Disclaimer

The following report(s) provides findings from a Food and Drug Administration (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

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_mpl1r_wp055_nsdp_v01

Request ID: cder_mpl1r_wp055_nsdp_v01

Query Description: The goal of this query was to estimate the proportion of incident oxycodone and oxymorphone users concomitantly using a selection of cytochrome P450 (CYP) enzyme inhibitors in the Sentinel Distributed Database (SDD).

Sentinel Modular Program Tool Used: Cohort Identification and Descriptive Analysis (CIDA) tool, version 4.0.0

Data Source: Data from January 1, 2013 to December 31, 2016 from 16 health plans contributing to the SDD were included in this report. This request was distributed on June 2, 2017. See Appendix A for a list of the latest dates of available data for each Data Partner.

Study Design: This request was designed to calculate background rates. The number of qualifying patients with the exposures of interest and concomitant product use was calculated overall and stratified by age group and sex.

Exposures of Interest: The exposures of interest were oxymorphone and oxycodone, which were defined using National Drug Codes. Concomitancy was defined as initiation of a CYP inhibitor within the 90 days before or three days after initiation of either oxymorphone or oxycodone. See Appendix B for a list of generic and brand names used to define exposures and concomitant use in this request.

Cohort Eligibility Criteria: Those included in the cohort were required to be continuously enrolled in plans with drug coverage for at least 90 days prior to their opioid dispensing date, during which gaps in coverage of up to 45 days were allowed. Members were excluded if they had the exposure of interest in the 90 days prior to the index date. The following age groups were included in the cohort: 0-18, 19-64, and 65+ years. All qualifying incident dispensings that occurred between January 1, 2013 to December 31, 2016 were included.

Exclusion Criteria : For each opioid of interest, three scenarios were considered:

1) No exclusions based on use of the other opioid
2) Exclusion based on use of the other opioid within the period before or up to three days after the index date
3) Exclusion based on use of the other opioid within the entire enrollment period

Limitations: Algorithms to define exposures are imperfect and, therefore, may be misclassified.

Please see Appendices C and D for the specifications of parameters used in the analyses for this request.

Notes: Please contact the Sentinel Operations Center Query Fulfillment Team (qf@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document.

Sentinel

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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

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). Care Setting, along with the Principal Diagnosis Indicator, 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 encou
- **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: (1) 01: Cohort includes only the first valid treatment episode during the query period; (2) 02: Cohort includes all valid treatment episodes during the query period; (3) 03: Cohort includes all valid treatment

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 bridged by the

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

Event Deduplication - specifies how events are counted by the MP algorithm: (0): Counts all occurrences of an 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 days are added after any episode gaps have been bridged

Lookback Period - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug

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

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

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

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 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: Summary of Concomitant Use of Oxymorphone or Oxycodone with Cytochrome P450 (CYP) Inhibitors in the Sentinel Distributed Database (SDD) between January 1, 2013 and December 31, 2016

	Number of Patients with Concomitant Opioid and CYP-Inhibitor Use	Number of Patients with Opioid Use	Prevalence of Concomitant CYP Inhibitor Use Among Patients with Opioid Use
Oxymorphone			
	1,400	43,009	3.26%
Oxycodone			
	44,423	1,574,505	2.82%
Oxymorphone without history of oxycodone use anytime before or up to 3 days after oxymorphone index date			
	567	17,601	3.22%
Oxycodone without history of oxymorphone use anytime before or up to 3 days after oxycodone index date			
	43,119	1,547,393	2.79%
Oxymorphone without history of oxycodone use during entire enrollment period			
	458	13,514	3.39%
Oxycodone without history of oxymorphone use during entire enrollment period			
	42,938	1,545,379	2.78%

Table 1b: Summary of Concomitant Use of Oxymorphone or Oxycodone with Cytochrome P450 (CYP) Inhibitors in the Sentinel Distributed Database (SDD) between January 1, 2013 and December 31, 2016, by Age Group

	Number of Patients with Concomitant Opioid and CYP-Inhibitor Use	Number of Patients with Opioid Use	Prevalence of Concomitant CYP Inhibitor Use Among Patients with Opioid Use
Oxymorphone			
00-18 Years	0	89	0.00%
19-64 Years	1,172	36,275	3.23%
65+ Years	228	6,694	3.41%
Oxycodone			
00-18 Years	816	82,959	0.98%
19-64 Years	28,660	1,042,523	2.75%
65+ Years	14,947	453,637	3.29%
Oxymorphone without history of oxycodone use anytime before or up to 3 days after oxymorphone index date			
00-18 Years	0	50	0.00%
19-64 Years	458	14,390	3.18%
65+ Years	109	3,183	3.42%
Oxycodone without history of oxymorphone use anytime before or up to 3 days after oxycodone index date			
00-18 Years	811	82,449	0.98%
19-64 Years	27,602	1,020,856	2.70%
65+ Years	14,706	448,552	3.28%
Oxymorphone without history of oxycodone use during entire enrollment period			
00-18 Years	0	45	0.00%
19-64 Years	363	10,892	3.33%
65+ Years	95	2,596	3.66%
Oxycodone without history of oxymorphone use during entire enrollment period			
00-18 Years	814	82,913	0.98%
19-64 Years	27,430	1,018,024	2.69%
65+ Years	14,694	448,937	3.27%

Table 1c: Summary of Concomitant Use of Oxymorphone or Oxycodone with Cytochrome P450 (CYP) Inhibitors in the Sentinel Distributed Database (SDD) between January 1, 2013 and December 31, 2016, by Sex

	Number of Patients with Concomitant Opioid and CYP-Inhibitor Use	Number of Patients with Opioid Use	Prevalence of Concomitant CYP Inhibitor Use Among Patients with Opioid Use
Oxymorphone			
Female	757	23,744	3.19%
Male	643	19,265	3.34%
Unknown	0	0	---
Oxycodone			
Female	20,752	849,003	2.44%
Male	23,666	725,406	3.26%
Unknown	5	96	5.21%
Oxymorphone without history of oxycodone use anytime before or up to 3 days after oxymorphone index date			
Female	320	10,417	3.07%
Male	247	7,184	3.44%
Unknown	0	0	---
Oxycodone without history of oxymorphone use anytime before or up to 3 days after oxycodone index date			
Female	20,072	833,863	2.41%
Male	23,042	713,436	3.23%
Unknown	5	94	5.32%
Oxymorphone without history of oxycodone use during entire enrollment period			
Female	265	8,031	3.30%
Male	193	5,483	3.52%
Unknown	0	0	---
Oxycodone without history of oxymorphone use during entire enrollment period			
Female	19,960	832,757	2.40%
Male	22,973	712,528	3.22%
Unknown	5	94	5.32%

Appendix A: Dates of Available Data for Each Data Partner up to Request End Date (June 2, 2017)

DP ID	Start Date	End Date
DP0001	1/1/2000	10/31/2014
DP0002	1/1/2000	5/31/2015
DP0003	1/1/2000	10/31/2015
DP0004	1/1/2012	12/31/2015
DP0005	1/1/2000	12/31/2015
DP0006	1/1/2000	6/30/2016
DP0007	1/1/2008	6/30/2016
DP0008	6/1/2007	7/31/2016
DP0009	1/1/2004	9/30/2016
DP0010	1/1/2006	10/31/2016
DP0011	1/1/2005	10/31/2016
DP0012	1/1/2008	11/30/2016
DP0013	1/1/2000	11/30/2016
DP0014	1/1/2000	11/30/2016
DP0015	1/1/2000	11/30/2016
DP0016	1/1/2000	12/31/2016

Appendix B: Generic and Brand Names Used to Define Exposures and Concomitant Use in this Request

Generic Name	Brand Name
Oxymorphone	
OXYMORPHONE HCL	Oxymorphone
OXYMORPHONE HCL	Opana ER
OXYMORPHONE HCL	Opana
Oxycodone	
OXYCODONE HCL	Oxycodone
OXYCODONE HCL	Oxycodone (bulk)
OXYCODONE HCL	OxyContin
OXYCODONE HCL	Roxicodone
OXYCODONE HCL	Oxecta
OXYCODONE HCL	Oxaydo
CYP Inhibitors	
BOCEPREVIR	Victrelis
CARBAMAZEPINE	Carbamazepine
CARBAMAZEPINE	Carbamazepine (bulk)
CARBAMAZEPINE	Carbatrol
CARBAMAZEPINE	Epitol
CARBAMAZEPINE	Equetro
CARBAMAZEPINE	Tegretol
CARBAMAZEPINE	Tegretol XR
COBICISTAT	Tybost
ELVITEGRAVIR	Vitekta
ENZALUTAMIDE	Xtandi
INDINAVIR SULFATE	Crixivan
ITRACONAZOLE	Itraconazole
ITRACONAZOLE	Onmel
ITRACONAZOLE	Sporanox
ITRACONAZOLE	Sporanox Pulsepak
KETOCONAZOLE	Extina
KETOCONAZOLE	Ketoconazole
KETOCONAZOLE	Ketoconazole (bulk)
KETOCONAZOLE	Ketodan
KETOCONAZOLE	Nizoral
KETOCONAZOLE	Nizoral A-D
KETOCONAZOLE	Xolegel
KETOCONAZOLE, MICRONIZED	Ketoconazole, micro (bulk)
LOPINAVIR/RITONAVIR	Kaletra
LOPINAVIR/RITONAVIR	Lopinavir-ritonavir
MITOTANE	Lysodren
MITOTANE	Mitotane (bulk)
OMBITASVIR/PARITAPREVIR/RITONAVIR	Technivie
OMBITASVIR/PARITAPREVIR/RITONAVIR/DASABUVIR SODIUM	Viekira Pak
OMBITASVIR/PARITAPREVIR/RITONAVIR/DASABUVIR SODIUM	Viekira XR
PHENYTOIN	Dilantin Infatabs
PHENYTOIN	Dilantin-125
PHENYTOIN	Phenytoin

Appendix B: Generic and Brand Names Used to Define Exposures and Concomitant Use in this Request

Generic Name	Brand Name
PHENYTOIN	Phenytoin (bulk)
PHENYTOIN SODIUM	Phenytoin sodium
PHENYTOIN SODIUM	Phenytoin sodium (bulk)
PHENYTOIN SODIUM EXTENDED	Dilantin
PHENYTOIN SODIUM EXTENDED	Dilantin Extended
PHENYTOIN SODIUM EXTENDED	Dilantin Kapseal
PHENYTOIN SODIUM EXTENDED	Phenytek
PHENYTOIN SODIUM EXTENDED	Phenytoin sodium extended
POSACONAZOLE	Noxafil
RIFAMPIN	Rifadin
RIFAMPIN	Rifampin
RIFAMPIN	Rifampin (bulk)
RITONAVIR	Norvir
RITONAVIR	Norvir Soft Gelatin
SAQUINAVIR MESYLATE	Invirase
TELAPREVIR	Incivek
TIPRANAVIR	Aptivus
VORICONAZOLE	Vfend
VORICONAZOLE	Vfend IV
VORICONAZOLE	Voriconazole
VORICONAZOLE	Voriconazole (bulk)

Appendix C: Specifications for Request: cder_mpl1r_wp055_nsdp_v01

The FDA's Center for Drug Evaluation and Research requested execution of Sentinel's Cohort Identification and Descriptive Analysis (CIDA) tool to examine concomitant use of oxymorphone or oxycodone with drugs that are strong inhibitors in the Sentinel Distributed Database.

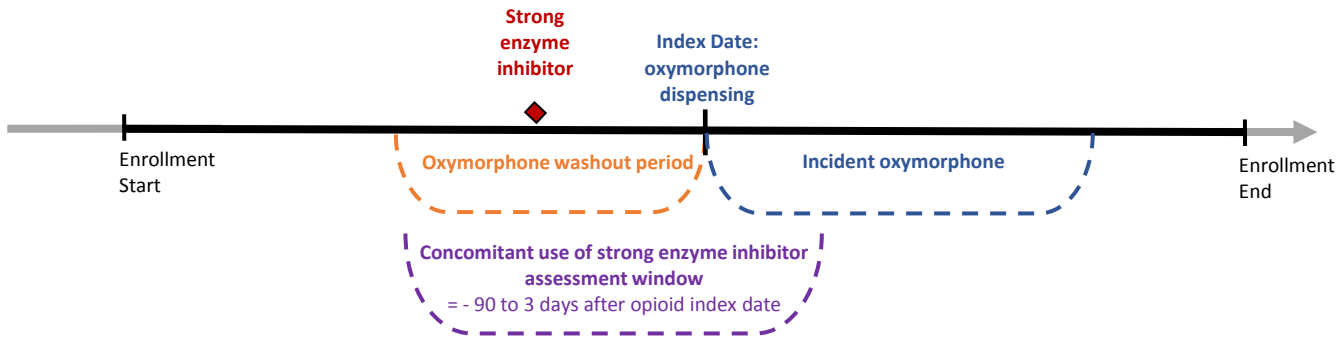
Query Periods: January 1, 2013 - latest available data
Coverage Requirement: Drug Coverage
Pre-Exposure Enrollment: 90 Days
Enrollment Gap: 45 Days
Age Groups: 0-18, 19-64, 65-120 years

		Event				Inclusion Criteria		Exclusion Criteria	
Scenario	Function	Incident Exposure	Incident w/ Respect to	Washout (Days)	Cohort Definition	Pre-Existing Condition	Lookback Period	Pre-Existing Condition	Lookback Period
1	Numerator	Oxymorphone	Oxymorphone	90	First valid event per patient	Strong enzyme inhibitors	-90 to 3 days	---	---
2	Denominator	Oxymorphone	Oxymorphone	90	All valid events per patient	---	---	---	---
3	Numerator	Oxycodone	Oxycodone	90	First valid event per patient	Strong enzyme inhibitors	-90 to 3 days	---	---
4	Denominator	Oxycodone	Oxycodone	90	All valid events per patient	---	---	---	---
5	Numerator	Oxymorphone	Oxymorphone	90	First valid event per patient	Strong enzyme inhibitors	-90 to 3 days	Oxycodone	Anytime prior to oxymorphone index date to 3 days after
6	Denominator	Oxymorphone	Oxymorphone	90	All valid events per patient	---	---	Oxycodone	Anytime prior to oxymorphone index date to 3 days after
7	Numerator	Oxycodone	Oxycodone	90	First valid event per patient	Strong enzyme inhibitors	-90 to 3 days	Oxymorphone	Anytime prior to oxycodone index date to 3 days after
8	Denominator	Oxycodone	Oxycodone	90	All valid events per patient	---	---	Oxymorphone	Anytime prior to oxycodone index date to 3 days after

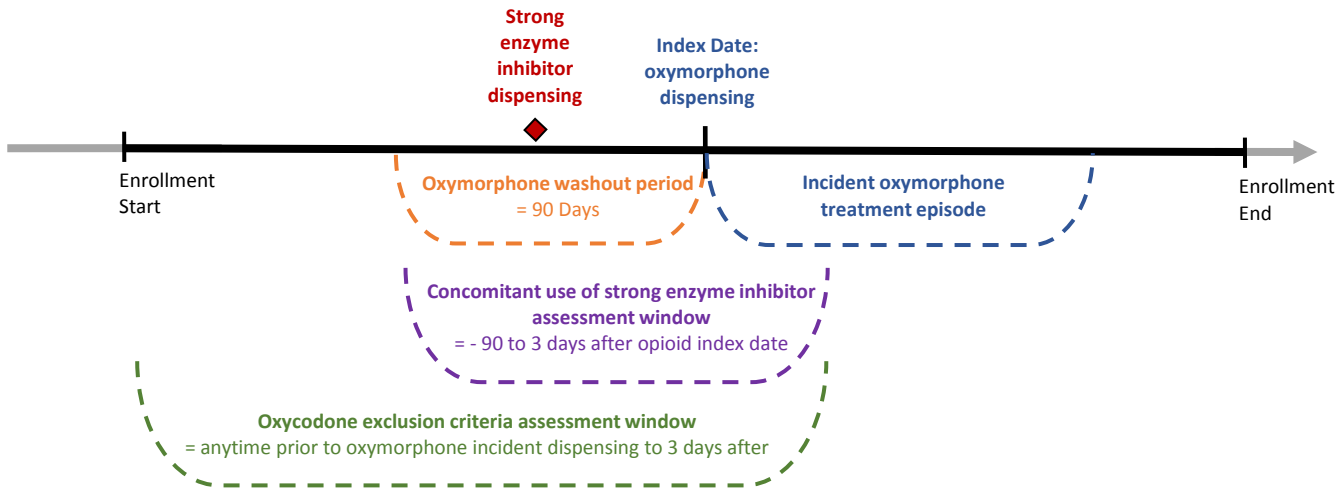
9	**Numerator**	Oxymorphone	Oxymorphone	90	First valid event per patient	Strong enzyme inhibitors	-90 to 3 days	Oxycodone	Anytime during enrollment history
10	**Denominator**	Oxymorphone	Oxymorphone	90	All valid events per patient	---	---	Oxycodone	Anytime during enrollment history
11	**Numerator**	Oxycodone	Oxycodone	90	First valid event per patient	Strong enzyme inhibitors	-90 to 3 days	Oxymorphone	Anytime during enrollment history
12	**Denominator**	Oxycodone	Oxycodone	90	All valid events per patient	---	---	Oxymorphone	Anytime during enrollment history
National Drug Codes (NDCs) are checked against First Data Bank's “National Drug Data File (NDDF®) Plus.”									

Appendix D: Pictorial Diagrams of Specifications

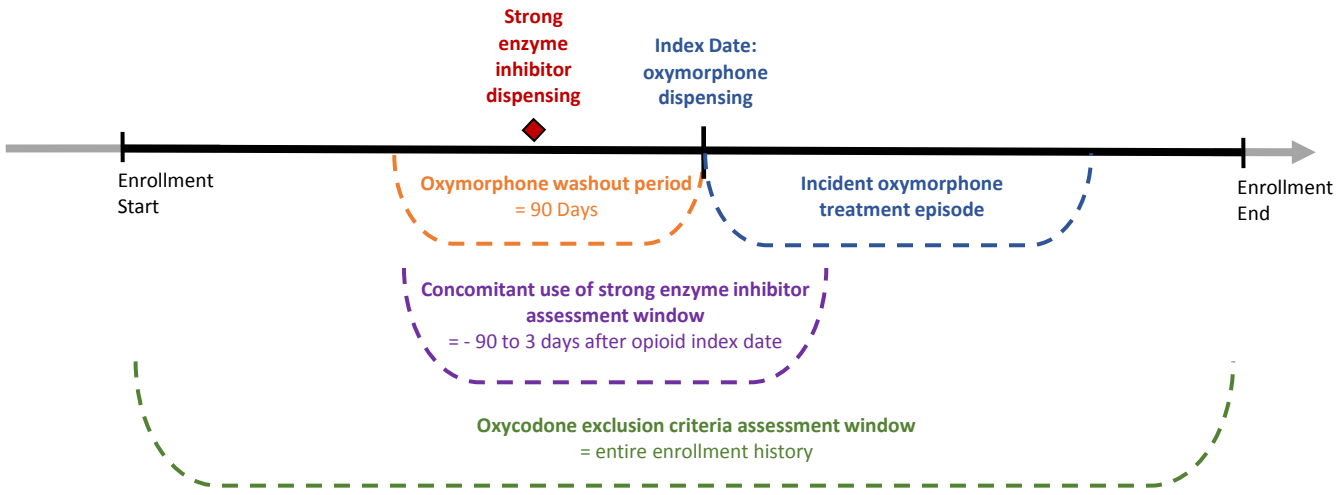
Pictorial Summary of Event Assessment for Scenario 1: Numerator



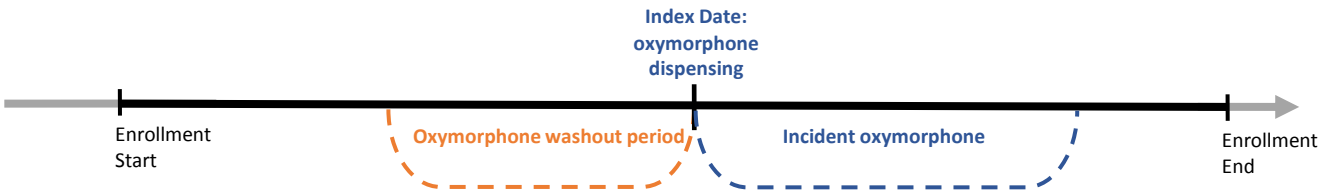
Pictorial Summary of Event Assessment for Scenario 5: Numerator



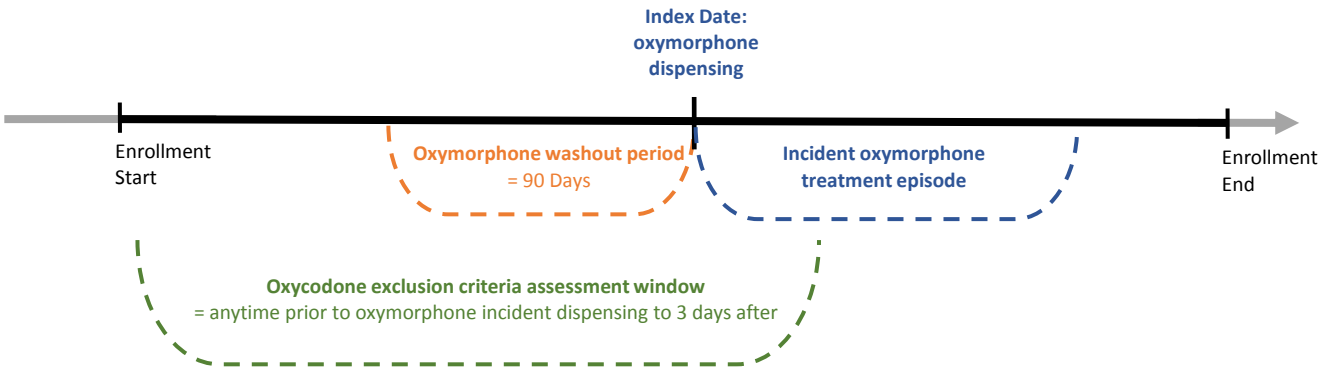
Pictorial Summary of Event Assessment <u>for Scenario 9: Numerator</u>



Pictorial Summary of Event Assessment <u>for Scenario 2: Denominator</u>



Pictorial Summary of Event Assessment <u>for Scenario 6: Denominator</u>



Pictorial Summary of Event Assessment <u>for Scenario 10: Denominator</u>