

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).

If you are using a web page screen reader and are unable to access this document, please contact the Sentinel Operations Center for assistance at info@sentinelssystem.org.

Overview for Request: cder_iqp_wp038

Request ID: cder_iqp_wp038

Request Description: In this report, we aimed to assess use of methotrexate (MTX) injection formulation products in the TriNetX Live™ platform.

Data Source: We ran this query in two parts: the first set on January 31 and February 1, 2024 and the second on February 2 and 5, 2024.

Section 1: This query contains data from 81 health care organizations (HCOs), provided through the TriNetX Live™ platform in their USA Network (with Natural Language Processing (NLP)) from January 1, 2022 to December 31, 2023.

Section 2: This query contains data from 81 health care organizations (HCOs), provided through the TriNetX Live™ platform in their USA Network (with NLP). The data used were over two distinct query periods: first from August 1, 2022 to December 31, 2023, and second from January 1, 2022 to December 31, 2023. Details are mentioned in the Study Design section.

TriNetX aggregates electronic health record (EHR) systems data from its partner HCOs to create queryable datasets. TriNetX datasets primarily comprise clinical patient data such as demographics, diagnoses, procedures, labs, and medications. For more information on the TriNetX Live™ platform and the TriNetX data visit their website here: <https://trinetx.com/>

Study Design: In this retrospective cohort study, we identified counts of individuals with evidence of exposure to MTX injection formulation (with focus on intravenous) products, stratified by age using the Query Builder module in the TriNetX Live™ platform. This query was conducted in two parts, complementary to each other.

The first part of this query focused on:

- The overall patient counts with a procedure code for injectable MTX administration among adult (aged 18 and older) and pediatric populations (0 to 17 years) over the query period of January 1, 2022, to December 31, 2023.
- Additionally, we stratified the counts in both age groups by care setting (inpatient, emergency and ambulatory) and by 3-month time intervals starting January 1, 2022.
- Last, we calculated the proportion of patients in both age groups with a cancer diagnosis code between 7 days prior to and 2 days after the index MTX date.

The second part of this query focused on:

- The monthly patient counts in both age groups with evidence of injectable MTX administration between August 2022 and December 2023.
- We also explored whether RxNorm codes for MTX (used to identify all formulations and doses of MTX in TriNetX) could be used, in conjunction with filters and concomitant diagnosis and procedure codes, to identify injectable MTX formulations.

Overview for Request: cder_iqp_wp038

Exposures of Interest:

We defined the exposure of interest, injectable MTX, using Healthcare Common Procedure Coding System (HCPCS) procedure codes (for both parts of the query) and RxNorm medication terms (in the second part only) in the Query Builder module.

HCPCS codes: We used two HCPCS procedure codes to identify administration of injectable MTX in the first part of the query and to ascertain monthly patient counts in the second part of the query.

RxNorm medication codes: We explored the use of the primary ingredient RxNorm code for MTX (representing all formulations and doses in the data) to identify injectable MTX (with focus on intravenous formulations) in the second part of the query by creating multiple cohorts:

Cohort 1: RxNorm medication code alone

Cohort 2: RxNorm medication code + route of administration: injectable (including intravenous, intramuscular, subcutaneous, etc.)

Cohort 3: RxNorm medication code + route of administration: injectable + care setting: inpatient, inpatient - non acute or short stay on same day as index MTX date

Cohort 4: RxNorm medication code + route of administration: injectable + codes for intravenous administration on the same day as index MTX date

Cohort 5: RxNorm medication code + route of administration: injectable + codes for intravenous administration between -1 day to +1 day of the index MTX date

Please see Appendix A for the list of RxNorm medication terms and HCPCS procedure codes used to define exposure to injectable MTX formulation in this request.

Please see Appendix B for the list of International Classification of Diseases-10-Clinical Modification (ICD-10-CM) diagnosis codes, Systemized Nomenclature of Medicine – Clinical Terms (SNOMED) codes, HCPCS and Current Procedural Terminology- I (CPT I) procedure codes used to define intravenous infusion/administration in this request.

Cohort Eligibility Criteria:

This section will describe the cohort eligibility criteria for each part of the query separately.

In the **first part of the query**, we created 24 cohorts over the query period of January 1, 2022 to December 31, 2023:

- Overall: Two cohorts (adult and pediatric age groups separately) of injectable MTX users
- Quarterly time intervals: 16 cohorts (8 for each age group) of injectable MTX users by each 3-month time period from January 2022 to December 2023.
- Care setting: Six cohorts (3 for each age group) of injectable MTX users with a visit on the same day with the following care settings - inpatient, emergency and ambulatory

In the **second part of the query**, we created 39 cohorts:

- Monthly time intervals: 34 cohorts (17 for each age group) of injectable MTX users, monthly from August 2022 to December 2023.
- 5 cohorts (detailed in the Exposures of Interest section) exploring use of RxNorm codes to identify users of injectable MTX (with focus on intravenous) formulation over the query period of January 2022 to December 2023

Please see Appendix C for the specifications of the cohort parameters for each of the 63 cohorts as included in the Query Builder.

Overview for Request: cder_iqp_wp038

Baseline Characteristics:

We utilized the Advanced Explore Cohort module to assess the presence of cancer (neoplasms) among adult and pediatric users of injectable MTX formulations (two overall cohorts from the first part of the query) in the following period: -7 days from index MTX date to +2 days from index MTX date (over the query period of Jan 2022 to Dec 2023). We identified cancer using available ICD-10-CM coding hierarchies in the TriNetX platform.

Please see Appendix D for details of the Analytic Module Specification with the ICD-10-CM parent codes used to define cancer (neoplasm) in this request.

Limitations: Algorithms used to define exposures, characteristics and mapping of source data to the data model are imperfect and susceptible to misclassification. Additionally, EHR data in the United States lacks longitudinality. The information before or after patients' healthcare encounters could be missing, especially if patient care was administered across different HCOs that may or might not participate in the TriNetX USA network. We are unable to determine if absence of evidence of a condition implies a true absence of a condition or if the condition was not observed in the data. Furthermore, not all HCOs provide brand name or route information for RxNorm terms or laboratory data. Therefore, data should be interpreted with these limitations in mind.

All counts provided through the TriNetX Live™ platform are rounded up to the nearest 10 to protect patient privacy. This rounding affects error, especially as sample sizes decrease. Error due to rounding can range from <0.09% when sample sizes are >10,000 to nearly 20% as sample sizes drop. Thus, all estimates should be interpreted as ranges, and small sample sizes should be interpreted with caution. Additionally, percentages are calculated based on these rounded numerators and denominators. Thus, due to rounding, the sum of each value in a category may not total to 100%.

We used HCPCS procedure codes and RxNorm codes to identify exposure to injectable (with focus on intravenous) MTX formulations. The HCPCS procedure codes could not further distinguish between an intravenous (IV), intramuscular or subcutaneous MTX formulation.

The TriNetX Live™ platform uses specifically the primary or main ingredient RxNorm terms to identify medications. In two of the cohorts from the second part of the request, we used concomitant IV infusion/administration codes to more accurately identify IV MTX users either on the same day as index MTX or within -1 to +1 days from index MTX. However, this makes an assumption that the IV administration code is related to the MTX code, which may not hold.

Notes: We ran this query in two parts: first on January 31, 2024, and the second on February 2 and 5, 2024. A re-run of this query for the same query period in the future may not yield the same results owing to the dynamic nature of the TriNetX Live™ network.

Please contact the Sentinel Operations Center (info@sentinelssystem.org) for questions and to provide comments/suggestions for future enhancements to this document. For more information on Sentinel's querying in the TriNetX platform, please refer to the Sentinel Website (<https://www.sentinelinitiative.org/methods-data-tools/methods/trinetx-rapid-querying>).

Table of Contents	
Glossary	Glossary of Terms for Analyses Using TriNetX Live™ Platform
Table 1	Counts of Users of Injectable Methotrexate in the TriNetX USA Network (with Natural Language Processing) from January 1, 2022 through December 31, 2023, Overall and by Quarter
Table 2	Counts of Users of Injectable Methotrexate in the TriNetX USA Network (with Natural Language Processing) from January 1, 2022 through December 31, 2023, by Healthcare Setting
Table 3	Counts of Users of Injectable Methotrexate with Diagnosis of Cancer in the TriNetX USA Network (with Natural Language Processing) from January 1, 2022 through December 31, 2023
Table 4	Counts of Users of Injectable Methotrexate in the TriNetX USA Network (with Natural Language Processing) from August 1, 2022 through December 31, 2023, by Month
Table 5	Exploration of Using RxNorm Medication Terms to Identify Users of Injectable Methotrexate (focus on Intravenous) Formulations in the TriNetX USA Network (with Natural Language Processing) from January 1, 2022 through December 31, 2023
Appendix A	List of RxNorm Medication Terms and Healthcare Common Procedure Coding System (HCPCS) Procedure Codes Used to Define Exposures in this Request
Appendix B	List of Diagnosis and Procedure Codes used to Define Intravenous Infusion/Administration in this Request
Appendix C	Specifications Defining Query Builder Modules in this Request
Appendix D	Specifications Defining Analytic Modules in this Request

Glossary of Terms for Analyses Using TriNetX Live™ Platform*

Characteristic - A medical fact (e.g., diagnosis, procedure, lab result) that occurred on or before the cohort-defining index event.

Explore Cohort - A description module on the TriNetX platform that presents a clinical profile of patients in a given cohort. Patient counts are rounded up to the nearest 10 before percentages are calculated, so the sum each of the values in one category may not total to 100%.

Date Shifting - A data obfuscation technique that some HCOs use to preserve patient privacy. Date shifting entails assigning each patient a random number of days (eg, -365 to +365 days) and consistently adjusting each of their dates by that number of days, thus maintaining temporal relationships between records within a single patient.

Fact - (Medical Fact) A unit of utilization that represents a medical observation on a patient (e.g., diagnosis, procedure, clinical observation).

Filter - A method of limiting terms included in queries to a specific subset of data. Filters include age at time of event, data source (electronic health record or natural language processing); brand name, route, and strength for medication terms; occurrence (first or most recent) for lab terms; and priority for diagnosis and procedure terms.

Group - A series of codes and terms defined with Boolean logic that are used to create a query cohort. For each group, users have the ability to specified time periods of interest, and the number of instances that the group must occur for cohort entry.

Subgroup - Within a group, additional subgroups can be specified to define temporal relationships between the terms in the subgroup (e.g., terms in subgroup B must occur within 5 days after terms in subgroup A). Users can require that these temporal constraints be applied to the 1) first, 2) last, or 3) any instance of each subgroup.

Health Care Organization (HCO) - Organizations that contribute electronic healthcare record data to the TriNetX data networks. HCOs include academic institutions and community health provider systems and a single HCO may contain one or more individual sites or facilities.

Index - The first date when a patient meets all of the cohort-defining criteria. In Analytics modules, the index can be defined as the date when a patient meets all of the cohort criteria, or only one specific group's criteria.

Module - A subsection of the TriNetX platform that performs a distinct functionality. Cohorts are created using the Query Builder module. Descriptive modules include Healthcare Organizations, Explore Cohorts, Rate of Arrival, Summary Statistics, and Analyze Criteria. Advanced analytic modules include Analyze Outcomes, Compare Outcomes, Compare Cohorts, Treatment Pathways, and Incidence and Prevalence.

Network - An aggregation of HCOs contributing data to the platform. Multiple networks are available for querying on the platform; the different networks represent subsets of HCOs organized by date-shifting practices or availability of downloadable datasets.

Outcome - A medical fact (e.g., diagnosis, procedure, lab result) that occurred on or after the cohort-defining index event.

Query - In the TriNetX platform, a query is a distinct cohort with a unique set of terms and logic. Query cohorts are created using the Query Builder platform module.

Risk - In Advanced Analytics modules, risk refers to the percentage of patients in each cohort with the specified outcome of interest.

Priority - An indication whether the code was the condition that the provider spent the most time evaluating or treating during a visit. Possible values include primary, secondary, or unknown.

Term - The codes used to specify patient cohort criteria in a query. Code options include diagnoses, procedures, medications, labs, demographics, genomics, and visits. Terms can be linked together using and/or Boolean logic. TriNetX also creates terms that group together multiple medical codes into single clinical concepts.

Cannot Have Term - A category of terms within a query group that patients must not have evidence of to be included in the cohort.

Must Have Term - A category of terms within a query group that patients must have evidence of to be included in the cohort.

Glossary of Terms for Analyses Using TriNetX Live™ Platform*

Time Constraint - used to define time periods of interest for each group within a query. Time constraints can be defined relative to the date the query was run (e.g., any time before today), or defined based on specific dates (e.g., January 1, 2015 to September 30, 2020).

Treatment Pathway - In Advanced Analytics modules, the Treatment Pathways module returns the order in which patients received treatment and the prevalence of treatments, including combination of medications, following an index event.

TriNetX Codes - For commonly used laboratory terms, TriNetX aggregates Logical Observation Identifiers Names and Codes (LOINC) laboratory codes at a clinically significant level to new queryable TNX:LAB terms.

Visit - A type of term used to specify the type of medical encounter or facility where the encounter was recorded. Visit terms are derived by TriNetX from the source data. Visits are recorded separately from the codes or labs that occurred during the encounter; care settings are not attached to individual codes. Values for visit terms include: ambulatory, emergency, field, home health, inpatient encounter, inpatient acute, inpatient non-acute, laboratory, observation, pharmacy, pre-admission, short stay, virtual, and unknown.

*all terms may not be used in this report

Table 1. Counts of Users of Injectable Methotrexate in the TriNetX USA Network (with Natural Language Processing) from January 1, 2022 through December 31, 2023, Overall and by Quarter

Quarter	0-17 years of age	18+ years of age
Jan-Mar 2022	740	1020
Apr-Jun 2022	750	1010
Jul-Sep 2022	800	1040
Oct-Dec 2022	780	970
Jan-Mar 2023	830	1000
Apr-Jun 2023	800	1030
Jul-Sep 2023	750	980
Oct-Dec 2023	690	800
Overall Total*	1900*	5380*

*The sum of the strata may not sum to the total patient count, as patients could be re-counted in each 3-month period if they had an additional exposure during the relevant period, but they would only count once towards the total.

Table 2. Counts of Users of Injectable Methotrexate in the TriNetX USA Network (with Natural Language Processing) from January 1, 2022 through December 31, 2023, by Healthcare Setting

Care setting	0-17 years of age	18+ years of age
Ambulatory	1420	3580
Inpatient	710	730
Emergency	70	1050
Overall Total*	1900*	5380*

*The sum of the strata may not sum to the total patient count, as patients could be re-counted in each healthcare setting if they had an additional exposure during the relevant setting, but they would only count once towards the total

Table 3. Counts of Users of Injectable Methotrexate with Diagnosis of Cancer in the TriNetX USA Network (with Natural Language Processing) from January 1, 2022 through December 31, 2023

	0-17 years of age N (%)	18+ years of age N (%)
Users of injectable MTX with a diagnosis code for cancer*	1450 (76%)	2360 (44%)
Overall Total*	1900 (100%)	5380 (100%)

*Presence of code for cancer (ICD-10 CM - C00 to D49) in the time period between 7 days before index MTX date to 2 days after index MTX date.

Table 4. Counts of Users of Injectable Methotrexate in the TriNetX USA Network (with Natural Language Processing) from August 1, 2022 through December 31, 2023, by Month

Month and Year	0-17 years of age	18+ years of age
Aug 2022	450	480
Sep 2022	450	490
Oct 2022	390	460
Nov 2022	420	460
Dec 2022	440	460
Jan 2023	480	460
Feb 2023	430	460
Mar 2023	480	480
Apr 2023	440	480
May 2023	460	490
Jun 2023	440	490
Jul 2023	420	440
Aug 2023	410	450
Sep 2023	400	440
Oct 2023	410	390
Nov 2023	370	370
Dec 2023	330	350

Table 5. Exploration of Using RxNorm Medication Terms to Identify Users of Injectable Methotrexate (focus on Intravenous) Formulations in the TriNetX USA Network (with Natural Language Processing) from January 1, 2022 through December 31, 2023

Cohorts	Number of users
1. Users of methotrexate overall (RxNorm 6851)	190270
2. Users of methotrexate overall, injectable (intravenous, intramuscular, subcutaneous, etc.)	28090
3. Users of methotrexate overall, injectable and inpatient stay (inpatient, inpatient - non acute, short stay) ^a	3640
4. Users of methotrexate overall, injectable and IV administration (same day)	6360
5. Users of methotrexate overall, injectable and IV administration (-1 to +1)	6960

^a This cohort was created on February 2, 2024. The other 4 cohorts were created on February 5, 2024.

Appendix A. List of RxNorm Medication Terms and Healthcare Common Procedure Coding System (HCPCS) Procedure Codes Used to Define Exposures in this Request

Code Type	Code	Description
RxNorm	6851	Methotrexate
HCPCS	J9260	Methotrexate sodium, 50 mg
HCPCS	J9250	Methotrexate sodium, 5 mg

Appendix B. List of Diagnosis and Procedure Codes* used to Define Intravenous Infusion/Administration in this Request

** International Classification of Diseases-10-Clinical Modification (ICD-10-CM) diagnosis codes, Systemized Nomenclature of Medicine – Clinical Terms (SNOMED) codes, Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) procedure codes*

Code Type	Code	Description
SNOMED	14152002	Intravenous infusion
SNOMED	431215000	Administration of substance via intravenous route
SNOMED	432054008	Infusion of drug or medicament via intravenous route
ICD-10-CM	Z51.11	Encounter for antineoplastic chemotherapy
HCPCS	G0498	Chemotherapy administration, intravenous infusion technique; initiation of infusion in the office/clinic setting using office/clinic pump/supplies, with continuation of the infusion in the community setting (e.g., home, domiciliary, rest home or assisted living) using a portable pump provided by the office/clinic, includes follow up office/clinic visit at the conclusion of the infusion
HCPCS	C8957	Intravenous infusion for therapy/diagnosis; initiation of prolonged infusion (more than 8 hours), requiring use of portable or implantable pump
CPT	96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
CPT	96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour
CPT	96367	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion of a new drug/substance, up to 1 hour
CPT	96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
CPT	96375	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of a new substance/drug
CPT	96376	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of the same substance/drug provided in a facility
CPT	96409	Chemotherapy administration; intravenous, push technique, single or initial substance/drug
CPT	96411	Chemotherapy administration; intravenous, push technique, each additional substance/drug (List separately in addition to code for primary procedure)
CPT	96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
CPT	96415	Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure)
CPT	96416	Chemotherapy administration, intravenous infusion technique; initiation of prolonged chemotherapy infusion (more than 8 hours), requiring use of a portable or implantable pump
CPT	96417	Chemotherapy administration, intravenous infusion technique; each additional sequential infusion (different substance/drug), up to 1 hour (List separately in addition to code for primary procedure)
CPT	1013438	Chemotherapy and Other Highly Complex Drug or Highly Complex Biologic Agent Administration
CPT	1019331	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug)
CPT	1013439	Injection and Intravenous Infusion Chemotherapy and Other Highly Complex Drug or Highly Complex Biologic Agent Administration
CPT	1013447	Chemotherapy administration, intravenous infusion technique

Appendix C. Specifications Defining Query Builder Modules in this Request

Cohort 1: Pediatric Methotrexate - Overall	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2022 - December 31, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 2: Adult Methotrexate - Overall	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2022 - December 31, 2023
<i>Global Filter: 18+ years</i>	
Cohort 3: Pediatric Methotrexate - Jan-Mar 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2022 - March 31, 2022
<i>Global Filter: 0-17 years</i>	
Cohort 4: Pediatric Methotrexate - Apr-Jun 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	April 1, 2022 - June 30, 2022
<i>Global Filter: 0-17 years</i>	
Cohort 5: Pediatric Methotrexate - Jul-Sep 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	July 1, 2022 - September 30, 2022
<i>Global Filter: 0-17 years</i>	
Cohort 6: Pediatric Methotrexate - Oct-Dec 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	October 1, 2022 - December 31, 2022
<i>Global Filter: 0-17 years</i>	
Cohort 7: Pediatric Methotrexate - Jan-Mar 2023	

Appendix C. Specifications Defining Query Builder Modules in this Request

Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2023 - March 31, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 8: Pediatric Methotrexate - Apr-Jun 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	April 1, 2023 - June 30, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 9: Pediatric Methotrexate - Jul-Sep 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	July 1, 2023 - September 30, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 10: Pediatric Methotrexate - Oct-Dec 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	October 1, 2023 - December 31, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 11: Adult Methotrexate - Jan-Mar 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2022 - March 31, 2022
<i>Global Filter: 18+ years</i>	
Cohort 12: Adult Methotrexate - Apr-Jun 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	April 1, 2022 - June 30, 2022
<i>Global Filter: 18+ years</i>	
Cohort 13: Adult Methotrexate - Jul-Sep 2022	
Group 1:	Time Restrictions

Appendix C. Specifications Defining Query Builder Modules in this Request

Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	July 1, 2022 - September 30, 2022
<i>Global Filter: 18+ years</i>	
Cohort 14: Adult Methotrexate - Oct-Dec 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	October 1, 2022 - December 31, 2022
<i>Global Filter: 18+ years</i>	
Cohort 15: Adult Methotrexate - Jan-Mar 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2023 - March 31, 2023
<i>Global Filter: 18+ years</i>	
Cohort 16: Adult Methotrexate - Apr-Jun 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	April 1, 2023 - June 30, 2023
<i>Global Filter: 18+ years</i>	
Cohort 17: Adult Methotrexate - Jul-Sep 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	July 1, 2023 - September 30, 2023
<i>Global Filter: 18+ years</i>	
Cohort 18: Adult Methotrexate - Oct-Dec 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	October 1, 2023 - December 31, 2023
<i>Global Filter: 18+ years</i>	
Cohort 19: Pediatric Methotrexate - Ambulatory Care Setting	
Group 1:	Time Restrictions
Subgroup 1A	

Appendix C. Specifications Defining Query Builder Modules in this Request

<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2022 - December 31, 2023
<i>Global Filter: 0-17 years</i>	
Subgroup 1B	
<i>Must Have:</i>	
Ambulatory visit	On the same day as Subgroup 1A (methotrexate)
Cohort 20: Pediatric Methotrexate - Emergency Department Care Setting	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2022 - December 31, 2023
<i>Global Filter: 0-17 years</i>	
Subgroup 1B	
<i>Must Have:</i>	
Emergency department visit	On the same day as Subgroup 1A (methotrexate)
Cohort 21: Pediatric Methotrexate - Inpatient Care Setting	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2022 - December 31, 2023
<i>Global Filter: 0-17 years</i>	
Subgroup 1B	
<i>Must Have:</i>	
Inpatient visit	On the same day as Subgroup 1A (methotrexate)
Cohort 22: Adult Methotrexate - Ambulatory Care Setting	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2022 - December 31, 2023
<i>Global Filter: 18+ years</i>	
Subgroup 1B	
<i>Must Have:</i>	
Ambulatory visit	On the same day as Subgroup 1A (methotrexate)
Cohort 23: Adult Methotrexate - Emergency Department Care Setting	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	

Appendix C. Specifications Defining Query Builder Modules in this Request

Methotrexate procedure code	January 1, 2022 - December 31, 2023
<i>Global Filter: 18+ years</i>	
Subgroup 1B	
<i>Must Have:</i>	
Emergency department visit	On the same day as Subgroup 1A (methotrexate)
Cohort 24: Adult Methotrexate - Inpatient Care Setting	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2022 - December 31, 2023
<i>Global Filter: 18+ years</i>	
Subgroup 1B	
<i>Must Have:</i>	
Inpatient visit	On the same day as Subgroup 1A (methotrexate)
Cohort 25: Pediatric Methotrexate - Aug 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	August 1, 2022 - August 31, 2022
<i>Global Filter: 0-17 years</i>	
Cohort 26: Pediatric Methotrexate - Sep 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	September 1, 2022 - September 30, 2022
<i>Global Filter: 0-17 years</i>	
Cohort 27: Pediatric Methotrexate - Oct 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	October 1, 2022 - October 31, 2022
<i>Global Filter: 0-17 years</i>	
Cohort 28: Pediatric Methotrexate - Nov 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	November 1, 2022 - November 30, 2022

Appendix C. Specifications Defining Query Builder Modules in this Request

<i>Global Filter: 0-17 years</i>	
Cohort 29: Pediatric Methotrexate - Dec 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	December 1, 2022 - December 31, 2022
<i>Global Filter: 0-17 years</i>	
Cohort 30: Pediatric Methotrexate - Jan 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2023 - January 31, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 31: Pediatric Methotrexate - Feb 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	February 1, 2023 - February 28, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 32: Pediatric Methotrexate - Mar 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	March 1, 2023 - March 31, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 33: Pediatric Methotrexate - Apr 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	April 1, 2023 - April 30, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 34: Pediatric Methotrexate - May 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	May 1, 2023 - May 31, 2023
<i>Global Filter: 0-17 years</i>	

Appendix C. Specifications Defining Query Builder Modules in this Request

Cohort 35: Pediatric Methotrexate - Jun 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	June 1, 2023 - June 30, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 36: Pediatric Methotrexate - Jul 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	July 1, 2023 - July 31, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 37: Pediatric Methotrexate - Aug 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	August 1, 2023 - August 31, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 38: Pediatric Methotrexate - Sep 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	September 1, 2023 - September 30, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 39: Pediatric Methotrexate - Oct 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	October 1, 2023 - October 31, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 40: Pediatric Methotrexate - Nov 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	November 1, 2023 - November 30, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 41: Pediatric Methotrexate - Dec 2023	

Appendix C. Specifications Defining Query Builder Modules in this Request

Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	December 1, 2023 - December 31, 2023
<i>Global Filter: 0-17 years</i>	
Cohort 42: Adult Methotrexate - Aug 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	August 1, 2022 - August 31, 2022
<i>Global Filter: 18+ years</i>	
Cohort 43: Adult Methotrexate - Sep 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	September 1, 2022 - September 30, 2022
<i>Global Filter: 18+ years</i>	
Cohort 44: Adult Methotrexate - Oct 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	October 1, 2022 - October 31, 2022
<i>Global Filter: 18+ years</i>	
Cohort 45: Adult Methotrexate - Nov 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	November 1, 2022 - November 30, 2022
<i>Global Filter: 18+ years</i>	
Cohort 46: Adult Methotrexate - Dec 2022	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	December 1, 2022 - December 31, 2022
<i>Global Filter: 18+ years</i>	
Cohort 47: Adult Methotrexate - Jan 2023	
Group 1:	Time Restrictions

Appendix C. Specifications Defining Query Builder Modules in this Request

Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	January 1, 2023 - January 31, 2023
<i>Global Filter: 18+ years</i>	
Cohort 48: Adult Methotrexate - Feb 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	February 1, 2023 - February 28, 2023
<i>Global Filter: 18+ years</i>	
Cohort 49: Adult Methotrexate - Mar 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	March 1, 2023 - March 31, 2023
<i>Global Filter: 18+ years</i>	
Cohort 50: Adult Methotrexate - Apr 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	April 1, 2023 - April 30, 2023
<i>Global Filter: 18+ years</i>	
Cohort 51: Adult Methotrexate - May 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	May 1, 2023 - May 31, 2023
<i>Global Filter: 18+ years</i>	
Cohort 52: Adult Methotrexate - Jun 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	June 1, 2023 - June 30, 2023
<i>Global Filter: 18+ years</i>	
Cohort 53: Adult Methotrexate - Jul 2023	
Group 1:	Time Restrictions
Subgroup 1A	

Appendix C. Specifications Defining Query Builder Modules in this Request

<i>Must Have:</i>	
Methotrexate procedure code	July 1, 2023 - July 31, 2023
<i>Global Filter: 18+ years</i>	
Cohort 54: Adult Methotrexate - Aug 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	August 1, 2023 - August 31, 2023
<i>Global Filter: 18+ years</i>	
Cohort 55: Adult Methotrexate - Sep 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	September 1, 2023 - September 30, 2023
<i>Global Filter: 18+ years</i>	
Cohort 56: Adult Methotrexate - Oct 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	October 1, 2023 - October 31, 2023
<i>Global Filter: 18+ years</i>	
Cohort 57: Adult Methotrexate - Nov 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	November 1, 2023 - November 30, 2023
<i>Global Filter: 18+ years</i>	
Cohort 58: Adult Methotrexate - Dec 2023	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate procedure code	December 1, 2023 - December 31, 2023
<i>Global Filter: 18+ years</i>	
Cohort 59: Methotrexate - RxNorm Overall	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	

Appendix C. Specifications Defining Query Builder Modules in this Request

Methotrexate RxNorm (6851)	January 1, 2022 - December 31, 2023
Cohort 60: Methotrexate - RxNorm + Injectable	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate RxNorm (6851)	January 1, 2022 - December 31, 2023
<i>Code Filter: Injectable Product</i>	
Cohort 61: Methotrexate - RxNorm + Injectable + Inpatient Care Setting	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate RxNorm (6851)	January 1, 2022 - December 31, 2023
<i>Code Filter: Injectable Product</i>	
Subgroup 1B	
<i>Must Have:</i>	
Inpatient visit	On the same day as Subgroup 1A (methotrexate)
Cohort 62: Methotrexate - RxNorm + Injectable + IV administration same day	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate RxNorm (6851)	January 1, 2022 - December 31, 2023
<i>Code Filter: Injectable Product</i>	
Subgroup 1B	
<i>Must Have:</i>	
IV administration codes	On the same day as Subgroup 1A (methotrexate)
Cohort 63: Methotrexate - RxNorm + Injectable + IV administration +/- 1 day	
Group 1:	Time Restrictions
Subgroup 1A	
<i>Must Have:</i>	
Methotrexate RxNorm (6851)	January 1, 2022 - December 31, 2023
<i>Code Filter: Injectable Product</i>	
Subgroup 1B	
<i>Must Have:</i>	
IV administration codes	[-1, 1] as Subgroup 1A (methotrexate)

Appendix D. Specifications Defining Analytic Modules in this Request

#	Module	Analysis Type	Cohort(s)	Window	Index Event(s)	Characteristics or Outcomes
1	Analytics Module	Advanced Explore Cohort	1 and 2 (pediatric methotrexate - overall; adult methotrexate - overall)	[-7, 2]	Methotrexate procedure code	C00-D49: Neoplasms