Study Design and Statistical Considerations for Neurothrombectomy Device Studies

Laura Thompson, Ph.D.
Mathematical Statistician
Division of Biostatistics
Office of Surveillance and Biometrics
Center for Devices and Radiological Health

Outline of Topics

- Issues with control groups
- Adaptive Designs
- Patient Selection mechanisms
- Blinding of assigned treatments
- Responder analysis versus ordinal ranking for outcome scales.
- Data Pooling/Leveraging: combining prior and current studies, or subgroups within a study

Issues with Control Groups

- Concurrent and randomized controls offer unbiased statistical inference.
- Historical controls may be an option if the control has a wealth of patient-level information.
  - A statistical adjustment is needed for the analysis to emulate a randomized controlled trial. (Not perfect!)
  - A compromise could be to incorporate some historical controls to reduce the size of concurrent controls.
- What is an appropriate control group?

Adaptive Designs

- Adaptively modify aspects of the trial using interim results in a prospectively specified way, while also controlling for potential bias.
  - Sample size re-estimation
  - Adaptive enrichment of patient population
  - Stopping a trial early for success or futility based on interim results
- Prospective specification is necessary to avoid inflicting bias.

Patient Selection Mechanisms

- Goal is to identify the broadest patient population expected to benefit from the new device, while also increasing precision of treatment effect.

  1. Restrict eligibility criteria based on predicted response to treatment.
  2. Use imaging modalities to select patients.
  3. Stratified randomization to reduce variability.
  4. Enrich patient population adaptively within the trial.

- How can patient selection be improved in these trials?

Blinding patients to treatment vs. Open-label trials

- Open-label trials have been typical.
- Risk of treatment bias, physician bias, enrollment difficulties.
- Are there alternative ways to mask patients/physicians?
- Is blinded evaluation a compromise?

Responder Analysis vs. Ordinal Scale Ranking

- Rating scales such as mRS are customarily dichotomized into success or failure for easier interpretation.
- Dichotomous endpoints typically have lower power to detect a treatment effect than do ordinal or interval scale endpoints.
- Should a proposed treatment be expected to result in more “responses” than a control, or could it instead increase the tendency to rate better on the scale?

Leveraging Information from Prior Studies

- Prior studies may be available from which to inform the analysis of a new study.
- The information may be incorporated quantitatively to reduce the amount of new information needed from the new study.
- The prior studies should be considered similar enough to the new study so that we wouldn't expect the new results to lead to a different conclusion.

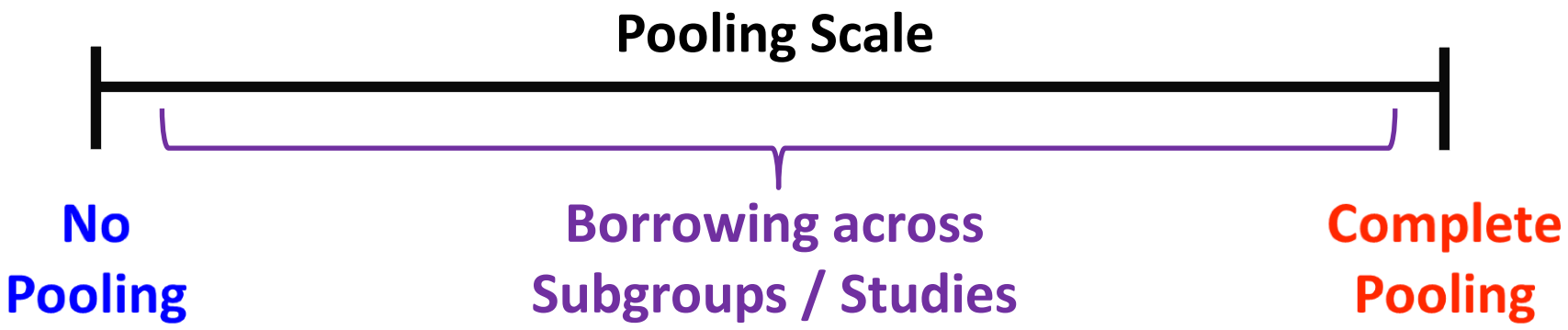
Leveraging Information from Prior Studies

- Various ways to leverage prior data
  - Statistically combine treatment effects across prior and current studies to increase precision in a current study.
  - Statistically combine outcomes from a control group across studies (e.g., combining historical and current controls).
  - Leverage information across *subgroups* within a study (e.g., stroke locations).

Leveraging vs. "Pooling"

- **No pooling:** New trial data (N) is completely separate from historical (H)
- **Complete pooling:** Subjects in H and N carry the same weight

- **Leveraging ("Partial" pooling):**
  - Weight of H depends on its similarity with N, and H's sample size
  - Evidence-based borrowing.



Data Pooling/Leveraging

- Recommendations for designing a study with leveraging:
  - Prospective selection of prior studies
  - Description of borrowing model.
- Leveraging across trials with different eligibility criteria
  - Baseline or concomitant variables may be useful to account for differences.
  - Information borrowed across trials will exclude this difference.
- Detailed presentation tomorrow…

Recommendations

- Discuss with FDA early re: study design
- Borrowing from prior studies may increase precision but require additional pre-meetings
- Adaptive designs and borrowing can address study design uncertainty but may need simulations to assess operating characteristics (e.g., type I error rate) under different trial scenarios.