



Signal Identification Studies in Sentinel

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Disclosures

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- The views expressed in this presentation are those of the authors and do not necessarily represent the official views of the US FDA.
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Signal Identification – Routine Pharmacovigilance

Risk-based approach for surveillance

- Product focus
 - New Molecular Entities (NMEs) and other novel medications
- Event focus
 - Serious, unlabeled adverse events
 - Adverse events of special interest (AESI)

Spontaneous reports, literature, and periodic safety reports are the main data sources surveilled

Best Practices for FDA Staff in
the Postmarketing Safety
Surveillance of Human Drug
and Biological Products

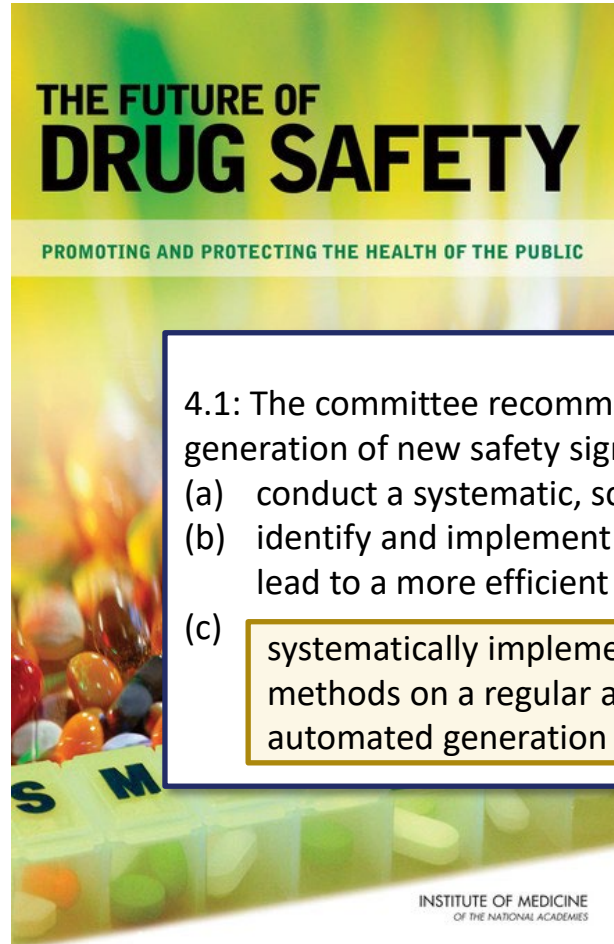
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2024
Drug Safety

Institute of Medicine Drug Safety System Assessment

In 2006, the FDA requested that the Institute of Medicine **examine the system of drug safety in the US**

Institute of Medicine published “The Future of Drug Safety: Promoting and Protecting the Health of the Public” in 2007 calling for a comprehensive approach to drug safety



- 4.1: The committee recommends that in order to improve the generation of new safety signals and hypotheses, CDER
- (a) conduct a systematic, scientific review of the AERS system,
 - (b) identify and implement changes in key factors that could lead to a more efficient system, and
 - (c) systematically implement statistical-surveillance methods on a regular and routine basis for the automated generation of new safety signals

FAERS vs. Sentinel for Signal Identification

FAERS Limitations

- Cannot determine incidence rates
- Vulnerable to underreporting and reporting bias
- Adverse events associated with long latency, worsening disease, or high background rates difficult to evaluate



Sentinel Strengths

- Estimates of population exposure available
- Risk quantification possible
- Exposure/event capture at the level of patient and based on billed medical encounters
- Longitudinal capture of medical history
- Ability to control for confounding

FAERS vs. Sentinel for Signal Identification

FAERS Strengths

- Detecting serious rare events, particularly obvious drug-induced events
- Captures all products and use settings; can provide patient perspectives
- Near real-time data from reporters available for analysis

Sentinel Limitations

- Need sufficient exposures & outcomes
- Capture based on billed medical encounters
- Claims maturation period; data lags

Sentinel Signal Identification- Where are we?

Credible source of signals? ✓

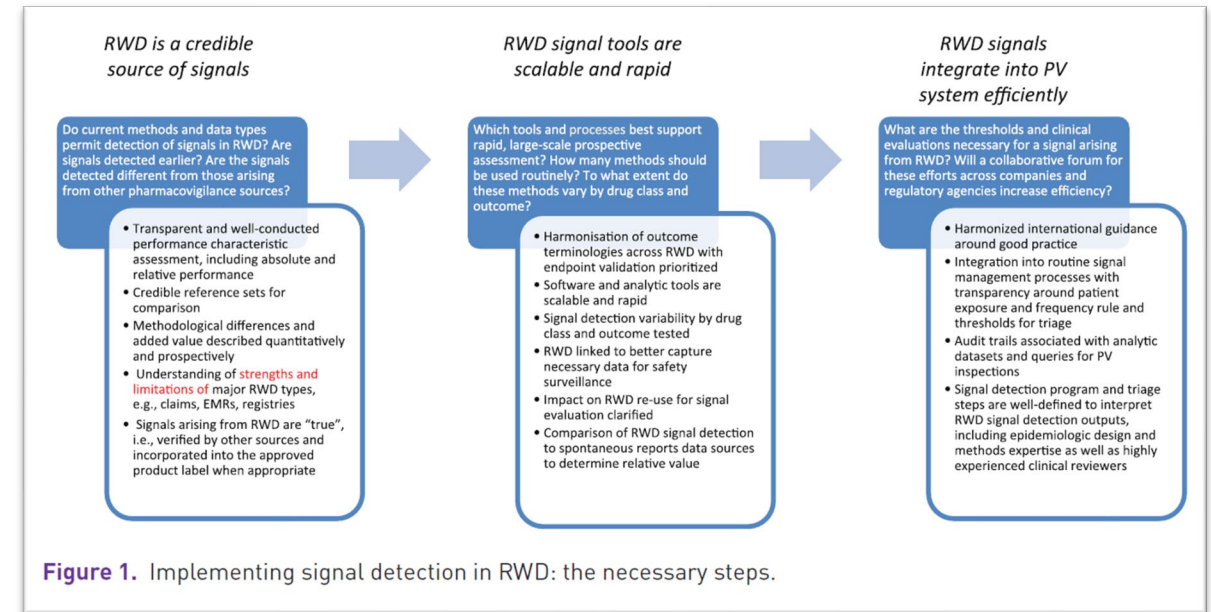
- Conceptual support, demonstration projects

Signal tools are scalable and rapid? ✓

- Foundational methods/infrastructure projects completed
- Enhancements implemented to facilitate Sentinel Signal Identification

Integrated into PV system efficiently?

- Pilots and ongoing projects are informing process development
- Expect tools and approaches will continue to evolve



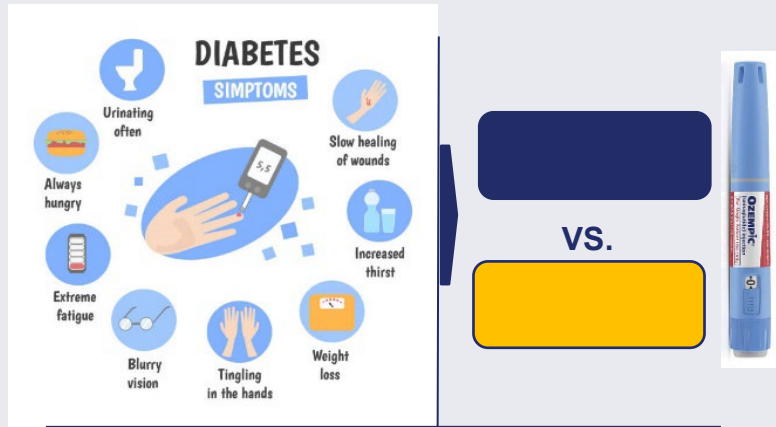
Bate A, et al. Ther Adv Drug Saf. 2019; 10: 2042098619864744.

The background is a dark blue field filled with a complex network of thin, light blue lines that swirl and crisscross. Scattered throughout this network are numerous small dots in various colors, including purple, green, yellow, and pink. A single, solid yellow horizontal line is positioned in the upper left quadrant of the slide.

Completed Sentinel Signal Identification Analyses

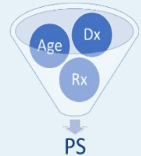
Signal Identification for Ozempic (semaglutide)

Background

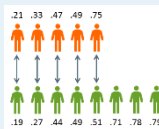


? Is there an increase in frequency of adverse events during Ozempic use as compared to sitagliptin?

Methods



1:1 PS Match & hdPS match



Analysis and Findings



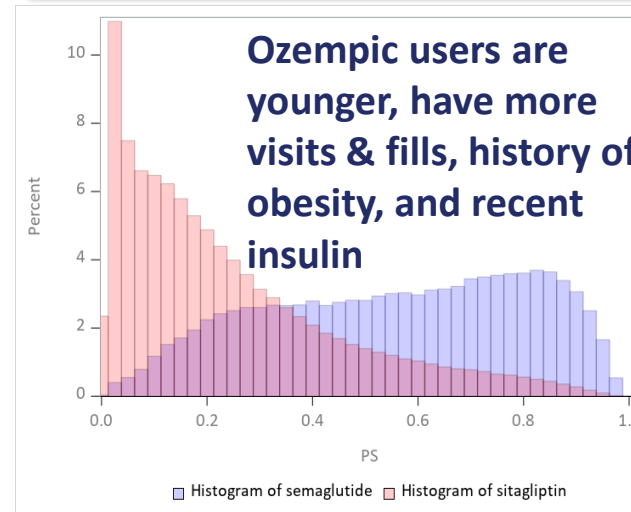
Sentinel Distributed Database



- Scanned ~83,000 non-pregnancy and non-cancer outcomes
- Sensitivities based on encounter setting



Jan. 2018 – Feb. 2022



134,007 1:1 Matched Pairs with Conventional PS
118,161 1:1 Matched Pairs with Conventional + hdPS

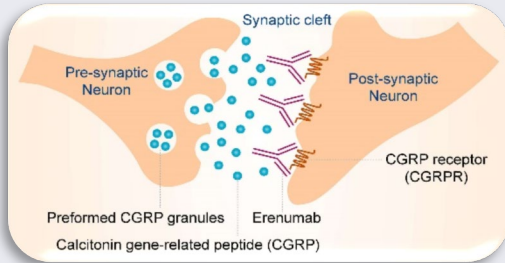
Ozempic users less adherent, more likely to stop treatment after a single dispensing

Significant Alerts: Nausea/Vomiting, Diarrhea, Constipation, GI distress / pain, Obesity, Abnormal Weight Loss, Metabolic Issues, Sleep Apnea

Conclusions: All of the alerts observed were either labeled adverse events, or comorbid conditions of people likely using Ozempic not only for glucose control but also for weight loss. None of the alerts required further follow-up.

Signal Identification for Aimovig (erenumab)

Background



Is there an increase in frequency of adverse events during erenumab risk period compared to control period?

Methods

Self-Controlled Risk Interval Design

- Variable risk window
- Fixed risk window with pre-exposure control window

Analysis and Findings



Sentinel
Distributed
Database



- Scanned ~83,000 non-pregnancy and non-cancer outcomes
- Sensitivities based on encounter setting



63,412 patients within variable risk window cohort
77,152 patients within fixed risk window cohort

Erenumab users were mostly female, had higher prevalence of hypertension, hyperlipidemia, and concomitant use of triptans

Significant Alerts: Constipation, Abnormal findings on diagnostic imaging of central nervous system, Headache, Other specified cerebrovascular disease

Other Significant Alerts: Sepsis, Pneumonia, Cough, COVID-19 (most likely related to a COVID outbreak)

Conclusions: The alert for “Other specified cerebrovascular disease” required follow-up with a Patient Episode Profile Retrieval (PEPR). Low suspicion that these diagnoses were related to erenumab exposure.

Signal Identification for Skyrizi (risankizumab)



Background

Interleukin-23 inhibitor
Approved in April 2019

- moderate-to-severe plaque psoriasis
- active psoriatic arthritis
- moderately to severely active Crohn's disease (CD)

Is there a significant elevation in frequency of outcomes following initiation of Skyrizi® (risankizumab)?



Two study designs used:

- Self-controlled risk interval design (SCRI)
- Active comparator (AC) propensity score (PS) matched design



Sentinel
Distributed
Database



04/2019
to
09/2023



Screen for any incident occurrence of non-cancer non-pregnancy outcomes (3rd-5th levels of pruned ICD-10-CM tree)

Self-controlled risk interval design: Three cohorts of adult non-pregnant new users of risankizumab

Tree only scan



Risk window
[1, 28 days post-index]



Control window
[-56, -29 days pre-index]

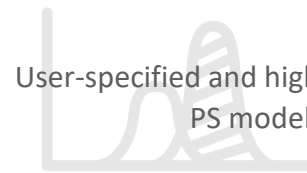


Tree temporal scan

Two variable risk windows for identifying temporal clusters

1 to 183 days post-index
1 to 84 days post-index

Active comparator design: Cohort of adult non-pregnant risankizumab vs. guselkumab new users



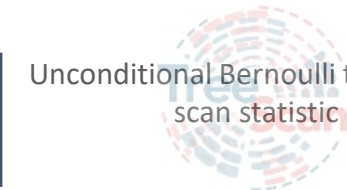
Created by Srinivas Agra
Project

SCRI:

Tree-only : 29,815 new use episodes
Tree-temporal [1, 183] : 21,095 new use episodes
Tree-temporal [1, 84] : 27,044 new use episodes



Follow "as treated" matched pairs for 183 days or until either is censored



Unconditional Bernoulli tree-based scan statistic

AC:



hdPS matched pairs : 14,819 pairs
User-specified PS pairs : 16,096 pairs

Relevant alerts (not indications or known risks)

Tree only scan (both SCRI and AC): No statistically significant alerts found

Tree temporal [1,183 days post-index]: **K80.20:** Calculus of gallbladder without cholecystitis without obstruction (clustered 9-11 days post-index) (RR: 15.16; p=0.036)
K80.2*: Calculus of gallbladder without cholecystitis (clustered 9-11 days post-index) (RR: 14.6; p=0.046)

Conclusions: The alert for "Calculus of gallbladder without cholecystitis" was followed up with a Patient Episode Profile Retrieval and was determined to be incidental to orders for radiology in support of hospitalization for more serious events.

Takeaways: Integrating Multi-Modal Data Streams

- FDA is working towards integrating Sentinel Signal Identification into its routine surveillance activities
 - Output complements surveillance of FAERS, periodic safety reports, literature, and other data streams
 - Best practice/process development underway
- Opportunities to refine approaches and processes
 - Curating additional “trees” (e.g., should we have a designated medical event-like tree?)
 - Exploring signaling in EHR-based signal detection

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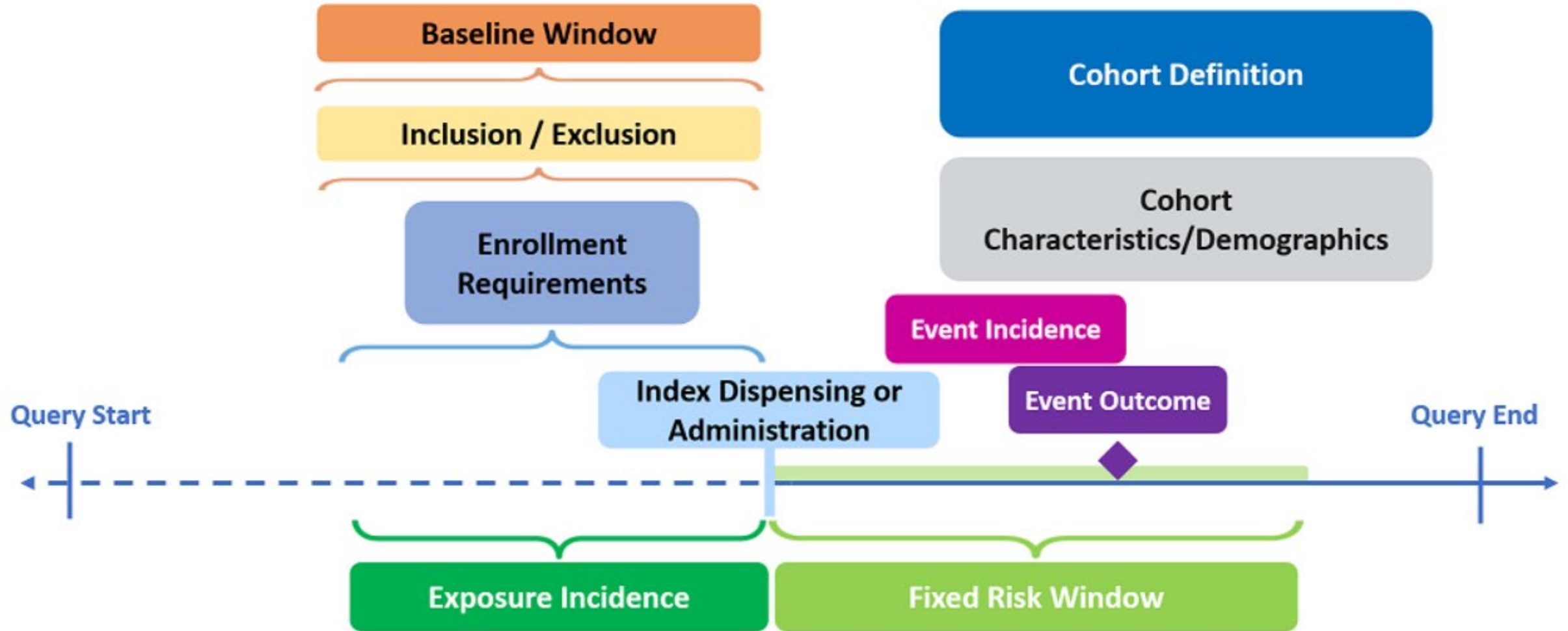


Thank You

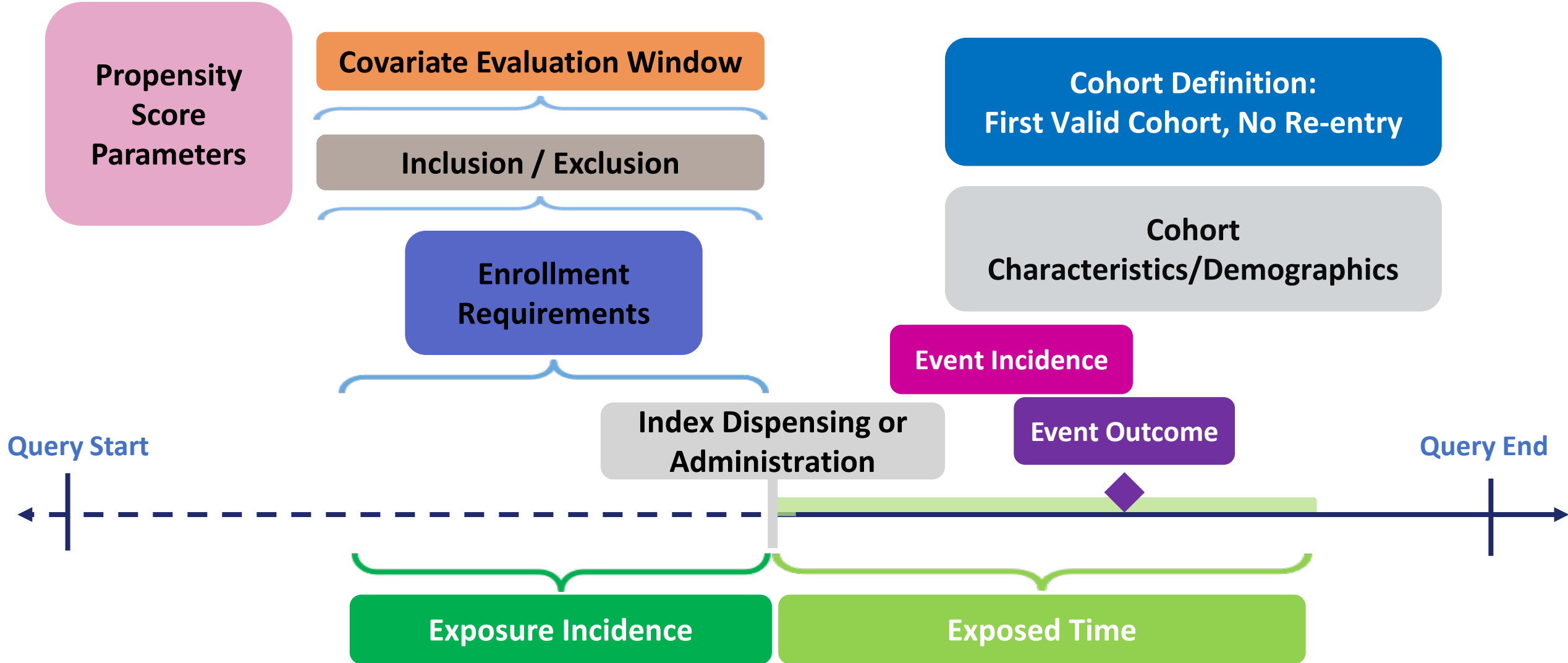
Choosing between Self-Controlled and Cohort Design

- Self-Control
 - Advantage is control for time-invariant characteristics by design
 - Asks the question: WHEN is there an etiological risk window for a particular outcome following medical exposure? It cannot detect if there is a sustained increase in an outcome over time.
 - Vulnerable to time-varying confounding and a poor choice for when there is a rapidly changing health state (e.g. people who are truly acutely ill)
- Cohort (Usually Active Concurrent Comparator but Historical Comparators are possible)
 - Advantage is clinical equipoise provided an appropriate comparator can be identified
 - Mitigates (but does not eliminate) concerns about time-varying confounding, latent coding, confounding by indication

Self Controlled Design



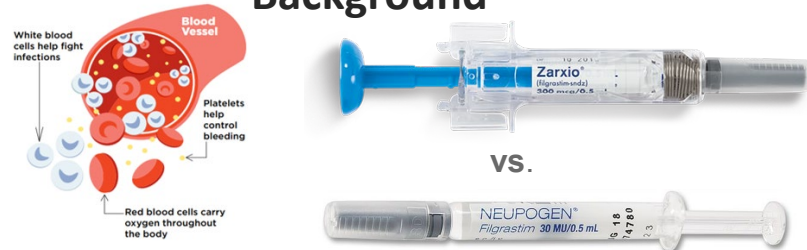
Propensity-Score Adjusted Design Diagram



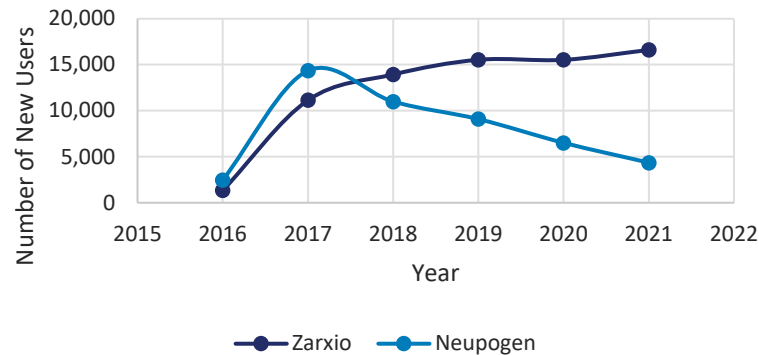
Adverse Events after Zarxio (filgrastim-sndz) as Compared to Neupogen (filgrastim)

1:1 PROPENSITY SCORE MATCHED SIGNAL IDENTIFICATION STUDY

Background



Substitution Effects



Is there any difference in medical product safety profiles between the originator product and its biosimilar?

Analysis and Findings



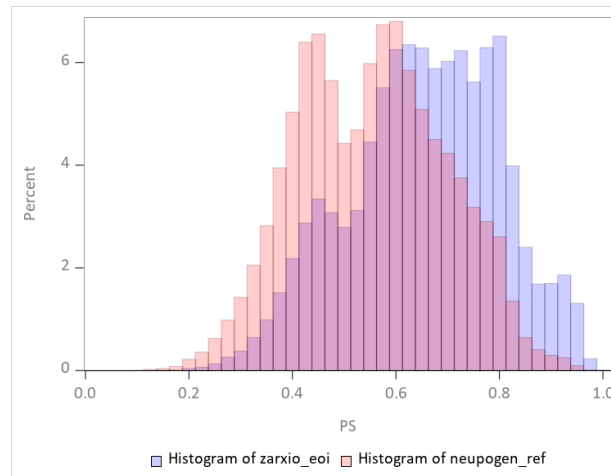
Sentinel
Distributed
Database



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- Sensitivities based on encounter setting



Nov. 2016 –
Feb. 2022



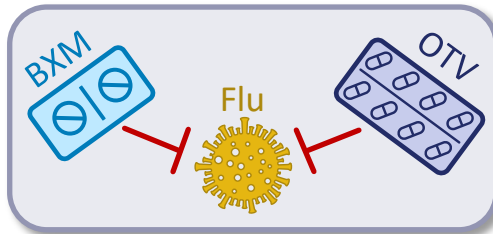
- 43,009 1:1 Matched Pairs with Conventional PS
- Imbalances on Indication, Year Before Matching
- Significant Alerts: Polyarthrititis, Pain in the Leg, Other Disorders of the Peripheral Nervous System

No alerts required further follow-up.

Comparative Post-Marketing Safety Assessment: Baloxavir Marboxil (BXM) vs Oseltamivir (OTV)

Background & Design

BXM is a new antiviral for influenza prophylaxis or treatment.



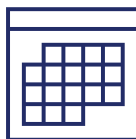
Are any safety issues more frequent among BXM vs. OTV new initiators?



Propensity score-matched (PSM) cohorts of community-dwelling, nonpregnant BXM & OTV users



Sentinel
Distributed
Database

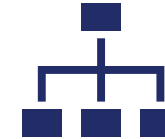


Oct 2018 –
Apr. 2023

Safety Signal Assessment



Follow “as treated” matched pairs for 84 days or until either is censored





Identify new safety outcomes in 3rd-5th levels of pruned ICD-10-CM tree



Unconditional Bernoulli tree-based scan statistic in 1) acute, and 2) all settings

Results

BXM **OTV**
 
N = 76,950 **N = 3,456,633**

In one sensitivity assessment, “Acute bronchitis” was more frequent in BXM (RR 1.09; p=0.01), but not determined to be a safety signal.

No new safety signals were identified for BXM as treatment or prophylaxis for influenza compared to OTV