New-user and prevalent-user designs

Klaus Kaae Andersen

Medical Evidence Scientific Lead, AstraZeneca

November 4rd 2021

One-day course

Intermediate methods in pharmacoepidemiology

Outline

- New-user cohort designs
- Challenges with new-user cohort designs
- Prevalent new-user designs
- Selection of comparator drug users in prevalent new-user designs:
  a) Time-based exposure
  b) Prescription-based exposure
- Time-conditional propensity scores
- Statistical models for prevalent new-user designs
- Pitfalls and perils with prevalent new-user designs

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2017; 26: 459–468
Published online 9 September 2016 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1

REFERENCE

ORIGINAL REPORT

Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores

Samy Suissa[1,2,3]*, Erica E. M. Moodie[1] and Sophie Dell'Aniello[2,3]

[1] *Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada*
[2] *McGill Pharmacoepidemiology Research Unit, McGill University, Montreal, Quebec, Canada*
[3] *Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, Quebec, Canada*

ABSTRACT

Purpose Studies of the real-world comparative effectiveness of drugs conducted using computerized healthcare databases typically involve an incident new-user cohort design for head-to-head comparisons between two medications, using exclusively treatment-naïve patients. However, the desired contrast often involves one new drug compared with an older drug, of which many users of the new drug may have switched from, seriously restricting the scope of incident new-user studies.

Methods We introduce prevalent new-user cohort designs for head-to-head comparative drug effect studies, where incident new users are scarce. We define time-based and prescription-based exposure sets to compute time-conditional propensity scores of initiating the newer drug and to identify matched subjects receiving the comparator drug. We illustrate this approach using data from the UK's Clinical Practice Research Datalink to evaluate whether the newer glucagon-like peptide-1 receptor agonists (GLP-1 analogs) used to treat type 2 diabetes increase the risk of heart failure, in comparison with the older similarly indicated sulfonylureas.

Results Of the 170 031 users of antidiabetic agents from 2000 onwards, 79 682 used sulfonylureas (first use 2000), while 6196 used GLP-1 analogs (first use 2007), 75% of which had previously used a sulfonylurea. After matching each GLP-1 analog user to a sulfonylurea user on the time-conditional propensity scores from prescription-based exposure sets, the hazard ratio of heart failure with GLP-1 use was 0.73 (95% CI: 0.57–0.93).

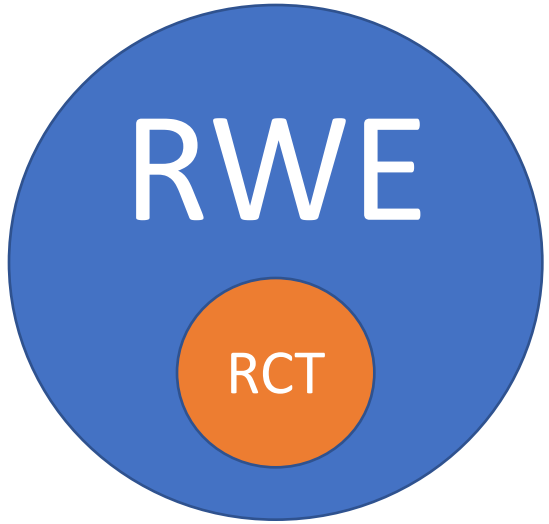
Conclusion The proposed prevalent new-user cohort design for comparative drug effects studies allows the use of all or most patients exposed to the newer drug, thus permitting a more comprehensive assessment of a new drug's safety. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—cohort studies; comparative effectiveness; database research; drug safety; epidemiologic design; pharmacoepidemiology; pharmacoepidemiology

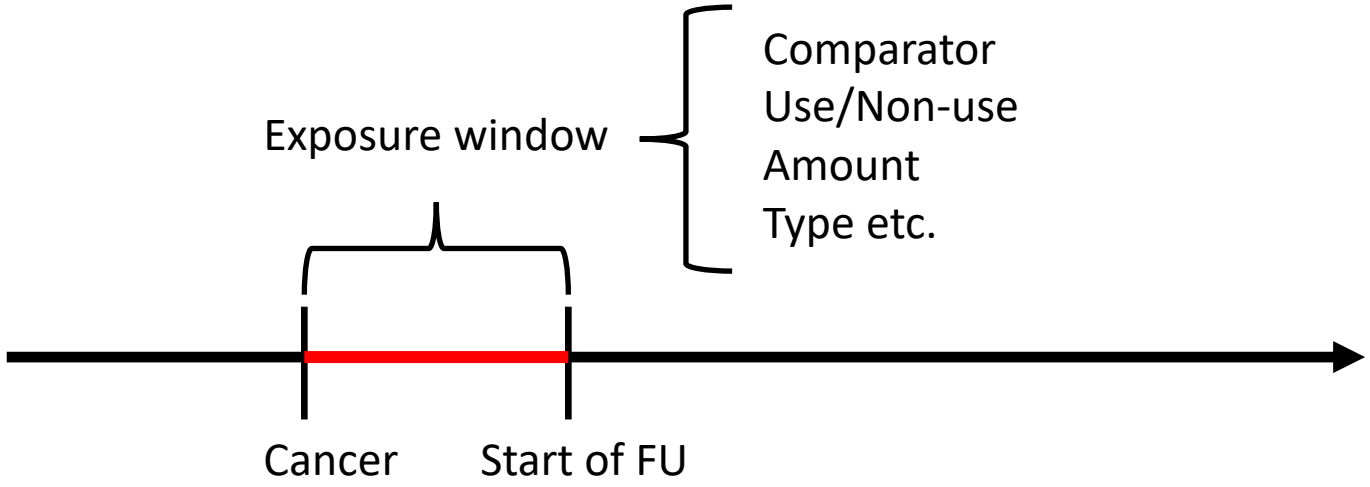
Received 15 February 2016; Revised 16 August 2016; Accepted 18 August 2016

New-user cohort designs

- **Observational studies** of comparative effects of drugs, including effectiveness and safety, are generally based on **cohort designs**.
- It is recommended that cohorts be defined by **new users** of the drug under study, also called incident users, to avoid missing potential early effects and properly time the confounders.
- New-users design ‘mimic’ the **trial setting** as it avoids the biases associated with the study of prevalent users



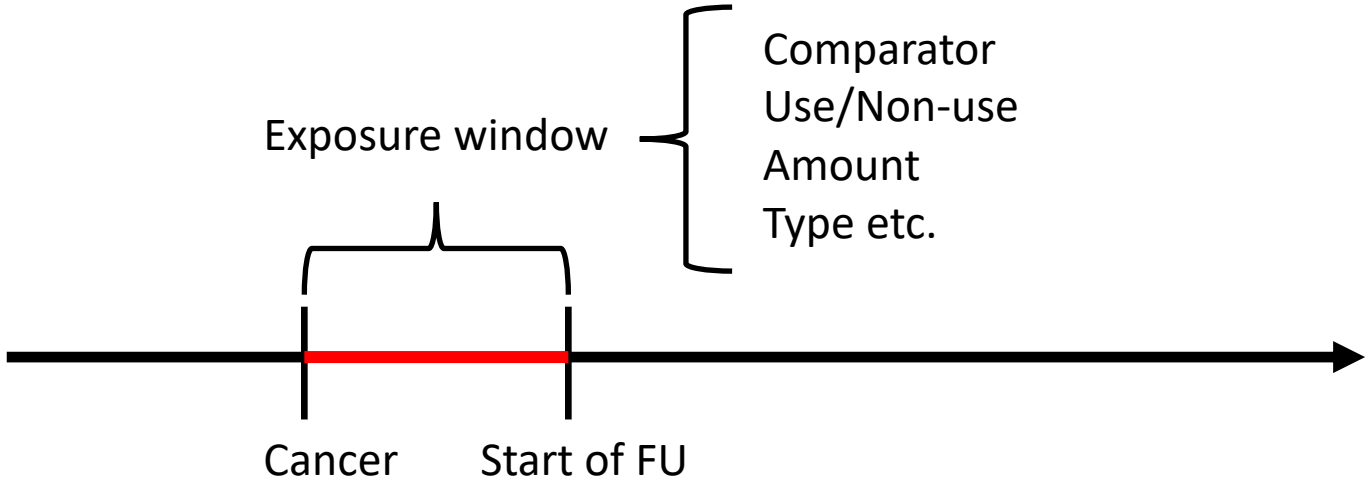
New-user design (with time-fixed exposure)



New-user cohort designs

- Some studies of comparative effects will involve the comparison of two drugs of similar indication that entered the market at around the same time, which makes the new user design adequate.
- Incident new-user comparative cohort studies are as relatively straightforward as observational studies can be. Different techniques of data analysis can then be used, such as regression or propensity scores, to match or adjust for differences in the baseline characteristics on the date of the first such prescription between the two groups.

New-user design (challenge with identifying subjects)



Challenges with new-user cohort designs

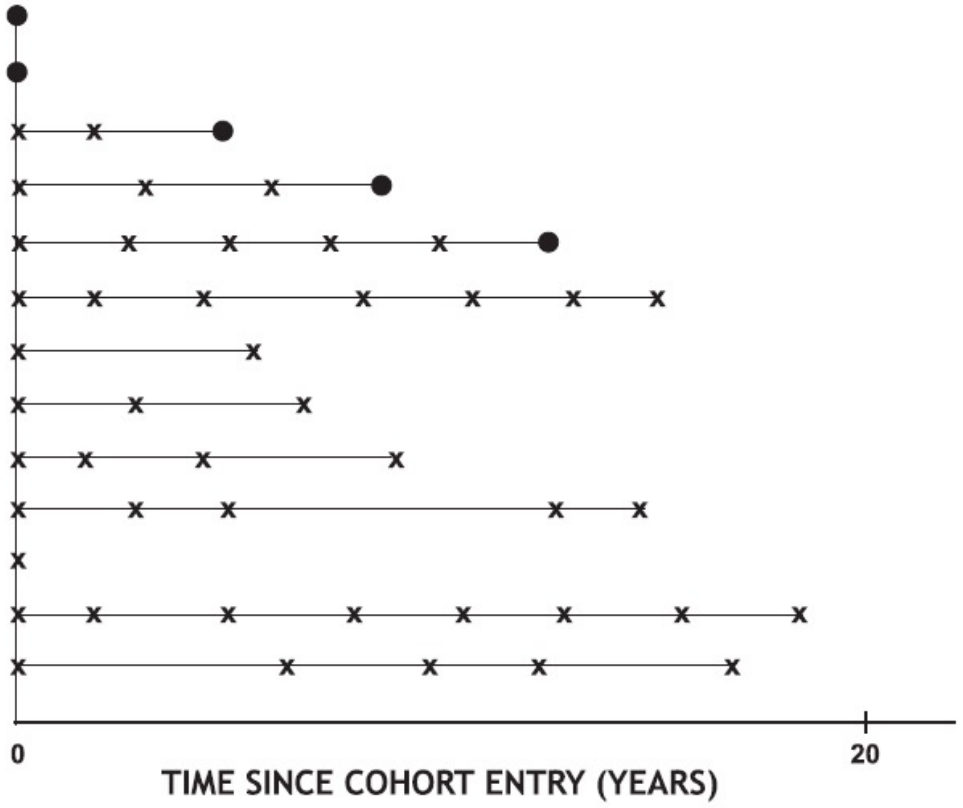
- Studies that are based strictly on treatment-naïve users, risk that the cohort only includes a small part of the real-life user population of the new drug, particularly during the early period of its availability.
- While studies of comparative effects will typically involve the head-to-head comparison of two similar drugs, one is often faced with evaluating the effect of a new drug, with no contemporaneous comparator.
- The most appropriate comparator is typically an older drug that has been on the market for a long time.
- This could greatly reduce the generalizability of study results, a key advantage of observational studies.
- Here, we discuss approaches to design cohort studies of head-to-head comparative drug effects, particularly focusing on the situation where the comparator drug is not contemporaneous.

Prevalent new-user design

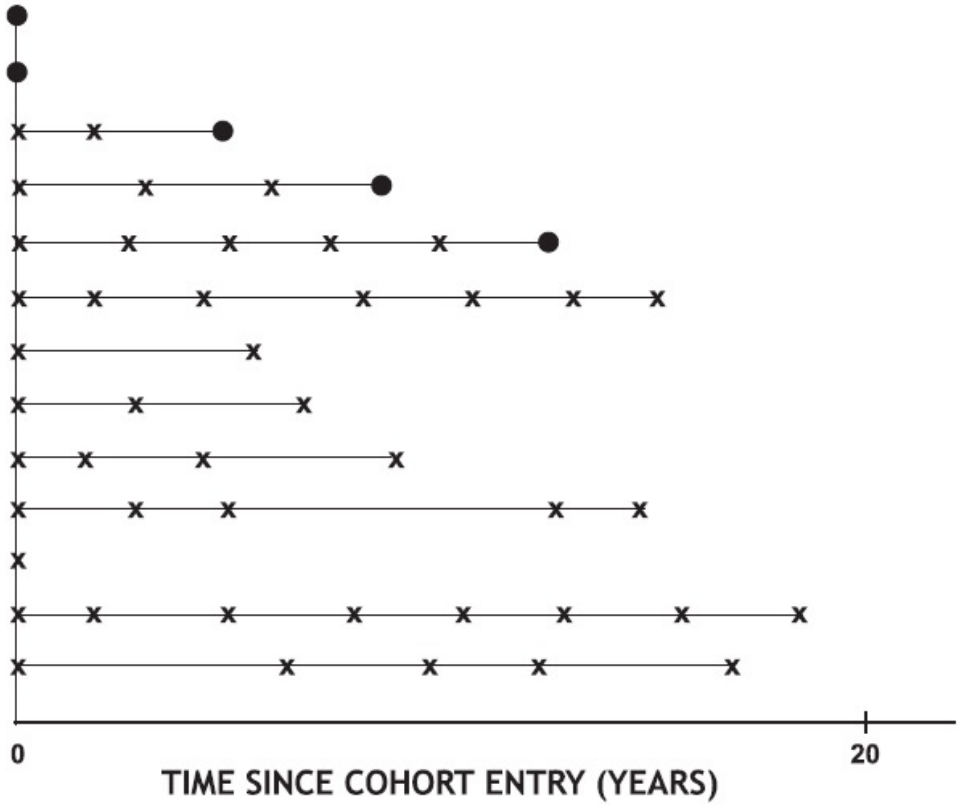
- A more common situation in pharmacoepidemiology involves the study of the effect of a new drug entering the market, in the absence of a direct contemporaneous comparator.
- In such instances, a prevalent new-user comparative cohort approach could be used.

Prevalent new-user design

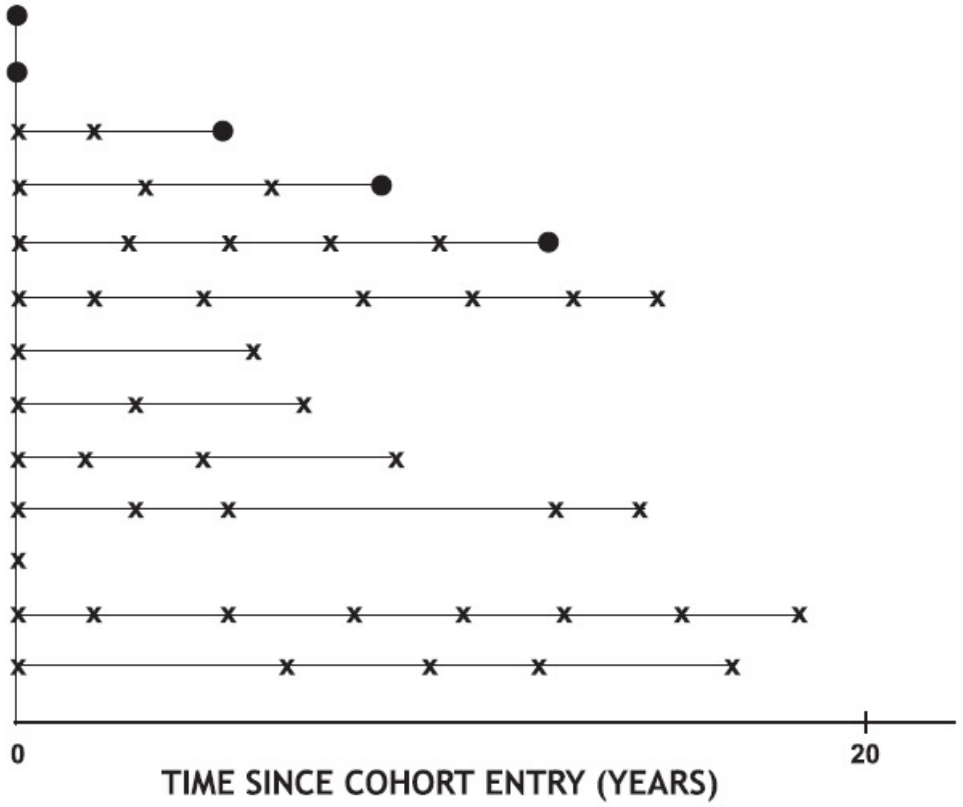
- The figure (next slide) depicts a base cohort formed of all subjects, some switching to the study drug, the others continuing on the comparator, as well as the subjects who initiated the study drug without ever using the comparator.



The main challenge with the design of prevalent new-user comparative cohort studies is the selection of comparator drug users for the subjects who switched from the comparator drug to the study drug.

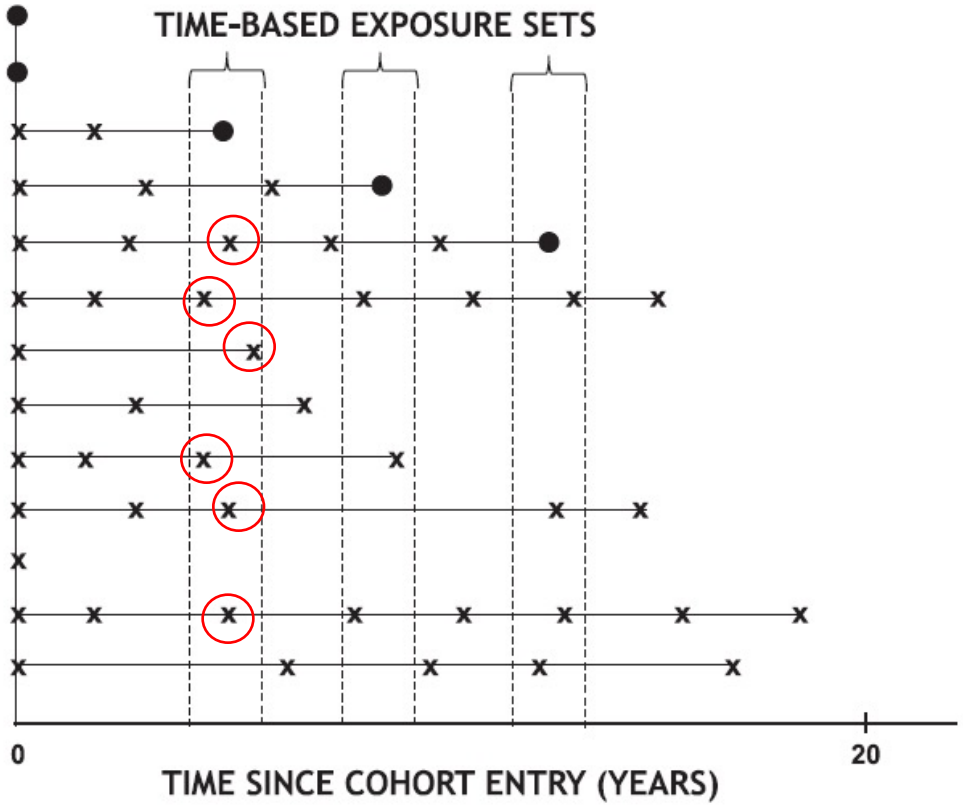

0
20
TIME SINCE COHORT ENTRY (YEARS)

time-based exposure sets must be defined with a time interval, such as ±1 month

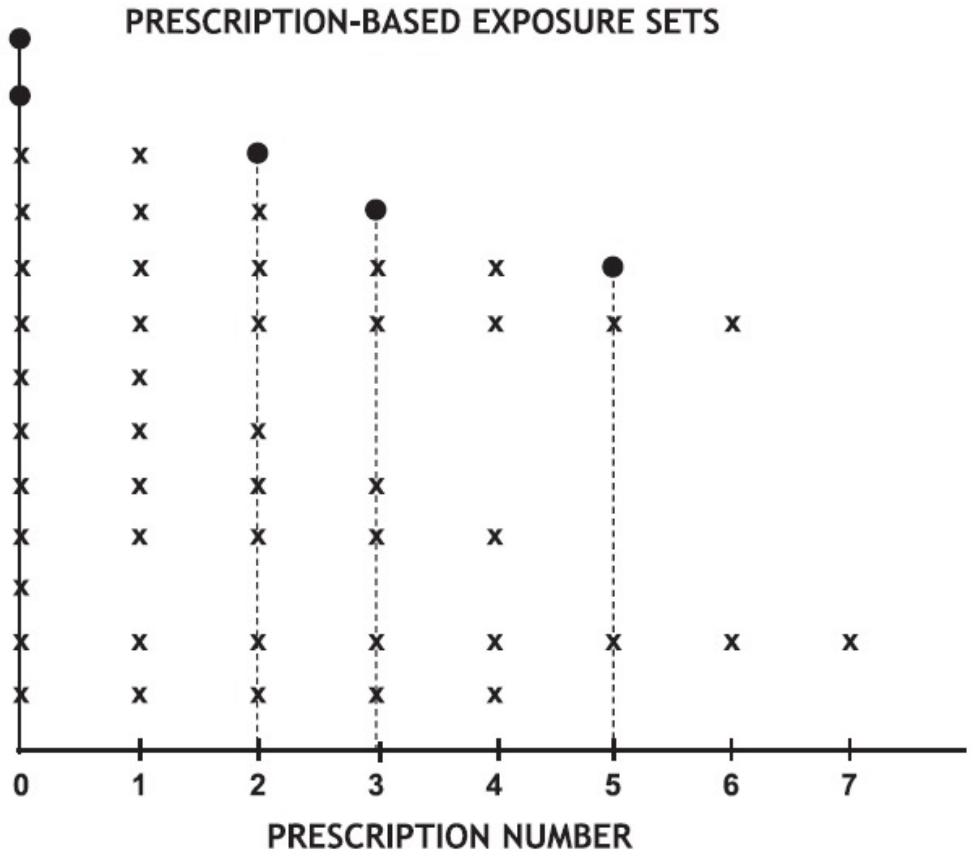


○ Potential comparator

Propensity scores can be used to chose comparator among those eligible



Prescription-based exposure sets do not consider the time between prescriptions.



Time-conditional propensity scores

- To identify the comparator drug user most similar to the patients who switched to the study drug, time-conditional propensity scores can be used.
- An estimated model is used to compute the time-conditional propensity score within each exposure set to identify the subject in the exposure set with the closest value to that of the switcher, thus identifying their matched comparator.
- A time-dependent Cox proportional hazards model, or its equivalent conditional logistic regression model, can be used to estimate the time-conditional propensity scores over time is distinctive.
- The label “time conditional” is added to the term propensity score to remind that its computation is carried out by updating the time-varying covariates at each exposure set and that matching is performed within the exposure sets, including the verification of the positivity assumption, which should be performed within each exposure set.

Time-conditional propensity scores

- For the purposes of the positivity assumption, the time-conditional propensity score of the switcher should lie within the range of the time-conditional propensity scores of the members of the corresponding exposure set.
- Once a patient has been selected into the comparator group, they are not considered any longer in subsequent exposure sets as potential comparators.
- Cohort entry is taken as the date of the first prescription of the study drug use and the corresponding date for the matched comparator drug user.

Statistical models for prevalent new-user designs

- Standard models, typically the Cox Proportional hazards model, can be used to model the rate of outcomes.
- It is possible to account for the matching (strata) in the statistical analysis.

$$\lambda(t, \mathrm{i}, x) = \lambda_{(i,\mathrm{t})} e^{\sum \beta_j f(x_j)}$$

Pitfalls and perils with prevalent new-user designs

- Most cohort studies involve exclusion criteria that define a homogenous population.
- Applying this exclusion is rather straightforward for the incident new-user comparative cohorts.
- For the prevalent new-user comparative cohort design, however, the potential for selection bias from exclusion criteria is high(er).
- Without a careful systematic approach, one could easily end up excluding outcome events, not only history events, or misclassifying history events as outcome events.
- To ensure that such selection bias is avoided, it is essential to perform the identification of matched comparator subjects in a systematic and chronological manner.

Pitfalls and perils with prevalent new-user designs

- First, this should be carried out blinded to the occurrence or timing of outcome events in the base cohort.
- Second, after propensity scores have been computed, identification of matched comparators should be conducted in chronological order, with the first new user of the study drug in calendar time matched first to a comparator, the second next,..
- If the new user of the study drug has a history of the exclusion event, they must be excluded outright from any further selection into the comparative cohort analysis.
- If the new user is eligible, a comparator with the closest propensity score is selected.
- If this comparator has a history of the exclusion event, they must be excluded from any further selection and the next closest match without such a history can be used to match to the new user.

Pitfalls and perils with prevalent new-user designs

- A second issue relates to the comparators that, during follow-up, switch from the old comparator drug to the new drug. Two choices are possible.

1) The first is to censor the comparator follow-up at the point of switch, then include the subject as a new user of the new drug from this point onwards while identifying a matched comparator at that point.
2) The second is to not reuse these subjects if they were selected as comparators while leaving the option open to censor or not the follow-up at the point of switch.

Conclusions

- The prevalent new-user design and new-user design both address unique questions of clinical and public health importance.
- Real-world evidence generated by pharmacoepidemiologic research is increasingly being used by regulators and other knowledge users to inform their decision-making.
- Understanding the causal questions addressed by different designs is crucial in this process.

Conclusions

- Studies of comparative effectiveness of drugs are becoming more widespread, particularly with the influx of new computerized healthcare databases.
- The traditional incident new-user comparative cohort design, exclusively based on treatment-naïve subjects, is a desirable approach for head-to-head comparisons between two medications, but often seriously restricts the size of studies.
- This calls for ways to incorporate prevalent users in epidemiologic studies.
- This may be achieved using a prevalent new-user comparative cohort designs, which includes all patients, and not only the treatment-naïve subjects