PROTECT

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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Signal detection in electronic medical records

PROTECT Symposium

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Uppsala Monitoring Centre

On behalf of PROTECT WP3 sub-package 10

Feb 19, 2015

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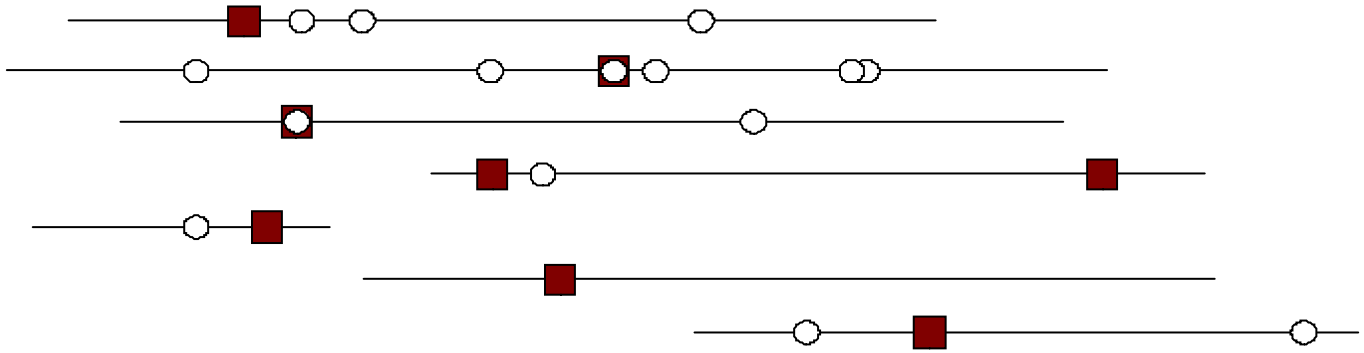
Are we fine-tuning an outdated model?

14 year old
presented w
elevated a

Can longitudinal observational data offer an alternative?



Pharmacovigilance

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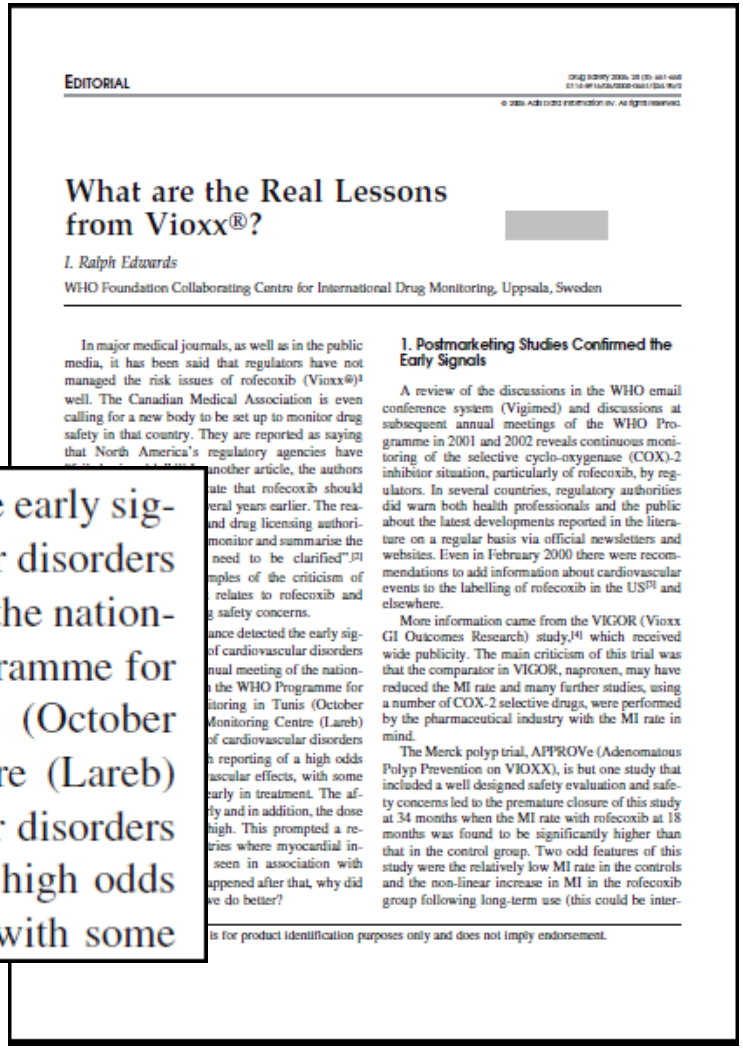
What would real-world signal detection in electronic medical records look like and what value can it bring?

Statistical signal detection is just the first step!

!

In fact, pharmacovigilance detected the early signals of an increased risk of cardiovascular disorders with rofecoxib. At the annual meeting of the national centres participating in the WHO Programme for International Drug Monitoring in Tunis (October 2000) the Netherlands Monitoring Centre (Lareb) presented new evidence of cardiovascular disorders related to rofecoxib, with reporting of a high odds ratio for adverse cardiovascular effects, with some



EDITORIAL

What are the Real Lessons from Vioxx®?

I. Ralph Edwards

WHO Foundation Collaborating Centre for International Drug Monitoring, Uppsala, Sweden

In major medical journals, as well as in the public media, it has been said that regulators have not managed the risk issues of rofecoxib (Vioxx®)[1] well. The Canadian Medical Association is even calling for a new body to be set up to monitor drug safety in that country. They are reported as saying that North America's regulatory agencies have

another article, the authors

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need to be clarified".[2]

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1. Postmarketing Studies Confirmed the Early Signals

A review of the discussions in the WHO email conference system (Vigimed) and discussions at subsequent annual meetings of the WHO Programme in 2001 and 2002 reveals continuous monitoring of the selective cyclo-oxygenase (COX)-2 inhibitor situation, particularly of rofecoxib, by regulators. In several countries, regulatory authorities did warn both health professionals and the public about the latest developments reported in the literature on a regular basis via official newsletters and websites. Even in February 2000 there were recommendations to add information about cardiovascular events to the labelling of rofecoxib in the US[3] and elsewhere.

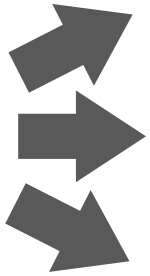
More information came from the VIGOR (Vioxx GI Outcomes Research) study,[4] which received wide publicity. The main criticism of this trial was that the comparator in VIGOR, naproxen, may have reduced the MI rate and many further studies, using a number of COX-2 selective drugs, were performed by the pharmaceutical industry with the MI rate in mind.

The Merck polyp trial, APPROVe (Adenomatous Polyp Prevention on VIOXX), is but one study that included a well designed safety evaluation and safety concerns led to the premature closure of this study at 34 months when the MI rate with rofecoxib at 18 months was found to be significantly higher than that in the control group. Two odd features of this study were the relatively low MI rate in the controls and the non-linear increase in MI in the rofecoxib group following long-term use (this could be inter-

is for product identification purposes only and does not imply endorsement.

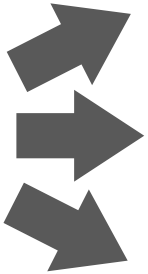
Recommendation

"Safety signal detection in longitudinal observational data should include **clinical, pharmacological, and epidemiological review** of identified temporal associations"



Sibutramine

Nifedipine



Oedema

Flushing

6 assessors

x

7 drugs per assessor

x

20 events per drug

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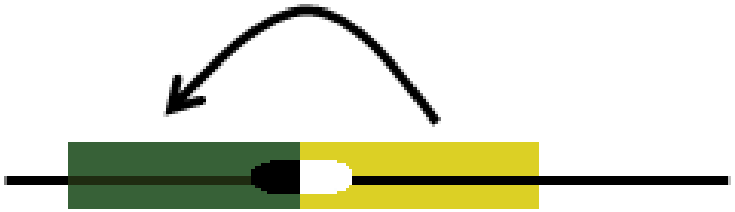
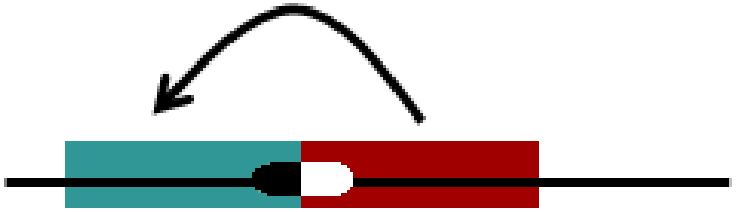
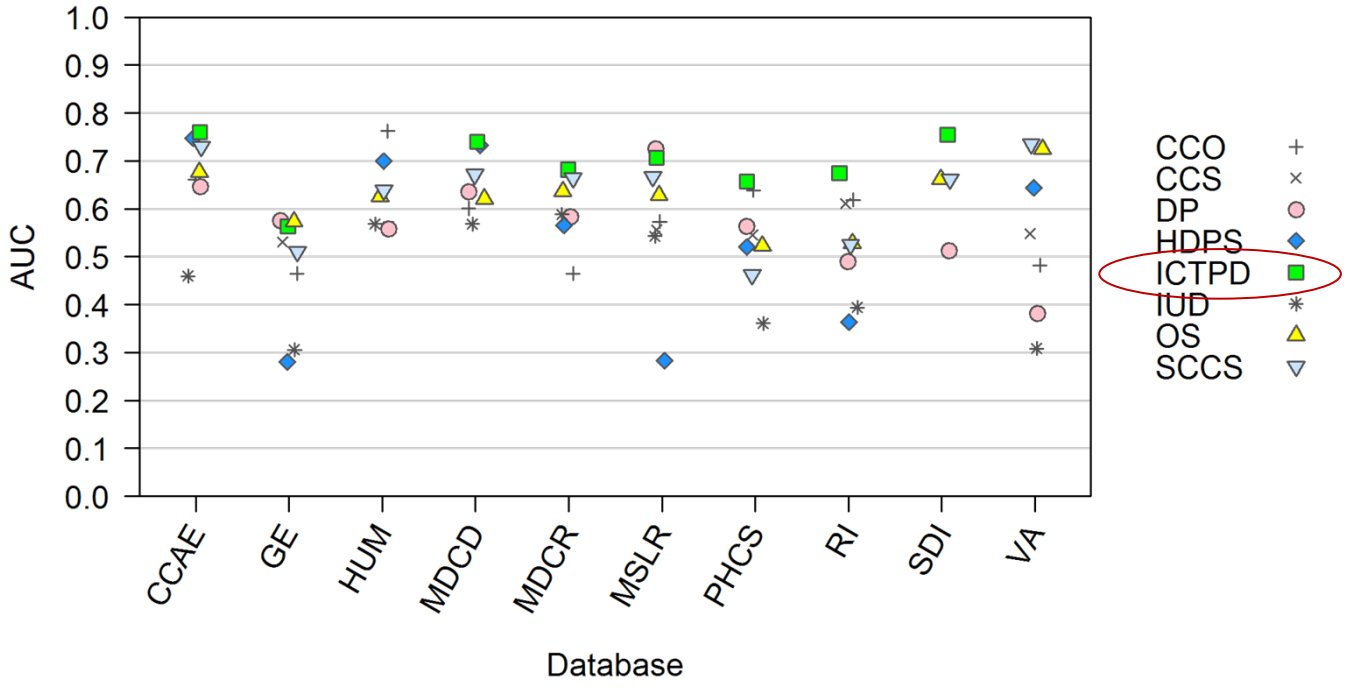
Comparator + self-control



VS



OMOP comparison of methods – Phase I



Preliminary results

820

Preliminary results

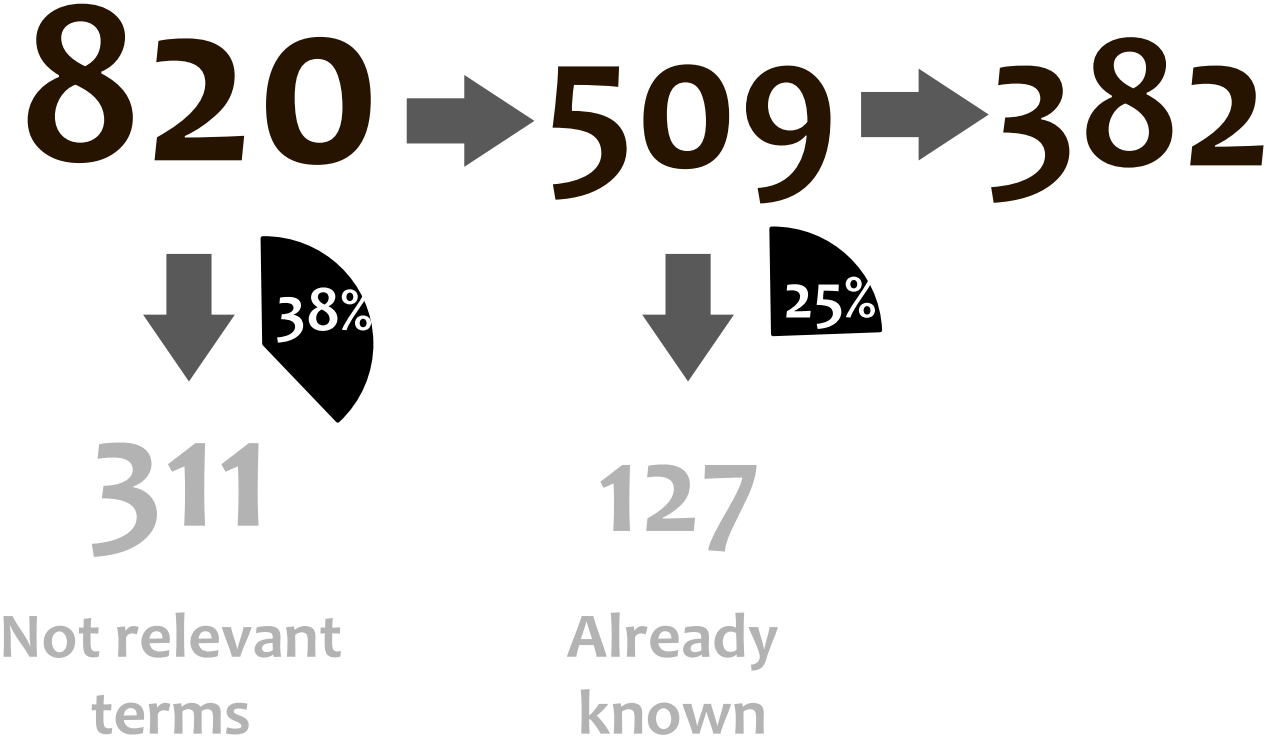
820 → 509

38%

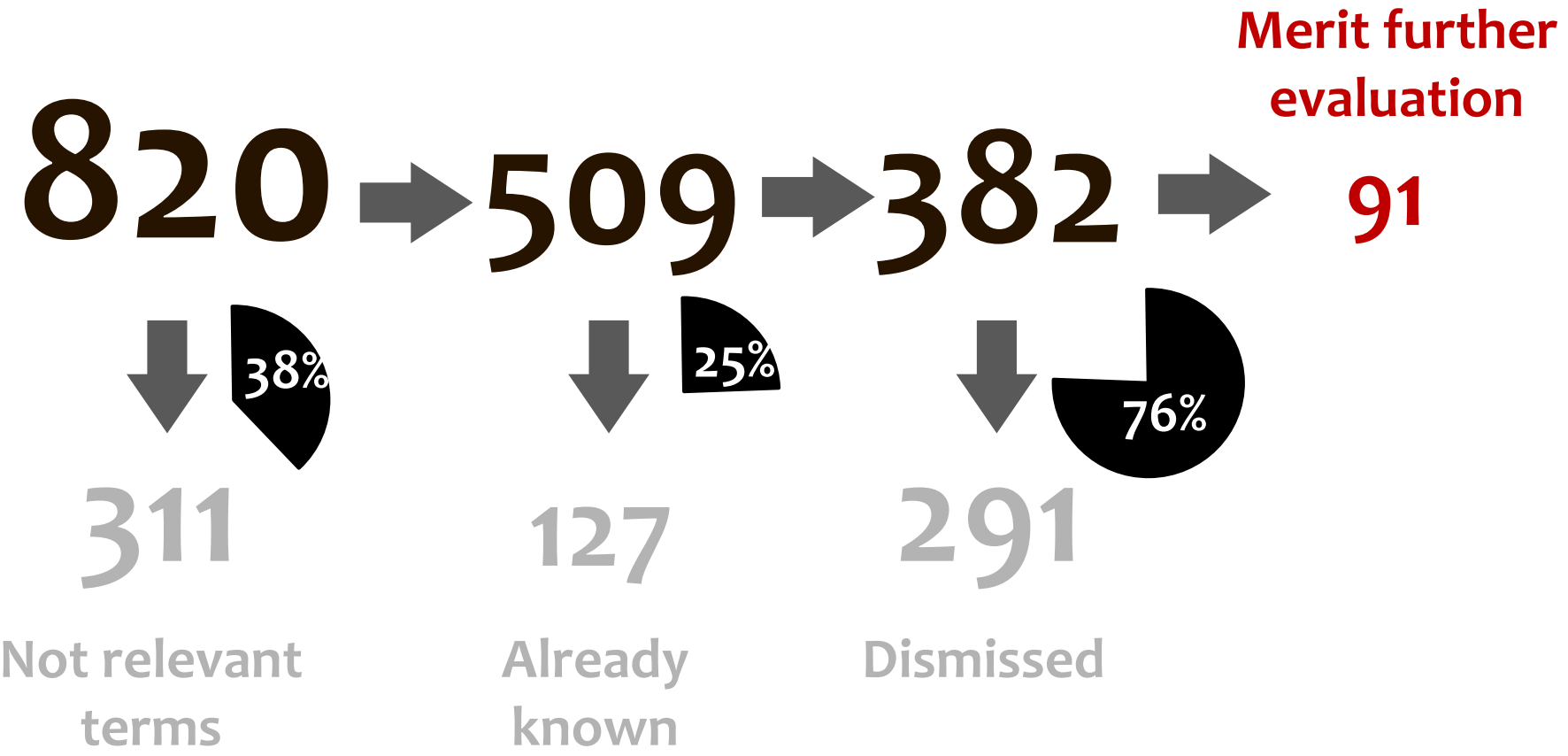
311

Not relevant terms

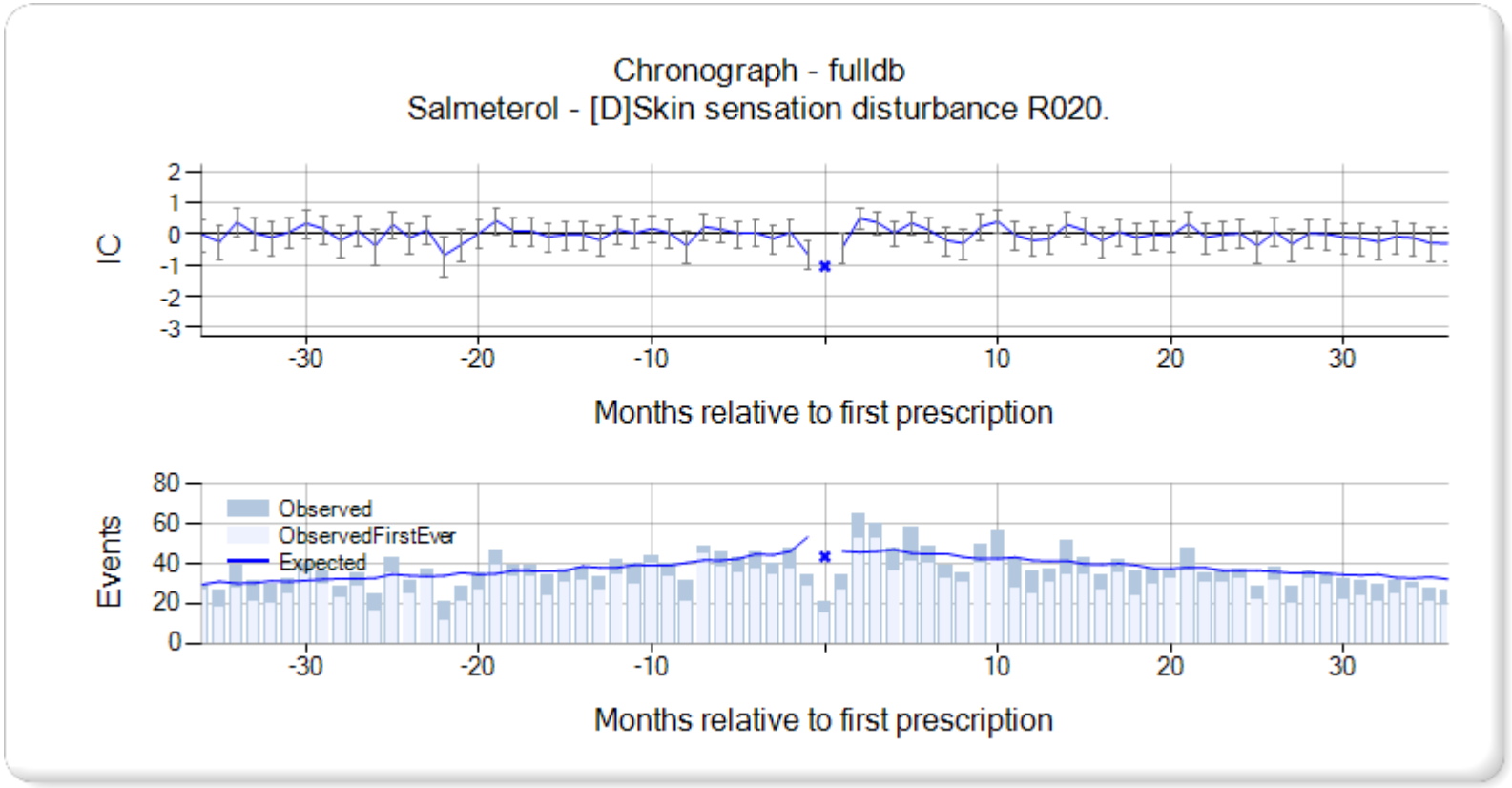
Preliminary results



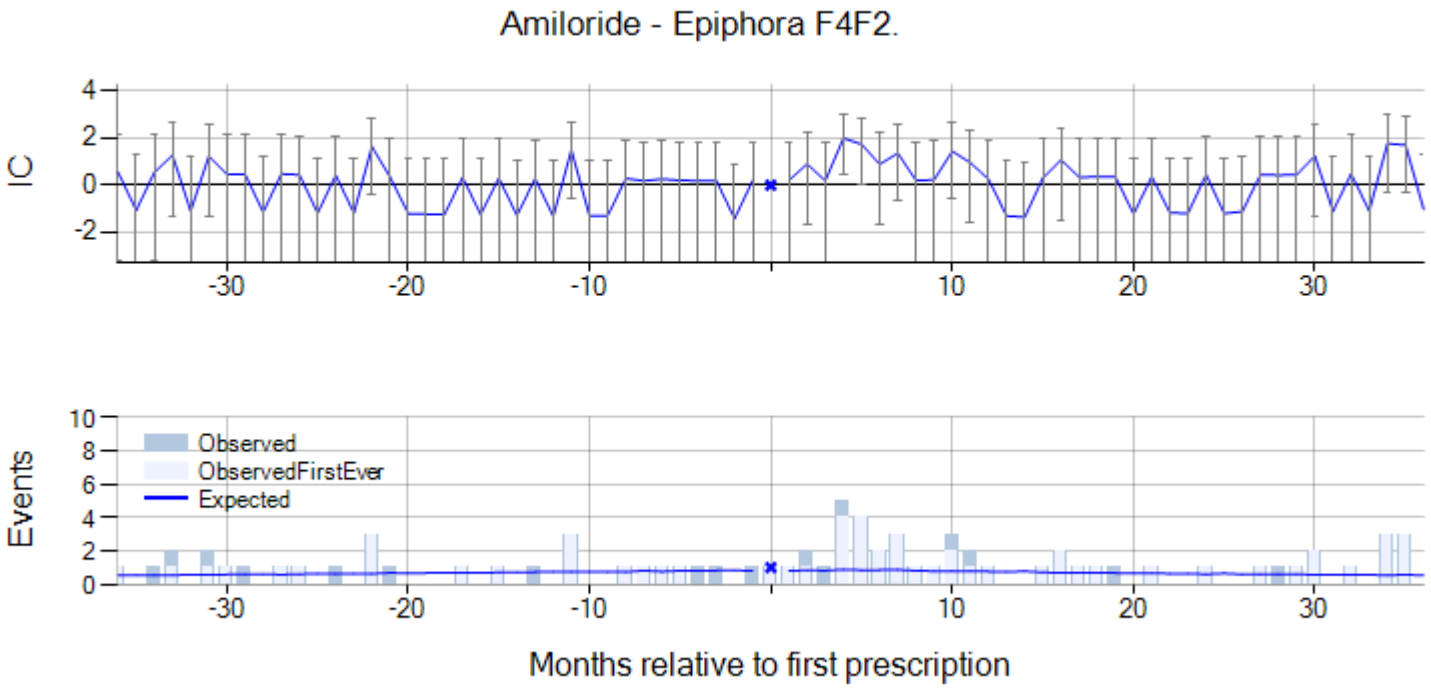
Preliminary results



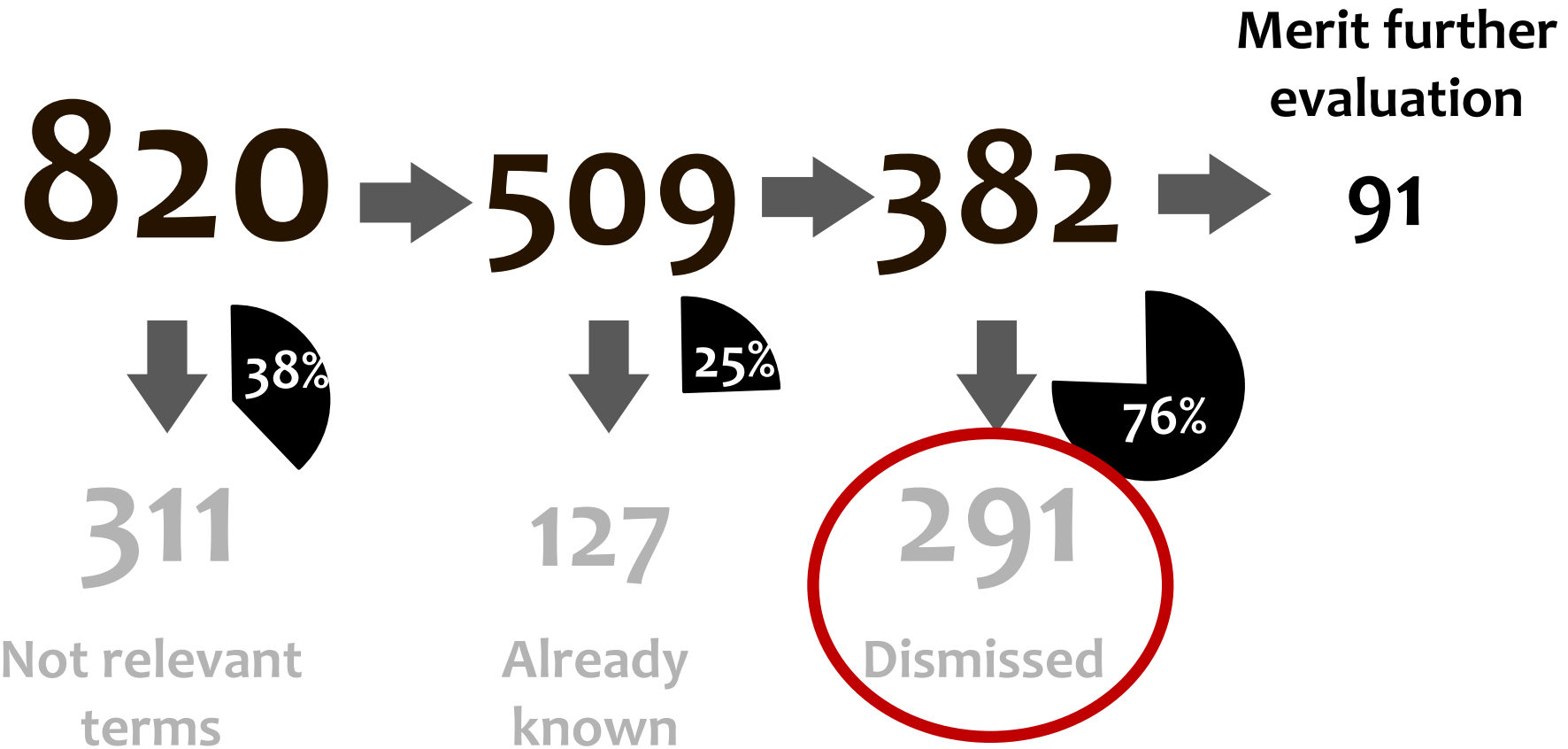
Skin sensation disturbance with salmeterol



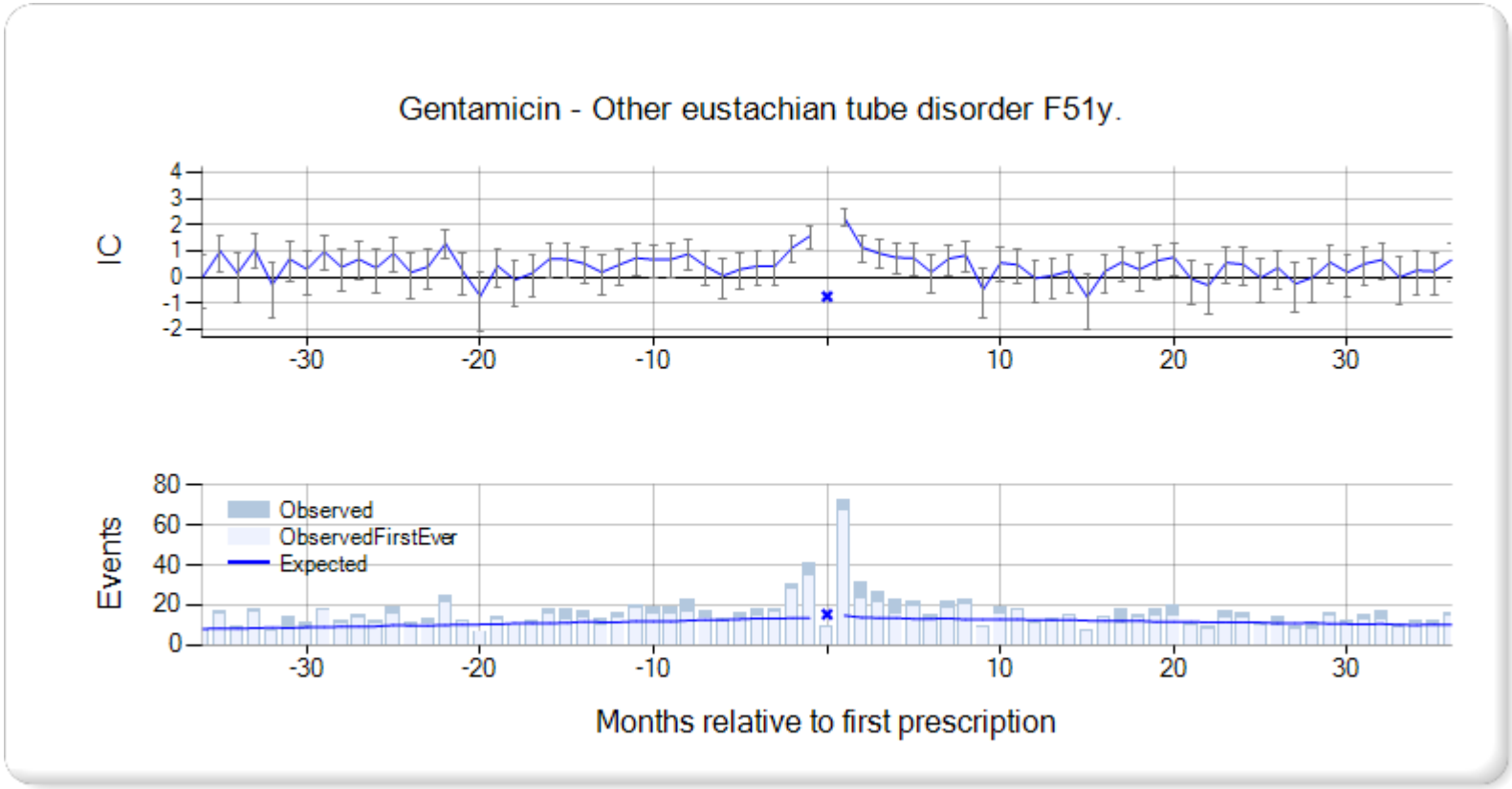
Epiphora with amiloride



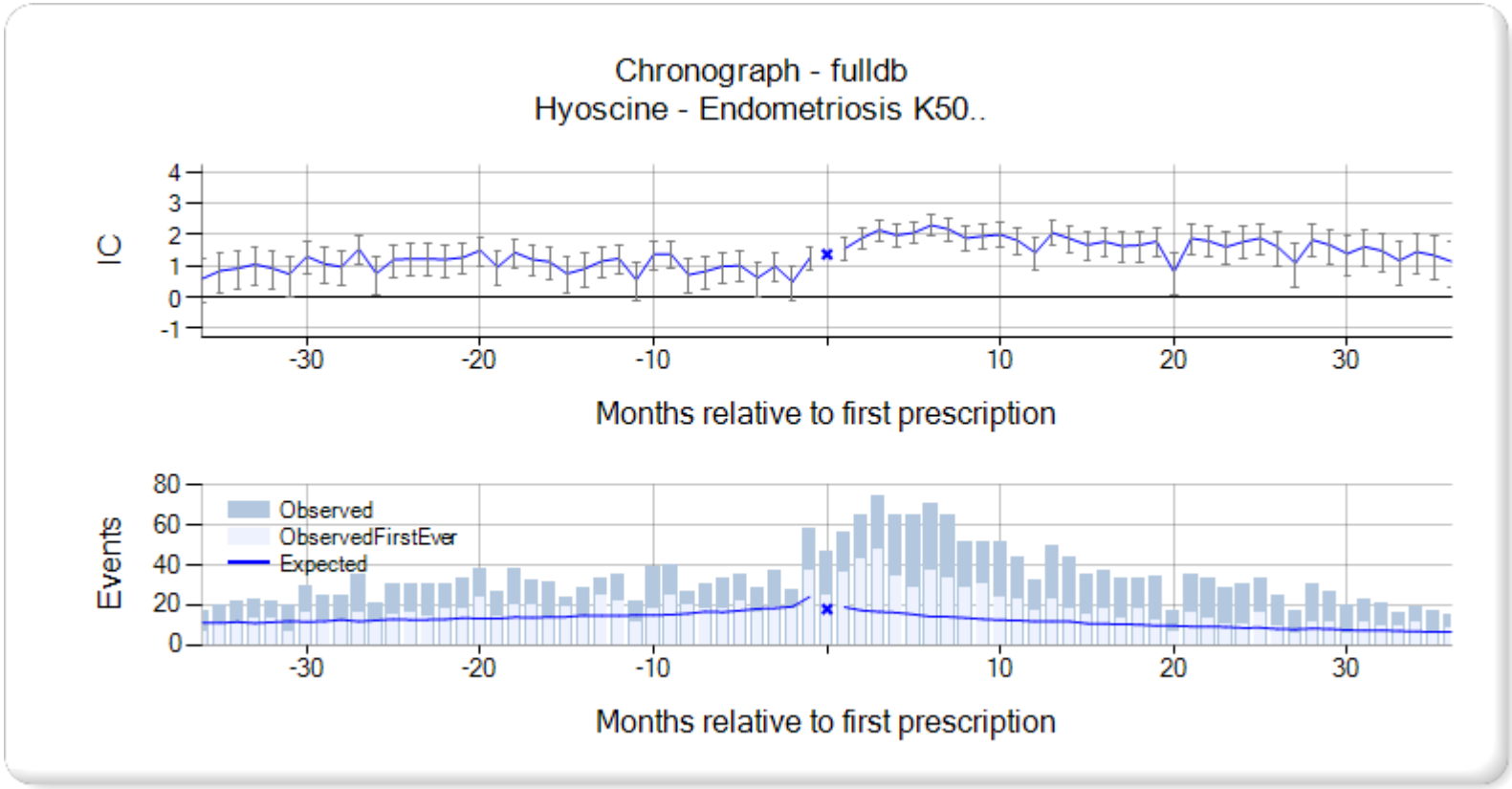
Preliminary results



Confounding by underlying disease

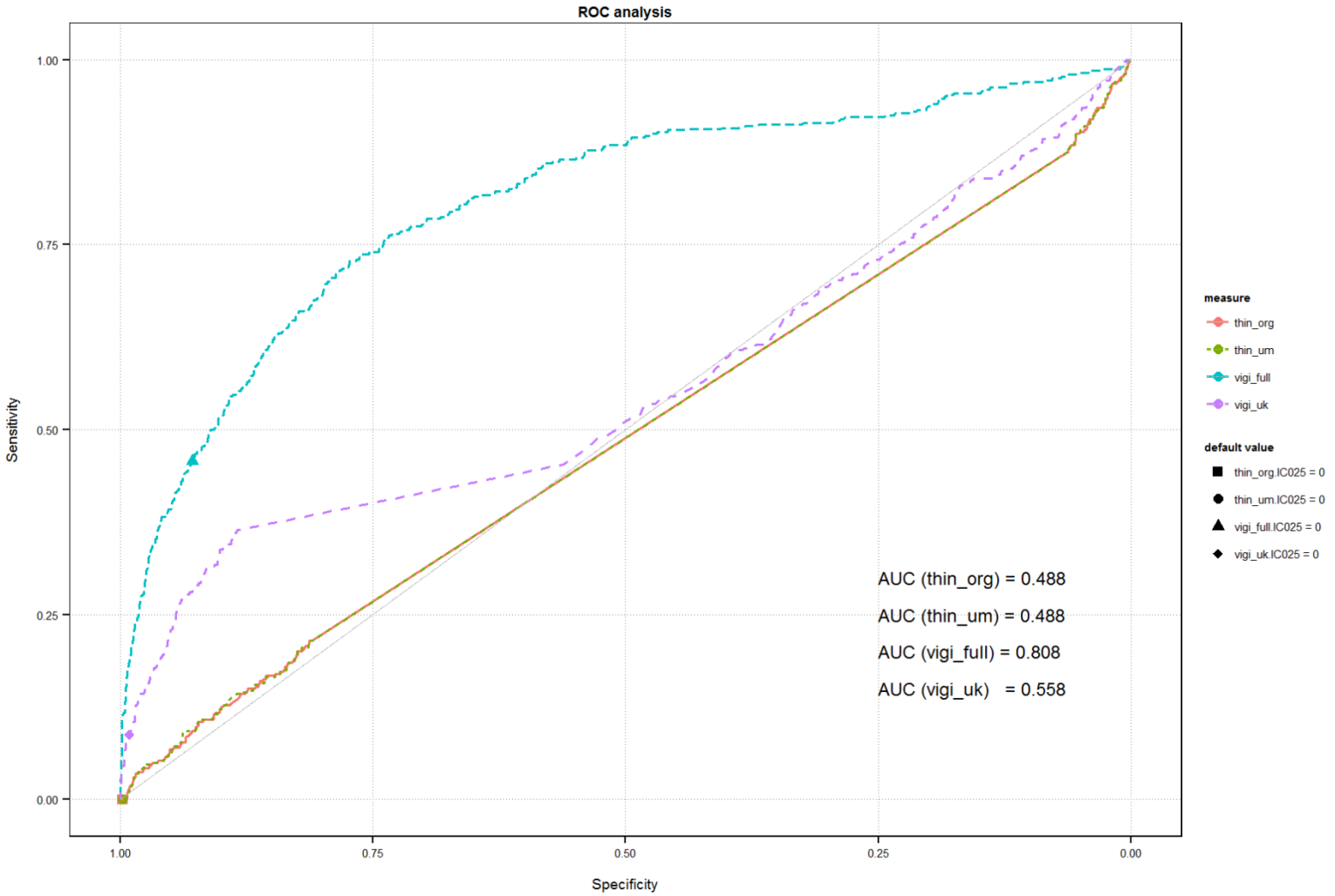


Protopathic bias?



Recommendation

"Longitudinal observational data should be further explored as a **complement** to individual case reports for safety signal detection, but are **not in a position to replace** individual case reports for this purpose"


ROC analysis
Sensitivity
1.00
0.75
0.50
0.25
0.00
Specificity
1.00
0.75
0.50
0.25
0.00
AUC (thin_org) = 0.488
AUC (thin_um) = 0.488
AUC (vigi_full) = 0.808
AUC (vigi_uk) = 0.558
measure
thin_org
thin_um
vigi_full
vigi_uk
default value
thin_org.IC025 = 0
thin_um.IC025 = 0
vigi_full.IC025 = 0
vigi_uk.IC025 = 0

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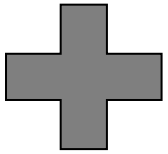
65%

of the drugs have less than 100 prescriptions in total in THIN

- Not marketed in the UK at the time
- Used in secondary care

Longitudinal observational data



Denominators

Longitudinal

'Objective'

No clinical suspicion

Data not collected for causality assessment

Restricted scope

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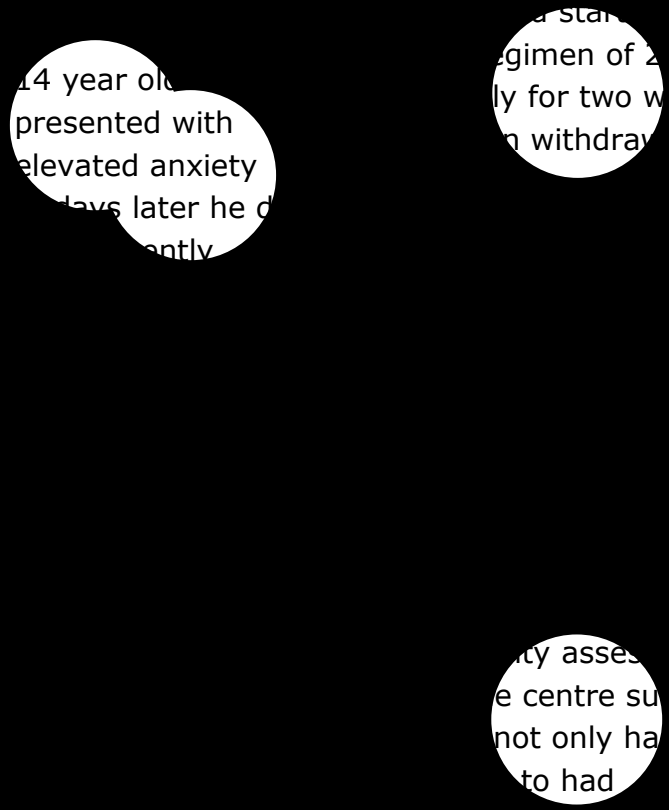
presented w
elevated a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References

1. Edwards IR. **What are the real lessons from Vioxx?** *Drug Safety*, 2004. **28**(8):651-8.
2. Norén GN, Hopstadius J, Bate A, Star K, Edwards IR. **Temporal pattern discovery in longitudinal electronic patient records**. *Data Mining and Knowledge Discovery*, 2010. **20**(3):361-387.
3. Norén GN, Hopstadius J, Bate A, Edwards IR. **Safety surveillance of longitudinal databases: results on real-world data**. *Pharmacoepidemiology and Drug Safety* 2012; **21**(6):673-675.
4. Norén GN, Bergvall T, Ryan P, Juhlin K, Schuemie MJ, Madigan D. **Empirical Performance of the Calibrated Self-Controlled Cohort Analysis within Temporal Pattern Discovery: Lessons for Developing a Risk Identification and Analysis System**. *Drug Safety* 2013; **36**(S1):107-121.
5. Cederholm S, Hill G, Asiimwe A, Bate A, Bhayat F, Persson Brobert G, Bergvall T, Ansell D, Star K, Norén GN. **Structured assessment for prospective identification of safety signals in electronic medical records: evaluation in The Health Improvement Network**. *Drug Safety*, 2015; **38**(1):87-100.