Trial designs for establishing efficacy and safety of anticoagulant reversal agents

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Need for Clinical Outcome Study

- No other way to assess safety in target population
- No guarantee that coagulation parameter reversal will improve outcomes
- Coagulation parameter reversal is not a ‘validated surrogate’

Clinical Studies Very Challenging

- Difficult Patient Populations
  - Actively Bleeding or emergency surgery
  - Eligible patients not common at any one centre
- What clinical response?
  - Cessation of, or reduced, bleeding?
  - Death, transfusion, length of stay?
- Safety evaluation difficult
  - Patients have thrombotic risk
  - Patients are already very sick

Randomized Trial

- Best design by far BUT technically challenging
  - Difficult to randomize acutely ill patients
  - Only several thousand eligible patients per year in USA actually eligible
  - Ethical concerns, no active control for any current agents
    - Especially difficult to finish trial if agents become commercially available during trial
  - Sample size challenging, depending on outcome

Stepped Wedge Randomized Trial

- Antidote introduced to centres progressively in waves
- Order of introduction randomized
- All eligible patients at centre get usual care before antidote introduced
  - All get antidote after its introduced
- Centres with antidote compared to those not having it yet, at each step (randomized)

Stepped Wedge: problems

- Difficult to establish complete capture of eligible patients
- Consent needed or not?
  - Getting consent challenging
- Problem of outcome assessment
- Unusual design for registration trial

Non-randomized designs

- Cohort Study of well defined bleeding patient population receiving reversal agent
  - Careful description of efficacy outcomes, adverse events, coagulation parameters, etc
- Advantage is practicality, ease of enrollment, no ethical issues
- Disadvantage is lack of comparative group
  - What if there are thrombotic events?
  - Are these natural history or due to reversal agent?

Non-Randomized Comparative groups

- Historical control patients
  - Do these exist?
- Contemporary control patients
  - group not receiving antidote
  - Different centres or different countries
- Contemporary control of patients on warfarin
  - Contemporary parallel cohort study

Two Contemporary Parallel Cohorts

- Two cohorts
  - NOAC patients receiving reversal agent
  - Warfarin patients receiving PCC/plasma
- Same inclusion criteria
  - Same outcome (possibly K-centra bleeding cessation outcome) with blinded adjudication
  - Patients enrolled at same centres
- No formal hypothesis testing because groups not randomized
  - Warfarin patients receiving PCC serve as ‘Comparative Reference Population’