	No
01/01/10 - 09/30/15, 10/1/15 - 12/31/19, 1/1/20 - 3/31/24	ANC Procedure Codes in Procedure Table During Incident Clozapine Treatment Episodes	Neutropenia Diagnoses During Incident Clozapine Treatment Episodes	ANC Procedure Codes in Procedure Table	Index	0	EpisodeEnd	0	1	1	Count	1-7, 8-14, 15-21, 22-28, 29-35, 36-42, 43-49, 50-56, 57-63, 64-70, 71-77, 78-84, 85-91, 92-98, 99-105, 106-112, 113-119, 120-126, 127-133, 134-140, 141-147, 148-154, 155-161, 162-168, 169-175, 176-182, 183+	Yes
""	ANC Procedure Codes in Laboratory Table During Incident Clozapine Treatment Episodes	""	ANC Procedure Codes in Laboratory Table	Index	0	EpisodeEnd	0	1	1	Count	""	No

Appendix D: Specifications Defining Parameters for this Request

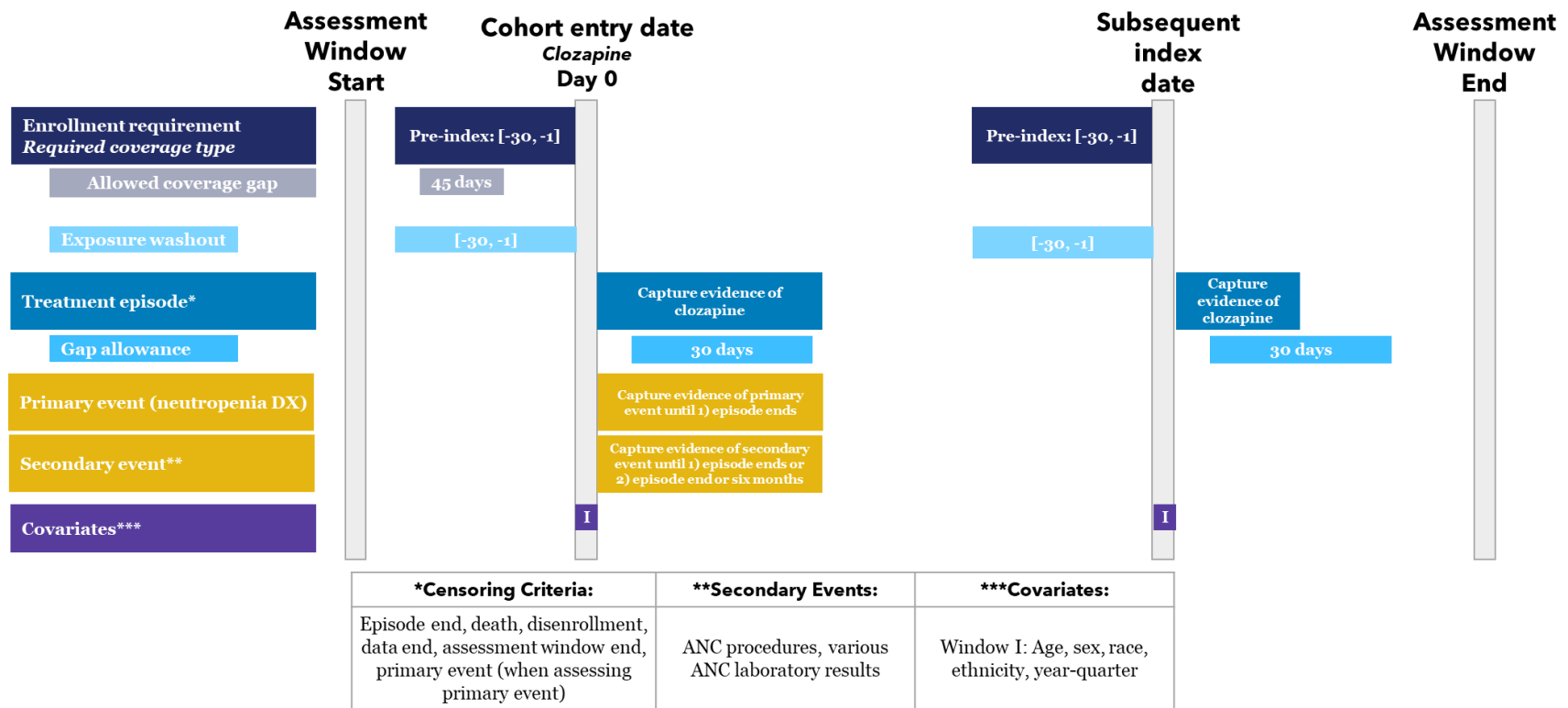|													
					Secondary Event Criteria								
Query Period	Analysis Group	Primary Episode	Secondary Episode	Observation From Anchor	Observation From:	Observation To Anchor	Observation To:	Secondary Ep to Use for Time to Secondary Ep Output	Minimum Cutoff to be Considered Adherent	Scale for Minimum Cutoff	Primary Episode Duration Categories	Create Baseline Table for this Primary-Secondary Episode Pair (AKA Analysis Group)
""	ANC Procedure Codes in Procedure or Laboratory Table During Incident Clozapine Treatment Episodes	""	ANC Procedure Codes in Procedure or Laboratory Table	Index	0	EpisodeEnd	0	1	1	Count	""	No
""	ANC Laboratory Result During Incident Clozapine Treatment Episodes	""	ANC Laboratory Result	Index	0	EpisodeEnd	0	1	1	Count	""	No
""	"Clean" ANC Laboratory Result (0 - 7.8 K/uL) During Incident Clozapine Treatment Episodes	""	"Clean" ANC Laboratory Result (0 - 7.8 K/uL)	Index	0	EpisodeEnd	0	1	1	Count	""	No
""	"Non-neutropenic" ANC Laboratory Result (1.5 - 7.8 K/uL) During Incident Clozapine Treatment Episodes	""	"Non-neutropenic" ANC Laboratory Result (1.5 - 7.8 K/uL)	Index	0	EpisodeEnd	0	1	1	Count	""	No
""	"Neutropenic" ANC Laboratory Result (0 - 1.499 K/uL) During Incident Clozapine Treatment Episodes	""	"Neutropenic" ANC Laboratory Result (0 - 1.499 K/uL)	Index	0	EpisodeEnd	0	1	1	Count	""	No

Appendix D: Specifications Defining Parameters for this Request

Query Period	Analysis Group	Primary Episode	Secondary Episode	Observation From Anchor	Observation From:	Observation To Anchor	Observation To:	Secondary Ep to Use for Time to Secondary Ep Output	Minimum Cutoff to be Considered Adherent	Scale for Minimum Cutoff	Primary Episode Duration Categories	Create Baseline Table for this Primary-Secondary Episode Pair (AKA Analysis Group)
							Secondary Event Criteria					
""	"Mildly-neutropenic" ANC Laboratory Result (1.0 - 1.499 K/uL) During Incident Clozapine Treatment Episodes	""	"Mildly-neutropenic" ANC Laboratory Result (1.0 - 1.499 K/uL)	Index	0	EpisodeEnd	0	1	1	Count	""	No
""	"Moderately-neutropenic" ANC Laboratory Result (0.5 - 0.999 K/uL) During Incident Clozapine Treatment Episodes	""	"Moderately-neutropenic" ANC Laboratory Result (0.5 - 0.999 K/uL)	Index	0	EpisodeEnd	0	1	1	Count	""	No
""	"Severely-neutropenic" ANC Laboratory Result (<0.5 K/uL) During Incident Clozapine Treatment Episodes	""	"Severely-neutropenic" ANC Laboratory Result (<0.5 K/uL)	Index	0	EpisodeEnd	0	1	1	Count	""	No

ANC means Absolute Neutrophil Count.
N/A means not applicable.

Design Diagram for Main Cohort

ANC means Absolute Neutrophil Count.