DEVELOPMENTS, APPLICATIONS, AND METHODOLOGICAL CHALLENGES TO THE USE OF PROPENSITY SCORE MATCHING APPROACHES IN FDA'S SENTINEL PROGRAM

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ABSTRACT

- In the Food and Drug Administration's Sentinel program, propensity scores can be used to minimize the need for data sharing while also addressing potential confounding in medical product safety surveillance activities. Recent developments in propensity score methodology led to the creation of a propensity score matching tool that was first added to the Sentinel program in 2013. To date, the propensity score matching methods utilized by the tool have been validated on several known positive and negative drug-outcome associations. Within Sentinel, the propensity score matching tool has also been used to successfully conduct post-approval safety surveillance of newly approved or older medications in both static and dynamic data sources. These experiences have highlighted areas of improvement for future versions of the tool, as well as unresolved questions regarding the use of propensity score methods in distributed and prospective data environments which include: 1) the optimal approach for estimating propensity score models with many covariates within small Data Partners where new users are scarce, 2) the optimal group in which to estimate the propensity score in sequential data, and 3) whether it is better to lock data on matched sets and outcomes from previous monitoring periods as new data accumulates, or instead allow for changes to past data with each data update

BACKGROUND

- Propensity scores (PSs) are an important tool for active post-approval medical product safety surveillance systems
- By reducing a vector of covariates into a single number, PSs facilitate adjustment for a large number of potential confounding variables without limitation by the number of outcome events
- Recent methodological advances have made the PS a particularly useful method in the distributed data setting when the number of outcome events is often very small within each individual DP, where analyses are performed
- PSs also help protect patient privacy by minimizing data sharing in distributed data settings
- For these reasons, PSs were incorporated into the Sentinel routine querying framework in 2013 in the form of a PS matching (PSM) tool
- The PSM tool combines a new user, active comparator cohort design with PS matching in order to avoid common biases and reduce confounding[1]

OBJECTIVES

- To describe the development, application, and performance of PS-based approaches used in Sentinel,[2] with a focus on early challenges and successes within Sentinel's distributed database

METHODS

- We summarized four retrospective applications of the PSM tool in Sentinel:
  - Dabigatran vs. warfarin on intracranial hemorrhage (ICH), gastrointestinal bleed, ischemic stroke, and acute myocardial infarction (AMI)
  - Apixaban vs. warfarin on gastrointestinal bleed, ICH, and stroke
  - Niacin vs. fenofibrate on gastrointestinal bleed, ICH, and stroke
  - Levetiracetam vs. lamotrigine/topiramate on agranulocytosis
- We also summarized two prospective assessments:
  - Rivaroxaban vs. warfarin on ischemic stroke, ICH and gastrointestinal bleed
  - Mirabegron vs. oxybutinin on stroke and AMI
- When summarizing each application, we sought to identify the following characteristics: the number of data partners to which the query was sent and returned, the outcome rate in the unmatched control group, the number of covariates, the expected strength of pre-adjustment confounding, the number of exposed and unexposed patients, and the number of outcome events in each exposure group, and any technical issues

RESULTS

- The number of included patients in these assessments ranged from 28,809 to 581,455
- The number of participating Data Partners (DPs) ranged from 4 to 10
- The number of outcome events ranged from 0.04 to 49 per 1000 person-years
- Unconditional analyses were determined to be more statistically efficient than analyses conditional on the matched set when 1:1 matching
- It was discovered that PS matched sets shifted between monitoring periods due to the dynamic nature of the data when performing prospective analyses in the rivaroxaban query
- A lack of new users caused model convergence issues at smaller DPs in some assessments and precluded sequential analysis in the mirabegron assessment

CONCLUSION

- The PSM tool has been successfully applied to multiple one-time and prospective safety assessments
- Future investigations into the use of PS matching methods in distributed databases should seek to address challenges related to loss of precision in conditional analyses, the dynamic nature of the underlying data for prospective analyses, and confounding adjustment in smaller DPs

Table 1. Tabular Summary of Queries Using the PSM Tool

Query	Outcomes	#DPs Returned/ Sent	Outcome Rate in unmatched control group	# Covariates	Expected Strength of Pre-adjustment Confounding	Primary Analysis	# Exposed	# Unexposed
One-time drug safety assessments								
Dabigatran vs. warfarin*	ICH GI Bleed Isch. Stroke AMI	4/4	ICH: 11/1000PY GI Bleed: 29/1000PY Isch. Stroke: 12/1000PY AMI: 9/1000PY	63 (73 total)	Strong	Age 21+ cohorts, 365 day baseline period	ICH: 26,176 GI Bleed: 26,171 Stroke: 26,166 AMI: 26,171	ICH: 64,404 GI Bleed: 64,403 Stroke: 64,392 AMI: 64.401
Apixaban vs. warfarin	GI Bleed ICH Stroke	4/4	GI Bleed: 35/1000PY ICH (IPP): 10/1000PY ICH (IPP/IPS): 14/1000PY Stroke: 15/1000PY	3 (13 total)	Strong	Pre-defined covariates, in-patient outcomes	GI Bleed: 4,384 ICH (IPP): 4,384 ICH (IPP/IPS): 4,384 Stroke: 4,384	GI Bleed: 24,423 ICH (IPP): 24,425 ICH (IPP/IPS): 24,425 Stroke: 24,418
Niacin vs. fenofibrate	GI Bleed ICH Stroke	4/4	GI Bleed: 15/1000PY ICH: 1/1000PY Stroke: 4/1000PY	68 (78 total)	Weak	Niacin only vs. Fenofibrates	GI Bleed: 225,174 ICH: 225,175 Stroke: 225,173	GI Bleed: 356,275 ICH: 356,280 Stroke: 356,278
Levetiracetam vs. lamotrigine/topiramate	Agranulocytosis	10/17	Lamotrigine: 0.09/1000PY Topiramate: 0.04/1000PY	12 (22 total)	Strong	Inpatient primary diagnosis	Lamotrigine: 90,092 Topiramate: 89,158	Lamotrigine: 240,346 Topiramate: 372,514
Dabigatran vs. warfarin*	ICH GI Bleed Isch. Stroke AMI	4/4	ICH: 11/1000PY GI Bleed: 29/1000PY Isch. Stroke: 12/1000PY AMI: 9/1000PY	63 (73 total)	Strong	Age 21+ cohorts, 365 day baseline period	ICH: 26,176 GI Bleed: 26,171 Stroke: 26,166 AMI: 26,171	ICH: 64,404 GI Bleed: 64,403 Stroke: 64,392 AMI: 64.401
Prospective drug safety assessments								
Rivaroxaban vs. warfarin	Isch. Stroke ICH GI Bleed	4/4	Isch. Stroke: 32/1000PY ICH: 12/1000PY GI Bleed: 49/1000PY	75 (83 total)	Strong	Pre-defined covariates only	Isch. Stroke: 24,334 ICH: 24,337 GI Bleed: 24,337	Isch. Stroke: 69,554 ICH: 69,566 GI Bleed: 69,557
Mirabegron vs. oxybutinin	Stroke AMI	4/4	Stroke: 9/1000PY AMI: 6/1000PY	35 Stroke, 42 AMI (45 total for stroke, 52 for AMI)	Weak	Pre-defined covariates, in-patient outcomes only	Stroke: 5,952 AMI: 4,472	Stroke: 60,588 AMI: 48,835

AMI - Acute Myocardial Infarction; ED - Emergency Department; GI - Gastrointestinal; ICH - Intracranial hemorrhage; IPP - Inpatient Primary Diagnosis; IPS - Inpatient Secondary Diagnosis; Isch. Stroke – Ischemic Stroke

*No preference between 365 day or 183 day lookback period for primary analysis

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