Sentinel

Signal Identification Studies in Sentinel

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Judith C. Maro

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Disclosures

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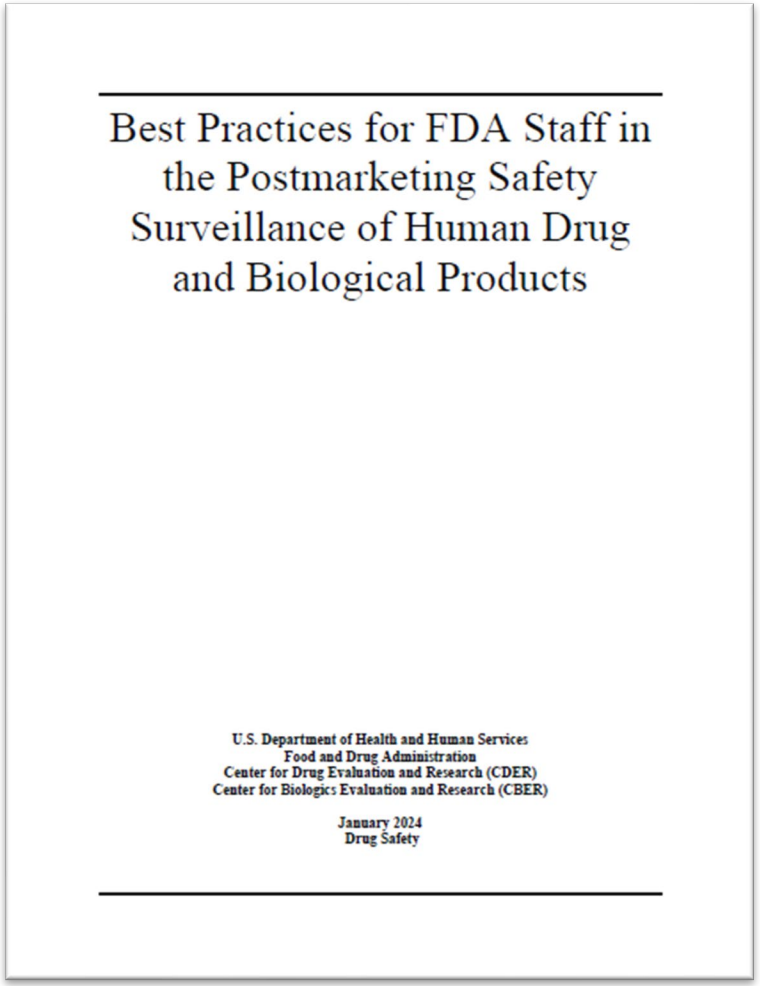
Signal Identification – Routine Pharmacovigilance

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)

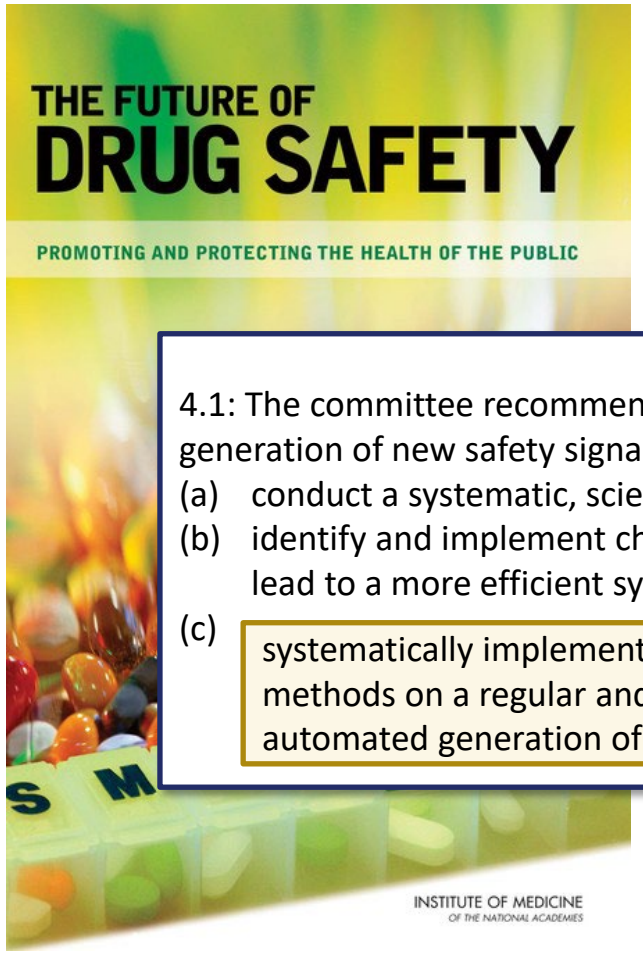
January 2024
Drug Safety

Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff. January 2024. https://www.fda.gov/media/130216/download

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

Committee on the Assessment of the US Drug Safety System; Board on Population Health and Public Health Practice; Institute of Medicine. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*; Stratton, K., Baciu, A., Burke, S. P., Eds.; National Academies Press: Washington, D.C., 2007. https://doi.org/10.17226/11750.

FAERS vs. Sentinel for Signal Identification

FAERS Limitations	Sentinel Strengths
• Cannot determine incidence rates	• Estimates of population exposure available • Risk quantification possible
• Vulnerable to underreporting and reporting bias	• Exposure/event capture at the level of patient and based on billed medical encounters
• Adverse events associated with long latency, worsening disease, or high background rates difficult to evaluate	• Longitudinal capture of medical history • Ability to control for confounding

FAERS = FDA Adverse Event Reporting System

FAERS vs. Sentinel for Signal Identification

FAERS Strengths	Sentinel Limitations
• Detecting serious rare events, particularly obvious drug-induced events	• Need sufficient exposures & outcomes
• Captures all products and use settings; can provide patient perspectives	• Capture based on billed medical encounters
• Near real-time data from reporters available for analysis	• Claims maturation period; data lags

FAERS = FDA Adverse Event Reporting System

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

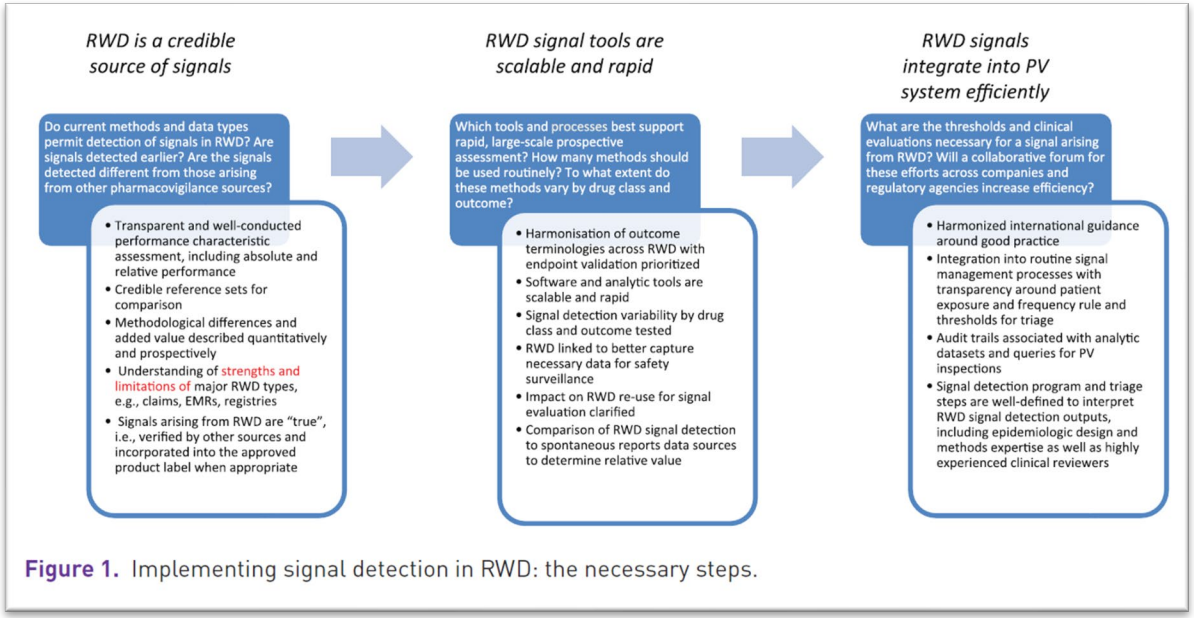


Figure 1. Implementing signal detection in RWD: the necessary steps.

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

Completed Sentinel Signal Identification Analyses

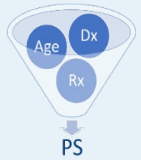
Signal Identification for Ozempic (semaglutide)

Background

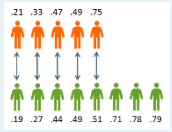
VS.

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

Methods



1:1 PS Match & hdPS match

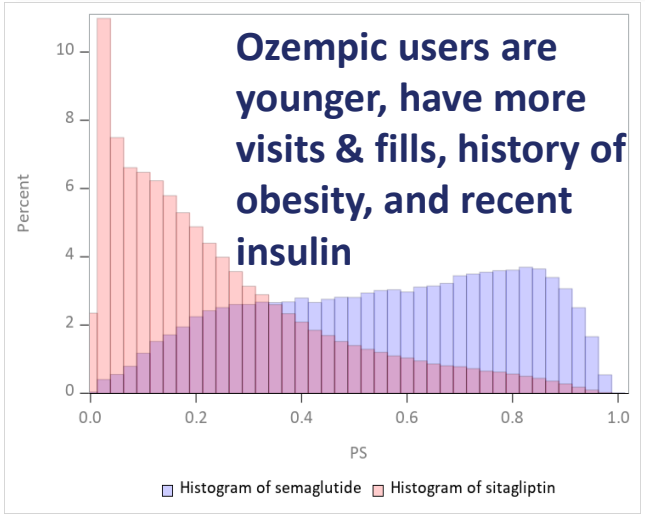


Analysis and Findings

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

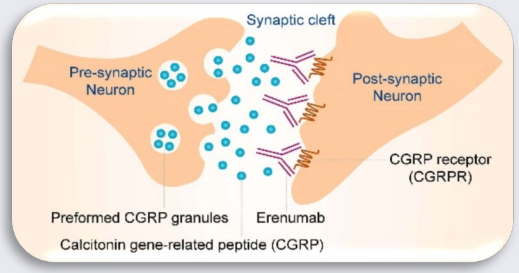
Significant Alerts: Nausea/Vomiting, Diarrhea, Constipation, GI distress / pain, Obesity, Abnormal Weight Loss, Metabolic Issues, Sleep Apnea

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.

https://sentinelinitiative.org/studies/drugs/individual-drug-analyses/outcome-monitoring-following-ozempic-use-patients-type-2

Signal Identification for Aimovig (erenuma)

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

TreeScan

- **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.

https://sentinelinitiative.org/studies/drugs/aimovig-erenumab-0

Signal Identification for Skyrizi (risankizumab)

Background

Skyrizi® risankizumab-rzaa

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

User-specified and high dimensional PS model

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

Unconditional Bernoulli tree-based scan statistic

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

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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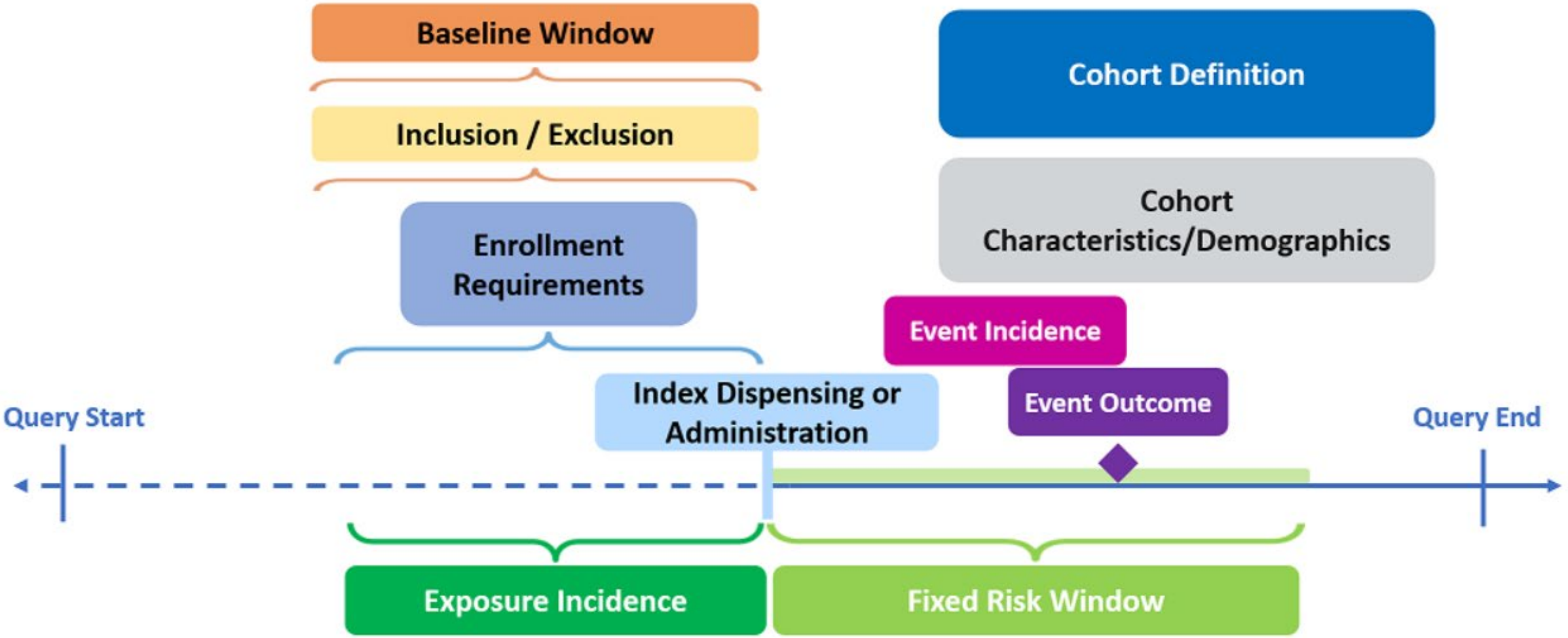
Sentinel

Thank You

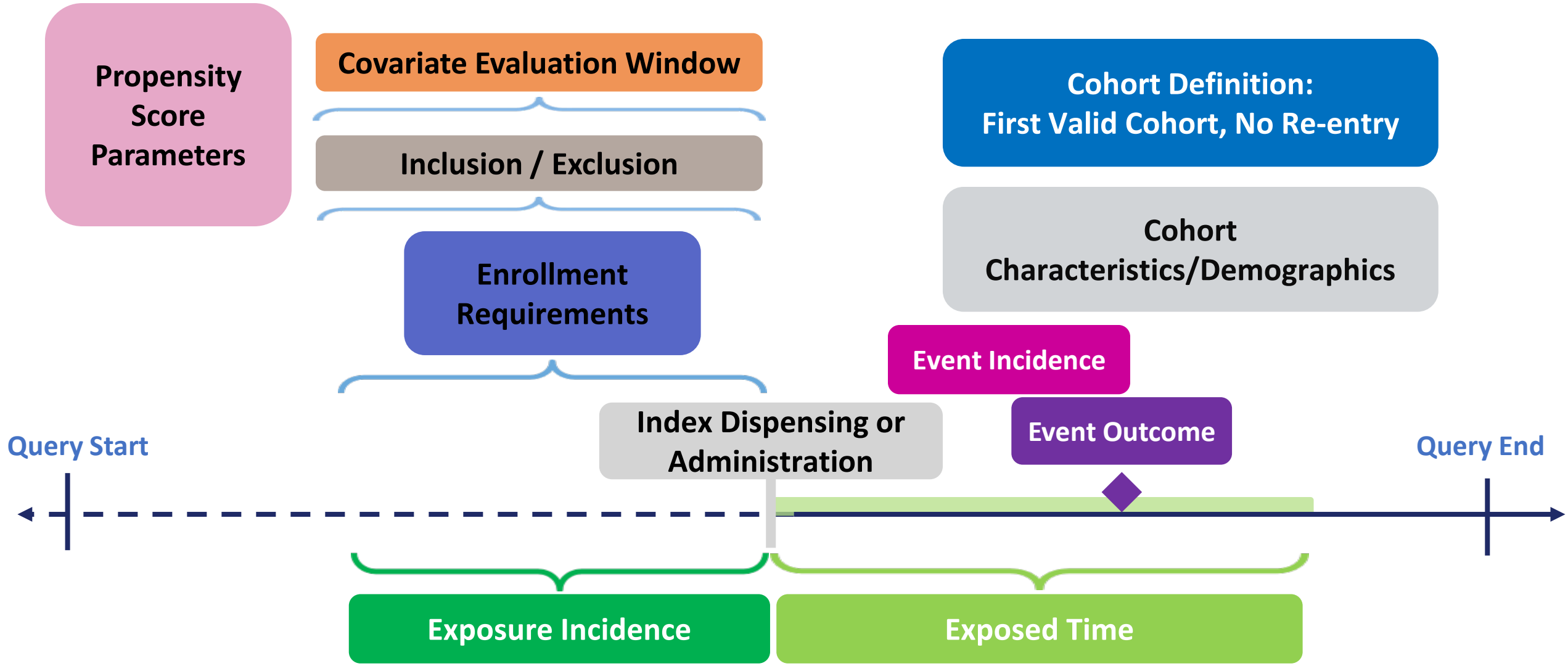
Choosing between Self-Controlled and Cohort Design

- 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

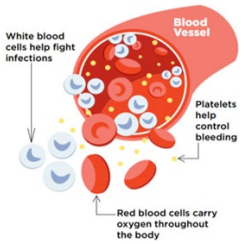


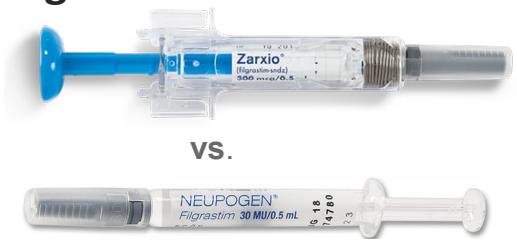
https://dev.sentinelsystem.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse/files/file350-type020304-sifunctional.md

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

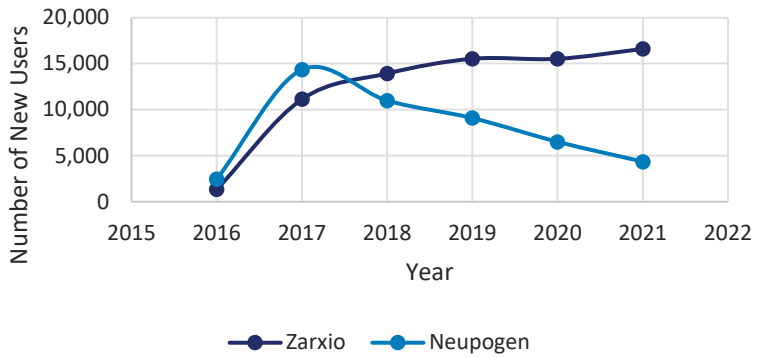
1:1 PROPENSITY SCORE MATCHED SIGNAL IDENTIFICATION STUDY

Background





Substitution Effects



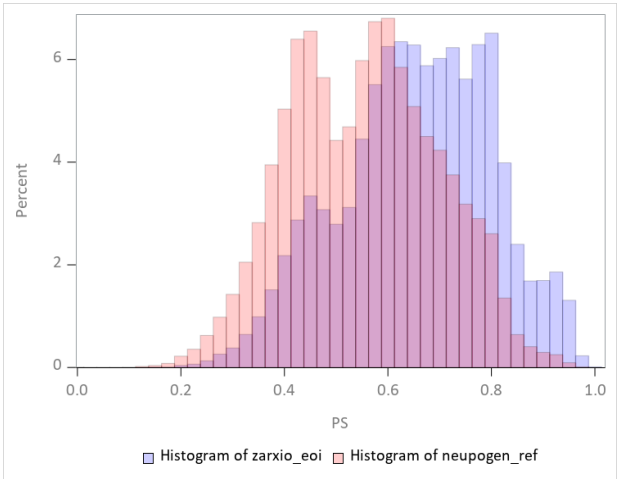
Is there any difference in medical product safety profiles between the originator product and its biosimilar?

Analysis and Findings

Sentinel Distributed Database

- Scanned ~83,000 non-pregnancy and non-cancer outcomes
- 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: Polyarthritis, Pain in the Leg, Other Disorders of the Peripheral Nervous System**

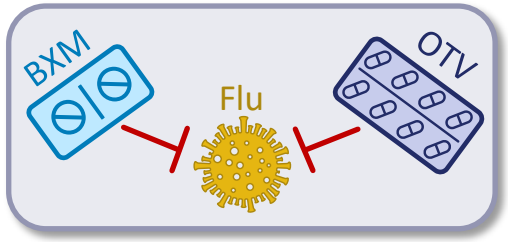
No alerts required further follow-up.

https://www.sentinelinitiative.org/studies/drugs/zarxio-filgrastim-sndz

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 N = 76,950

OTV 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

https://www.sentinelinitiative.org/studies/drugs/xofluza-baloxavir