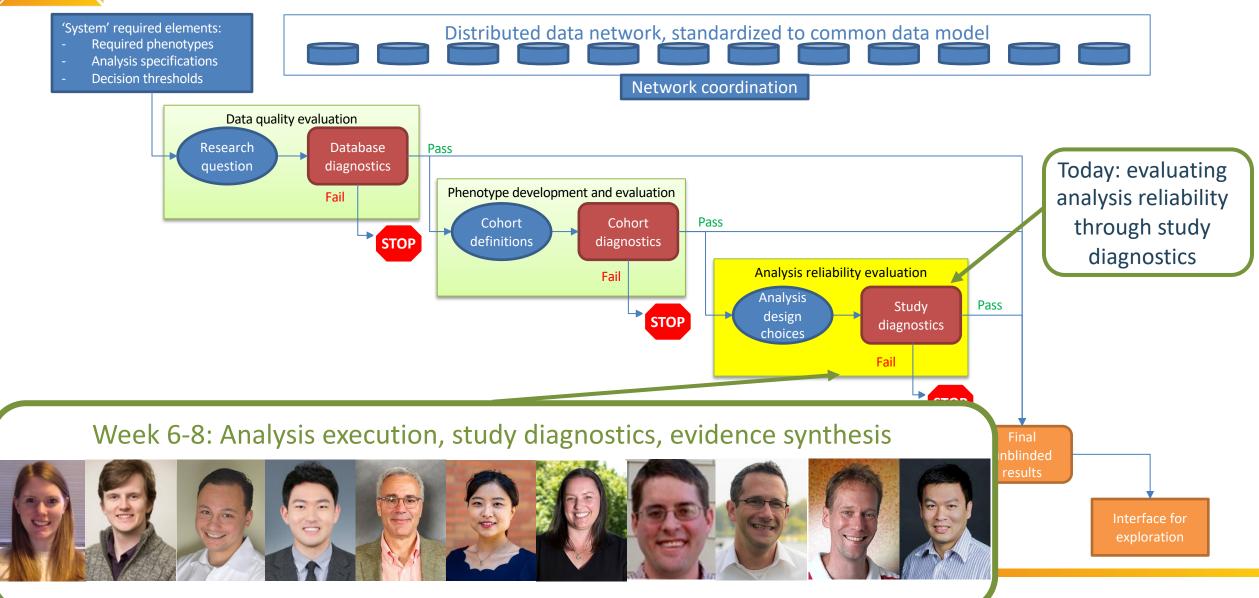


## SOS Challenge Week 7: Study Diagnostics

Anti-VEGF and kidney failure

Fan Bu and George Hripcsak

# Engineering open science systems that build trust into the real-world evidence generation and dissemination process





## **Revisiting 2022 Global Symposium Plenary**

#### Plenary: Objective Diagnostics: A pathway to provably reliable evidence

The plenary presentation from the 2022 OHDSI Symposium was led by **Martijn Schuemie (Johnson & Johnson)** and focused on 'Objective Diagnostics: A pathway to provably reliable evidence.' **Patrick Ryan (Johnson & Johnson, Columbia University)** also took part in this session.

This session introduced a series of diagnostics that can be evaluated to determine database, phenotype, and analysis fitness-for-use for generating reliable evidence. The presentation demonstrates the empirical performance of these objective diagnostics across the LEGEND-HTN result set to illustrate how objective diagnostics can be used and how they improve the quality of evidence generated.

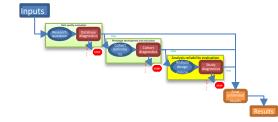


Recording: <u>https://youtu.be/DJZP5z6r-QE</u>

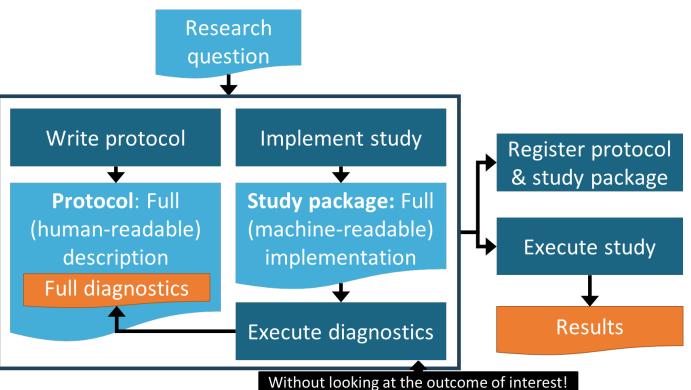
Key message: To reduce post-hoc investigator bias, we need prespecified objective diagnostics rules for evaluating the reliability of analyses. Results should be blinded if study fails diagnostics.



Avoiding investigator bias when interpreting diagnostics

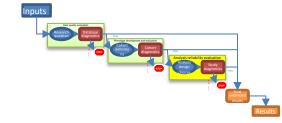


- Diagnostics need to be performed *before* looking at study results
- Protocol can contain diagnostics results, or
- Protocol can contain
   prespecified diagnostics
   rules (so long as they are
   not modified post-hoc)





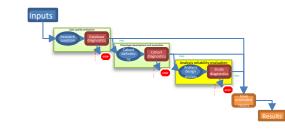
## Study diagnostics



- Characterization
  - Feature summary, incidence, cohort pathways
    - Temporal stability, subpopulation heterogeneity, heterogeneity across data sources
- Population-level Estimation
  - Comparative cohort
    - Statistical power, comparator similarity, between-person confounding, generalizability, residual bias
  - Self-controlled case series
    - Statistical power, time-varying confounding, protopathic bias, residual bias
  - Meta-analysis
    - Statistical power, heterogeneity across data sources
- Patient-level prediction
  - PROBAST criteria (<u>https://doi.org/10.7326/M18-1376</u>) : embedded in PatientLevelPrediction package



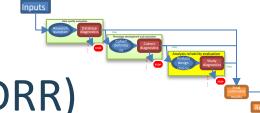
Study diagnostics: A (short) checklist



- Statistical power: minimum detectable relative risk
- Target-comparator similarity: empirical equipoise
- Between-person confounding: covariate balance
- Generalizability: attrition fraction
- Residual bias: expected absolute systematic error
- Other design/analysis-specific checks:
  - SCCS: time trends, pre-exposure outcomes, etc.
  - Prediction: PROBAST criteria



Statistical power:



- Minimum detectable relative risk (MDRR)
- Statistical power = probability of detecting an effect if a true effect exists
  - = 1- Type II error rate
  - Interventional studies: given hypothesized effect size & background incidence, determine sample size needed
  - Non-interventional studies (e.g., OHDSI network studies): sample size already exists, so we ask "given the available data, what effect size would the analysis be able to detect?"
- Usually, more data provide greater power
  - Design and analysis choices impact how much data are used to generate estimates
  - But, is less data definitely better than no data (or no results) at all?
- Rationale: to avoid producing hard-to-interpret, under-powered estimates
  - E.g., RR = 6.7 (0.5, 37.6)



### Statistical power: Minimum detectable relative risk (MDRR) Examples from LEGEND-HTN

Good: T = lisinopril C = hydrochlorothiazide O = cough

All databases have MDRR < 1.75 (ability to detect 75% increased risk if present), and 5 databases have MDRR < 1.1 (ability to detect 10% increased risk)

**Table 1a.** Number of subjects, follow-up time (in years), number of outcome events, and event incidence rate (IR) per 1,000 patient years (PY) in the target (*Lisinopril*) and comparator (*Hydrochlorothiazide*) group after stratification, as well as the minimum detectable relative risk (MDRR). Note that the IR does not account for any stratification.

Source	Target subjects	Comparator subjects	Target years	Comparator years	Target events	Comparator events	Target IR (per 1,000 PY)	Comparator IR (per 1,000 PY)	MDRR
CUMC	3,565	3,387	4,563	5,555	284	288	62.23	51.84	1.26
IMSG	2,980	1,443	2,034	683	96	26	47.19	38.04	1.72
MDCD	45,283	24,993	20,591	9,038	3,249	1,206	157.79	133.42	1.09
MDCR	60,853	28,461	48,503	22,586	4,831	1,514	99.60	67.03	1.08
Optum	364,307	154,543	261,838	100,906	25,947	7,631	99.10	75.62	1.03
CCAE	548,859	243,878	380,386	163,469	30,942	9,419	81.34	57.62	1.03
Panther	583,608	189,242	207,470	66,877	21,366	5,369	102.98	80.28	1.04
Summary	1,609,455	645,947	925,388	369,118	86,715	25,453	93.71	68.96	1.02



### Statistical power: Minimum detectable relative risk (MDRR) Examples from LEGEND-HTN

Bad: T = candesartan C = chlorthalidone O = rhabdomyolysis

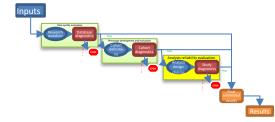
All databases have MDRR > 6 (underpowered to detect 600% increased risk if present), and two databases have MDRR > 15 <5 cases in target and comparator

**Table 1a.** Number of subjects, follow-up time (in years), number of outcome events, and event incidence rate (IR) per 1,000 patient years (PY) in the target (*Candesaran*) and comparator (*Chlorthalidone*) group after stratification, as well as the minimum detectable relative risk (MDRR). Note that the IR does not account for any stratification.

Source	Target subjects	Comparator subjects	Target years	Comparator years	Target events	Comparator events	Target IR (per 1,000 PY)	Comparator IR (per 1,000 PY)	MDRR
Optum	4,510	7,682	3,394	5,037	<5	<5	<1.47	<0.99	>6.27
CCAE	4,897	14,092	4,179	8,519	0	<5	0.00	<0.59	>17.53
Panther	3,148	15,105	877	5,626	0	<5	0.00	<0.89	>27.56



### Statistical power: MDRR in the Anti-VEGF study



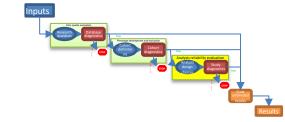
Results ShinyApp: <u>https://data.ohdsi.org/AntiVegfKidneyFailure/#use</u>

Database	Target	Comparator	Outcome	Max SDM	Shared Max SDM	Equipoise	MDRR	EASE
CCAE	aflibercept	ranibizumab	ESRD	0.065	0.135	0.607	2.05	0.054
CCAE	ranibizumab	bevacizumab	ESRD	0.051	0.097	0.834	1.89	0.054
CCAE	aflibercept	bevacizumab	ESRD	0.055	0.113	0.822	1.82	0.067

All analyses have MDRR <= 2.05 (ability to detect 105% increased risk if present). The last two analyses have MDRR <= 1.9 (ability to detect 90% increased risk if present).



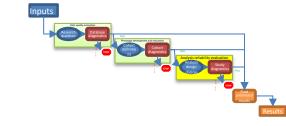
#### Empirical Equipoise: Preference score



- Randomized clinical trials assign treatments to subjects with the same probabilities
  - E.g., 1:1 randomized head-to-head trial: each subject 50%-50% chance to target/comparator group, regardless of patient/provider characteristics
  - Randomization ---> persons assigned to target cohort are exchangeable at baseline with persons assigned to comparator cohort
- Non-interventional studies (OHDSI studies) involve observing treatment choices, which can be influenced by patient or provider characteristics
  - Comparator selection is a pre-analysis design choice
  - **Preference** = probability of patient assigned to target vs. comparator, given baseline features
  - "Preference = 50%" means indifference between treatments for a patient, akin to random assignment
- Similarity between target & comparator: equipoise measured by preference scores
  - what proportion of the target population is close to treatment indifference? (**PS between 0.3 and 0.7**)
  - want this proportion to be large (> 0.5, as suggested by literature)



## **Empirical Equipoise:** Preference score



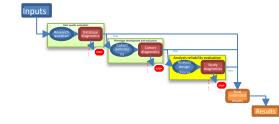
## **Examples from LEGEND-HTN**

Good: Even with >40,000 patients on each drug, large-scale T = valsartan propensity score model could not meaningfully discriminate C = olmesartan between the two treatments; >90% of persons in 'empirical DB = CCAEequipoise' with a preference score between 0.3 and 0.7 Valsartan Olmesar 90.8% is in equipoise 0.00 0.25 0.50 0.75 1.00 Preference score

> Figure 2. Preference score distribution. The preference score is a transformation of the propensity score that adjusts for differences in the sizes of the two treatment groups. A higher overlap indicates subjects in the two groups were more similar in terms of their predicted probability of receiving one treatment over the other.

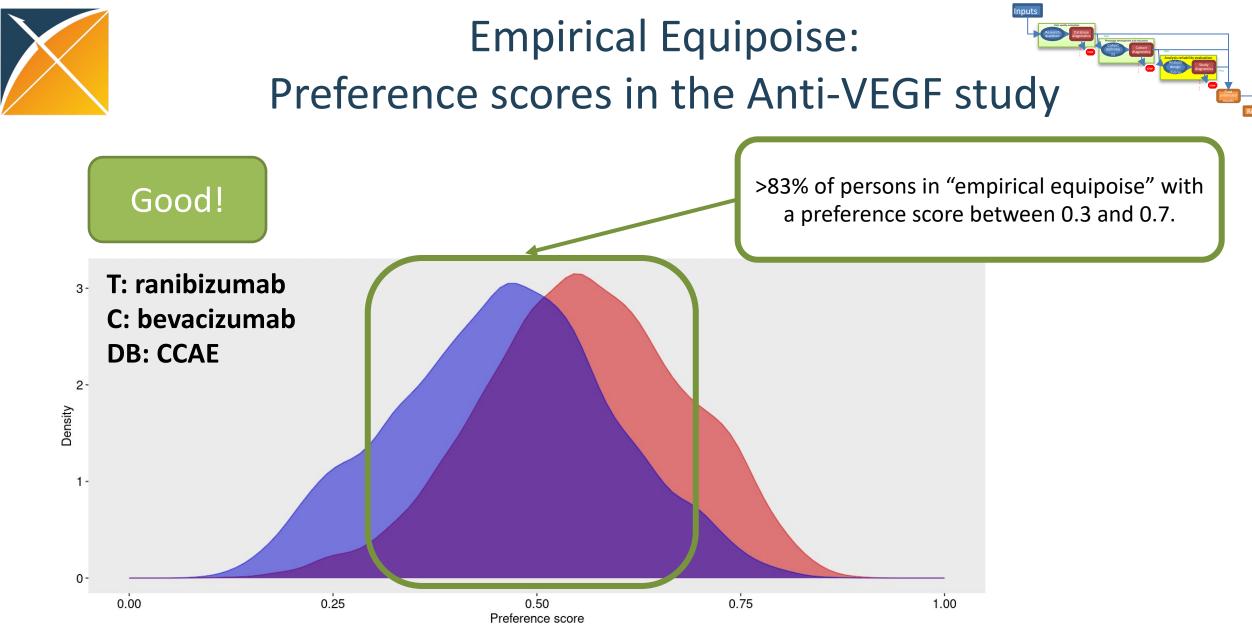


#### Empirical Equipoise: Preference score Examples from LEGEND-HTN



#### Bad: Baseline characteristics can clearly discriminate most new T = valsartan users of valsartan vs. chlorthalidone; <30% of persons in C = chlorthalidone'empirical equipoise' with a preference score between 0.3 DB = CCAEand 0.7 Valsartan Chlorthalidon 27.9% is in equipoise 0.25 1.00 0.00 0.50 0.75 Preference score

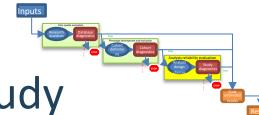
Figure 2. Preference score distribution. The preference score is a transformation of the propensity score that adjusts for differences in the sizes of the two treatment groups. A higher overlap indicates subjects in the two groups were more similar in terms of their predicted probability of receiving one treatment over the other.



**Figure 2.** Preference score distribution. The preference score is a transformation of the propensity score that adjusts for differences in the sizes of the two treatment groups. A higher overlap indicates subjects in the two groups were more similar in terms of their predicted probability of receiving one treatment over the other.



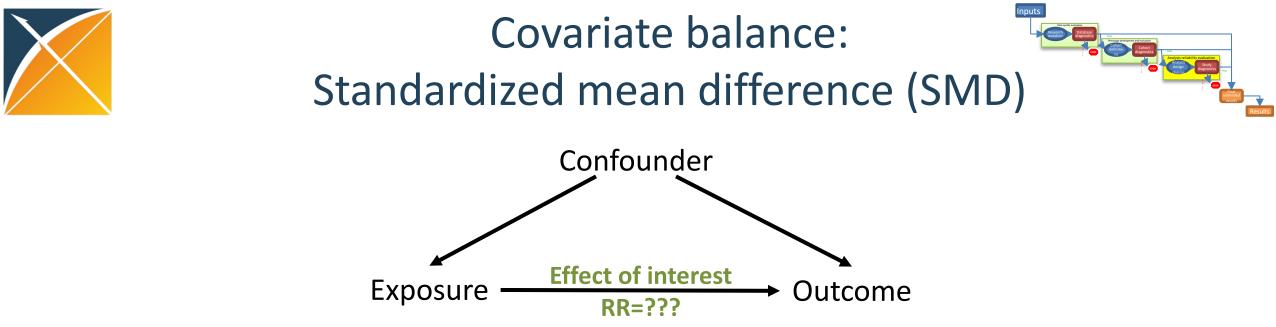
Empirical Equipoise:



Results ShinyApp: <u>https://data.ohdsi.org/AntiVegfKidneyFailure/#use</u>

Database	Target	Comparator	Outcome	Max SDM	Shared Max SDM	Equipoise	MDRR	EASE
CCAE	aflibercept	ranibizumab	ESRD	0.065	0.135	0.607	2.05	0.054
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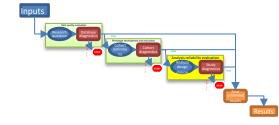
All three TC comparisons have at least 50% persons in "empirical equipoise", which is usually a good sign. The first TC pair has slightly lower proportion of persons in equipoise (we can check out the PS plot).



- Confounding variables can bias effect estimates if not properly addressed
- Various design and analysis choices (restriction, matching, propensity score adjustment) offer strategies to reduce the effect of confounding by balancing confounder prevalence in target and comparator cohort
- **Covariate balance**: are all observed baseline characteristics sufficiently similar between target and comparator cohorts?
  - Measured by standardized mean difference (SMD) on each covariate
  - Usually, we want to see max SMD < 0.1 (rule of thumb)</li>



### Covariate balance: Standardized mean difference Examples from LEGEND-HTN



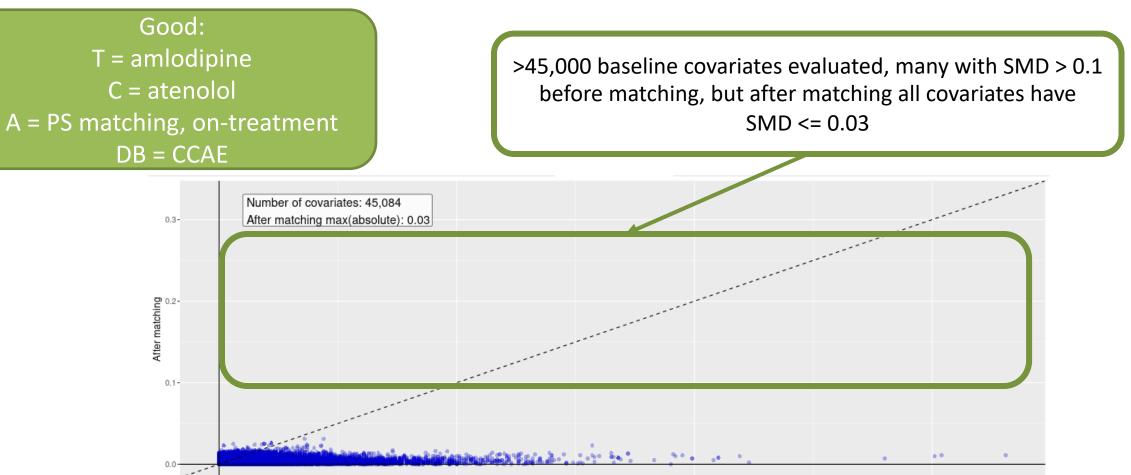


Figure 3. Covariate balance before and after matching. Each dot represents the standardized difference of means for a single covariate before and after matching on the propensity score. Move the mouse arrow over a dot for more details.

Before matching

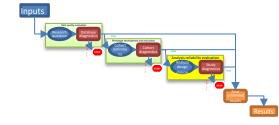
0.2

0.3

0.1



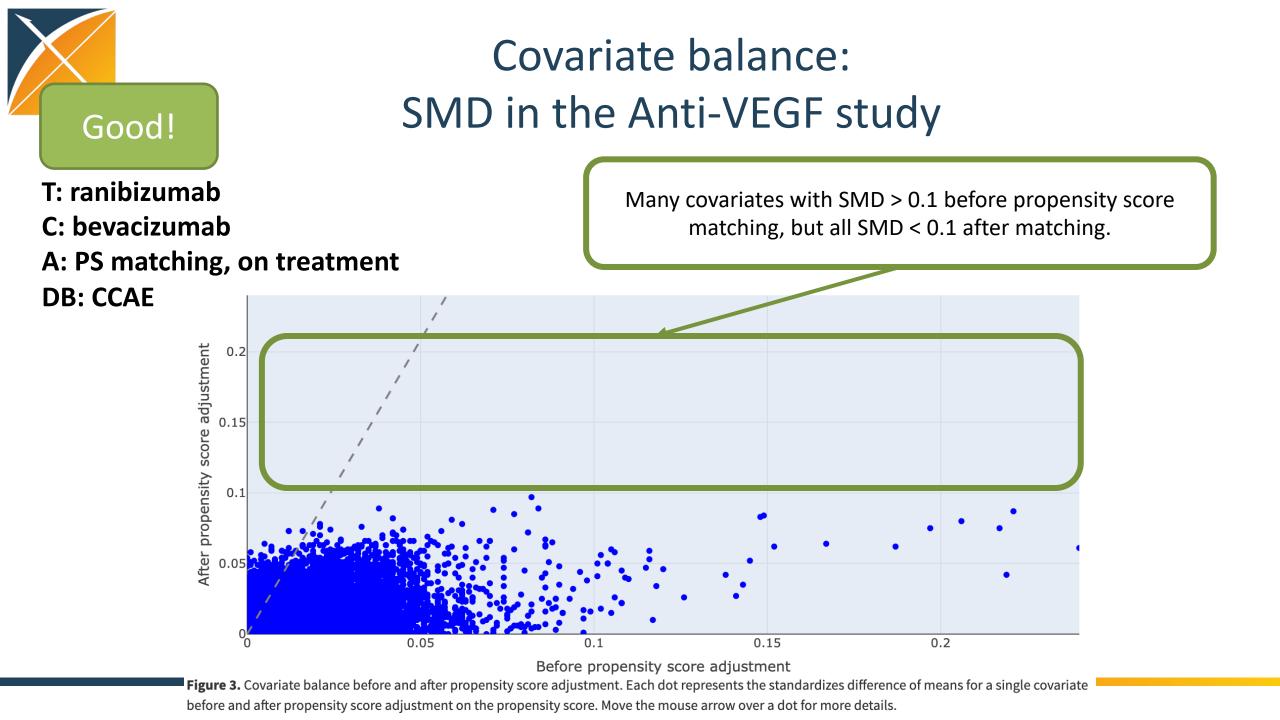
### Covariate balance: Standardized mean difference Examples from LEGEND-HTN



#### Bad: >50,000 baseline covariates evaluated, many with SMD > 0.1 T = candesartan before stratification. After stratification, many covariates C = atenolol have higher SMD than pre-stratification, many covariates A = PS stratification, on-treatment with SMD > 0.1DB = CCAENumber of covariates: 50,427 0.3-After stratification max(absolute): 0.20 After stratification 0.1-0.3 0.1 0.2

Figure 3. Covariate balance before and after stratification. Each dot represents the standardized difference of means for a single covariate before and after stratification on the propensity score. Move the mouse arrow over a dot for more details.

Before stratification





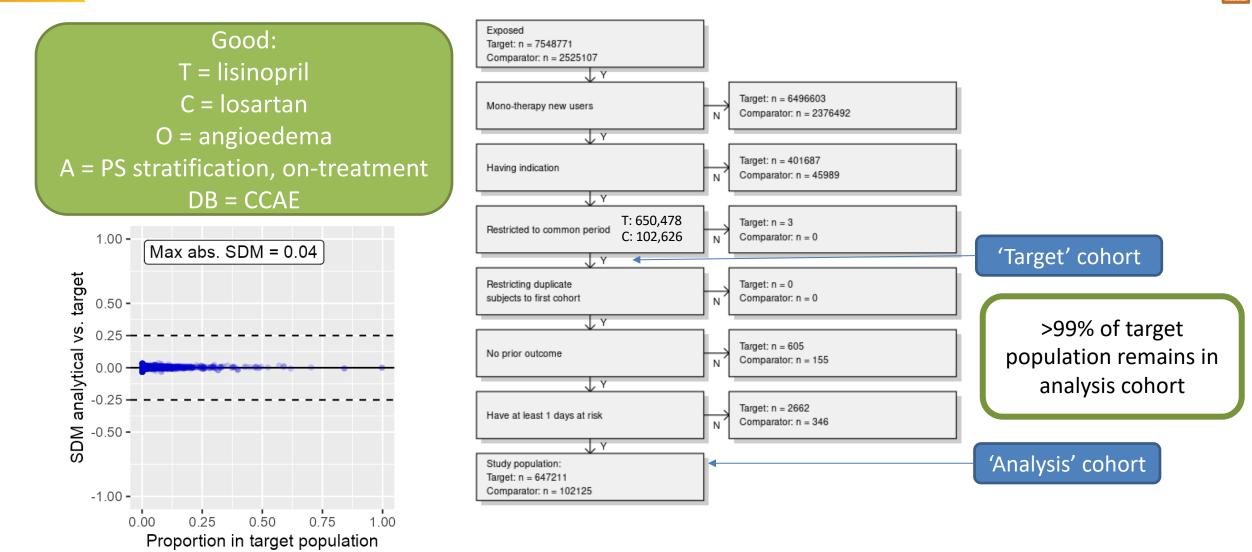
Generalizability:

Attrition fraction & standardized mean difference

- Generalizability: to what extent can a study result be applied to a target population of interest?
- The same design and analytic strategies employed to improve internal validity by reducing confounding can potentially decrease external **validity** by shifting the composition of the analytic cohort away from the original target population
- Similarity between target population and analytic cohort:
  - does a substantial fraction of the initial target cohort remain in the analytic target cohort? (attrition fraction)
  - are all observed baseline characteristics sufficiently similar between the preadjustment target and post-adjustment analytic cohorts? (SMD)

#### Generalizability:

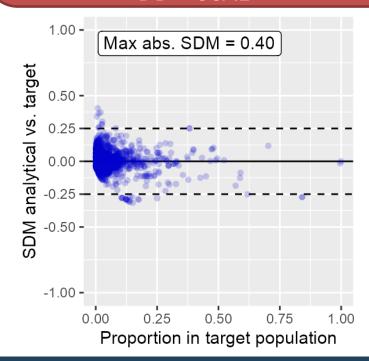
Attrition fraction & standardized mean difference

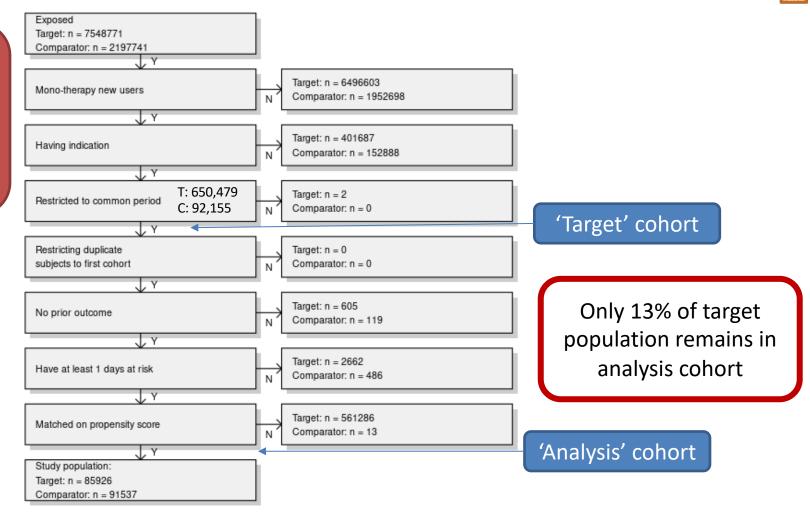


#### Generalizability:

A construction of the second o Attrition fraction & standardized mean difference

Bad: T = lisinopril C = atenololO = angioedema A = PS matching, on-treatment DB = CCAE



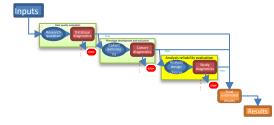


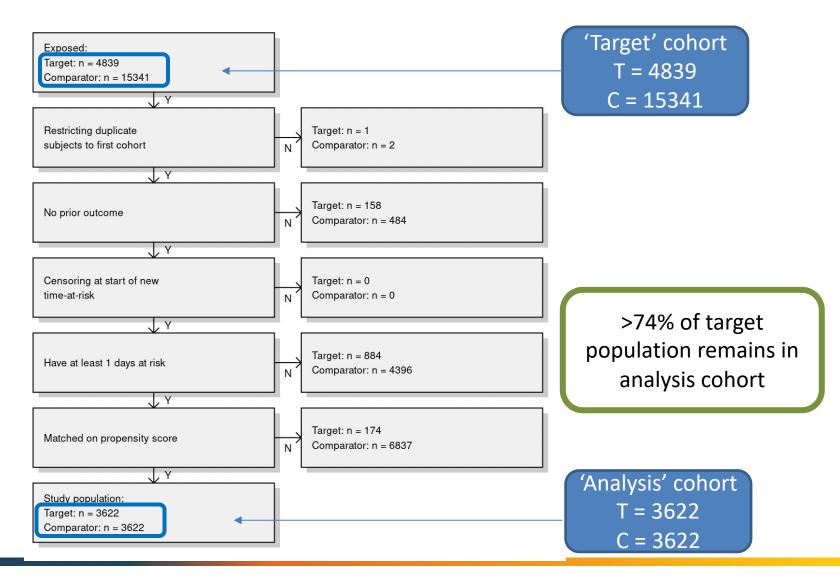


T: ranibizumab C: bevacizumab O: ESRD A: PS matching, on treatment DB: CCAE

# Good!

#### Generalizability: In the Anti-VEGF study







**Residual bias:** 

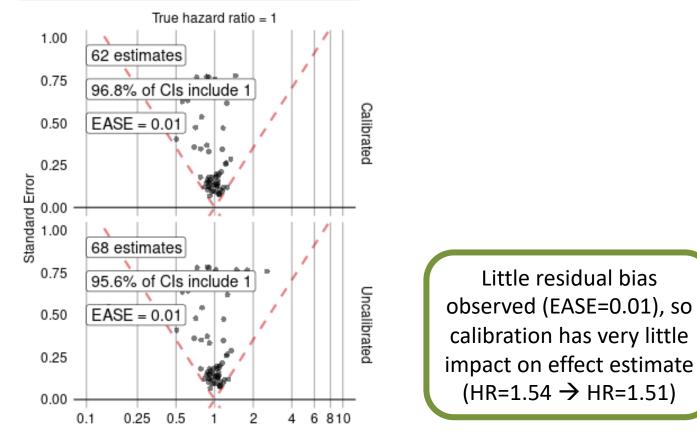
**Expected Absolute Systematic Error (EASE)** 

- Residual systematic error can exist due to model misspecification inherent to analysis or data
- Measure bias by expected absolute systematic error (EASE) - average of abs(log(estimated RR) - log(true RR)) across negative control outcomes
- **Residual bias**: is the estimated residual bias (EASE) small enough to accept that calibrated effect estimates can be trusted as unbiased?
  - we advocate for empirical calibration, but calibrated results are harder to trust if there is huge bias

#### **Residual bias:**

**Expected Absolute Systematic Error (EASE)** 

Good: T = hydrochlorothiazide C = chlorthalidone O = acute myocardial infarction A = PS stratification, on-treatment DB = CCAE

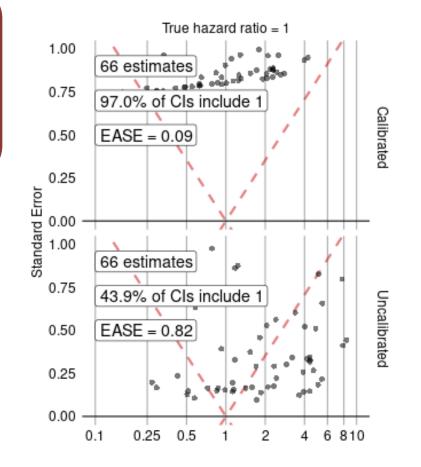


Cal.HR Analysis LB Cal.UB Cal.P Data source HR UB Cal.LB PS stratification, on-treatment CCAE 1.54 0.88 3.00 0.17 1.51 0.82 2.79 0.18 \_\_\_\_

#### **Residual bias:**



Bad: T = furosemide C = labetalol O = acute myocardial infarction A = PS stratification, on-treatment DB = CCAE

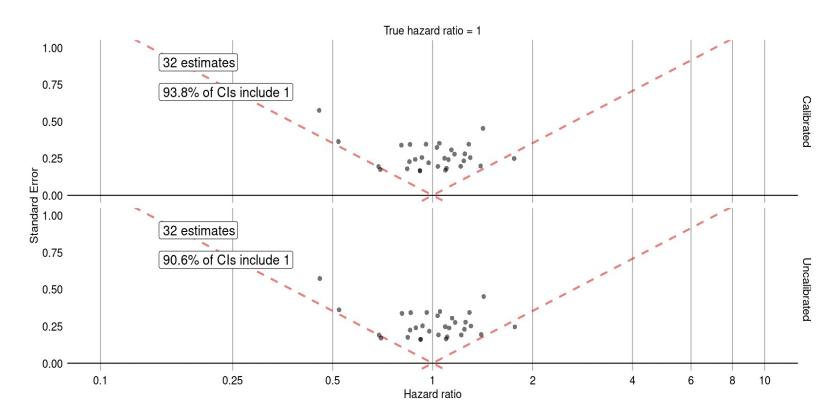


Substantial positive bias and variance observed (EASE=0.82), so calibration has substantial impact on effect estimate (HR=5.55, p<0.01 → HR=2.86, p<0.20)

Analysis	Data source	♦ HR	<b>≜ LB</b>		<b>♦ ₽</b>	Cal.HR	🔶 Cal.LB	🔶 Cal.UB	🔷 Cal.P	\$
PS stratification, on-treatment	CCAE	5.55	3.50	9.25	0.00	2.86	0.59	17.78	0.20	



### Residual bias: EASE in the Anti-VEGF study



T: ranibizumab C: bevacizumab O: ESRD A: PS matching, on treatment DB: CCAE

Little residual bias observed (EASE=0.054). Calibration has little impact on effect estimate (HR=0.79 unchanged).

Good!





Remarks: diagnostics thresholds are rules of thumb We can pre-specify thresholds given empirical objectives

Diagnostics metric	Literature- derived	Strategus interface	Data-driven (LEGEND-HTN)
Statistical power (MDRR)	< 10	< Inf; < 10 (SCCS)	-
Equipoise	> 0.50	> 0.20	> 0.50
Covariate balance (SDM)	< 0.10	< 0.10	< 0.50
Generalizability (attrition)	-	<= 1	-
Systematic error (EASE)	< 0.25	< 0.25	-
Interpretability: MDRR Internal validity: equipoise, SDM , EAS External validity: attrition (or SDM)	Ε	thresholds	ed to pre-specify and run diagnostics e seeing results!



### Let's see the Strategus user interface

(Already seen pieces of cohort diagnostics)



#### Strategus standard user interface

OHDSI Analysis Viewer	× +	∨ – Ø ×
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OHDSI Analysis	≡	
i About () CohortGenerator ()	i About OHDSI Viewer	
🗳 CohortDiagnostics 👔	OHDSI Analysis Viewer	Population-level effect estimation
Characterization     (1)	Table of contents	The OHDSI community have developed several packages that enable users with data in the OMOP common data model to perform causal inference studies.
Prediction 🕕	1. Introduction 2. How to use the viewer	CohortMethod     SelfControlledCaseSeries
Estimation (1)	3. Analysis types 1. Characterization	SelfControlledCohort
iii sccs 🕕	2. Population-level effect estimation 3. Patient-level prediction	Patient-level prediction The OHDSI community have developed several packages that enable users with data in the OMOP common data model to develop and validate patient-level prediction models.
	Introduction	PatientLevelPrediction     EnsemblePatientLevelPrediction
	This is an interactive shiny app for exploring standardized outputs for OHDSI analyses including:	DeepPatientLevelPrediction
	<ul> <li>characterization (descriptive studies)</li> <li>population-level effect estimation(causal inference)</li> <li>patient-level prediction (inference)</li> </ul>	
	Full details of all the analysis tools can be found on the HADES website	
	How to use the viewer	
	Please use the left hand menu to select the type of analysis to explore (click on a button). This show the results that	can be interactively explored.
	Analysis types	
	Characterization	
	The OHDSI community have developed a suite of tools for conducting characterization studies including:	
	<ul> <li>incidence rate calculation</li> <li>baseline characterization</li> <li>treatment pathways</li> </ul>	
	and more	

#### Population-level effect estimation

The OHDSI community have developed several nackages that enable users with data in the OMOP common data model to perform causal inference studies



	OHDSI Analysis
i	About
	CohortGenerator
2	CohortDiagnostics
⊞	Characterization
₩.	Prediction
	Estimation
iH	SCCS

Cohort Level Diagnostics	
Select Report	
Cohort Counts	•
Patabase(s)	
IBM Health MarketScan® Commercial Claims and Encounters Database	•
Cohorts	
C1782164: [SOS] End-stage renal disease, C1782480: [SOS Phenotype Devt] persons with blinding diseases, C1782481: [SOS Phenotype Devt] ranibizumab exposures after new use with 3	exposures in 21-70d windows, C1782482: [SOS Phenotype Devt] bevacizumab expc 🔻
Cohort Counts	+
C1782164: [SOS] End-stage renal disease	
C1782480: [SOS Phenotype Devt] persons with blinding diseases	
C1782481: [SOS Phenotype Devt] ranibizumab exposures after new use with 3 exposures in 21-70d windows	
C1782482: [SOS Phenotype Devt] bevacizumab exposures after new use with 3 exposures in 21-70d windows	
C1782483: [SOS Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d windows	

**OHDSI** 

#### Display

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● Both ○ Persons ○ Records

				Search
			IBM Health MarketScan	<sup>®</sup> Commercial Claims and Encounters D
	Cohort Id	Cohort Name	Persons	Records
0	1782164	[SOS] End-stage renal disease	249,258	249,258
$\bigcirc$	1782480	[SOS Phenotype Devt] persons with blinding diseases	1,294,165	1,294,165
$\bigcirc$	1782481	[SOS Phenotype Devt] ranibizumab exposures after new use with 3 exposures in 21-70d windows	4,846	6,022
$\bigcirc$	1782482	[SOS Phenotype Devt] bevacizumab exposures after new use with 3 exposures in 21-70d windows	15,440	19,874
$\bigcirc$	1782483	[SOS Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d windows	4,115	5,192

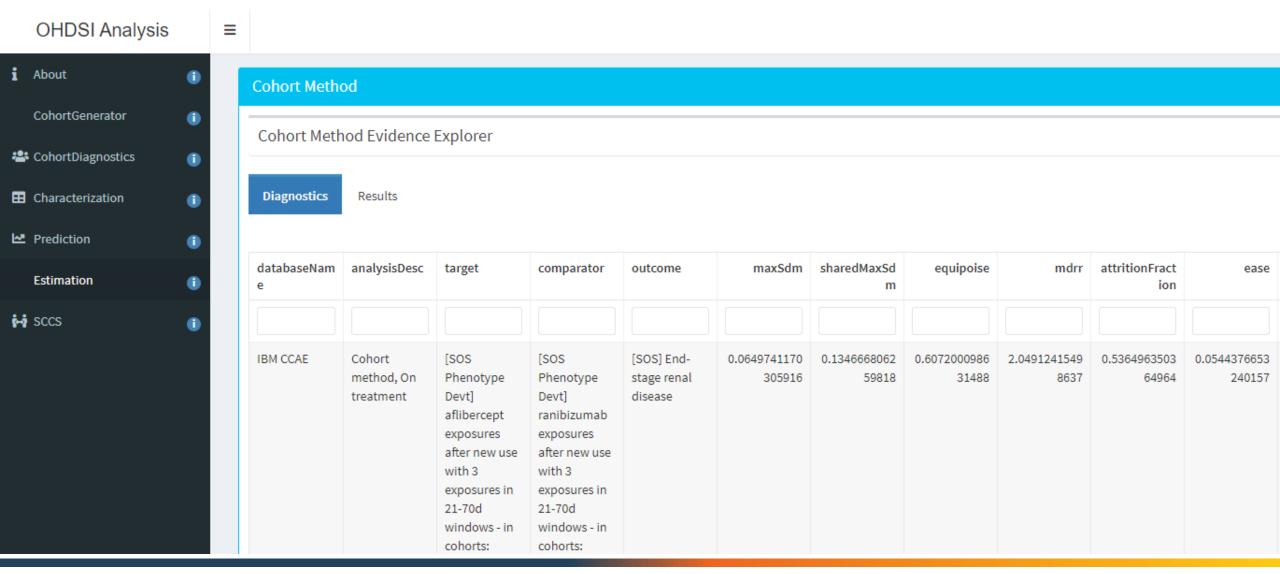


### Characterization: Time-to-event

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	👥 Characterizatio	on Viewer																				
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	Time-to-events																					+
	Options																					-
	Target id:									Outco	me id:											
	[SOS Phenotype	e Devt] aflibercept ex	posures after new	use with 3 e	exposures in 2	21-70d wir	ndows		•	[SO	S] End-stag	ge renal dise	ease								-	•
	Generate Report																					
	Selected: Target: [SOS Phenoty	ype Devt] aflibercept	t exposures after n	ew use with	1 3 exposures	s in 21-70d	windows			Outco	<b>me:</b> [SOS]	End-stage r	renal dis	ease								
	🌣 Results																					
	Databases:										per 1-day											
	IBM CCAE		3								IBM CCAE											
	Timespan:		2				_	_										1.				
			0	100			50									50				100		
				100			-00				per 30-day									100		
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			20								_						_					
		Characterization	Characterization Viewer Target Viewer Outcome Stratified Time-to-events Options Target id: [SOS Phenotype Devt] aflibercept ex Generate Report Selected: Target: [SOS Phenotype Devt] aflibercept Results Databases: IBM CCAE Timespan: Per 30-day per 30-day per 365-day	Target Viewer Outcome Stratified Incidence Rate   Time-to-events   Options   Target id:   [SOS Phenotype Devt] aflibercept exposures after new   Generate Report   Selected:   Target: [SOS Phenotype Devt] aflibercept exposures after new   © Results   Databases:   © IBM CCAE   Timespan:   © per 30-day   © per 365-day   © per 1-day	Characterization Viewer  Target Viewer Outcome Stratified Incidence Rate Time  Time-to-events  Options  Target id: [SOS Phenotype Devt] aflibercept exposures after new use with a d Generate Report  Selected: Target: [SOS Phenotype Devt] aflibercept exposures after new use with  Results Databases: Immespan: Per 30-day Per 365-day Per 1-day	Characterization Viewer  Target Viewer Outcome Stratified Incidence Rate Time To Event  Time-to-events  Options Target id:  SOS Phenotype Devt] aflibercept exposures after new use with 3 exposures in Generate Report  Selected: Target: [SOS Phenotype Devt] aflibercept exposures after new use with 3 exposures  Results Databases: BitaM CCAE Timespan: Pi per 306-day Pi per 365-day Pi per 1-day  Outcome Stratified  Time To Event  Outcome Stratified  Time To Event  Outcome Stratified  Time To Event  Time To Event  Time To Event  Databases: Pi BM CCAE  Timespan: Pi per 365-day Pi per 1-day  Outcome Stratified  Outcome Stratified  Time To Event  Databases: Pi BM CCAE  Timespan: Pi Per 30-day Pi per 365-day Pi Per 1-day  Database: Pi Per 1-day  Databases: Pi Per 1	E Characterization Viewer     Target Viewer   Outcome Stratified   Incidence Rate   Time To Event   Dechalle   Time-to-events   Options   Target id:   [SOS Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d wire   Generate Report   Selected:   Target:   [SOS Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d wire   Selected:   Target:   [SoB Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d   Patabases:   IBM CCAE   Timespan:   Per 30-day   Per 30-day   Per 1-day	Characterization Viewer  Target Viewer Outcome Stratified Incidence Rate Time To Event Dechallenge Rechalle Time-to-events  Options Target id: [SOS Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d windows  Generate Report Selected: Target: [SOS Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d windows  Results Databases: I IBM CCAE Timespan: Per 30-day Per 305-day Per 1-day  Outcome Stratified Databases: Databases: Detabases: Detab	Characterization Viewer     Target Viewer     Outcome Stratified     Inne-to-events        Options     Target ii:     [SoS Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d windows     Cenerate 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Paraget:   Sos Phenotype Devt] affibercept exposures after new use with 3 exposures in 21-70d windows   Timespan: Image Provide Comparison   Image Provide Comparison   Image Provide Comparison   Image Provide Comparison   Timespan: Image Provide Comparison	E: Characterization Viewer     Target Viewer   Outcome Stratified   Incidence Rate   Time-to-events   Options   Target I:   SDS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows   Outco   Selected:   Target [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows   Outco   Selected:   Target [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows   Outco   Image: Particity Partity Particity Particity Particity Particity Particity Pa	El Characterization Viewer     Target Viewer   Outcome Stratified   Inne-to-events     Options   Target Id:   [Sos Phenotype Devt] affibercept exposures after new use with 3 exposures in 21-70d windows     Selected:   Target Sos Phenotype Devt] affibercept exposures after new use with 3 exposures in 21-70d windows     Outcome I (Sos)     Selected:   Target Sos Phenotype Devt] affibercept exposures after new use with 3 exposures in 21-70d windows   Outcome: [Sos]   Per alorgan:   Image: Ima	E Characterization Viewer  Target Viewer Outcome Stratified Incidence Rate Time To Event Dechallenge Rechallenge Time-to-events  Options  Target id: Dottoms Cenerate Report  Selected: Target: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cenerate Report  Selected: Target: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cutcome: [SOS] End-stage renal disc  Parget: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cutcome: [SOS] End-stage renal disc  Parget: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cutcome: [SOS] End-stage  Parget: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cutcome: [SOS] End-stage  Parget: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cutcome: [SOS] End-stage  Parget: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cutcome: [SOS] End-stage  Parget: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cutcome: [SOS] End-stage  Parget: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cutcome: [SOS] End-stage  Parget: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cutcome: [SOS] End-stage  Parget: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cutcome: [SOS] End-stage  Parget: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cutcome: [SOS] End-stage  Parget: [SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Cutcome: [SOS] End-stage  Parget: [SOS Phenotype Devt] allibercept exposure exposures after new use with 3 exposure in 21-70d windows Cutcome: [SOS] End-stage  Parget: [SOS Phenotype Devt] allibercept exposure exposure exposure	E3 Characterization Viewer     Target Viewer   Outcome Stratified   Ince To Event   Characterization Viewer   Time-to-events   Options   Target Id:   Isols Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21:70d windows   Outcome: [SOS] End-stage renal disease   Selected:   Target IS   Perso-day   Imegan:   I per 30-day   I per 30-day   I per 30-day   I per 30-day   Outcome: [SOS] End-stage renal disease   Imegan:   I per 30-day   I per 30-day   I per 30-day   I per 30-day   Outcome: [SOS] End-stage renal disease   Imegan:   I per 30-day   I per 30-day   I per 30-day   Outcome: [SOS] End-stage renal disease   Imegan:   I per 30-day   I per 30-day   I per 30-day   I per 30-day <pi 30-day<="" p="" per=""> I per 30-day I per 30-</pi>	E Characterization Viewer   Target Viewer Outcome Stratified Incidence Rate Time to Event   Diffuse   Target Id: Outcome Id:   [SOS Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d windows Outcome Id:   Selected:   Target IS:   Selected:   Target IS:   Parget IS:   Devtlatiblercept exposures after new use with 3 exposures in 21-70d windows   Outcome I: [SOS] End-stage renal disease   Prime: SoS Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d windows   Outcome: [SOS] End-stage renal disease   Prime: SoS Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d windows   Outcome: [SOS] End-stage renal disease   Prime: SoS Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d windows   Outcome: [SOS] End-stage renal disease   Outcome: [SOS] End-stage renal disease   Prime: Distribution: Distribution	Characterization Viewer  Target Viewer Outcome Stratified Incidence Rate Inter to Exercite  Coptions  Target Id:  Dots Devel affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Selected:  Target (SDS Phenotype Devel) affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Selected:  Parget SDS Phenotype Devel) affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Parget SDS Phenotype Devel) affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Parget SDS Phenotype Devel) affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Parget SDS Phenotype Devel) affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Parget SDS Phenotype Devel) affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Parget SDS Phenotype Devel) affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Parget SDS Phenotype Devel) affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Parget SDS Phenotype Devel) affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Parget SDS Phenotype Devel) affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Parget SDS Phenotype Devel) affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Parget SDS Phenotype Devel) affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Parget SDS Phenotype Devel affibercept exposures after new use with 3 exposures in 21-70d windows Cererate Report  Parget SDS Phenotype Devel affibercept exposures after new use with 3 exposures after	Chracterization Viewer  Target Viewer Outcome Stratified Indience Rate Time to Even Dechallenge Rechallenge Time-to-events  Options Target I: Options Target I: Options Target I: Options Selected: Target (SOS Phenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows Outcome (SOS) End-stage renal disease  Results Databases: Per 3 ob ay	Characterization Viewer  Target Viewer Outcome Stratifie Incidence Rate Incidence Incidenc	Chraceterization Viewer   Target Viewer Outcome Stattlifed   Target Viewer Outcome Rate   Time-to-events   Options   Target All   Dot Sphenotype Devt] allibercept exposures after new use with 3 exposures in 21-70d windows   Generate Report   Selected:   Target Sis   Outcome (5OS) End-stage renal disease   The state of the state of the stage renal disease   Selected:   Target Sis   Outcome (SOS) End-stage renal disease   The state of the state of the stage renal disease   Selected:   Target Sis Allow   Outcome (SOS) End-stage renal disease   The state of the state renal disease   Selected:   Target Sis Allow   Outcome (SOS) End-stage renal disease   The state of the state renal disease   Selected:   Target Sis Allow   Outcome (SOS) End-stage renal disease   The state of the state renal disease   Selected:   Target Sis Allow   Outcome (SOS) End-stage renal disease   The state of the s	Characterization Viewer  Target Viewer  Outcome Statisfied  Indexese Rate  Time-to-events  Options  Target Ail  Second State  Consende Report  Second State  Second State State  Second State  Second State State Sec	Claractorization Viewer  Taget Viewer  Dutcome Strattlind  inclence Rate  Time-to-events  Diptions  Taget Report  Selected:  Selected: Selecte	



#### Estimation: Cohort method diagnostics





# Estimation: Cohort method diagnostics pass/fail based on a priori decision thresholds

target	comparator	outcome	maxSdm	sharedMaxSd m	equipoise	mdrr	attritionFract ion	ease	balanceDiagn ostic	sharedBalar eDiagnostic	equipoiseDia gnostic	mdrrDiagnos tic	attritionDiag nostic	easeDiagnost ic	unblind
[SOS Phenotype Devt] aflibercept	[SOS Phenotype Devt] ranibizumab	[SOS] End- stage renal disease	0.0649741170 305916	0.1346668062 59818	0.6072000986 31488	2.0491241549 8637	0.5364963503 64964	0.0544376653 240157	PASS	FAIL	PASS	PASS	PASS	PASS	1
exposures after new use with 3 exposures in 21-70d windows - in cohorts:	exposures after new use with 3 exposures in 21-70d windows - in cohorts:		<0.1	NA	>0.2	NA	<1	<0.25			haredResource oduleSpecifi { { {		[		
										8	"version": "remoteRep "remoteUse "settings" "cmAnaly "target0 "refitPs "refitPs "cmDiagn "mdrr1 "ease1 "sdmTh "equip "attri	oo": "gith ername": " ysisList": Comparator sForEveryO sForEveryS nosticThre Threshold" hreshold": poiseThres itionFract	ub.com", ohdsi", <u>[</u> OutcomesLi utcome": f tudyPopula sholds": { : "Inf", : 0.25, 0.1, hold": 0.2 ionThresho	st": [ false, ation": fals	



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#### Estimation: Cohort method diagnostic drilldown: Minimum Detectable Relative Risk (MDRR)

OHDSI Analysis	≡																
About 🕕		Cohort Method															
CohortGenerator () CohortDiagnostics ()		Cohort Method Evidence Explorer												+			
Characterization (1)		Diagnostics Results										-			- Lup		
Prediction ()		[SOS Phenotype Devt] aflibercept exposures after new use	A	nalysis	Dat	ta source	HR		LB		UB	P	Cal.HR	Cal.LB	Cal.UB	Cal.P	_
Estimation (1)		with 3 exposures in 21-70d windows - in cohorts: (1782480)															
sccs ()		starts within D: -99999 - D: 0 of cohort start and ends D: -99999 - D: 99999 of cohort start, first ever occurence with at least 365 days prior observation and 1 days follow up	<u> </u>	ohort metho n treatment	1	I CCAE	1.23	3	0.74		2.09	0.43	1.27	0.75	2.13	0.38	
		observation, males, females aged 18+	Power	Attritio	n Po	pulation ch	aracterist	ics P	ropensity m	odel	Propensity scores	Covariate balance	e Systematic e	rror Kapl	an-Meier		
		Comparator Table 1a. Number of subjects, follow-up time (in years), number of outcome events, and event incidence rate (IR) per 1,000 patient years (PY) in the target (1782483001) and comparator (17824 after propensity score adjustment, as well as the minimum detectable relative risk (MDRR). Note that the IR does not account for any stratification.											tor (17824810	DI P			
		[SOS Phenotype Devt] ranibizumab exposures after new use	Target su	· ·	-	nt, as well a tor subject		imum det get years		ator years		Comparator even	-		Comparator IR (pe	r 1,000 PY)	MDRR
		with 3 exposures in 21-70d windows - in cohorts: (1782480) starts within D: -99999 - D: 0 of cohort start and ends D: -99999 - D: 99999 of cohort start, first ever occurence with <b>a</b> t	1,905		1,905		1,89	2	1,535		37	24	19.55		15.63		2.05
		least 365 days prior observation and 1 days follow up observation, males, females aged 18+	Table 1b. Time (days) at risk distribution expressed as minimum (min), 25th percentile (P25), median, 75th percentile (P75), and maximum (max) in the target (1782483001) and comparator (1782481001) cohort after propensity score adjustment.         Schort       P25       P25       P25       P25       P25       P25       P25														
			Cohort	Min	<b>P10</b>		Median		P90 Max								
		Outcome	Target	2			220										
		[SOS] End-stage renal disease 🔹	Compara	lor 2	37	79 1	177	558	598 2,82	18							

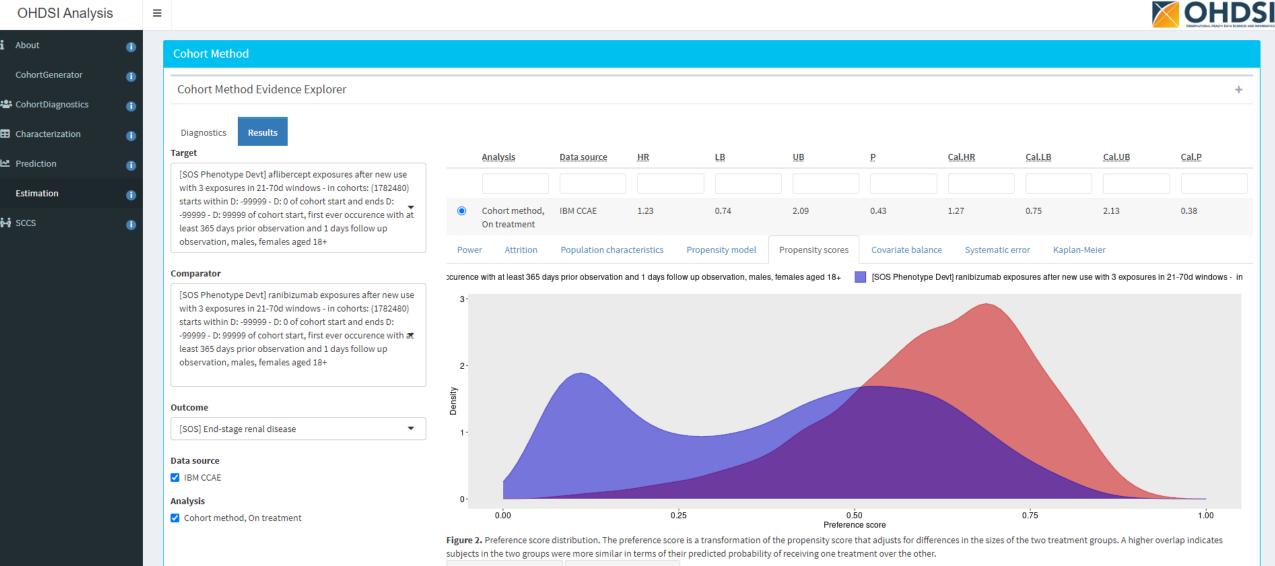


#### Estimation: Cohort method diagnostic drilldown: Attrition Fraction

OHDSI Analysis	≡											
i About (i) CohortGenerator (i)		Cohort Method										
CohortDiagnostics		Cohort Method Evidence Explorer										+
Characterization		Diagnostics Results										
Prediction 👔		Target [SOS Phenotype Devt] aflibercept exposures after new use	Analysis	Data source	HR	LB	UB	P	Cal.HR	Cal.LB	Cal.UB	Cal.P
Estimation (1)		with 3 exposures in 21-70d windows - in cohorts: (1782480) starts within D: -99999 - D: 0 of cohort start and ends D:										
👬 sccs 🕕		-99999 - D: 999999 of cohort start, first ever occurence with at least 365 days prior observation and 1 days follow up	<ul> <li>Cohort method,</li> <li>On treatment</li> </ul>	IBM CCAE	1.23	0.74	2.09	0.43	1.27	0.75	2.13	0.38
		observation, males, females aged 18+	Power Attrition	Population char	acteristics	Propensity model	Propensity sco	res Covariate	balance System	natic error Kap	an-Meier	
		Comparator										
		[SOS Phenotype Devt] ranibizumab exposures after new use with 3 exposures in 21-70d windows - in cohorts: (1782480) starts within D: -99999 - D: 0 of cohort start and ends D: -99999 - D: 99999 of cohort start, first ever occurence with st least 365 days prior observation and 1 days follow up observation, males, females aged 18+	Restricting duplicate subjects to first cohort	, Y		arget: n = 1 omparator: n = 1						
		Outcome [SOS] End-stage renal disease	No prior outcome			arget: n = 131 omparator: n = 151						
		Data source	Censoring at start of ne time-at-risk	y Y		arget: n = 0 omparator: n = 0						
		Analysis ✓ Cohort method, On treatment	Have at least 1 days at	risk		arget: n = 665 omparator: n = 707						
			Matched on propensity	score		arget: n = 1408 omparator: n = 1237						
ttos://data.obdsi.org/Antii/egfKidnevEail		2277.0	Study population: Target: n = 1905 Comparator: n = 1905	, γ								



### Estimation: Cohort method diagnostic drilldown: Equipoise



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## Estimation: Cohort method diagnostic drilldown: Covariate balance maxSDM

Analysis	=											
٥		Cohort Method										
ator 👔												
stics 👔		Cohort Method Evidence Explorer										
on 👔		Diagnostics Results										
		Target	Analysis	Data source	HR	LB	UB	B	Cal.HR	Cal.LB	Cal.UB	Cal.P
·		[SOS Phenotype Devt] aflibercept exposures after new use with 3 exposures in 21-70d windows - in cohorts: (1782480)										
•		starts within D: -99999 - D: 0 of cohort start and ends D: -99999 - D: 99999 of cohort start, first ever occurence with at least 365 days prior observation and 1 days follow up	Cohort me On treatme		1.23	0.74	2.09	0.43	1.27	0.75	2.13	0.38
		observation, males, females aged 18+	Power Attri	on Population cl	naracteristics	Propensity model	Propensity score	s Covariate	balance System	atic error Kapl	an-Meier	
		Comparator										
		[SOS Phenotype Devt] ranibizumab exposures after new use with 3 exposures in 21-70d windows - in cohorts: (1782480) starts within D: -99999 - D: 0 of cohort start and ends D:	e 0.4					-				
		-99999 - D: 99999 of cohort start, first ever occurence with <b>a</b> t least 365 days prior observation and 1 days follow up observation, males, females aged 18+	0.4 0.3 0.3				-					
		Outcome									_	
		[SOS] End-stage renal disease	0.2									
		Data source			÷. •					· · ·	• • •	
		IBM CCAE	<		يد الله الحو		Se para	• •	••	•		
		Analysis	0	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45
		Cohort method, On treatment	-				Before propen	sity score adju	istment			
			-	balance before and aft . Move the mouse arro			lot represents the sta	ndardizes differe	nce of means for a si	ngle covariate before	e and after propens	ity score adjustr
			Lownload	. Move the mouse and		ore details.						



**OHDSI Analysis** 

# Estimation: Cohort method diagnostic drilldown: Expected Average Systematic Error (EASE)

**OHDSI** 

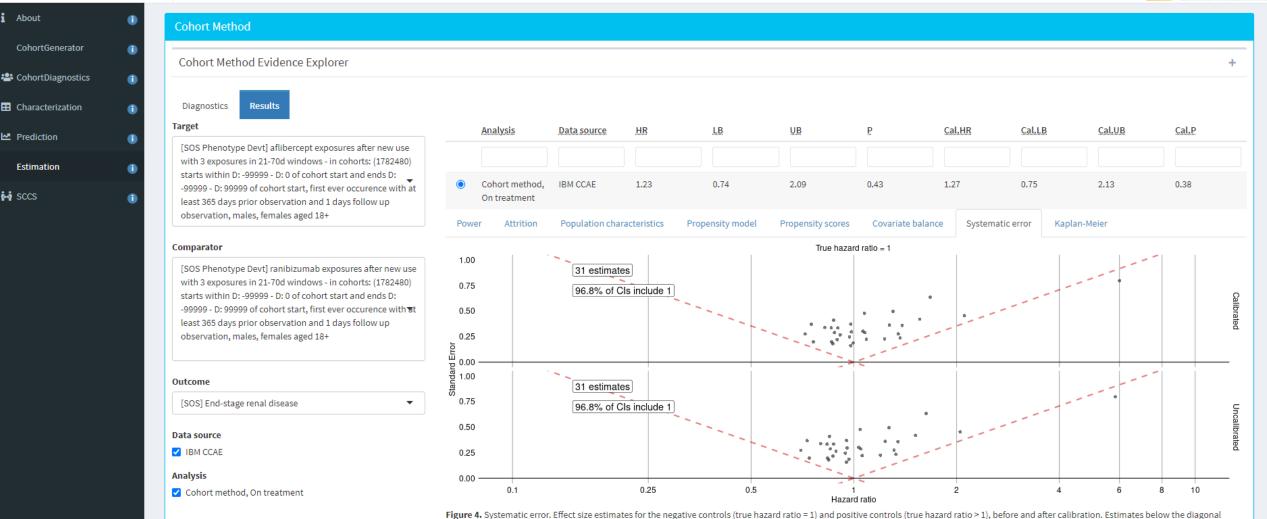


Figure 4. Systematic error. Effect size estimates for the negative controls (true hazard ratio = 1) and positive controls (true hazard ratio > 1), before and after calibration. Estimates below the diagonal dashed lines are statistically significant (alpha = 0.05) different from the true effect size. A well-calibrated estimator should have the true effect size within the 95 percent confidence interval 95 percent of times.

🛓 Download plot as PNG 🛛 🛓 Download plot as PDF



**OHDSI Analysis** 

i About

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🖽 Chara

🗠 Predi

🙀 sccs

Estim

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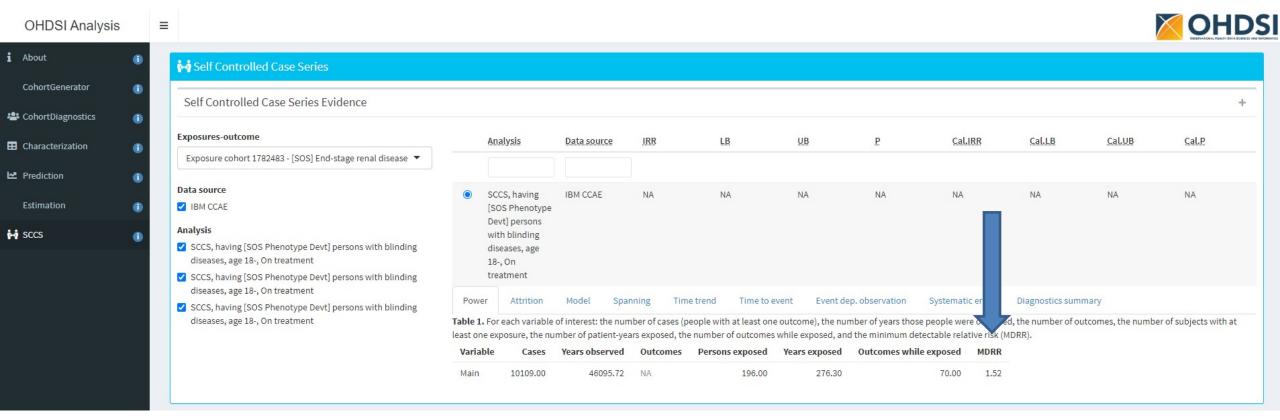
# Estimation: Self-controlled case series (SCCS) pass/fail based on a priori decision thresholds

**OHDSI** 

Self Controlled Case Series				
Self Controlled Case Series Evidence				
Exposures-outcome	Analysis Data source	IRR	F	
Exposure cohort 1782483 - [SOS] End-stage renal disease			Ľ.	"sharedResources": [ "moduleSpecifications": [
Data source	<ul> <li>SCCS, having IBM CCAE</li> </ul>	NA	Ē	{
IBM CCAE	[SOS Phenotype Devt] persons		¢.	{
Analysis     Acceleration Deutlearners with blind	with blinding		Ē	
<ul> <li>SCCS, having [SOS Phenotype Devt] persons with blindi diseases, age 18-, On treatment</li> </ul>	diseases, age 18-, On			{
SCCS, having [SOS Phenotype Devt] persons with blindi diseases, age 18-, On treatment	treatment		Ę	{
SCCS, having [SOS Phenotype Devt] persons with blindi		ning T	'ime tren	<pre>"module": "SelfControlledCaseSeriesModule", "version": "0.1.3",</pre>
	hold Diagnostic	Value	Status	"remoteRepo": "github.com",
	Minimum detectable relative risk (MDRR)	1.52	PASS	"remoteUsername": "ohdsi",
	.05 Time trend P	0.00	FAIL	"settings": {
	Pre-exposure gain P	0.74	PASS	"sccsAnalysisList": [
	.25 Expected absolute systematic error (EASE)	0.05	PASS	"exposuresOutcomeList": [
			-	<pre>"analysesToExclude": {     "combineDataFetchAcrossOutcomes": false,</pre>
			Ē	"sccsDiagnosticThresholds": {
				"mdrrThreshold": 10,
				"easeThreshold": 0.25,
				"timeTrendPThreshold": 0.05,
				"preExposurePThreshold": 0.05,
				"attr_class": "SccsDiagnosticThresholds"
				J

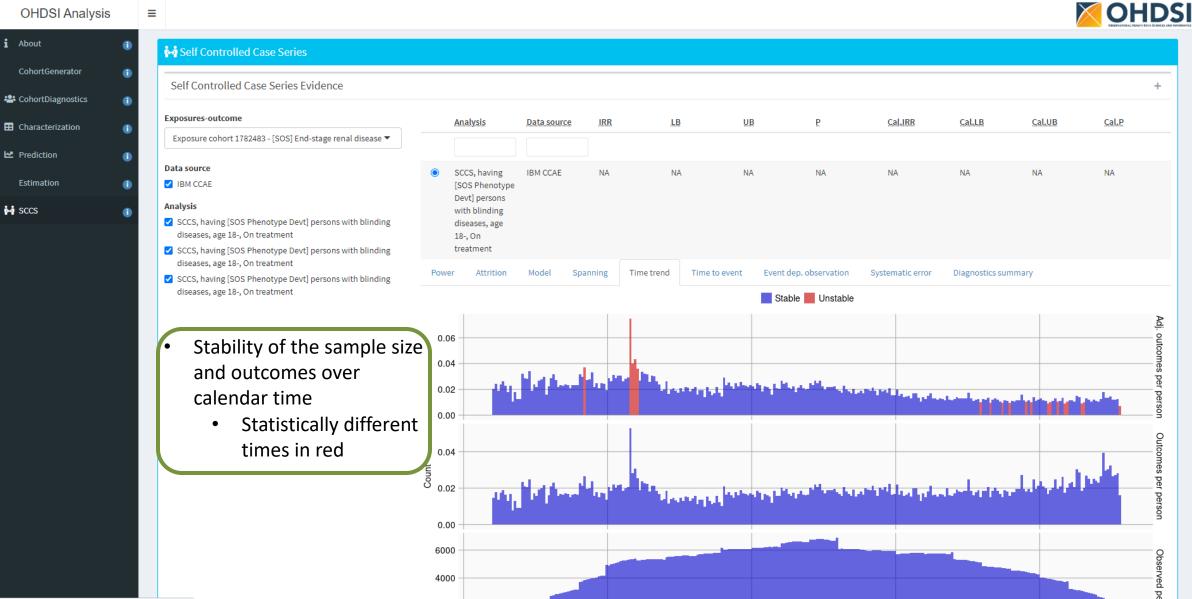


# Estimation: SCCS diagnostic drilldown: Minimum detectable relative risk (MDRR)





### Estimation: SCCS diagnostic drilldown: Time trend





### Estimation: SCCS diagnostic drilldown: Bad time trend

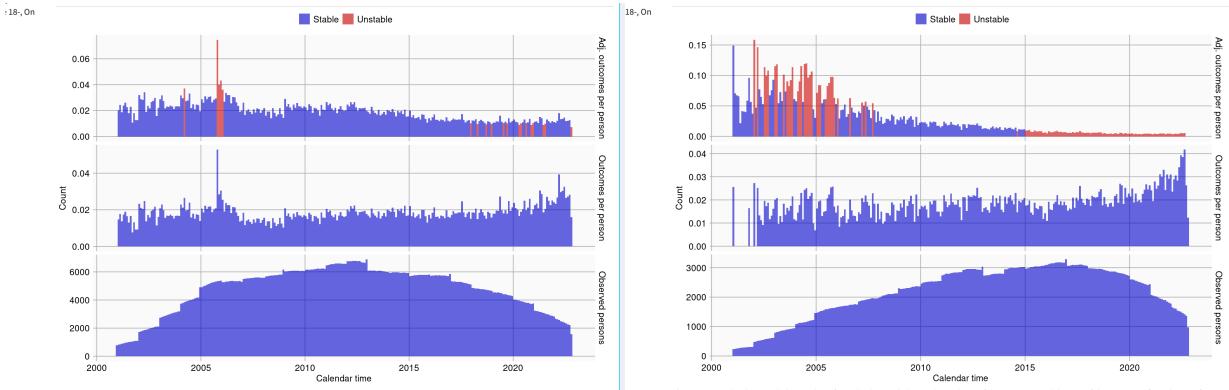


Figure 4. Per calendar month the number of people observed, the unadjusted rate of the outcome, and the rate of the outcome after adjusting for age, season, and calendar time, if specified in the model. Red indicates months where the adjusted rate was significantly different from the mean adjusted rate.

Figure 4. Per calendar month the number of people observed, the unadjusted rate of the outcome, and the rate of the outcome after adjusting for age, season, and calendar time, if specified in the model. Red indicates months where the adjusted rate was significantly different from the mean adjusted rate.

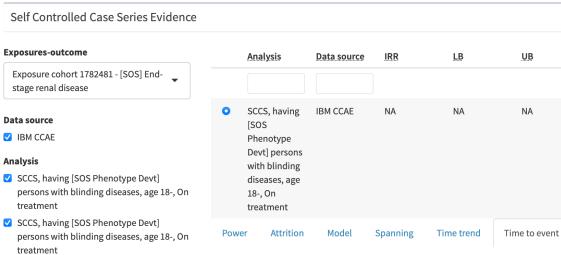


 Distribution of outcomes over time w.r.t. index event

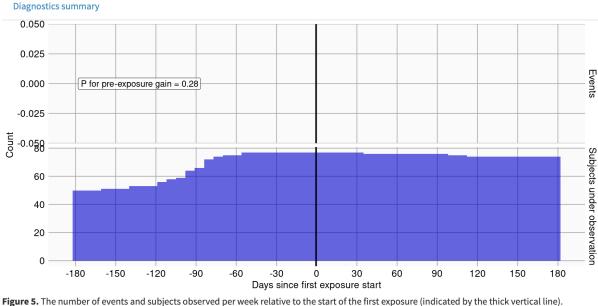
> Are there more outcomes just before exposure?

### Estimation: SCCS diagnostic drilldown: Time to event

#### self Controlled Case Series



SCCS, having [SOS Phenotype Devt] persons with blinding diseases, age 18-, On treatment



Ρ

NA

Event dep. observation

Cal.IRR

NA

Cal.LB

NA

Systematic error

+

Cal.

NA



# Patient-level prediction (PLP): View diagnostics

odel Desig	ns Summary	/											
Design ID	Model Type	Target Pop	Outcome	TAR	min AUROC	mean AUROC	max AUROC	Num. Diagnostic Dbs	Num. Development Dbs	Num. Validation Dbs			
1	logistic	Cohort: 1782483001	[SOS] End- stage renal disease	(cohort start + 1) - (cohort start + 365)	0.929	0.929	0.929	1	1	1	View Diagnostics	View Results	View Repor
2	logistic	Cohort: 1782481001	[SOS] End- stage renal disease	(cohort start + 1) - (cohort start + 365)	0.887	0.887	0.887	1	1	1	View Diagnostics	View Results	View Repor
3	logistic	Cohort: 1782482001	[SOS] End- stage renal disease	(cohort start + 1) - (cohort start + 365)	0.929	0.929	0.929	1	1	1	View Diagnostics	View Results	View Report



# Patient-level prediction: PROBAST criteria

Diagnostic											
diagnosticId	databaseNam e	targetName	outcomeNam e	<u>1.1</u>	<u>1.2</u>	<u>2.1</u>	2.2	<u>2.3</u>	3.4	3.6	<u>4.1</u>
1	IBM CCAE	Cohort: 1782483001	[SOS] End- stage renal disease	✓ Pass	✓ Pass	✓ Pass	✓ Pass	? Unkown	✓ Pass	✓ Pass	🗙 Fail

- 1.1 Appropriate data sources
- 1.2 Appropriate inclusions/exclusions
- 2.1 Predictors defined similarly for all
- 2.2 Predictor assessed without outcome knowledge
- 2.3 Predictor available when model is to be used
- 3.4 Outcomes defined similarly for all
- 3.6 Time interval from predictor to outcome is okay
- 4.1 Are there enough outcomes (200)

# PLP model results are diagnostics: discrimination

≡							
Prediction Viewer							
i ← Back To Models Summary							
Full Result Explorer							
1							
modelDesignId : 1     developmentDb : IBM CCAE		modelType : logistic validationDb : IBM C		Target : Cohort: 1782483001 outcome : [SOS] End-stage renal disease			
	Threshold Dependant Discrimination	Calibration Net Benefit	Validation				
Summary							
Click view to see the corresponding	ıg plots:						
	performanceId	evaluation	AUROC	95% lower AUROC	95% upper AUROC	AUPRC	
View	1	Test	0.9287261	0.8663226	0.9911296	0.363808	
View		Train	0.9549709	0.9337148	0.9762270	0.495689	
View	ROC Plot	ROC Plot 💿 🔍 🕂 🖬 🖬	i Precisio	on recall plot PR Plo	t	1632	
	0.6 0.6						

# PLP model results are diagnostics: calibration

#### **OHDSI** Analysis

i About

CohortGenerator

CohortDiagnostics

E Characterization

Market Prediction

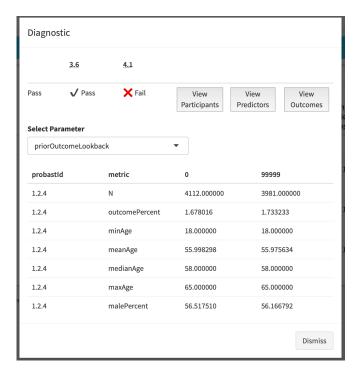
i sccs

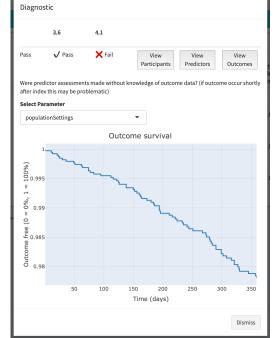
Estimation

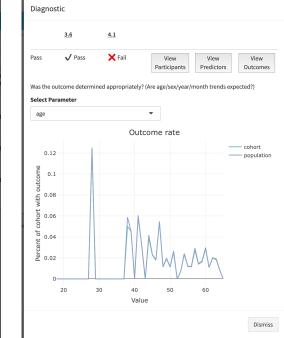
Prediction Viewer									
← Back To Models Summary									
Full Result Explorer									
modelDesignId : 1 developmentDb : IBM CCAE			ype : logistic onDb : IBM CCAE			Target : Cohort: 1782483001 outcome : [SOS] End-stage re	enal disease		
Design Settings Model Thres	hold Dependant Discrimination	on Calibration Ne	t Benefit Validation						
Summary									
Click view to see corresponding plots:									
pe	erformanceId evaluation	E90	Emax	calibrationInLarge mean prediction	calibrationInLar observed risk	ge calibrationInLarge intercept	weak calibration intercept	weak calibration gradient	I
View	1 Test	0.0126729	0.0732649	0.0201014	0.0170854	-0.2045637	-0.0010278	1.0852866	
View	1 Train	alibration Plot			iDe	mographic Plot			
View	1 CV 0	).5-			~	Female		Male	
[	o o	0.4-			Models 0.1	5-			
	to 1		· .		- Ideal Loess				
	Ö .				1.0 DJ	•	A		-
	0	0.0 0.1	0.2 Predicted Probability	0,4 0,5	0.0	5-			
	ount of				label			h	
	2 per son O	20 -			No Outcome 0.0 Outcome	0.24 0.24 0.249 0.549 0.540		4 6 4 6 4 6	

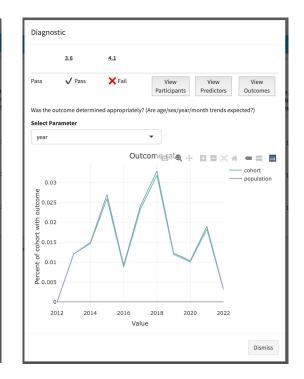


# PLP model diagnostics: pulldowns









# Session 2: fluoroquinolone and aortic aneurysms

