Approaching Interim Analysis

Yuko Y. Palesch, PhD
Renee L. Martin, PhD
Sharon Yeatts, PhD

Medical University of South Carolina
Advantages of Early Stopping

• Cost savings
  ⇒ not wasting resources on duds if futile
  ⇒ getting effective tx to market earlier

• Ethical issues
  ⇒ not exposing subjects to inferior tx
  ⇒ getting effective drug to patients earlier
Statistical Challenges of Interim Analysis

• High variability in early stages of the study with small N.
• If stop early for efficacy, tend to overestimate tx effect and its precision\textsuperscript{1}.
• This bias may or may not affect meta-analysis that includes truncated RCTs\textsuperscript{2-4}.

\textsuperscript{2} Bassler D, et al. *JAMA* 2010; 303: 1180-7; letters to the editors *JAMA* 2010;304:157-160.
\textsuperscript{3} Bassler D, et al. SMMR 2011;
\textsuperscript{4} Schou IM, Marschner IC. *SIM* 2013;32:4859-74.
Considerations for Interim Analysis

- Slow recruitment (hence, long study period)
- Multiple protocol amendments (unplanned AD)
  - change in medical management (e.g., new tx)
  - change in patient characteristics
  - affect cond’l power assumption?
• Large # of clinical sites
  ➡ variability in medical management
  ➡ learning curves amplified (with protocol, tx admin)
  ➡ may lead to dilution of tx effect
  ➡ treatment-by-site interaction could complicate the interpretation of IA results.
Example of IMS III Trial*

• Compare IV tPA (CTL) vs IV tPA + endovascular thromboysis (TX) in acute ischemic stroke patients.
• N=900; # sites ≈ 60.
• Had 4 protocol amendments with introduction of new devices with each.
• Very slow recruitment of subjects (~10/mo).
• 3 IAs planned with OF boundaries for efficacy.
• 3 conditional power analysis planned for futility.

Example of IMS III Trial*

Was conditional power affected by slow recruitment, multiple amendments, and learning curves?

N=656 from 58 sites

N=225 CP=42%  N=347 CP=30%  N=450 CP=23%  N=587 CP=4%

Example of ALIAS Parts 1* & 2** Trials

• Compare Saline (SAL) vs Albumin (ALB), above and beyond std of care (tPA or not), in acute ischemic stroke patients.
• N=1,800 in Part 1; N=1,100 in Part 2 with ~90 sites.
• Part 1 - stopped for safety concerns.
• Part 2 - 3 IAs planned with OF boundaries for both efficacy and futility.

Example of ALIAS Parts 1* & 2** Trials

Like the Part 1 Trial, except in opposite direction.

Part 1 (N=434; ~50 sites)

Part 2 (N=841; ~90 sites)

SAL similar to CTL in IMS III


Example of ALIAS Part 2 Trial*

Had we used PK boundary, we’d had stopped for efficacy

What, if anything, was happening in the SAL group over time?

Summary

• Choose IA timing (esp. the first one) carefully – don’t plan on one too early.
• Assess and address the learning curve, if any, of tx administration and protocol adherence.
• Be cognizant of temporal trends in patient characteristics, clinical standards of care, potential treatment-by-site interaction, etc. (Simulation accounting for above factors at the design stage may be helpful.)
• Expect the unexpected.
Acknowledgement:

Lydia Foster, MS
Jamie Speiser, MS
Yanqiu Weng, DDS, PhD
ALIAS and IMS 3 Investigators

Funding from NINDS (U01-NS54630, U01-NS077306, U01-059041)

Thank You