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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Overview for Request: cder_iqp_wp028

Request ID: cder_iqp_wp028

Requester: Center for Drug Evaluation and Research (CDER)

Request Description: In this report we aimed to characterize patients with evidence of cannabis-derived product use, excluding FDA-approved cannabidiol.

Data Source: We ran this query on September 07, 2022. This query contains data from 76 health care organizations (HCOs), provided through the TriNetX Live™ platform in their USA Network from July 01, 2018 to June 30, 2022.
TriNetX aggregates electronic health record (EHR) systems data from its partner HCOs to create queryable datasets. TriNetX datasets are primarily comprised of 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: We identified counts of individuals with evidence of cannabis-derived product use among a cohort of patients with a history of healthcare utilization. This was done using the Query Builder module in the TriNetX Live™ platform. We additionally summarized the length of individuals' patient record using the Summary Statistics module. We finally utilized the Analyze Outcomes Analytics module to determine the number of patients in the cohort with our baseline characteristics of interest, which were pregnancy, lactation, co-exposures, and subsequent cannabis-derived product exposures.

Exposures of Interest: Our exposures of interest in this request were a prescription for any cannabis-derived products, excluding FDA-approved cannabidiol (Epidiolex), or positive lab results for tetrahydrocannabinol (THC) from July 01, 2018 to June 30, 2022. We identified Epidiolex for exclusion based on evidence of the brand name or a cannabidiol product with a strength of 100 mg/ml. In our first cohort we included evidence of exposures from any data source (structured EHR data or data sourced from natural language processing (NLP)). In our second cohort we required that the evidence of cannabis-derived products be sourced from NLP data. Please see Appendix A for the List of RxNorm medication terms and Logical Observation Identifiers, Names and Codes (LOINC) laboratory codes Used to define exposures in this request.

Cohort Eligibility Criteria: We required every patient included in each cohort to have a history of healthcare visits prior to their cannabis-derived product exposure. We looked for evidence of any type of visit term in the two years prior to any cannabis-derived product or positive THC lab exposure that occurred during the query period. Patients of all ages were included in the cohorts.

Baseline Characteristics: We utilized the Characteristics section of the Analyze Outcomes analytic module to evaluate the following baseline characteristics in the 365 days prior to and including the date of the first qualifying cannabis-derived product exposure (index exposure): attention-deficit hyperactivity disorders (ADHD), anxiety disorders, autism, cancer, cannabis-related disorders, cerebrovascular diseases, chronic kidney disease, chronic pain (unspecified), chronic respiratory conditions, dementia (unspecified), dementia (vascular), diabetes, Dravet syndrome, dystonia, eating disorders, glaucoma, human immunodefficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS), Huntington's disease, hypertension, intracranial injury, irritable bowel syndrome, ischemic heart diseases, Lennox-Gastaut syndrome, liver disease, mood disorders, multiple sclerosis, nicotine dependence, nicotine use, obesity, other epilepsies, Parkinson's disease, personality disorders, post-traumatic stress disorder, psychologic developmental conditions, psychotic disorders, rheumatologic and inflammatory conditions, sleep disorders, spinal cord injury, Tourette syndrome, tuberous sclerosis complex, and vaping-related disorders. We additionally looked for evidence of a diagnosis code for a positive pregnancy test in the 270 days prior to and including the index date, and lactation in the 183 days prior to and including the index date. We further assessed co-exposures in the 30 days prior to and including the index date. These co-exposures included: anticonvulsants, antidepressants, antidiabetic agents, antiemetic agents, antihistamines, antipsychotics, anxiolytic and hypnotic drugs, cardiovascular medications, chemotherapeutics, central nervous system (CNS) stimulants, corticosteroids, dronabinol, nabilone, opioids, and other immunosuppressants.

Overview for Request: cder_iqp_wp028

Baseline Characteristics, continued: In the TriNetX platform, all pre-index characteristics must be defined by a single branch within the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) hierarchy or by a single Veterans Affairs (VA) formulary classification. Please see Appendix B for a list of the codes used to approximate these baseline characteristics.

We utilized the Outcomes section of the Analyze Outcomes analytics module to assess additional post-index characteristics for each cohort. We looked for evidence of the co-exposures and a positive pregnancy test or diagnosis code for a positive test in the 30 days after the index exposure. We finally summarized subsequent cannabis-derived product exposure in the 365 days following the initial index exposure. We evaluated all cannabis-derived products, and then separately assessed cannabidiol and THC labs. For the subsequent cannabis-derived product exposures we report both the number of patients in each cohort with a subsequent exposure, and the mean number of exposures per patient. Please see Appendix C for a list of the codes used to define the post-index characteristics in this request.

Please see Appendices D, E and F for the specifications of parameters used in this request and a design diagram.

Limitations: Algorithms used to define exposures and characteristics, and mapping of source data to the data model are imperfect and susceptible to misclassification. Additionally, EHR data in the US lacks longitudinality. The information before or after patients' healthcare encounters could be missing, especially if patient care was administered across different HCOs that 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, only 15 out of the 76 contributing HCOs provide data through NLP, and not all HCOs provide brand name information for RxNorm terms. Therefore, data should be interpreted with these limitations in mind.

A subset of HCOs contributing data across the TriNetX Networks date shift between 1 and 365 days in either direction at the level of the patient record. All records for a patient are shifted the same number of days. Data should be interpreted with these limitations in mind, especially when they are relevant to a specific calendar period, like an approval date.

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%.

Notes: We ran this query on September 07, 2022. 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@sentinelsystem.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).

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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.

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. Baseline Characteristics Among Patients with Cannabis-Derived Product Exposures from July 1, 2018 through June 30, 2022

	Cannabis-Derived Product or THC Exposure, Excluding Epidiolex		Cannabis-Derived Product (from NLP) or THC Exposure, Excluding Epidiolex	
	Number	Percent[1]	Number	Percent[1]
Total Number of Patients	76,150		69,770	
Baseline Clinical Characteristics [-365, 0][2]	**72,900**		**66,060**	
Attention-deficit hyperactivity disorders (ADHD)	4,230	6%	3,960	6%
Anxiety disorders	19,190	26%	18,160	27%
Autism	1,040	1%	680	1%
Cancer[3]	12,140	17%	10,990	17%
Cannabis-related disorders	10,220	14%	10,140	15%
Cerebrovascular diseases	4,710	6%	4,370	7%
Chronic kidney disease (CKD)	3,740	5%	3,520	5%
Chronic liver disease	6,200	9%	5,960	9%
Chronic pain (unclassified)	13,820	19%	13,050	20%
Chronic respiratory conditions	11,490	16%	10,750	16%
Dementia (vascular)	140	0%	130	0%
Dementia (unspecified)	530	1%	490	1%
Diabetes	8,540	12%	8,030	12%
Dravet syndrome	110	0%	40	0%
Dystonia	590	1%	470	1%
Eating disorders	740	1%	700	1%
Glaucoma	1,060	1%	980	1%
HIV/AIDS	1,700	2%	1,690	3%
Huntington's disease	80	0%	80	0%
Hypertension	17,420	24%	16,100	24%
Irritable bowel syndrome	1,400	2%	1,230	2%
Ischemic heart diseases	5,830	8%	5,440	8%
Lennox-Gastaut syndrome	1,190	2%	310	0%
Mood disorders	22,840	31%	21,930	33%
Multiple sclerosis	700	1%	610	1%
Nicotine Use	16,930	23%	16,680	25%
Obesity	7,850	11%	7,260	11%
Other epilepsies	4,530	6%	3,020	5%
Other neurological or developmental conditions	3,110	4%	2,110	3%
Parkinson's disease	530	1%	440	1%
Personality disorders	1,050	1%	1,030	2%
Post-traumatic stress disorder (PTSD)	3,630	5%	3,540	5%
Psychotic disorders	4,420	6%	4,380	7%
Rheumatologic and inflammatory conditions	3,770	5%	3,510	5%
Sleep disorders	11,340	16%	10,300	16%
Spinal cord injury	40	0%	40	0%
Tourette syndrome	90	0%	80	0%
Traumatic brain injury or intracranial hemorrhage	2,000	3%	1,870	3%
Tuberous sclerosis complex	150	0%	60	0%

Table 1. Baseline Characteristics Among Patients with Cannabis-Derived Product Exposures from July 1, 2018 through June 30, 2022

	Cannabis-Derived Product or THC Exposure, Excluding Epidiolex		Cannabis-Derived Product (from NLP) or THC Exposure, Excluding Epidiolex	
	Number	Percent[1]	Number	Percent[1]
Vaping-related disorder	50	0%	50	0%
Baseline Clinical Characteristics [-270, 0][2]	**71,880**		**66,300**	
Positive pregnancy test (diagnosis code)	950	1%	950	1%
Baseline Clinical Characteristics [-183, 0][2]	**71,920**		**66,060**	
Lactation	50	0%	50	0%
Pre-Index Co-Exposures [-30, 0][2]	**73,280**		**65,810**	
Anticonvulsants	34,200	47%	27,030	41%
Antidepressants	18,580	25%	17,340	26%
Antidiabetic agents	10,650	15%	10,000	15%
Antiemetics	22,470	31%	21,540	33%
Antihistamines	18,060	25%	17,020	26%
Antipsychotics	9,960	14%	9,640	15%
Anxiolytic and hypnotic drugs	22,580	31%	20,570	31%
Cardiovascular medications	29,430	40%	27,150	41%
Central nervous system (CNS) stimulants	5,800	8%	5,470	8%
Chemotherapeutics	4,900	7%	4,540	7%
Corticosteroids	13,660	19%	12,520	19%
Dronabinol[4]	2,120	3%	2,030	3%
Nabilone	10	0%	10	0%
Opioids	26,850	37%	25,570	39%
Other immunosuppressants	1,490	2%	1,350	2%
Post-Index Co-Exposures [1, 30]	**76,150**		**69,770**	
Anticonvulsants	15,070	20%	13,370	19%
Antidepressants	12,910	17%	12,480	18%
Antidiabetic agents	7,620	10%	7,170	10%
Antiemetics	13,270	17%	12,530	18%
Antihistamines	12,010	16%	11,470	16%
Antipsychotics	7,220	9%	7,100	10%
Anxiolytic and hypnotic drugs	14,350	19%	13,170	19%
Cardiovascular medications	20,110	26%	18,910	27%
Central nervous system (CNS) stimulants	4,200	6%	4,110	6%
Chemotherapeutics	3,860	5%	3,730	5%
Corticosteroids	10,190	13%	9,420	14%
Dronabinol[4]	920	1%	920	1%
Nabilone	10	0%	10	0%
Opioids	19,450	26%	18,590	27%
Other immunosuppressants	970	1%	930	1%
Post-index Clinical Characteristics [1, 30]	**76,150**		**69,770**	
Positive pregnancy test (positive test result or diagnosis code)	150	0%	150	0%

Table 1. Baseline Characteristics Among Patients with Cannabis-Derived Product Exposures from July 1, 2018 through June 30, 2022

	Cannabis-Derived Product or THC Exposure, Excluding Epidiolex		Cannabis-Derived Product (from NLP) or THC Exposure, Excluding Epidiolex	
	Number	Percent[1]	Number	Percent[1]
Post-index Subsequent Cannabis-Derived Product Exposures [1, 365]	**76,150**		**69,770**	
Any Cannabis-Derived Product	14,080	18%	11,870	17%
Mean Number of Any Cannabis-Derived Product Exposure	3.7	5.9	3.4	5.0
Cannabidiol	13,000	17%	10,820	16%
Mean Number of Cannabidiol Exposures	3.7	5.9	3.5	5.1
THC positive lab test	8,330	11%	8,330	12%
Mean Number of THC positive lab tests	2.1	2.8	2.1	2.8

[1]Value represents standard deviation where no % follows the value.

[2]All characteristics assessed in the pre-index period are taken from a convenience sample of the full cohort. Values in header rows represent the sample size for each look back period. Percentages for each section are calculated using these values as the denominator.

[3]Cancer baseline characteristic definition includes malignant, benign, and in situ neoplasms.

[4]Dronabinol is a subset of the overall antiemetics category. Counts for dronabinol will be counted in both co-exposures.

NOTE: All counts provided through the TriNetX Live™ platform are rounded up to the nearest 10 to protect patient privacy. Thus, all estimates should be interpreted as ranges, with the lower value of the range ≤ 0.09% less than the presented value unless otherwise noted.

Figure 1. Distribution of Length of Patient Record for Patients with Cannabis-Derived Product Exposures or a Positive Lab Test for Tetrahydrocannabinol (THC) from July 1, 2018 through June 30, 2022

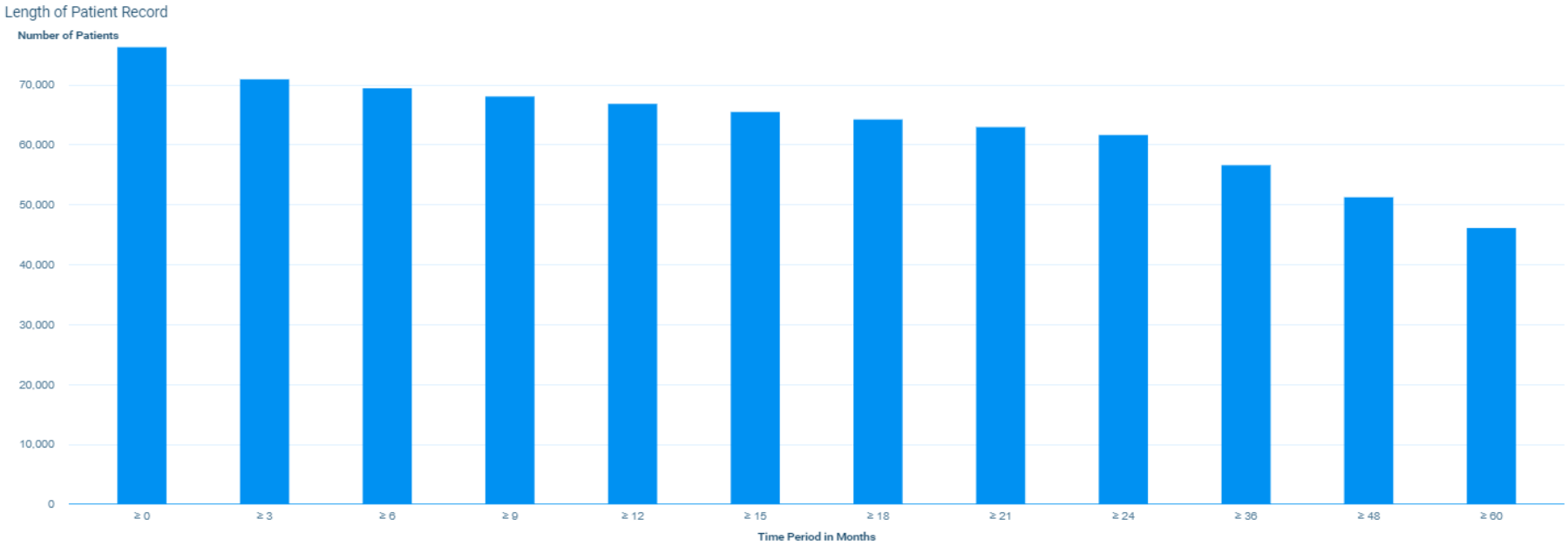
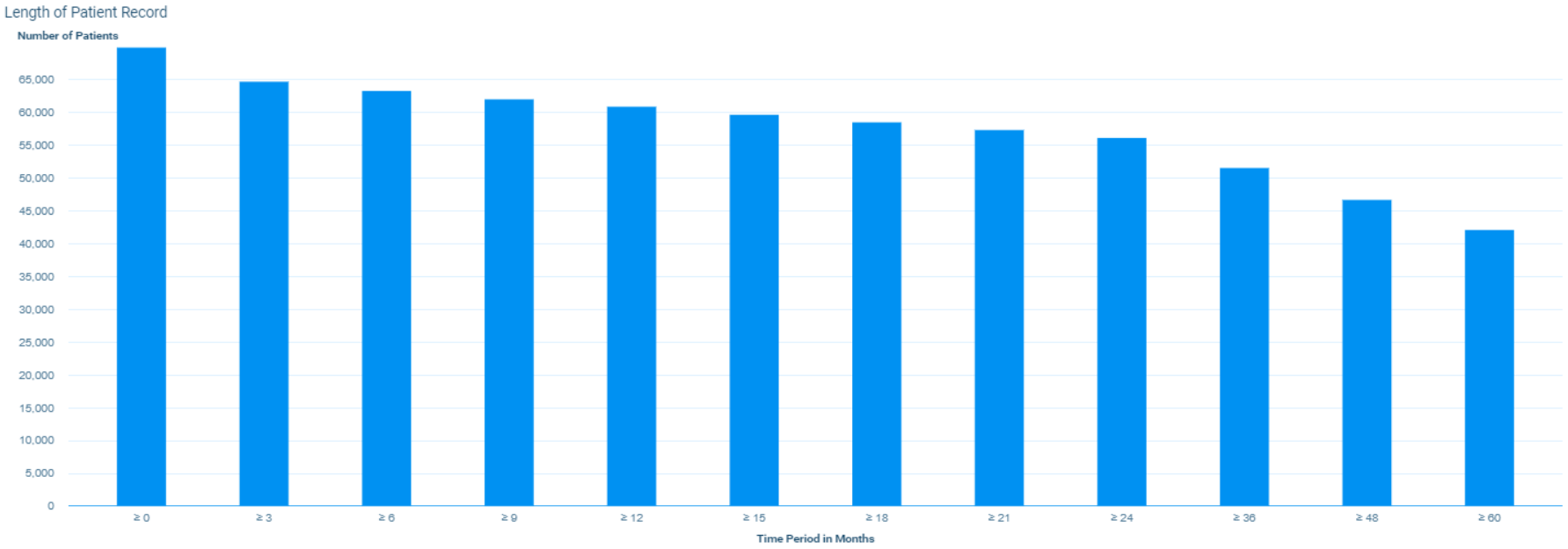


Figure 2. Distribution of Length of Patient Record for Patients with Cannabis-Derived Product Exposures, Derived from Natural Language Processing (NLP) Sources, or a Positive Lab Test for Tetrahydrocannabinol (THC) from July 1, 2018 through June 30, 2022



Appendix A. List of RxNorm Medication Terms and Logical Observation Identifiers, Names and Codes (LOINC) Laboratory Codes Used to Define Exposures in this Request

Code	Description	Filter	Code Category	Code Type
	Cannabis and Cannabis-Derived Products			
2045371	Cannabidiol	N/A	Medication	RxNorm
1976	Cannabinol	N/A	Medication	RxNorm
1788846	Hemp	N/A	Medication	RxNorm
1305550	Cannabis sativa seed oil	N/A	Medication	RxNorm
2177094	Cannabis Sativa subsp. Sativa whole extract	N/A	Medication	RxNorm
2464938	Cannabigerol (*note: this term has 0 patients)	N/A	Medication	RxNorm
2279519	Cannabigerolate (*note: this term has 0 patients)	N/A	Medication	RxNorm
2585216	Cannabichromene (*note: this term has 0 patients)	N/A	Medication	RxNorm
2168435	Cannabis sativa susp. indica top extract (*note: this term has 0 patients)	N/A	Medication	RxNorm
1484855	Cannabis Sativa subsp. Flowering top extract (*note: this term has 0 patients)	N/A	Medication	RxNorm
2002575	Cannabis sativa pollen extract (*note: this term has 0 patients)	N/A	Medication	RxNorm
2048033	Cannabis sativa whole extract (*note: this term has 0 patients)	N/A	Medication	RxNorm
1429926	Cannabis sativa seed extract (*note: this term has 0 patients)	N/A	Medication	RxNorm
	Epidiolex			
2045371	Cannabidiol	Brand Name, or 100 mg/ml strength	Medication	RxNorm
	Tetrahydrocannabinol (THC) Lab Tests			
19415-9	Tetrahydrocannabinol [presence] in urine by screen method	Positive result	Laboratory Test	LOINC
14312-3	Tetrahydrocannabinol [presence] in urine by screen method >50 ng/ml	Positive result	Laboratory Test	LOINC
3426-4	Tetrahydrocannabinol [presence] in urine	Positive result	Laboratory Test	LOINC
21556-6	Tetrahydrocannabinol [presence] in urine by screen method >20 ng/ml	Positive result	Laboratory Test	LOINC
19416-7	Tetrahydrocannabinol [presence] in urine by confirmatory method	Positive result	Laboratory Test	LOINC
8175-2	Tetrahydrocannabinol [presence] in urine by samhsa screen method	Positive result	Laboratory Test	LOINC
21557-4	Tetrahydrocannabinol [presence] in urine by screen method >100 ng/ml	Positive result	Laboratory Test	LOINC
43834-1	Tetrahydrocannabinol [presence] in specimen	Positive result	Laboratory Test	LOINC
58047-2	Tetrahydrocannabinol [presence] in blood by confirmatory method (*note: 0 positive patients)	Positive result	Laboratory Test	LOINC

Appendix A. List of RxNorm Medication Terms and Logical Observation Identifiers, Names and Codes (LOINC) Laboratory Codes Used to Define Exposures in this Request

Code	Description	Filter	Code Category	Code Type
3435-5	Carboxy tetrahydrocannabinol [presence] in urine	Positive result	Laboratory Test	LOINC
19381-3	Carboxy tetrahydrocannabinol [presence] in urine by screen method	Positive result	Laboratory Test	LOINC
19382-1	Carboxy tetrahydrocannabinol [presence] in urine by confirmatory method	Positive result	Laboratory Test	LOINC
42492-9	Carboxy tetrahydrocannabinol [presence] in blood	Positive result	Laboratory Test	LOINC
26743-5	Carboxy tetrahydrocannabinol [presence] in serum or plasma	Positive result	Laboratory Test	LOINC
61063-4	Carboxy tetrahydrocannabinol [presence] in specimen	Positive result	Laboratory Test	LOINC
74678-4	Carboxy tetrahydrocannabinol [presence] in saliva (oral fluid) by confirmatory method	Positive result	Laboratory Test	LOINC
78754-9	11-hydroxy delta-9 tetrahydrocannabinol [presence] in urine by screen method (*note: 0 positive patients)	Positive result	Laboratory Test	LOINC
14313-1	Tetrahydrocannabinol [Mass/volume] in Urine by Confirmatory method	15 ng/ml - 800 ng/ml	Laboratory Test	LOINC
3530-3	Tetrahydrocannabinol [Mass/volume] in Urine	50 ng/ml - 800 ng/ml	Laboratory Test	LOINC
3528-7	Tetrahydrocannabinol [Mass/volume] in Serum or Plasma	2 ng/ml - 125 ng/ml	Laboratory Test	LOINC
44049-5	Tetrahydrocannabinol [Mass/volume] in Serum or Plasma by Confirmatory method	2 ng/ml - 125 ng/ml	Laboratory Test	LOINC
73935-9	Tetrahydrocannabinol [Mass/volume] in Serum, Plasma, or Blood by Confirmatory method	2 ng/ml - 125 ng/ml	Laboratory Test	LOINC

Appendix B. List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Hierarchy Codes and Veterans Affairs (VA) Formulary Classifications used to Define Baseline Characteristics in this Request

Characteristic	ICD-10 Hierarchy Term/VA Code and Description
ADHD	F90 (Attention-deficit hyperactivity disorders)
Anxiety Disorders	F41 (Other anxiety disorders)
Autism	F84.0 (Autistic disorder)
Cancer	C00-D49 (Neoplasms)
Cannabis-Related Disorders	F12 (Cannabis related disorders)
Cerebrovascular diseases	I60-I69 (Cerebrovascular diseases)
Chronic Kidney Disease	N18 (Chronic kidney disease)
Chronic Liver Disease	K70-K77 (Diseases of liver)
Chronic Pain	G89 (Pain, not elsewhere classified)
Chronic Respiratory Conditions	J40-J47 (Chronic lower respiratory diseases)
Dementia (vascular)	F01 (Vascular dementia)
Dementia (unspecified)	F03 (Unspecified dementia)
Diabetes	E08-E13 (Diabetes mellitus)
Dravet Syndrome	G40.83 (Dravet syndrome)
Dystonia	G24 (Dystonia)
Eating Disorders	F50 (Eating disorders)
Glaucoma	H40-H42 (Glaucoma)
HIV/AIDS	B20 (Human immunodeficiency virus [HIV] disease)
Huntington's Disease	G10 (Huntington's disease)
Hypertension	I10 (Essential (primary) hypertension)
Irritable Bowel Syndrome	K58 (Irritable bowel syndrome)
Ischemic Heart Diseases	I20-I25 (Ischemic heart diseases)
Lennox-Gastaut Syndrome	G40.81 (Lennox-Gastaut syndrome)
Mood Disorders	F30-F39 (Mood [affective] disorders)
Multiple Sclerosis	G35 (Multiple sclerosis)
Nicotine Use	F17 (Nicotine dependence)
Obesity	E66 (Overweight and obesity)
Other Epilepsies	G40.9 (Epilepsy, unspecified)
Other Neurological Or Developmental Conditions	F80-F89 (Pervasive and specific developmental disorders)
Parkinson's Disease	G20 (Parkinson's disease)
Personality Disorders	F60 (Specific personality disorders)
Post-Traumatic Stress Disorder	F43.1 (Post-traumatic stress disorder (PTSD))
Psychotic Disorders	F20-F29 (Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders)
Rheumatologic And Inflammatory Conditions	M05-M14 (Inflammatory polyarthropathies)
Sleep Disorders	G47 (Sleep disorders)
Spinal Cord Injury	S34 (Injury of lumbar and sacral spinal cord and nerves at abdomen, lower back and pelvis level)
Tourette Syndrome	F95.2 (Tourette's disorder)
Traumatic Brain Injury Or Intracranial Hemorrhage	S06 (Intracranial injury)
Tuberous Sclerosis Complex	Q85.1 (Tuberous sclerosis)
Vaping-Related Disorders	U07.0 (Vaping-related disorder)
Positive Pregnancy Test	Z32.01 (Encounter for pregnancy test, result positive)

Appendix B. List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Hierarchy Codes and Veterans Affairs (VA) Formulary Classifications used to Define Baseline Characteristics in this Request

Characteristic	ICD-10 Hierarchy Term/VA Code and Description
Lactation	Z39.1 (Encounter for care and examination of lactating mother)
Anticonvulsants	CN400 (Anticonvulsants)
Anxiolytic And Hypnotic Drugs	CN300 (Sedatives/hypnotics)
Antidepressants	CN600 (Antidepressants)
Antipsychotics	CN700 (Antipsychotics)
Opioids	CN101 (Opioid analgesics)
Central Nervous System (CNS) Stimulants	CN800 (CNS stimulants)
Cardiovascular Medications	CV000 (Cardiovascular medications)
Antidiabetic Agents	HS500 (Blood glucose regulation agents)
Corticosteroids	HS050 (Adrenal corticosteroids)
Chemotherapeutics	AN000 (Antineoplastics)
Other Immunosuppressants	IM600 (Immune suppressants)
Antiemetic Agents	GA605 (Antiemetics)
Antihistamine	AH000 (Antihistamines)
Dronabinol	10402 (Dronabinol)
Nabilone	31447 (Nabilone)

Appendix C. List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes, RxNorm Medication Terms, and Logical Observation Identifiers, Names and Codes (LOINC) Laboratory Codes Used to Define Post-Index Characteristics in this Request

Code	Description	Filter	Code Category	Code Type
	Pregnancy			
80385-8	Choriogonadotropin (pregnancy test) [Presence] in Serum by Rapid immunoassay	Positive result	Laboratory Test	LOINC
2118-8	Choriogonadotropin (pregnancy test) [Presence] in Serum or Plasma	Positive result	Laboratory Test	LOINC
2106-3	Choriogonadotropin (pregnancy test) [Presence] in Urine	Positive result	Laboratory Test	LOINC
80384-1	Choriogonadotropin (pregnancy test) [Presence] in Urine by Rapid immunoassay	Positive result	Laboratory Test	LOINC
2110-5	Choriogonadotropin.beta subunit (pregnancy test) [Presence] in Serum or Plasma	Positive result	Laboratory Test	LOINC
2112-1	Choriogonadotropin.beta subunit (pregnancy test) [Presence] in Urine	Positive result	Laboratory Test	LOINC
Z32.01	Encounter for pregnancy test, result positive		Diagnosis	ICD-10-CM
	Cannabis and Cannabis-Derived Products			
2045371	Cannabidiol	N/A	Medication	RxNorm
1976	Cannabinol	N/A	Medication	RxNorm
1788846	Hemp	N/A	Medication	RxNorm
1305550	Cannabis sativa seed oil	N/A	Medication	RxNorm
2177094	Cannabis Sativa subsp. Sativa whole extract	N/A	Medication	RxNorm
2464938	Cannabigerol (*note: this term has 0 patients)	N/A	Medication	RxNorm
2279519	Cannabigerolate (*note: this term has 0 patients)	N/A	Medication	RxNorm
2585216	Cannabichromene (*note: this term has 0 patients)	N/A	Medication	RxNorm
2168435	Cannabis sativa susp. indica top extract (*note: this term has 0 patients)	N/A	Medication	RxNorm
1484855	Cannabis Sativa subsp. Flowering top extract (*note: this term has 0 patients)	N/A	Medication	RxNorm
2002575	Cannabis sativa pollen extract (*note: this term has 0 patients)	N/A	Medication	RxNorm
2048033	Cannabis sativa whole extract (*note: this term has 0 patients)	N/A	Medication	RxNorm
1429926	Cannabis sativa seed extract (*note: this term has 0 patients)	N/A	Medication	RxNorm
	Cannabidiol			
2045371	Cannabidiol	N/A	Medication	RxNorm
	Tetrahydrocannabinol (THC) Lab Tests			
19415-9	Tetrahydrocannabinol [presence] in urine by screen method	Positive result	Laboratory Test	LOINC
14312-3	Tetrahydrocannabinol [presence] in urine by screen method >50 ng/ml	Positive result	Laboratory Test	LOINC
3426-4	Tetrahydrocannabinol [presence] in urine	Positive result	Laboratory Test	LOINC
21556-6	Tetrahydrocannabinol [presence] in urine by screen method >20 ng/ml	Positive result	Laboratory Test	LOINC

Appendix C. List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes, RxNorm Medication Terms, and Logical Observation Identifiers, Names and Codes (LOINC) Laboratory Codes Used to Define Post-Index Characteristics in this Request

Code	Description	Filter	Code Category	Code Type
19416-7	Tetrahydrocannabinol [presence] in urine by confirmatory method	Positive result	Laboratory Test	LOINC
8175-2	Tetrahydrocannabinol [presence] in urine by samhsa screen method	Positive result	Laboratory Test	LOINC
21557-4	Tetrahydrocannabinol [presence] in urine by screen method >100 ng/ml	Positive result	Laboratory Test	LOINC
43834-1	Tetrahydrocannabinol [presence] in specimen	Positive result	Laboratory Test	LOINC
58047-2	Tetrahydrocannabinol [presence] in blood by confirmatory method (*note: 0 positive patients)	Positive result	Laboratory Test	LOINC
3435-5	Carboxy tetrahydrocannabinol [presence] in urine	Positive result	Laboratory Test	LOINC
19381-3	Carboxy tetrahydrocannabinol [presence] in urine by screen method	Positive result	Laboratory Test	LOINC
19382-1	Carboxy tetrahydrocannabinol [presence] in urine by confirmatory method	Positive result	Laboratory Test	LOINC
42492-9	Carboxy tetrahydrocannabinol [presence] in blood	Positive result	Laboratory Test	LOINC
26743-5	Carboxy tetrahydrocannabinol [presence] in serum or plasma	Positive result	Laboratory Test	LOINC
61063-4	Carboxy tetrahydrocannabinol [presence] in specimen	Positive result	Laboratory Test	LOINC
74678-4	Carboxy tetrahydrocannabinol [presence] in saliva (oral fluid) by confirmatory method	Positive result	Laboratory Test	LOINC
78754-9	11-hydroxy delta-9 tetrahydrocannabinol [presence] in urine by screen method (*note: 0 positive patients)	Positive result	Laboratory Test	LOINC
14313-1	Tetrahydrocannabinol [Mass/volume] in Urine by Confirmatory method	15 ng/ml - 800 ng/ml	Laboratory Test	LOINC
3530-3	Tetrahydrocannabinol [Mass/volume] in Urine	50 ng/ml - 800 ng/ml	Laboratory Test	LOINC
3528-7	Tetrahydrocannabinol [Mass/volume] in Serum or Plasma	2 ng/ml - 125 ng/ml	Laboratory Test	LOINC
44049-5	Tetrahydrocannabinol [Mass/volume] in Serum or Plasma by Confirmatory method	2 ng/ml - 125 ng/ml	Laboratory Test	LOINC
73935-9	Tetrahydrocannabinol [Mass/volume] in Serum, Plasma, or Blood by Confirmatory method	2 ng/ml - 125 ng/ml	Laboratory Test	LOINC

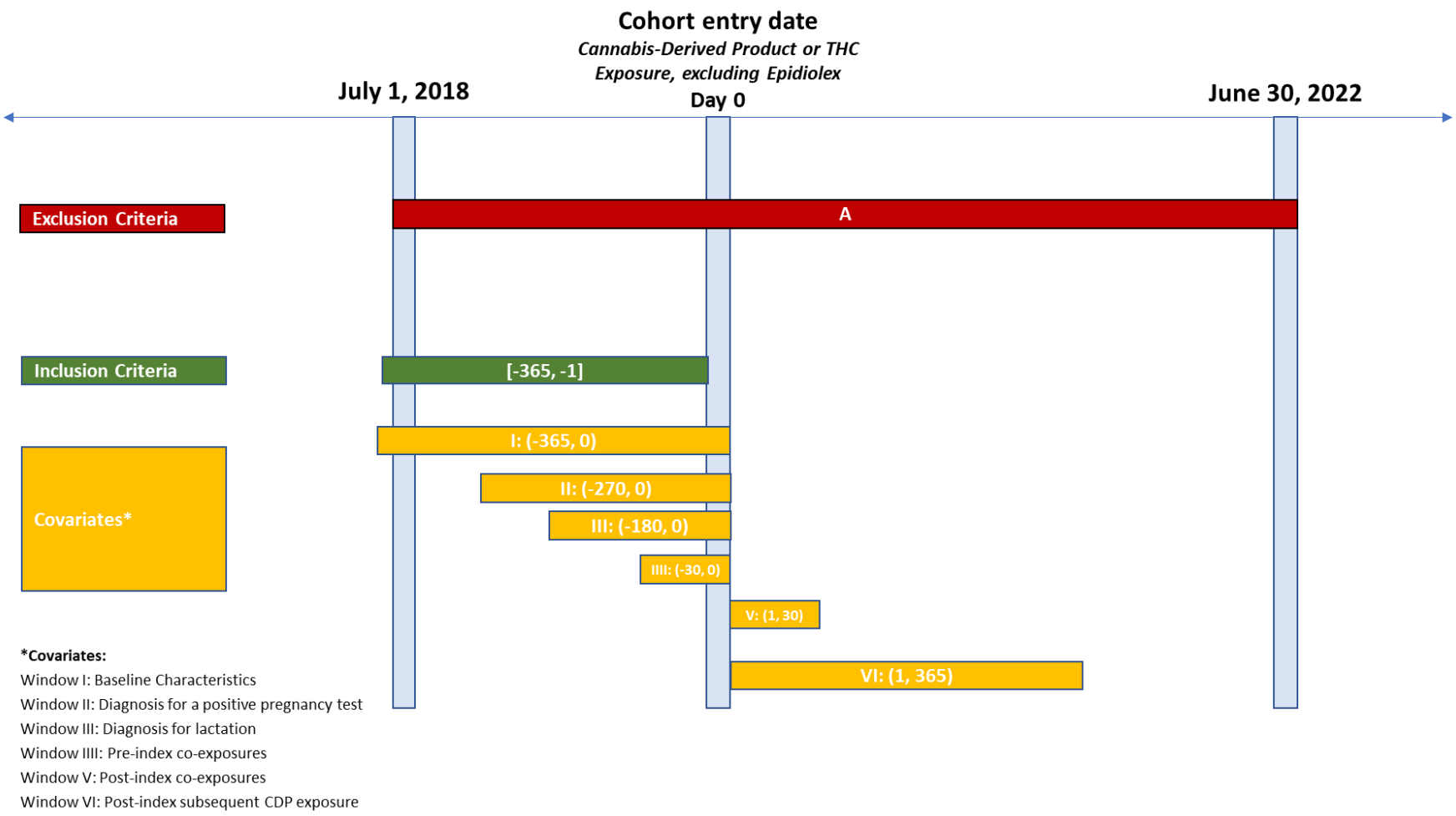
Appendix D. Specifications Defining Query Builder Modules in this Request

Cohort 1: Cannabis-derived product or THC Exposure, excluding known Epidiolex	
Group 1: Cannabis-derived Product	**Time Restrictions**
Must Have:	
Cannabis-derived product THC Presence Lab Test [FILTER: Positive Result]	7/1/2018 - 6/30/2022
Cannot Have:	
Cannabidiol [FILTER: Epidiolex brand] Cannabidiol [FILTER: 100 mg/ml strength]	7/1/2018 - 6/30/2022
Group 2: History of Healthcare Visits	**Time Restrictions**
Must Have:	
Visit	2 years prior to Group 1 (cannabis-derived product) [-720, -1]
Cohort 2: Cannabis-derived product (from NLP) or THC Exposure, excluding known Epidiolex	
Group 1: Cannabis-derived Product or Lab	**Time Restrictions**
Must Have:	
Cannabis-derived product [FILTER: NLP-derived] THC Presence Lab Test [FILTER: Positive Result]	7/1/2018 - 6/30/2022
Cannot Have:	
Cannabidiol [FILTER: Epidiolex brand] Cannabidiol [FILTER: 100 mg/ml strength]	7/1/2018 - 6/30/2022
Group 2: History of Healthcare Visits	**Time Restrictions**
Must Have:	
Visit	2 years prior to Group 1 (cannabis-derived product) [-720, -1]

Appendix E. Specifications Defining Analytic Modules in this Request

#	Module	Analysis Type	Cohort(s)	Window	Index Event(s)	Characteristics
1	Analyze Outcomes	Characteristics	All Cohorts	[-365, 0]	All cohort-defining criteria	Baseline characteristics (See Appendix B for a full list of conditions)
2	Analyze Outcomes	Characteristics	All Cohorts	[-270, 0]	All cohort-defining criteria	Pregnancy test (diagnosis)
3	Analyze Outcomes	Characteristics	All Cohorts	[-30, 0]	All cohort-defining criteria	Co-Exposures
4	Analyze Outcomes	Characteristics	All Cohorts	[-183,0]	All cohort-defining criteria	Lactation
5	Analyze Outcomes	Risk	All Cohorts	[1,30]	All cohort-defining criteria	Pregnancy test (lab or diagnosis), and co-exposures
6	Analyze Outcomes	Risk/Number of instances	All Cohorts	[1,365]	All cohort-defining criteria	cannabidiol, positive THC test, Epidiolex, cannabis or other CDP

Appendix F. Cohort Design Diagrams for this Request



***Covariates:**
Window I: Baseline Characteristics
Window II: Diagnosis for a positive pregnancy test
Window III: Diagnosis for lactation
Window IIII: Pre-index co-exposures
Window V: Post-index co-exposures
Window VI: Post-index subsequent CDP exposure