Tree-Based Safety Signal Identification for Infliximab Biosimilars vs. Reference Product

42nd Annual Meeting

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Presented at the International Society for Pharmacoepidemiology 42nd Annual Meeting

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31 August 2026

Disclosures

- The contents of this presentation are those of the authors and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS, or the U.S. Government.
- This project was supported by Task Order 75F40125F19015 under Master Agreement 75F40119D10037 from the U.S. Food and Drug Administration (FDA).
- A.I.M., J.C.H., L.H., M.L., J.C.M., A.P., and B.R. are employees of Harvard Pilgrim Health Care Institute, a non-profit organization that conducts work for government and private organizations, including pharmaceutical companies.
- In line with the Sentinel System's transparency principals,[1] the results of this study are placed in the public domain. While data is not available, the code for creating the analytical dataset from the source data warehouse and the code for generating the tables, figures, and analysis results are available online.[2]

[1]Sentinel System. *Principles & Policies: Communications*. 2026.
[2]Sentinel System. *Outcome Monitoring Following Infliximab Biosimilar Product Use: An Active Comparator Signal Identification Analysis*; 2026.

Overview

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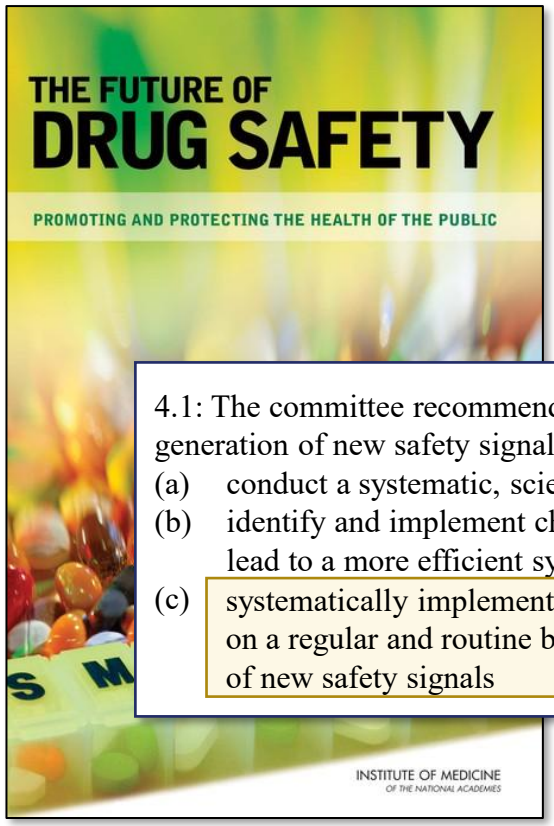
History of Safety Signal Identification at the U.S. FDA

- In 2006, the U.S. FDA requested the Institute of Medicine to **examine the system of drug safety in the U.S.**



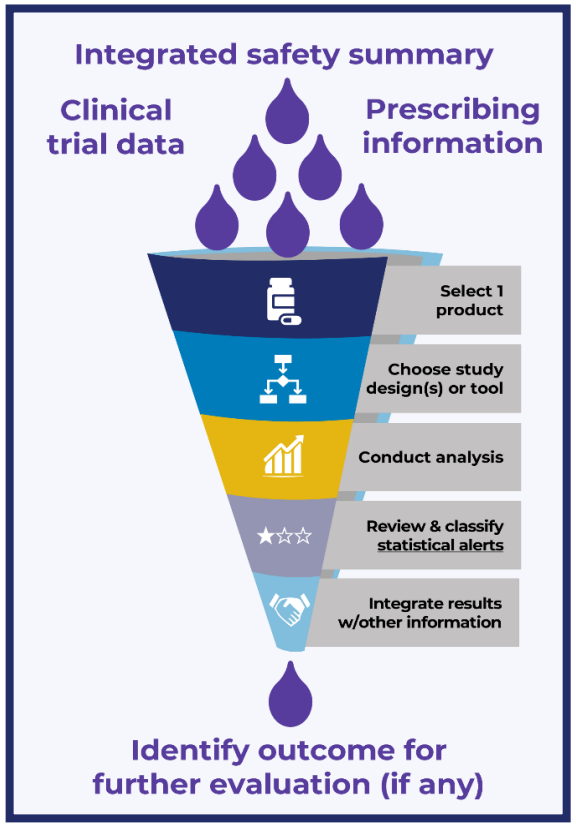
4.1: The committee recommends that in order to improve the generation of new safety signals and hypotheses, CDER

(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

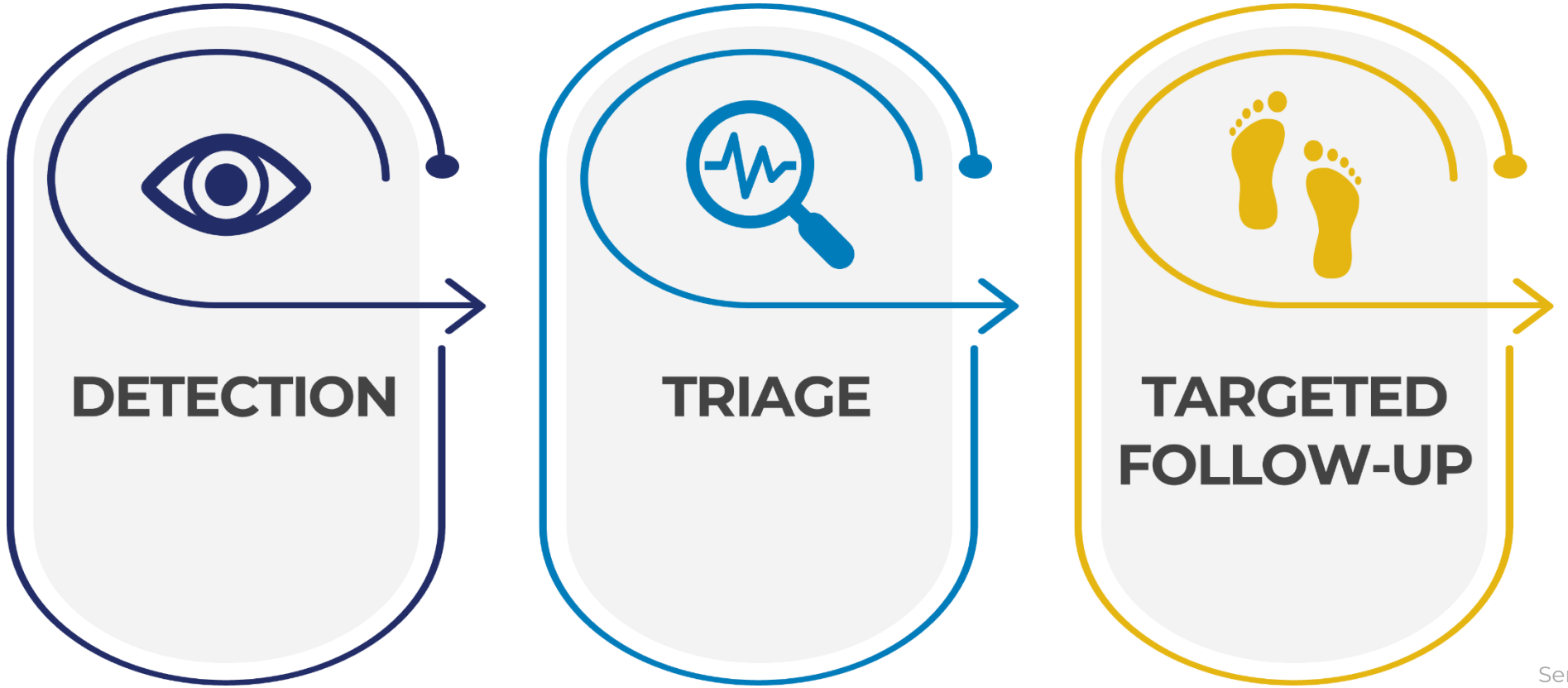
- In 2018, the U.S. FDA proposed a **process for safety signal identification** in Sentinel and integration with other sources of information



Institute of Medicine. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*; National Academies Press: Washington, D.C., 2007. https://doi.org/10.17226/11750.
Nguyen M. FDA convening presented at: *Implementation of Signal Detection Capabilities in the Sentinel System*; December 3, 2018; Bethesda, Maryland.

Safety Signal Identification in the Sentinel System

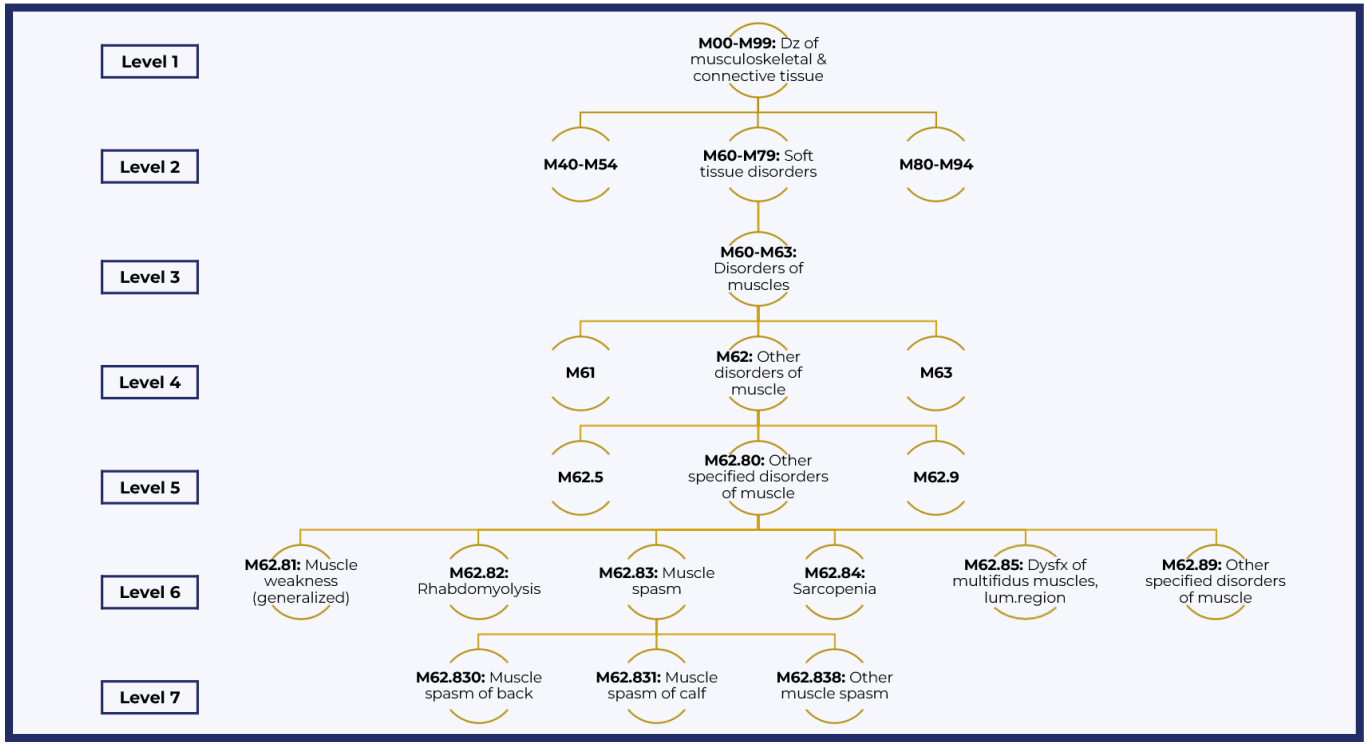
- Process includes **systematically evaluating** potential adverse events related to the use of medical products **without prespecifying an outcome** of interest
  - Detect unexpected, higher numbers of health outcomes
  - Clinical review and/or targeted epidemiology safety study follows signal identification



Tree-Based Scan Statistics for Signal Identification

- Several signal identification techniques have been developed and used within pharmacoepidemiology; the Sentinel System uses **tree-based scan statistics (TBSS)**.
  - Implemented via the TreeScan® software
  - Scans different groupings of related codes leveraging hierarchical outcome structures
  - Compatible with multiple epidemiologic study designs and confounding control methods while automatically adjusting for multiple outcomes being scanned

www.treescan.org



This tree represents section from a hierarchical tree of International Classification of Diseases, 10th Edition, Clinical Modification (ICD-10-CM) codes.

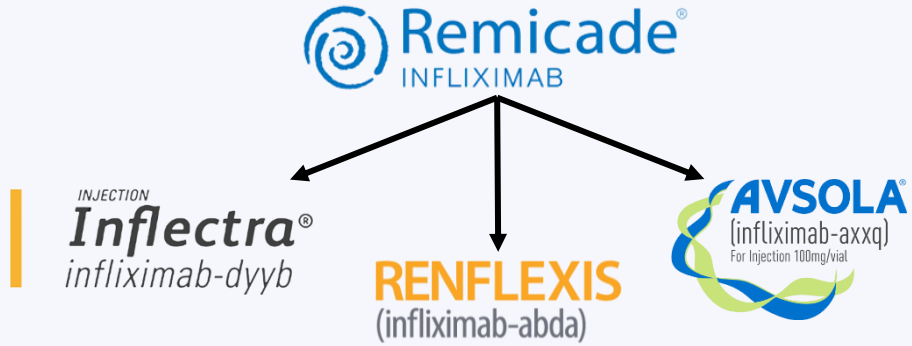
Kulldorff M et al. *Biometrics*, 2003,59:323-331
Kulldorff M et al. *Pharmacoepidemiology and Drug Safety*, 2013, 22:517-523.
Signal Identification in the Sentinel System. 2026. https://www.sentinelinitiative.org/methods-data-tools/signal-identification-sentinel-system

Studying Safety of Biosimilar Products

- Biosimilar products (BPs) are highly similar to and have no clinically meaningful differences from their reference products (RPs).
  - Post-marketing surveillance is essential to support both BP and RP safety in clinical practice.

Product of Interest: Infliximab

- Infliximab (Remicade®, RP) was approved in the U.S. in 1998. It is now used to treat severe chronic autoimmune conditions (such as Crohn's disease and rheumatoid arthritis).



- **Study objective:** To *address the possibility for differing safety profiles between infliximab RP and its BPs*, use tree-based scan statistics to identify new potential safety signals following infliximab BPs vs. RP initiation.

Active Comparator New User Retrospective Cohort

Study Period Starts
01/01/2017

Cohort Entry*
(Infliximab biosimilar product (BP); infliximab RP)
Day 0

Follow-Up Ends
Most Recent Data
(Max 5/31/25)

ENROLLMENT REQUIREMENT
(Pre-Index)
Days [-400, 0]; Allow 45-Day Gap

EXCL
(Age < 18 years)
Days [0, 0]

EXCL
(Ongoing pregnancy)
Days [-183, 183]

EXCL
(Pregnancy Delivery)
Days [0, 183]

EXCL
(Anti-TNF biological products)
Days [-400, 0]

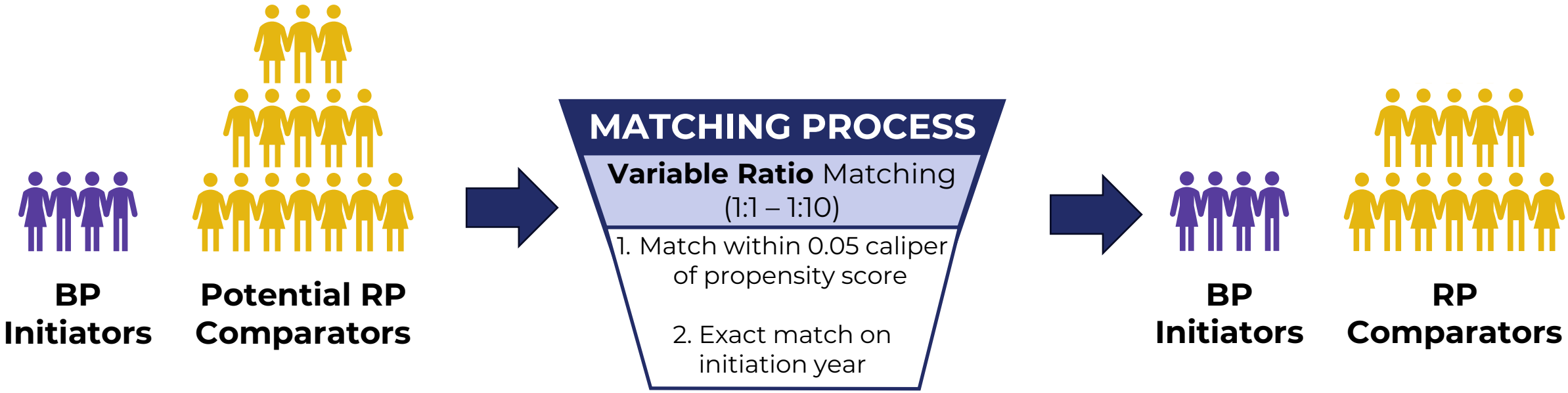
WASHOUT WINDOW
(Exposure and Comparator)
Days [-400, -1]

Exposure	**** Cohort entry***
Any BP	***01/01/2017***
Inflectra®	*01/01/2017*
Renflexis®	*01/01/2018*
Avsola®	*01/01/2021*

Time

BP: biosimilar product; ED: event date; RP: reference product; TNF: tumor necrosis factor

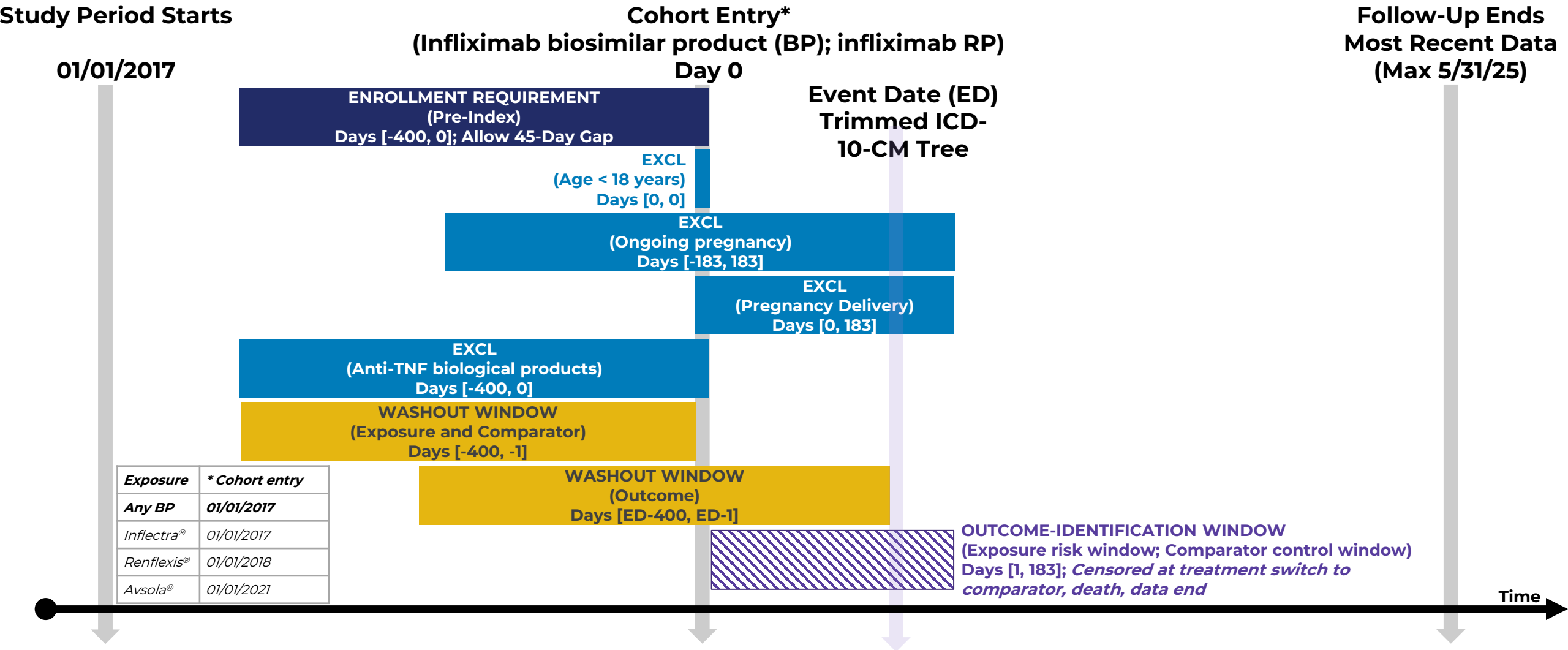
Variable Ratio Exact and Propensity Score Matching



Propensity score used a general model[1] including baseline demographics, socioeconomic status [SES], chronic comorbidities, and healthcare utilization.

[1] Wang SV, Maro JC, Gagne JJ, et al. "A General Propensity Score for Signal Identification Using Tree-Based Scan Statistics." *Am J Epidemiol.* 2021;190(7):1424-1433. doi:10.1093/aje/kwab034

Active Comparator New User Retrospective Cohort



Exposure	** Cohort entry*
Any BP	***01/01/2017***
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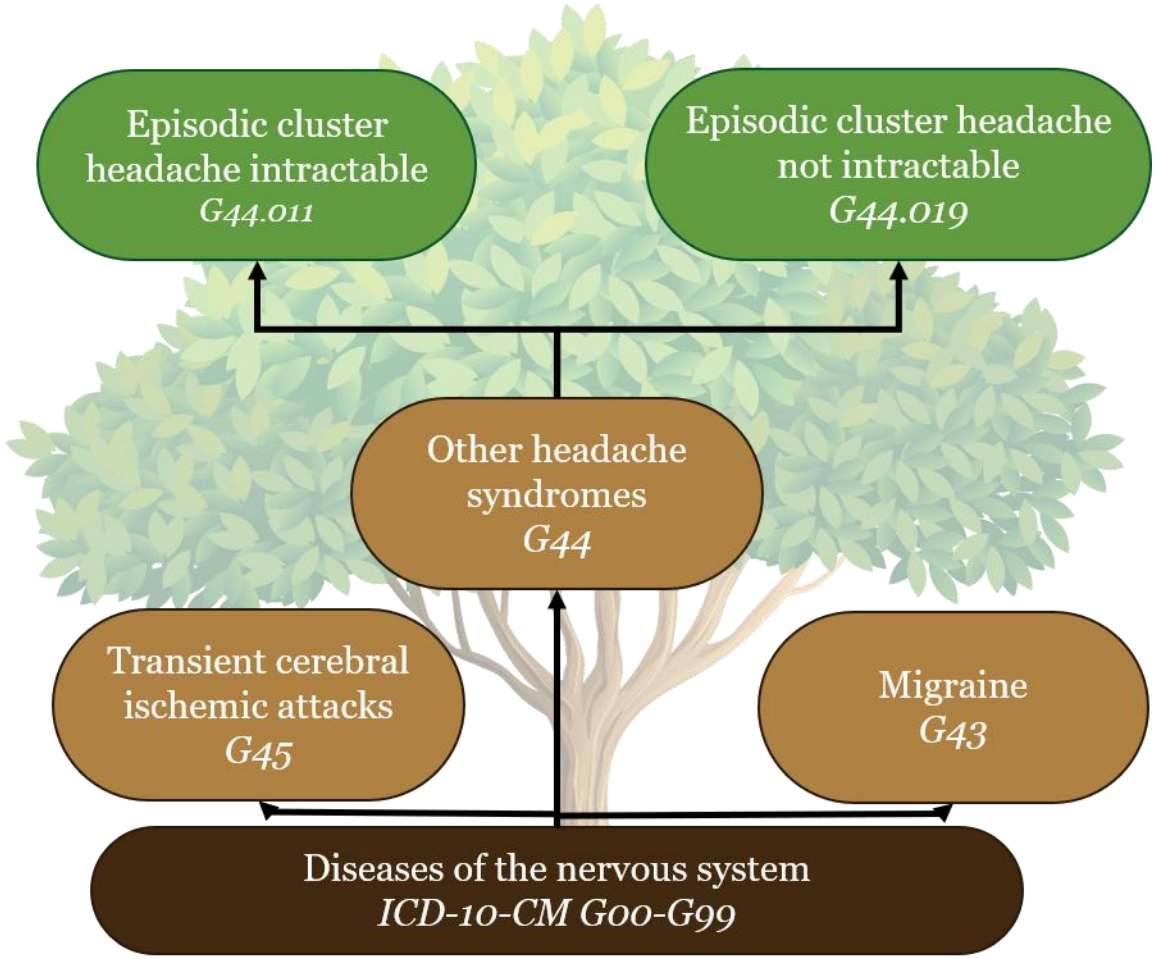
Avsola®	*01/01/2021*

BP: biosimilar product; ED: event date; RP: reference product; TNF: tumor necrosis factor

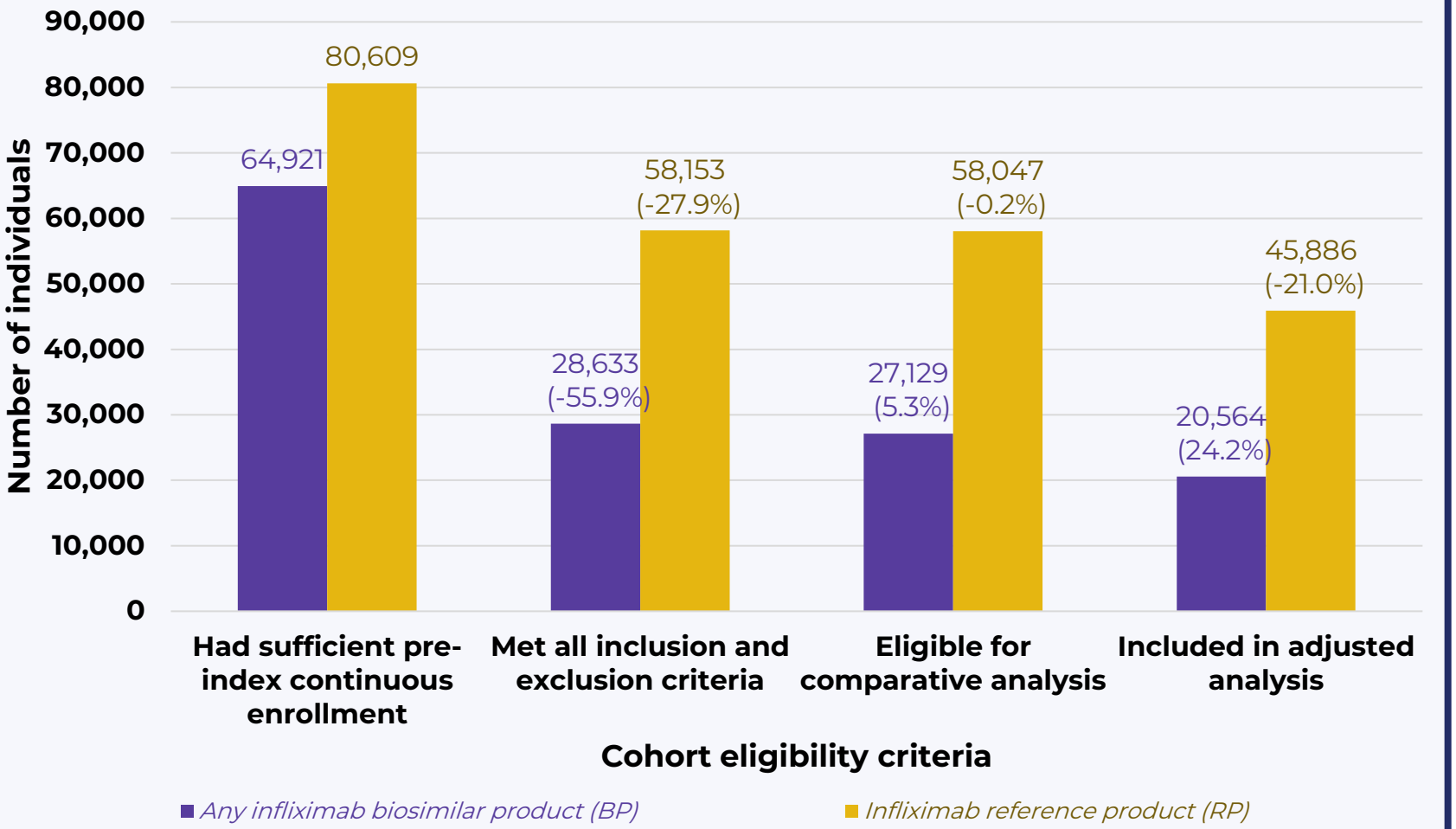
Hierarchical Safety Outcome Trees

- Primary analyses used a "pruned" tree of nearly **70,000 ICD-10-CM diagnosis codes**
  - Included all codes except those unlikely to be related to drug use within our risk window, such as pregnancy and cancer
  - Primary analyses restricted to diagnosis codes in the 3rd – 5th levels of the tree in *inpatient* and *emergency department* settings
- Secondary analyses used a smaller tree of ~3,000 codes indicating serious medical adverse events, known as **designated medical events (DMEs)**[1]
- Scans used a variable probability unconditional Bernoulli tree-based scan statistic



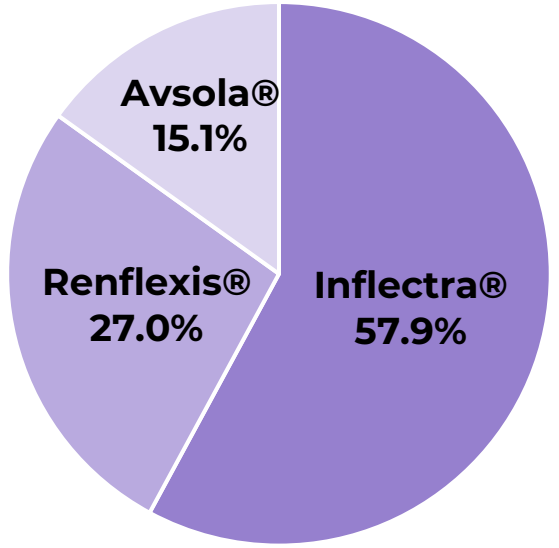
[1]The Sentinel DME tree includes codes pertinent to serious (often drug-related) events from the US FDA and EMA lists, and other clinically important events such as stroke, myocardial infarction, and venous thromboembolism. We used the Sentinel DME tree for analyses involving comparisons with fewer than 4,000 exposed new users in order to maximize power

Formation of Infliximab BP and RP New User Cohorts



Counts reflect the number of individuals remaining at each step of cohort attrition; percentages reflect the proportion lost from the prior step.

Biosimilar Products in "Any BP" Comparison



Successful Balance with Variable-Ratio Matching Techniques

	Unadjusted		Adjusted	
	Any infliximab BP	Infliximab RP	Any infliximab BP	Infliximab RP
Unique patients	27,129	58,047	20,564	45,886
Demographics				
Age (years)	54.9 ± 12.9	57.6 ± 12.8	59.0 ± 12.5	59.4 ± 12.2
Race				
Unknown	29.5%	25.6%	16.7%	16.8%
Non-white	40.1%	35.2%	27.8%	28.2%
Highest social deprivation[1]	19.2%	17.4%	18.8%	18.6%
Clinical characteristics				
Combined comorbidity score	2.5 ± 3.0	2.5 ± 2.9	2.7 ± 3.1	2.8 ± 3.1
Immunocompromised	99.2%	99.0%	99.2%	99.2%
Hypertension	48.5%	54.0%	55.6%	56.4%
Hyperlipidemia	42.9%	48.8%	49.7%	51.3%
Infliximab indications	90.2%	92.2%	90.1%	89.7%
Rheumatoid arthritis	34.6%	37.2%	40.4%	39.7%
Crohn's disease	30.0%	30.7%	26.3%	25.9%
Ulcerative colitis	25.6%	25.7%	22.0%	22.2%

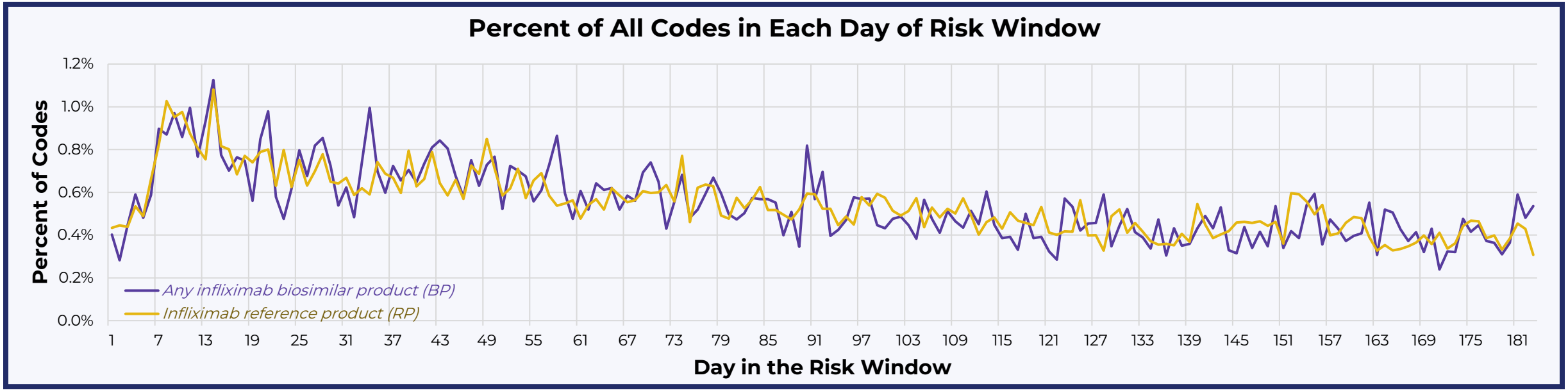
BP: biosimilar product; RP: reference product

Teal text indicates an imbalance (|SMD| ≥ 0.1) between exposed and comparator groups

[1] Social deprivation measured using the "Social Deprivation Index" (https://www.graham-center.org/content/brand/rgc/maps-data-tools/social-deprivation-index.html)

No Statistically Significant Elevations in Health Outcomes Were Detected in the 6 Months after Infliximab BP Initiation

- In the primary analysis comparing individuals initiating any infliximab BP compared to those initiating the RP:
  - 108,645 codes were identified during the risk window, 36,783 (33.4%) among BP initiators
  - Code volume over the risk window was similar between groups



- No primary or secondary analyses for all BPs combined nor for the individual BPs identified statistically significant differences

BP: biosimilar product; RP: reference product

Conclusions

In this active comparator new user retrospective cohort study, we did not identify any new potential safety signals associated with use of infliximab BP compared to the infliximab RP

Strengths

- Variable ratio matching allowed us to maximize the number of exposed individuals retained in the adjusted analysis
- Generalized propensity score and exact matching on year of initiation balanced baseline differences between biosimilar (BP) and reference product (RP) users
- Even smaller exposure groups for newer BPs were able to be assessed using smaller outcome trees

Limitations

- Signal identification, by nature, is designed for broad screening and is not built around specific confounding control for targeted outcomes
- While outcome timing was generally similar between groups over the risk window, we did not assess temporal trends within codes or code groups

BP: biosimilar product; RP: reference product

Thank You!

Questions?

Acknowledgements:
Many thanks are due to the Sentinel Data Partners who provided data: CVS Health (Aetna), Blue Bell, PA; Duke University School of Medicine, Department of Population Health Sciences, Durham, NC, through the Centers for Medicare and Medicaid Services which provided Medicare and Medicaid data; Carelon Research/Elevance Health, Wilmington, DE; Humana Healthcare Research Inc., Louisville, KY; OptumInsight Life Sciences Inc., Boston, MA.

Lexie Jaquish and Josie Anderson of Harvard Pilgrim Health Care Institute provided administrative support.

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