Plans for heart attack surveillance in users of anti-diabetes drugs

Notes on methods for Sentinel

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Four topics

1. Proposal for a new user cohort design, comparing MI risk in Saxagliptin users versus active comparators;

   Should we also examine on-drug v. off-drug variation over time (within persons)?

2. How to split and lump the study population; How to split and lump the outcomes

3. Refinement of reassurance: it is not simply the flip side of signal refinement

4. A pilot of surveillance that is outcome-centered can supplement the cohort design

Research question:
How is risk of AMI affected by Saxagliptin?

Sentinel team refined the question to:

How does the risk of AMI in Saxagliptin users differ from what it would have been if they instead used

(a) sitagliptin (b) pioglitazone (c) long-acting insulin (d) sulfonylurea?

A new-user cohort design is proposed:

- Active comparators, rather than comparison of use versus nonuse
- New users only; prevalent users ignored
- Each pair-wise analysis addresses a part of the research question; the 4 comparators may differ in risk from each other and from nonuse
- Follow-up is censored when users are non-adherent or switch drugs

Thus, variation in exposure within persons (over time) is ignored; inference is only from variation between persons

1st topic: When can within-person variation be ignored When and how can it be informative?

- Our proposal ignores within-person variation because
  - Its association with risk may be driven by unmeasured confounders
  - It may be "downstream" on a relevant causal pathway (from use of Saxagliptin or Comparator to an outcome event)
- But, these issues could also be problematic for our proposed design; so we plan to monitor non-adherence, switching and other censoring, and we plan secondary ITT-style analyses.

- If a lot of users stop and restart the drugs of interest, or if we otherwise expect a start and stop to the period of risk, and if within-person confounders are measured or negligible, then we might
  - condition analysis on the person, and base inference on variation within persons (e.g. vaccine safety studies done by SCCS)
  - use a model that permits inference from both kinds of variation: within people and between people.

2nd topic: how to split and lump

- Refinement of research question: how does Saxagliptin affect risk of AMI, or acute coronary syndrome, in diabetics with or without history of CVD?
- How we proposed to split and lump the study population
  - 4 comparator drugs: separate pair-wise comparisons, no lumping, no Bonferroni or other such “correction” for multiple comparisons
  - 5 sites (data partners): assessment of heterogeneity for signs of bad data, potential confounding, or possible interactions of drug effects with unmeasured demographic factors (that may vary by site)
  - CVD history versus no CVD history: separate models to make the propensity score and disease risk score, separate relative risk estimates, separate sequential tests in those with and without CVD and also in the larger lumped population. The latter are primary.
  - Subgroups defined by DRS, anchor date of risk sets (time period of follow-up): assessment of heterogeneity (and proportionality)

How we split and lump the outcomes

- Primary outcome: acute myocardial infarction (AMI)
- Secondary outcome: AMI plus acute coronary syndrome
- Not to be examined as outcomes: heart failure, stroke, sudden cardiac death, other CVD outcome

Outcomes may be split out or lumped together according to

- Pathophysiology, severity (hepatitis and liver failure)
- Place on possible pathway from drug to outcome (data on fever facilitated inference about febrile seizure and MMRV)
- Confidence in validity of available data

3rd topic: Reassurance

- As we plan how Sentinel can refine signals, we also should plan how Sentinel can refine the reassurance that is appropriate when good timely data are well-analyzed, and signals don't arise or else fade out.
- The absence of a compelling signal is insufficient to convey reassurance about drug safety.

In other words: failing to reject the null hypothesis provides little reason to accept it as true, if the relative risk estimate is far from the null and/or the CI is wide. Even if Sentinel looks at data on tens of millions of people, an early look at a new drug like Saxagliptin, or any look at a very rare outcome, will yield results with a degree of uncertainty that will be challenging to convey appropriately.

Reassurance: not the flip side of a signal

- The upper bound of a 95% CI might let us say: “a relative risk of 2.0 or more can be ruled out with 95% confidence”. While a CI needs special clarification in sequential surveillance, it can be meaningful and useful.
- The upper bound of the risk difference can also be useful.
- There is asymmetry between our interest in the null and our interest in specific alternative hypotheses (hard-to-reverse decisions rarely hinge on specific alternatives). Our sequential tests are one-sided.
- Post-hoc power is less relevant to reassurance than the CI, because it ignores the extent to which the data favor the drug of concern or its comparator.
- “Repeated confidence intervals”, such as are formed by inverting sequential tests, are also less appropriate for reassurance than are nominal CIs.

4th topic: Piloting surveillance that is outcome-centered

- Saxagliptin use may stay low
- There is interest in surveillance of AMI in relation to anti-diabetes drugs more generally
- Comparisons among our 4 comparator drugs will be powerful even if Saxagliptin use stays low. Analyses stratified by the proposed disease risk score can estimate relative risks for all pair-wise comparisons
- Many newly-licensed drugs may turn out to get less use than expected. Sentinel surveillance should be designed to yield useful analyses even if uptake of a target drug is slower than anticipated.

Piloting outcome-centered surveillance

- Without greatly burdening the data partners and researchers, we may be able to
  - ascertain all AMIs in the broader study population, including new users of all anti-diabetes drugs
  - identify an appropriate risk set corresponding to each MI, permitting stratified Cox regression
  - anchor baseline covariates to the 1st drug use, and anchor time-varying covariates to the date of the risk set (which is the date of the MI).
- Such outcome-centered surveillance is especially promising for outcomes – including heart attack, liver failure, and suicide – that are interesting in relation to many drugs.

Questions and comments are welcome on

- Inference about drug safety from variation over time
- How to split and lump the population and outcomes of interest
- Implications of active surveillance for reassurance (in the absence of a compelling signal)
- Piloting active surveillance that is outcome-centered

Or on other aspects of the design we are proposing for heart attack surveillance in users of anti-diabetes drugs