

Building a Generalized Framework for Signal Refinement

Reactor comments

Andrew Bate

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In Active Medical Product Surveillance

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Comments on presentations

- Three interesting, and insightful presentations, very different focuses but some clear common themes.
 - All speakers emphasize that there are elements that are hard/impossible to standardize in the use of a surveillance framework for signal refinement
 - Different diseases, drugs, populations, data sets etc
 - General emphasis of the importance of the signal refinement process including other data in addition to observational databases
- Walker discussed the risks of ‘Signal amplification’ and role of re-analysis of original data and consideration of alternative hypothesis
 - How much of this should have been in signal detection phase?
- Santanello provided a check list of steps and challenges with signal refinement
 - Goals is deciding what signals need to go to evaluation,
 - But also in facilitating the development a well-specified hypothesis
- Morris made some suggestions for design choices that are ‘necessary causes’ for sustainability of Sentinel
 - One needs to ensure these design choices are indeed essential by extensive evaluation



Need for increased clarity on goal of signal refinement

- Some aspects to consider
 - Produce a testable hypothesis
 - Glean as much information as possible from the available data in a timely manner
 - Construction of an audit trail of what potential hypotheses have been considered and how, in an iterative signal refinement process
- Signal refinement needs to focus on providing more information about signals not just more data related to the signals
- Need to communicate and educate on the value of refinement
 - E.g. When signal evaluation confirms a refined signal some will question the necessity for the time to do evaluation

Specific challenges in refinement using multiple observational databases

- **Need to focus on specific challenges; consider signal amplification**
- **Size of data sets (one or several) important for refinement of potentially rare spontaneous report signals (power)**
- Consideration of more data can readily reduce chance variability, but less likely to reduce bias... increase precision, not necessarily accuracy
- **‘Accurate but imprecise’ better than ‘inaccurately precise’**
 - Can give an unhelpful impression that have clear actionable answer
- **Ensure that analysis of multiple databases avoids inaccurate precision**
 - Focus on approaches to use on ensembles of data sets to detect and minimize biases present in one or another data set
 - If can reliably detect and show variability across data sets, including biases, this will lead to increased visibility in the imprecision in a signal refinement analysis; so approaches to minimize the imprecision can be considered and prioritized in the design of an evaluation phase