Active PM surveillance and considerations for an active comparator NOAC Reversal Agents

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Concepts that I will cover

- Active Surveillance
- Identification/selection of comparators
- Benefit-Risk balance

What is ‘Active Surveillance’

- Systematic process for capturing and analyzing health care data sources to better understand the effects of medical products (in combination with data from RCTs, Pharmacovig, etc)
- Minimal lag in data availability
- Characterize ‘actual use’
- Provide insight into benefit-risk

What is the exact question we are trying to address?

- Usage (appropriate) of NOAC reversal agents?
- Events associated with NOAC reversal agents?
- Compared to what?
- Both are tied to selection of patients for NOAC vs. alternative and the rates of events for each leading to use of reversal agent.

What drives decisions: Implementing Active Surveillance

- Capture of Exposure
  - Can we 'see' use of NOAC reversal agent
    - Inpt, Outpt, Nursing homes
- Frequency of events (use of reversal agent)
  - Indication for reversal agents (MB) <3%
- Outcomes
  - Can we follow patient and 'see' outcomes of interest
- How representative must the sample be?
- Comparison/Control group

Possible study designs for Active Surveillance

PROSPECTIVE and Concurrent

- Cluster randomization/stepped wedge
- Registry
- Case-control monitoring

RETROSPECTIVE

- Database
- Registry

What you may/may not 'see' or not see clearly enough

- Seeing claim requires specific reimbursement, particularly outpatient
  - Procedure code but must be billed separately
  - Potential comparators (prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) in combination with vitamin K) may not be visible
- How much was administered
- Who administered/ordered it and what was the setting for administration?
- Was the NOAC stopped? When?
- Site of bleed, how severe or was there actually a bleed?
- Rationale for reversal agent
  - initiated prophylactically (e.g., start of emergency surgery because you are on a NOAC) or once you started to bleed?
  - Will you be given the right reversal agent? May not know what NOAC you are on when they see you.

Site (place) of Use Will Influence Capture of Information

- Outpatient
- Inpatient on floor
- In the OR
- In the ER

Comparators for NOAC Reversal Agents?

- Warfarin: Discontinuation, Fresh frozen plasma, PCC, etc
- Among comparable patients (warfarin vs. NOAC or NOAC1 vs. NOAC2), how frequently are reversals undertaken and what is the outcome?
  - Comparable patients (propensity)
- Or is the question, among anti-coagulated patients who receive ‘reversal treatment’, is there a substantive difference in use and outcome?

Different ways to get to comparators

- Self-controlled designs
- Clinical rationale
- Empiric selection from database using propensity score to assure clinical equipoise
- Specify alternatives based on clinical insight
- Historical: what has happened without agents, ‘standard of care’

One approach Using Hospital Data

- Is there a situation that would meet criteria for using a NOAC reversal agent in an office setting without immediate ER/hospital referral?
- Assume that NOAC reversal agents will be administered in hospital setting
  - PREMIER -G.Magee, C. Peters, A. Zbrozek. Analysis of Inpatient Use of Fresh Frozen Plasma and Other Therapies and Associated Outcomes in Patients with Major Bleeds from Vitamin K Antagonism. Clin Ther. 2013;35:1432–1443
  - Will not know which NOAC patient was taking but can do source record abstraction (xx%)
- Can then 'count' instances of use outside of hospital in broader database that will also capture broader outcome
- Historical controls
- Comparison of rates
- Nested case-control study with record abstraction