How should studies be designed to evaluate new carotid protection devices and stents?

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A good---no, a great---question! There is no “one” answer

- The answer will depend on:
  - Goals of the new technology
    - “Me too” vs. new/improved
    - Regulatory approval?
  - Chosen comparator
    - CEA
    - Pre-existing class of CAS devices: yes or no
    - Pre-existing CAS outcomes
  - Capacity for duration, size and cost of the trial

What are the options for study designs?

- Trial types
  - RCT vs. CEA (or CAS)
  - Single-arm vs. a performance goal (PG)
- Primary endpoints
  - Clinical: death/stroke/MI (DSMI)
  - Composite Morbidity Measure (CMM)
  - Surrogate: MR-DWI or neuropsychometric testing
- Study populations
  - Standard or high-risk for CEA
  - Symptomatic and/or asymptomatic

Generic considerations

- The event rates of interest (death/stroke) for a new device in carotid intervention---CEA or CAS---are very low
  - This means that if the goal is to prove superiority of a new device, a large (several thousand) trial is necessary
    - Even with inclusion of only symptomatic patients, it is difficult to adequately “enrich” the population to increase events and lower trial numbers
- Experimental environment is key (willingness to change practice patterns for the study of new device)

Considerations: Trial type

- RCT vs. CEA (or CAS)
  - Highest level of evidence
  - Typically reserved for proof of superiority
  - If done on clinical outcomes basis are large, expensive, lengthy trials
- Single-arm vs. a performance goal (PG)
  - Most common
  - Non-inferiority with a PG with upper boundary of 95% CI
  - Much smaller and shorter study, even with clinical endpoints

Considerations: primary endpoints

- Clinical
  - Death/stroke for new devices most relevant (MI less so), but for US regulatory purposes it will be a composite of all 3 endpoints. If a comparison to CEA, all are important
    - FDA-driven standard for new devices
    - The composite also helps with increasing the event rate and therefore reduces the size of the trial

Considerations: primary endpoints

- Surrogate
  - MR-DWI is a very sensitive marker of embolic activity, represents cellular edema
    - A reasonable set of data exist for indirect comparison
    - Direct (randomized) comparison does not require nearly the number of patients as clinical endpoint trial, especially if “treatment effect” is substantial (e.g., device results in significant reduction of embolic activity)
  - Neuropsychometric (cognative) testing is too “blunt” a tool to distinguish outcomes

Considerations: Secondary endpoints

- Composite Morbidity Measure (CMM)
  - cranial/peripheral nerve injury
  - vascular injury
  - non-cerebral bleeding
  - wound complications related to the neck incision/femoral puncture site
  - anesthetic complications

Considerations: study population

- High vs. standard CEA risk
  - PG event rates are higher in high-risk patients= smaller trial
- Symptomatic and/or asymptomatic
  - If randomized trial, can be any combination
  - If PG trial, can also be any combination since the PG will be adjusted for the final mix of patients
  - Practical point: there are many more potential asymptomatic patients for inclusion

Conclusion

- For new devices seeking regulatory approval:
  - a single-arm in high-surgical risk patients in a mixed symptom population using an established clinical PG
- For new devices seeking to demonstrate greater procedural effectiveness
  - Single-arm or randomized in any population of patients using surrogate endpoint of MR-DWI
  - clinical endpoints will also need to be collected/compared, but the trial does not need to be powered to show differences there

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