Sentinel

Evaluation of Three Self-Controlled Methods for Signal Identification

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- The views expressed are the authors' and not necessarily those of the Food and Drug Administration, or the Department of Health and Human Services.

Methods

Signal Identification within the Sentinel System

Signal Identification Methods

Study Designs	TreeScan Analytics	Information Component Temporal Pattern Discovery (ICTPD)	Sequence Symmetry Analysis
Self-Controlled Design	X	X	X
Propensity Score or other Fixed Ratio Match Design	X		
Stratified Cohort Design	X		

Primary Objective: Explore the use of self-controlled study designs with longitudinal database signal identification across several methods.

- Signal Identification: Evaluating the risk of adverse events following medication use without pre-specifying **particular** adverse events

Data Sources and Exposures

MarketScan IBM Research Databases: January 1, 2010 – September 30, 2015 (ICD-9-CM only)

- Adults Only
- Large (nearing 140M covered lives), claims-based, de-identified patient-level dataset
- Provides Medical and Pharmacy Coverage information on primarily commercially insured individuals but also includes some Medicare coverage

Two Study Exposures, ~8000 Outcome Codes

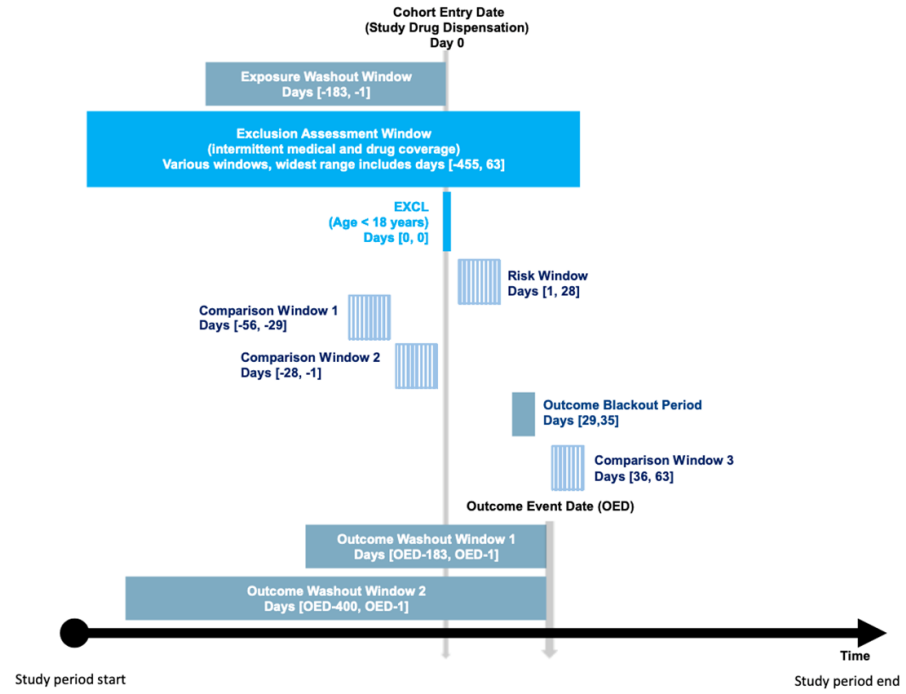
1. Levetiracetam, approval 1999, single indication (anti-seizure)
2. Lamotrigine, approval 1994, multi-indication (anti-seizure, mood disorder)

1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021035s102,021505s042lbl.pdf
2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020241s060,020764s053,022251s024lbl.pdf

Main Design Diagram and Sensitivity Analyses

1. Timing and Number of Comparison Windows
2. Length of Outcome Washout Window
3. Inclusion of Ambulatory Care Setting in Outcome Definition
4. Use of a Tree of Clinically-related groupings of Diagnosis Codes

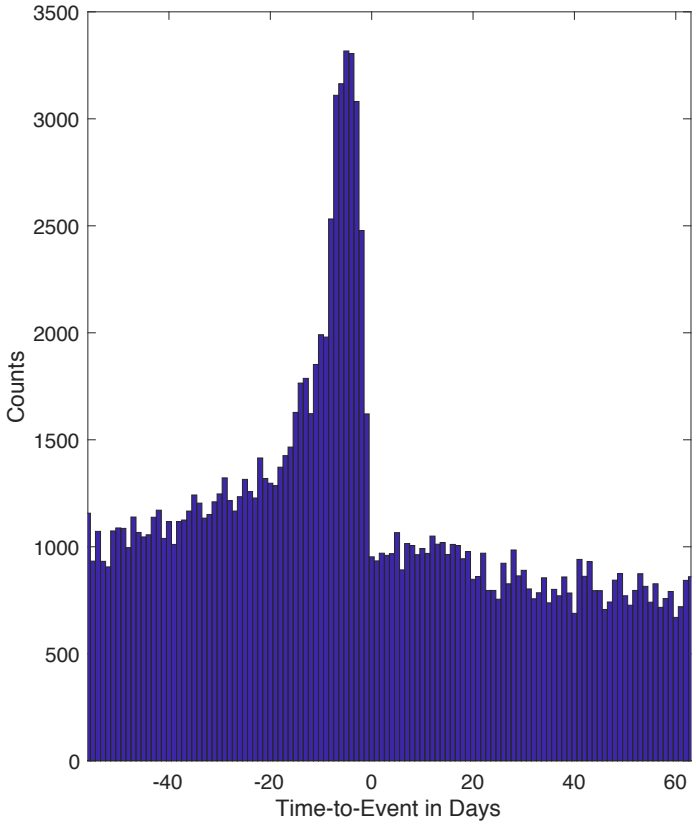
Figure 1. Design Diagram

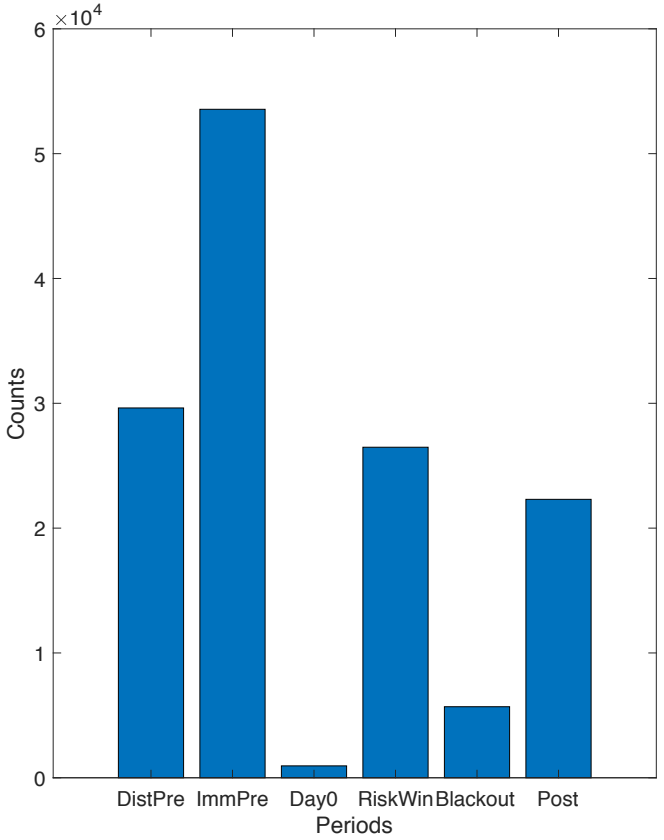


https://www.sentinelinitiative.org/sites/default/files/Methods/Evaluation_of_Three_Self-Controlled_Methods_for_Signal_Detection_Protocol-v2.pdf

Results

Total Outcome Distribution among Lamotrigine Users





- 180K patients, 82.9K incident outcomes*
- Average of 0.5-2.5 incident outcomes per patient
- General outcome volume is highest in Immediate Pre-Dispensing Period (shown as ImmPre)

*An incident outcome is defined as a single ICD-9-CM diagnosis code. In this case, it was the first observed in 400 days.

More Labeled Events for Lamotrigine

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LAMICTAL safely and effectively. See full prescribing information for LAMICTAL.

LAMICTAL (lamotrigine) tablets, for oral use
LAMICTAL (lamotrigine) tablets for oral suspension
LAMICTAL ODT (lamotrigine) orally disintegrating tablets, for oral use
Initial U.S. Approval: 1994

WARNING: SERIOUS SKIN RASHES
See full prescribing information for complete boxed warning.

- **Cases of life-threatening serious rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, and/or rash-related death have been caused by lamotrigine. The rate of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash include:**
  - **coadministration with valproate.**
  - **exceeding recommended initial dose of LAMICTAL.**
  - **exceeding recommended dose escalation for LAMICTAL. (5.1)**
- **Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious or life threatening. LAMICTAL should be discontinued at the first sign of rash, unless the rash is clearly not drug related. (5.1)**

---------- RECENT MAJOR CHANGES ----------

Warnings and Precautions, Hemophagocytic Lymphohistiocytosis (5.2)	8/2019

---------- INDICATIONS AND USAGE ----------

- Tablets for oral suspension: 2 mg, 5 mg, and 25 mg. (3.2, 16)
- Orally disintegrating tablets: 25 mg, 50 mg, 100 mg, and 200 mg. (3.3, 16)

---------- CONTRAINDICATIONS ----------

Hypersensitivity to the drug or its ingredients. (Boxed Warning, 4)

---------- WARNINGS AND PRECAUTIONS ----------

- Life-threatening serious rash and/or rash-related death: Discontinue at the first sign of rash, unless the rash is clearly not drug related. (Boxed Warning, 5.1)
- Hemophagocytic lymphohistiocytosis: Consider this diagnosis and evaluate patients immediately if they develop signs or symptoms of systemic inflammation. Discontinue LAMICTAL if an alternative etiology is not established. (5.2)
- Fatal or life-threatening hypersensitivity reaction: Multiorgan hypersensitivity reactions, also known as drug reaction with eosinophilia and systemic symptoms, may be fatal or life threatening. Early signs may include rash, fever, and lymphadenopathy. These reactions may be associated with other organ involvement, such as hepatitis, hepatic failure, blood dyscrasias, or acute multiorgan failure. LAMICTAL should be discontinued if alternate etiology for this reaction is not found. (5.3)
- Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia): May occur, either with or without an associated hypersensitivity syndrome. Monitor for signs of anemia, unexpected infection, or bleeding. (5.4)
- Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.5)
- Aseptic meningitis: Monitor for signs of meningitis. (5.6)
- Medication errors due to product name confusion: Strongly advise patients to visually inspect tablets to verify the received drug is correct. (5.7, 16, 17)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020241s060,020764s053,022251s024lbl.pdf

Lamotrigine Results (1/3)

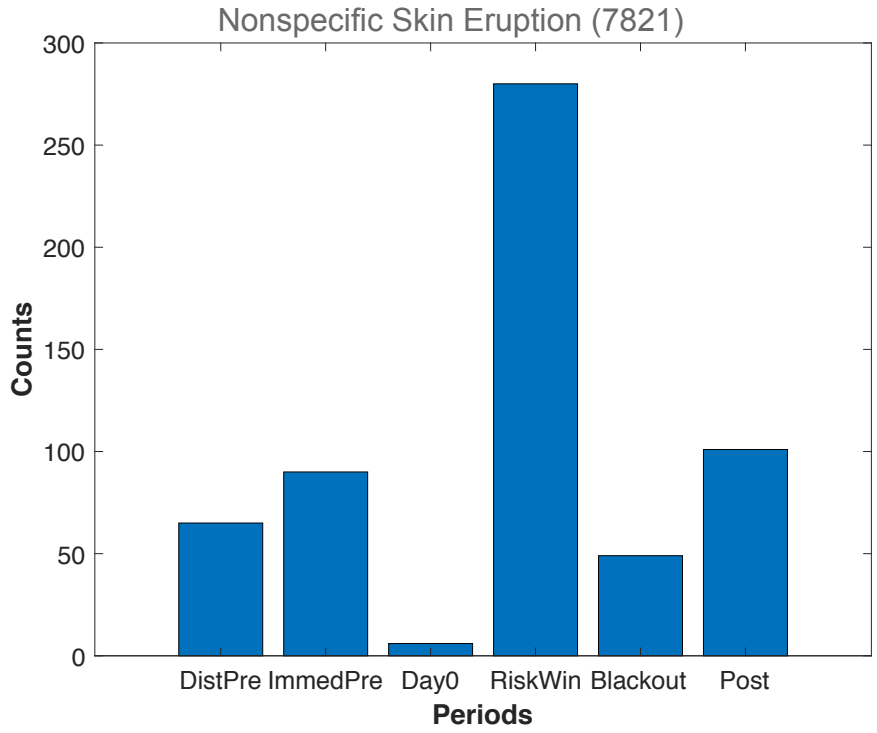
- All methods pick up **labeled events** such as allergic reactions, toxic use of the medicine, and serious skin conditions
- TreeScan picks up suicides (labeled) but mood disorders are also an indication for lamotrigine so there is a high volume of pre-exposure outcome counts (see backup)

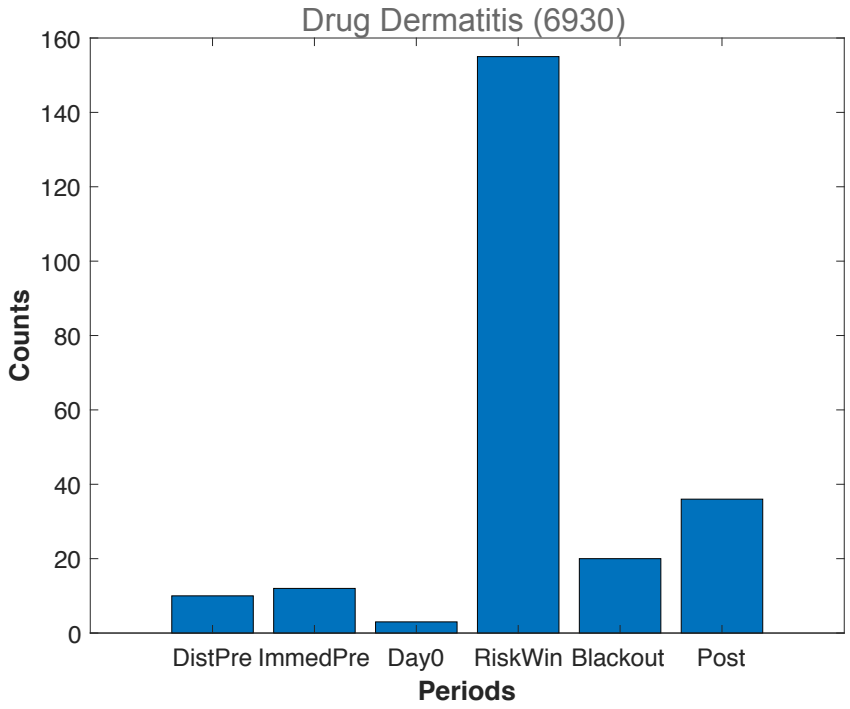
Outcome Name	Outcome ID	CTS	ICTPD3	SSA	Labeled
Allergic reactions	17010900	1	X	1	L (W/P, AR)
Dermatitis, unspecified	6929			18	L (AR, skin-related)
Drug dermatitis, unspecified	6930	2	X	4	L (AR, skin-related)
Allergic urticaria	7080		X	23	L (W/P, AR, skin-related)
Angioneurotic edema	9951		X		L (W/P)
Allergy, unspecified	9953		X	8	L (W/P)
Unspecified adverse effect of unspecified drug, medicinal and biological substance	99520		X	11	L
Drug allergy, not elsewhere classified	99527	6	X	10	L (W/P, AR)
Unspecified adverse effect of other drug, medicinal and biological substance	99529		X		L
Poisoning by other medications and drugs	16110200	7		7	L (Overdosage)
Poisoning by other and unspecified anticonvulsants	9663		X	17	L (Overdosage)
Other inflammatory condition of skin	12020000		X	9	L (W/P)
Pruritic disorder, unspecified	6989		X	19	L (AR, skin-related)
Other skin disorders	12040000	4	X	3	L (W/P)
Nonspecific skin eruption, not elsewhere classified	7821	3	X	2	L (AR, skin-related)
Suicide and intentional self-inflicted injury	05130000	5			L (W/P)
Suicide ideation	V6284	8			L (W/P)

Blue Font is a group of similar clinical codes (i.e., analogous to a Preferred Term level); A number is listed as the rank of the alert for single comparison window analyses. Abbreviations: CTS = Conditional TreeScan, ICTPD = Information Component Temporal Pattern Discovery, SSA = Sequence Symmetry Analysis; CI = Contraindications; W/P=Warnings and Precautions; AR-Adverse Reactions, ** indicates 1 or zero comparison window counts

Agreement in Methods when Data tell a Clear Story

- Risk Window Counts exceed Comparison Window Counts across the board.





Lamotrigine Results (2/3)

- SSA and ICTPD pick up many labeled signs and symptoms that appear to be part of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- DRESS typically presents with fever, rash, and lymphadenopathy, sometimes resembling an acute viral infection

Outcome Name	Outcome ID	CTS	ICTPD3	SSA	Labeled
Other non-traumatic joint disorders	13020300			14	L (AR)
Lumbago	13030303			27	L (AR)
Lumbago	7242			28	L (AR)
Fever of unknown origin	17012000			5	L (W/P)
Fever, unspecified	78060			6	L (W/P)
Abdominal pain	17017000			12	L (AR)
Abdominal pain, left lower quadrant	78904			24	L (AR)
Lymphadenitis	17010300			25	L (W/P)
Lymphadenitis, unspecified	2893		X		L (W/P)
Other and unspecified upper respiratory infections	08010504			21	L (AR, infection-related)
Acute pharyngitis	462			13	L (AR, infection-related)
Disorders of teeth and jaw	09020000			22	L (AR, xerostomia-related)
Diseases of mouth; excluding dental	09030000		X	15	L (AR, xerostomia-related)
Cellulitis/Abscess mouth**	5283		X		L (AR, infection-related)
Glossodynia**	5296		X		L (AR, xerostomia-related)
Other and unspecified viral infection	01030303			16	L (AR, infection-related)
Campylobacter enteritis**	00843		X		L (AR, infection-related)
Viral exanthem, unspecified	0579		X		L (AR, infection-related)
Viral infection, unspecified	7999			20	L (AR, infection-related)

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Lamotrigine Results (3/3)

- SSA picks up an indication (mood disorders)
- ICTPD picks up Intermediate Coronary Syndrome, which is not labeled or part of the disease process
- Standalone codes with asterisks are those with zero or small cell counts in the comparison window. These are deemed uninformative because of small cell counts.

Outcome Name	Outcome ID	CTS	ICTPD3	SSA	Labeled
Personality disorders	05090000			26	Disease/Indication-related
Borderline personality disorder	30183			29	Disease/Indication-related
Unstable angina (intermediate coronary syndrome)	07020402		X		
Intermediate coronary syndrome	4111		X		
DM1 with renal manifestations**	25043		X		
Conjunctivitis in mucocutaneous disease**	37233		X		
Ill-defined disorders of eye, not elsewhere classified	37999		X		
Acute serous otitis media**	38101		X		
Spontaneous pneumothorax, not elsewhere classified**	5128		X		
Stomatitis/mucositis, unspecified	52800		X		
Sicca syndrome**	7102		X		

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Strengths and Limitations

- First study to compare signal identification methods using a self-controlled design
- Adapted the "usual" implementation of each method to use identical analytic datasets
  - For TreeScan, used the Bernoulli scan statistic instead of tree-temporal
  - For ICTPD, added a hierarchical tree to allow testing for clinical groupings; multiple comparison windows included one post-exposure comparison window; used more stringent "alerting" criteria
  - For SSA, implemented a cutoff
- Biggest differences were choice of comparison windows
  - Why Not Pre-Exposure Windows: Generates notable outcome counts due to indication/disease process which informs calibration mechanisms, Induces selection bias through "healthy user" effect
  - Why Not Post-Exposure Windows: Inability to distinguish sustained risk of adverse event

Summary

- Methods Project evaluating three methods using self-controlled designs highlighted the differences among these methods but surfaced no new alerts needing further follow-up
  - Intermediate Coronary Syndrome signaling with ICTPD was considered an artifact of the way ICTPD creates contrasts with an external control group (see backup slides)
- If FDA pursues a self-controlled design and given the same analytic dataset…
  - ICTPD will pick up imbalances in counts at a lower threshold of total events
    - Therefore, it has more power to detect a TRUE event with lower outcome counts, BUT it also generates more false positive events across the same datasets (alerts on a 3/0 split)
    - The same pattern is repeated in a companion simulation study (where ground truth is fixed)
  - TreeScan and ICTPD have tuning parameters that can be used to balance false positive and false negative errors
  - SSA can be easily calculated from the same analytic dataset as another source of information

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- Martin Kulldorff

Backup

Similarities and Differences Among Methods

	Signal Identification Methods		
	TreeScan Analytics	Information Component Temporal Pattern Discovery (ICTPD)	Sequence Symmetry Analysis
Self-Controlled Design	X	X	X

How are these different?

- Tree Structure: TreeScan is built around the concept of a tree.
- Comparison Windows: TreeScan uses post-exposure observation window and scans across it. ICTPD and SSA use pre-exposure comparison windows
- Calibration Methods: Both TreeScan and ICTPD use different calibration mechanisms.
- Multiplicity Control: TreeScan uses formal multiplicity control. ICTPD and SSA do not. ICTPD uses multiple comparison windows (usually minimum of 3) and requires statistical "alerts" in all windows to be considered an alert.

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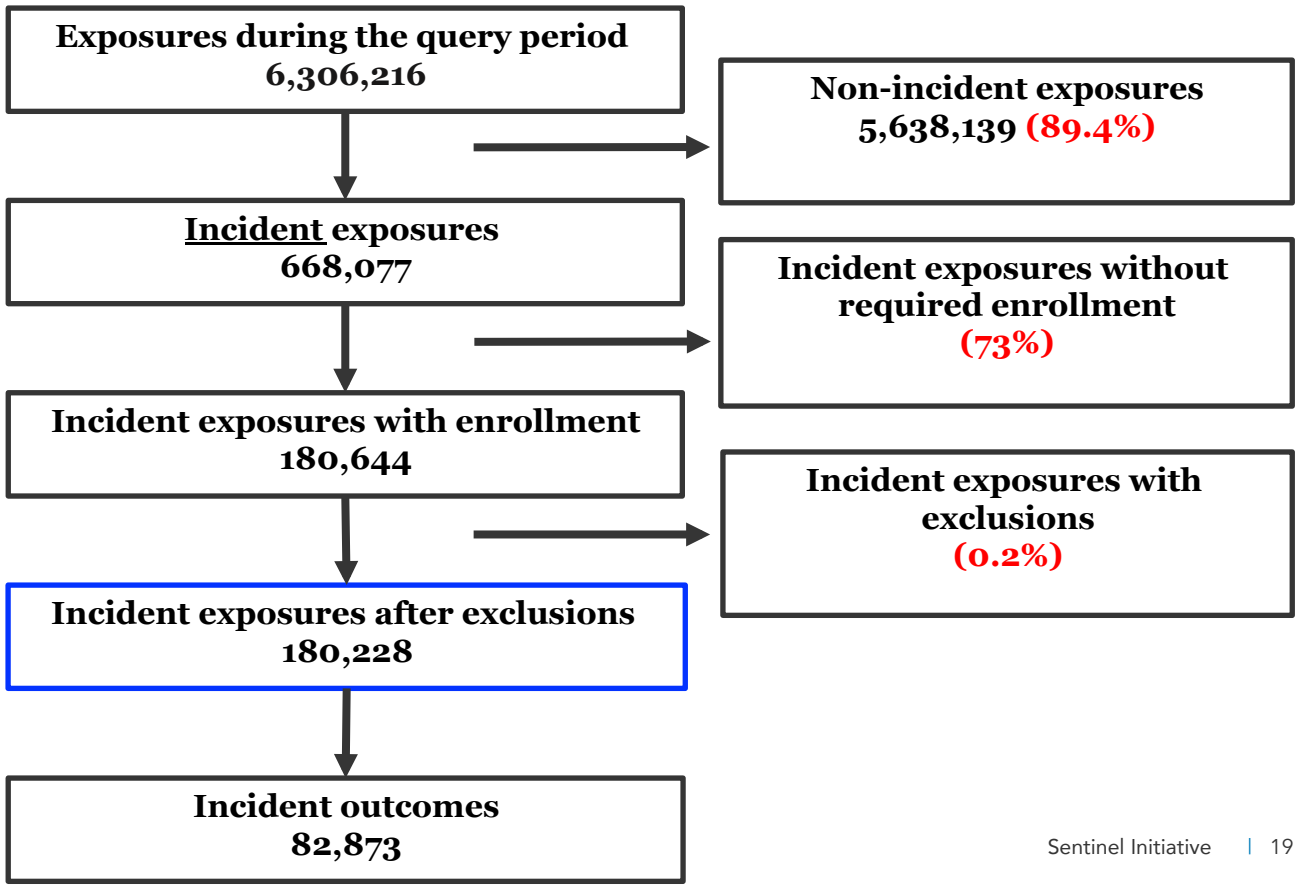
Lamotrigine Cohort Attrition



Exposed Cohort

Analytic Cohort

Alert Triage

1. Check the labeled conditions, commonly reported adverse reactions in the literature and in patient-facing medical materials (e.g., Cleveland Clinic, Mayo Clinic, etc.)
2. Check for latent indications or infrequently coded comorbidities (Table 1 data) that are co-coded upon occurrence of another adverse event.

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---------- INDICATIONS AND USAGE----------

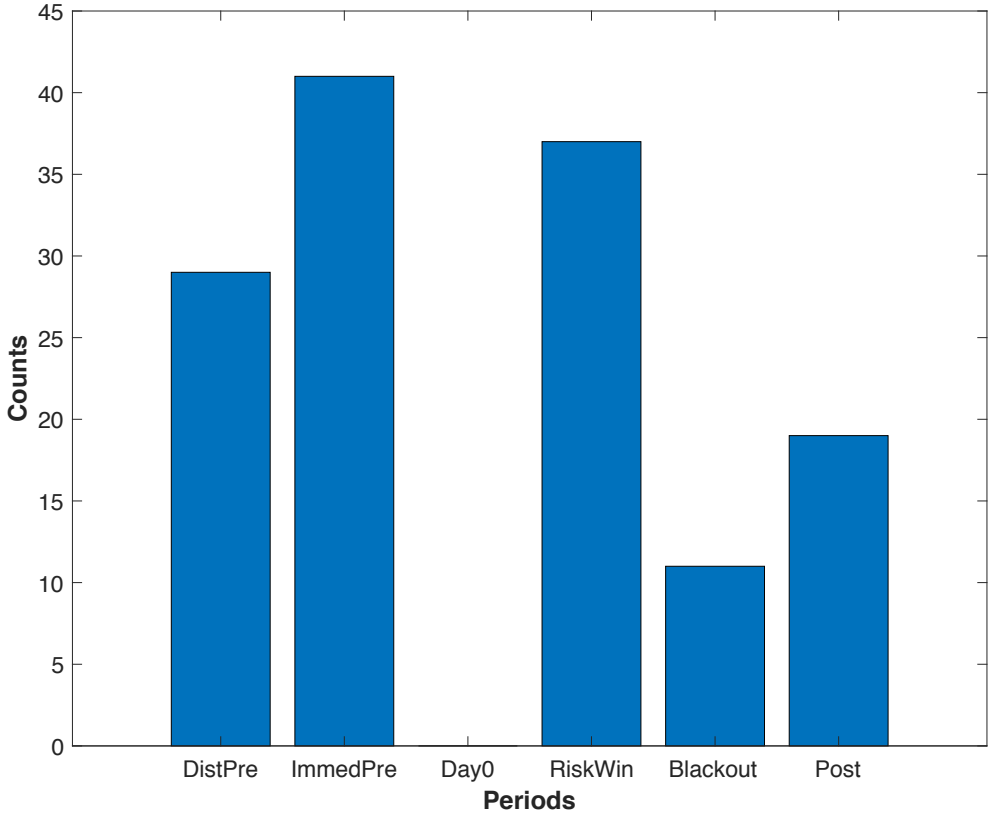
Alert Load in Primary Analysis (400 day lookback, Tree)

	Comparison Window	Risk Window Counts	TreeScan	ICTPD3	SSA
Lamotrigine	Distant Pre (1)	26,481	NA	29	29
	Immediate Pre (2)	27,510	NA		NA
	Post (3)	27,204	8		NA

Abbreviations: CTS = Conditional TreeScan, ICTPD = Information Component Temporal Pattern Discovery, SSA = Sequence Symmetry Analysis;

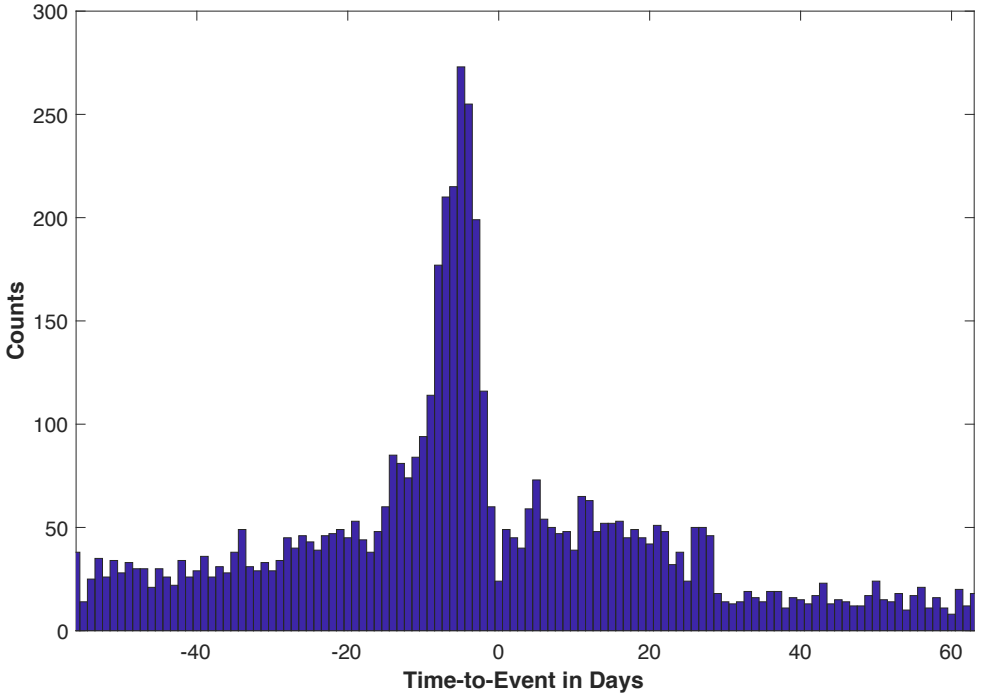
Understanding the Math of ICTPD Calibration

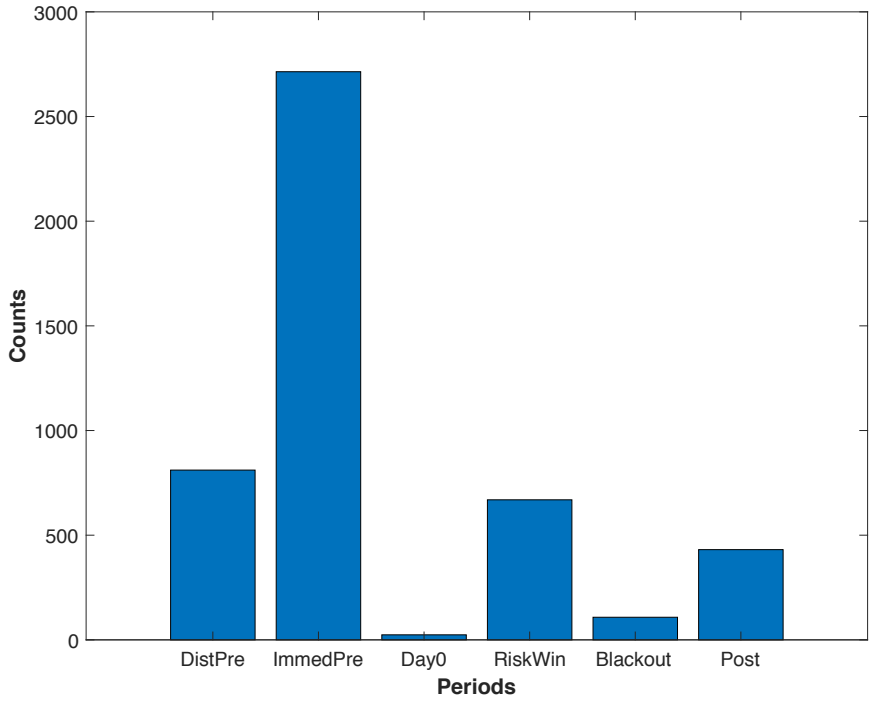
- ICTPD only alert
- ImmedPre Comparison Window counts > Risk Window counts
- O/E in ImmedPre: 0.88 with 79 total outcomes
- Calibration Population O/E in ImmedPre: 0.27 with 8798 total outcomes
- So, in the calibration population, there are many more comparison window outcomes than risk window and the study population has a more unusual ratio
- Post calibration adjustment O/E: 1.19



Consider Suicide Ideation Again….

- Lamotrigine indicated for mood disorders AND has a warning and precaution for Suicide Ideation





- The dominance of counts in the ImmedPre window means that any comparison that uses this pre-exposure window is unlikely to observe an alert, even after calibration.