Adaptive Clinical Trial Design: A Case Study

Statistical Considerations

Rebecca A. Betensky, Ph.D.
VALOR trial adaptive design: advantages

- **Feasible**: proven!
- **Simple**: one possible adaptation, pre-defined
- **Potentially efficient**:  
  - Initial partial investment; fully investment only when evidence for effect  
  - May yield positive result, where standard design would not  
  - May avoid need for second, larger trial  
  - May lead to discovery of effective treatment, where standard design would not
VALOR trial design: complexities

- Decisions for Data Safety Monitoring Board
- Influence on patients: drop-out, compliance, entry
- Technical issues regarding statistical inference
Data Safety Monitoring Board

• DSMB’s role is critical and difficult; must evaluate safety in light of three possible interim results:
  • Favorable (no increase in sample size)
  • Promising (increase in sample size)
  • Unfavorable (no increase in sample size)

• A decision to continue the trial based on a mixed safety profile will be informed by favorable vs. promising vs. unfavorable outcome.
  • Combined decision (based on safety and efficacy) not pre-specified.
  • Burden of decision to continue the trial is greater with potential to increase sample size.
Influence on patients

• At interim, based on decision, treatment effect estimate may be narrowly defined
  • If sample size increased, known to be within \((X_1,X_2)\)
  • If sample size not increased, known to be within \((X_2,X_3)\) or \((X_0,X_1)\); prior studies, or continuation in light of known safety concerns may make one of these very likely

• This may influence mix of patients who enter the trial and/or who drop out of the trial.

• Thus, patient population may change during the course of the trial as a result of treatment effect seen at interim.
Statistical Issues

• Even if interim results have no influence on patients’ decisions, inference about treatment effect (e.g., estimates, p-values, confidence intervals) is non-standard.

• Complex selection bias mechanisms (drop-out, compliance, entry) induced at interim make valid assessment of treatment effect even more difficult.
Extensions?

- Safety could be formally included with efficacy in the interim analysis decision.

- Examine interim results within pre-defined subgroups of patients; increase enrollment in those subgroups if they appear promising.

- Any circumstances under which to decrease sample size?

- Would a second interim every be worthwhile? Further increase in sample size?