DIA 2026 GLOBAL ANNUAL MEETING | PHILADELPHIA, PA JUNE 14-18

Safety Signal Identification for Infliximab Biosimilars:

An Exact- and Propensity Score-Matched Cohort Study Using Variable Probability Tree-Based Scan Statistics

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Proposed Sentinel Signal Identification Process

Integrated Safety Summary

Clinical Trial Data | **Prescribing Information**

Signal identification led by **Divisions of Pharmacovigilance** and Sentinel Program Team

Follow up investigations to be conducted by **Divisions of Epidemiology**

1. Select 1 product
2. Choose study design(s) or tool
3. Conduct analysis
4. Review and classify statistical alerts
5. Integrate results with other sources of information

Identify Outcome for Further Evaluation (if any)

https://healthpolicy.duke.edu/events/implementation-signal-detection-capabilities-sentinel-system

Design: Single Outcome Study → Multiple Outcome Study

Steps for an observational single outcome study in claims data:		Steps for an observational multiple outcome study in claims data:	
Identify a cohort	→	Identify a cohort	✓
Classify exposure based on records of medication dispensings	→	Classify exposure based on records of medication dispensings	✓
Identify the outcome using a validated algorithm	→	**Create an outcome tree with multiple outcomes of interest**	
Control for confounding using propensity score methods	→	Control for confounding using propensity score methods	✓
Calculate a point estimate for the exposure-outcome association	→	**Calculate test statistics for each outcome using TreeScan**	

Tree-Based Scan Statistics Enabled by:

- A signal identification / data-mining method
- Automatically adjusts for multiplicity in outcome assessment
- Scans electronic health data that are grouped into hierarchical tree structures

http://www.treescan.org

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? ✓
  - Expect tools and approaches will continue to evolve

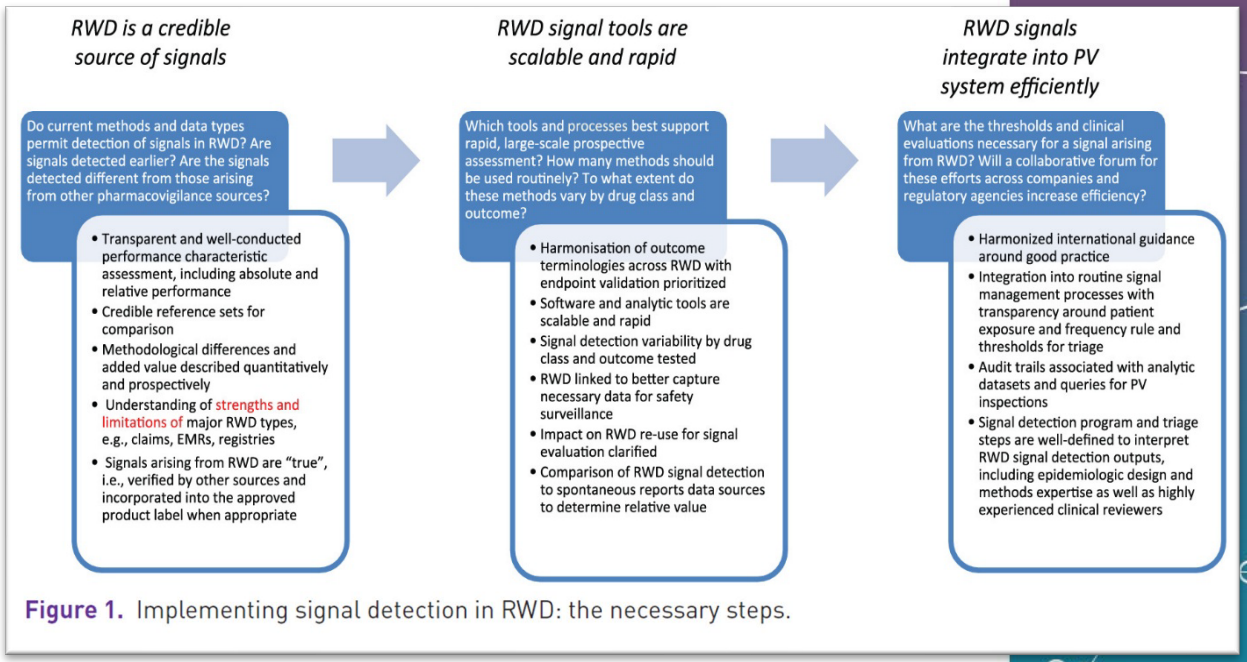


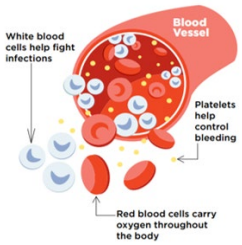
Figure 1. Implementing signal detection in RWD: the necessary steps.

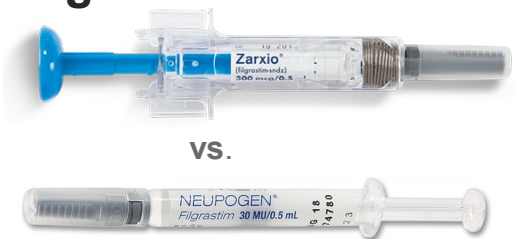
Bate A, et al. Ther Adv Drug Saf. 2019; 10: 2042098619864744.

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

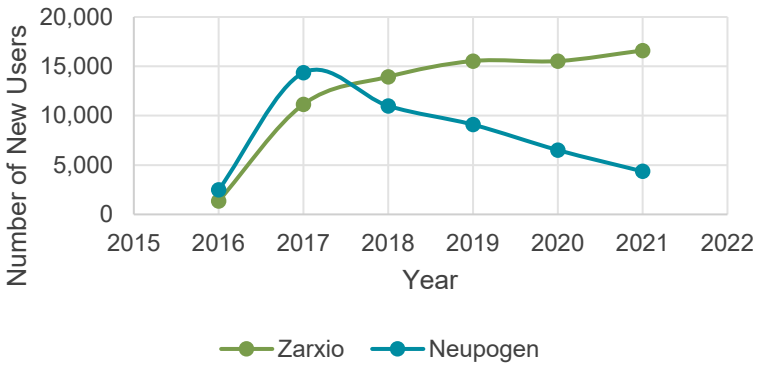
1:1 PROPENSITY SCORE MATCHED SIGNAL IDENTIFICATION STUDY

Background





Substitution Effects



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

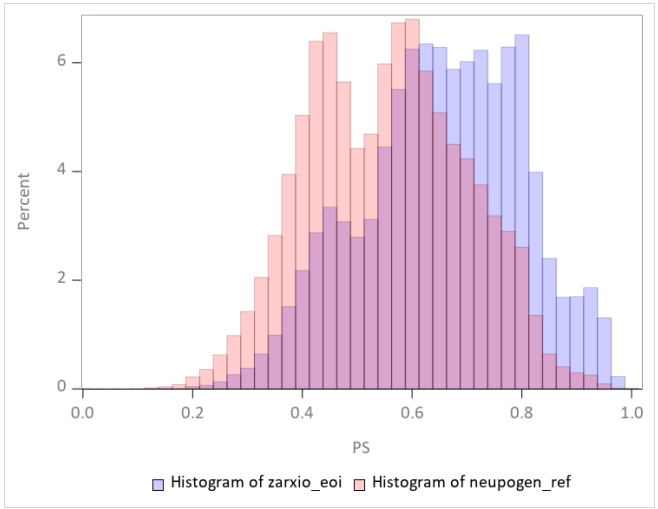
Analysis and Findings

Sentinel Distributed Database

TreeScan

- 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.

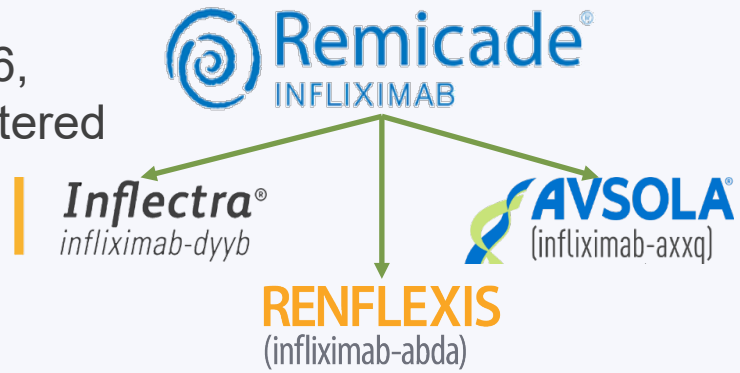
https://www.sentinelinitiative.org/studies/drugs/zarxio-filgrastim-sndz

Infliximab Biosimilars Safety Signal Identification

Background

- 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.**

- Infliximab (Remicade®, RP) was approved in 1998. It is used to treat severe, chronic autoimmune conditions (such as Crohn's disease and rheumatoid arthritis).
  - Since late 2016, 3 BPs have entered the market.



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.

Data & Population

National insurers in the Sentinel Distributed Database

Jan. 2017 – May 2025

New users included: non-pregnant adults with continuous medical & drug coverage in the 400 days prior to initiation *without comparator infliximab or another drug in the same pharmaceutical class*

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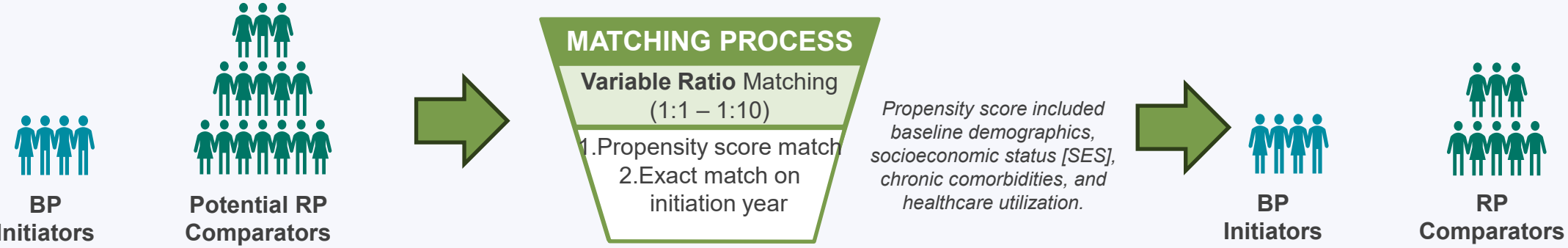
Safety Signal Assessment

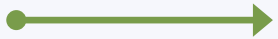
Comparisons

1. RP vs. any BP
2. RP vs. Inflectra®
3. RP vs. Renflexis®
4. RP vs. Avsola®

Confounding Adjustment



Identifying Safety Signals



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

Identify new safety outcomes in 3rd-5th levels of pruned (if sufficient outcome accrual) or designated medical event (DME) ICD-10-CM tree

Variable probability unconditional Bernoulli tree-based scan statistic in 1) acute, and 2) all settings

Unmatched New Initiators of Infliximab Biosimilars and the Originator/Reference Product

	Medical Product				Covariate Balance	
	Any Infliximab Biosimilar		Infliximab Reference			
Patient Characteristics[1]	Number/ Mean	Percent/ Standard Deviation[2]	Number/ Mean	Percent/ Standard Deviation[2]	Absolute Difference	Standardized Difference
Unique patients	27,129	100.0%	58,047	100.0%	N/A	N/A
Demographic Characteristics						
Age (years)	54.9	12.9	57.6	12.8	-2.602	-0.202
18-44 years	9,024	33.3%	15,761	27.2%	6.111	0.133
45-64 years	6,845	25.2%	13,756	23.7%	1.533	0.036
≥ 65 years	11,260	41.5%	28,530	49.1%	-7.644	-0.154
Sex*						
Female	16,341	60.2%	35,402	61.0%	-0.754	-0.015
Male	10,788	39.8%	22,645	39.0%	0.754	0.015
Race[3]						
American Indian or Alaska Native	154	0.6%	278	0.5%	0.089	0.012
Asian	402	1.5%	690	1.2%	0.293	0.026
Black or African American	2,052	7.6%	4,176	7.2%	0.37	0.014
Multi-racial	230	0.8%	348	0.6%	0.248	0.029
Native Hawaiian or Other Pacific Islander	39	0.1%	48	0.1%	0.061	0.018
Unknown	7,994	29.5%	14,874	25.6%	3.843	0.086
White	16,258	59.9%	37,633	64.8%	-4.903	-0.101
Hispanic origin						
Yes	1,247	4.6%	1,963	3.4%	1.215	0.062
No	18,002	66.4%	40,843	70.4%	-4.005	-0.086
Unknown	7,880	29.0%	15,241	26.3%	2.79	0.062

Unmatched New Initiators of Infliximab Biosimilars and the Originator/Reference Product

	Medical Product					
	Any Infliximab Biosimilar		Infliximab Reference		Covariate Balance	
Patient Characteristics[1]	Number/ Mean	Percent/ Standard Deviation[2]	Number/ Mean	Percent/ Standard Deviation[2]	Absolute Difference	Standardized Difference
Unique patients	27,129	100.0%	58,047	100.0%	N/A	N/A
Demographic Characteristics						
ZCTA Social Deprivation Index Score, National Quartile[4]						
Q1 (Least deprived)	7,854	29.0%	18,126	31.2%	-2.276	-0.05
Q2	7,507	27.7%	16,340	28.1%	-0.478	-0.011
Q3	6,513	24.0%	13,363	23.0%	0.987	0.023
Q4 (Most deprived)	5,220	19.2%	10,114	17.4%	1.818	0.047
Unknown	35	0.1%	104	0.2%	-0.05	-0.013
Year*						
2017	54	0.2%	9,325	16.1%	-15.866	-0.607
2018	2,099	7.7%	10,040	17.3%	-9.559	-0.292
2019	2,376	8.8%	8,403	14.5%	-5.718	-0.179
2020	3,001	11.1%	7,433	12.8%	-1.743	-0.054
2021	5,264	19.4%	6,921	11.9%	7.48	0.207
2022	6,436	23.7%	6,064	10.4%	13.277	0.358
2023	3,881	14.3%	4,686	8.1%	6.233	0.199
2024	3,477	12.8%	4,650	8.0%	4.806	0.158
2025	541	2.0%	525	0.9%	1.09	0.091
Census Bureau region						
Midwest	7,866	29.0%	13,992	24.1%	4.89	0.111
Northeast	4,218	15.5%	11,615	20.0%	-4.462	-0.117
South	7,296	26.9%	20,406	35.2%	-8.261	-0.179
West	7,714	28.4%	11,924	20.5%	7.893	0.184
Unknown[5]	35	0.1%	110	0.2%	-0.06	-0.015

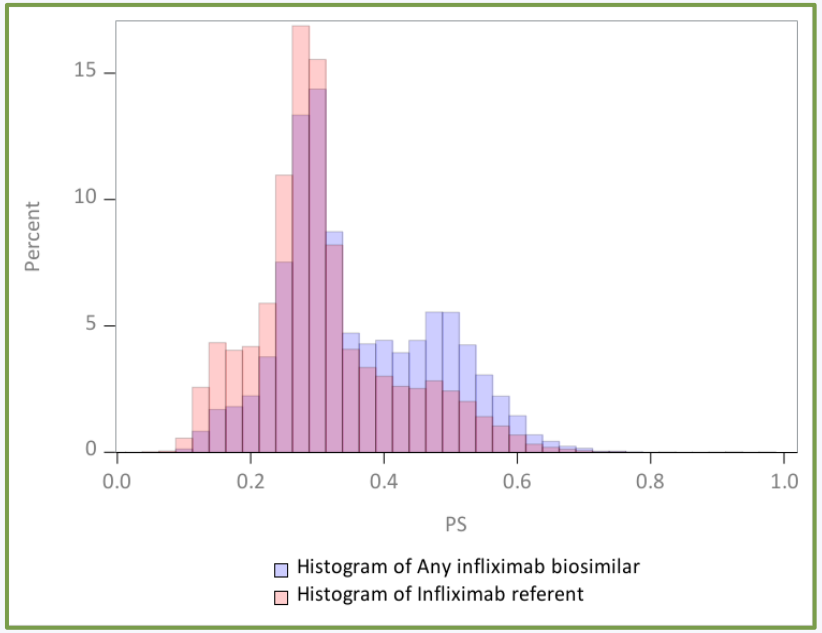
Unmatched New Initiators of Infliximab Biosimilars and the Originator/Reference Product

	Medical Product				Covariate Balance	
	Any Infliximab Biosimilar		Infliximab Reference			
Patient Characteristics[1]	Number/ Mean	Percent/ Standard Deviation[2]	Number/ Mean	Percent/ Standard Deviation[2]	Absolute Difference	Standardized Difference
Unique patients	27,129	100.0%	58,047	100.0%	N/A	N/A
Health Characteristics						
Combined comorbidity score[*,6]	2.5	3	2.5	2.9	0.003	0.001
Hyperlipidemia[*]	11,641	42.9%	28,313	48.8%	-5.866	-0.118
Hypertension[*]	13,153	48.5%	31,320	54.0%	-5.473	-0.11
Immunocompromised	26,909	99.2%	57,484	99.0%	0.159	0.017
Systemic biologic non-anti-TNF treatments[*]	0	0.0%	0	0.0%	NaN	NaN
Crohn's Disease*	8,142	30.0%	17,807	30.7%	-0.665	-0.014
Ulcerative Colitis[*]	6,958	25.6%	14,913	25.7%	-0.043	-0.001
Rheumatoid Arthritis[*]	9,382	34.6%	21,581	37.2%	-2.596	-0.054
Psoriatic Arthritis[*]	2,938	10.8%	6,673	11.5%	-0.666	-0.021
Ankylosing Spondylitis[*]	1,422	5.2%	3,401	5.9%	-0.617	-0.027
Plaque Psoriasis[*]	2,661	9.8%	6,050	10.4%	-0.614	-0.02
No Indications	2,661	9.8%	4,508	7.8%	2.043	0.072
Medical Product Use						
Systemic biologic non-anti-TNF treatments after initiation	468	1.7%	996	1.7%	0.009	0.001
Corticosteroids after initiation	14,828	54.7%	31,531	54.3%	0.338	0.007
Health Service Utilization Intensity Metrics						
Mean number of ambulatory encounters[*]	31.4	24.2	32.5	23.4	-1.064	-0.045
Mean number of emergency room encounters[*]	1.1	2.1	0.9	1.9	0.173	0.086
Mean number of inpatient hospital encounters[*]	0.5	1.1	0.5	1.1	0.005	0.005
Mean number of non-acute institutional encounters	0	0.3	0.1	0.3	-0.007	-0.021
Mean number of other ambulatory encounters	12.2	26.9	11.1	23	1.147	0.046
Mean number of filled prescriptions[*]	43.1	38.3	43.5	36.8	-0.42	-0.011
Mean number of non-proprietary meds dispensed	12.4	7.6	12.6	7.5	-0.2	-0.026

Safety Signal Identification Results

Analytical Cohort

- Confounding adjustment was successful and resulted in balanced groups
- Average matching ratio was 1:2.2

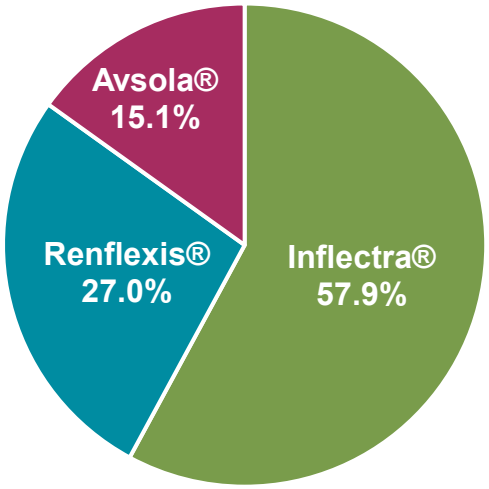


- Matched **20,564** "Any Infliximab Biosimilar Product (BP)" users to **45,886** Infliximab Originator Product Users
- Across all comparisons, the most common method of identifying BP use was presence of a procedure code (HCPCS) alone (50-89%).
  - About ¼ of BP new users also had evidence of an NDC, and <10% had only an NDC.

Results

There were no statistically significant elevations in health outcomes in the six months after infliximab BP initiation compared to RP initiation, either as a composite or when individual BPs were assessed.

Biosimilar Products in "Any BP" Comparison



Signal Identification Takeaways

- Infliximab and its Biosimilar Products had very similar safety profiles
- These products are easily distinguishable in longitudinal data using normal coding practices (i.e., existing NDC and HCPCS codes)
- Analysis is subject to typical limitations, common to observational data studies
- Signal identification, by nature, is designed for broad screening, and is not built around specific confounding control for targeted outcomes.
- All analytic packages and results are publicly available.

https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sip_wp002

Acknowledgements

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Thank You

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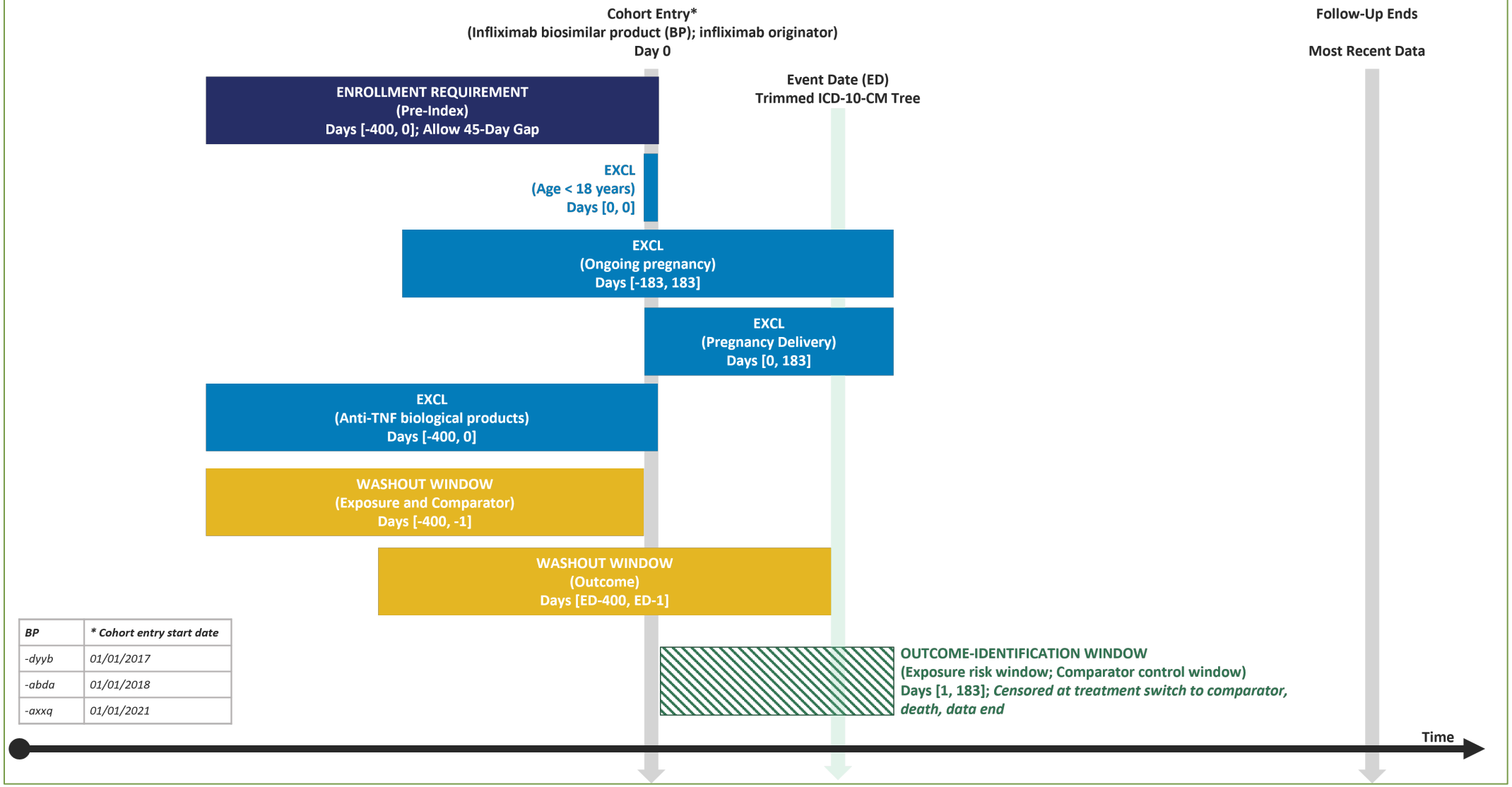
Associate Professor

Harvard Pilgrim Health Care Institute and Harvard Medical School

A propensity-score matched active comparator design with Tree-Only Scan



BP	* Cohort entry start date
-dyyb	01/01/2017
-abda	01/01/2018
-axxq	01/01/2021