

# Flexible Clinical Trial Designs Based on Bayesian Methods

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# Basic Features of Bayesian Adaptive Trials

- ▶ Adaptive Randomization
- ▶ Sequential Stopping Rules
- ▶ Bayesian Decision Criteria
- ▶ Aim is to protect interests (minimize harms) of subjects in trial

## c.f. Conventional Trial Design

- ▶ Balanced: equal samples in each group
- ▶ Total sample size is pre-determined
  - ▶ subject to interim analysis and early termination
  - ▶ early stopping rules generally conservative
- ▶ Frequentist analysis
  - ▶ ttest, chisquare and associated intervals
- ▶ Optimizes benefits for those treated subsequent to trial.

# Limitations of "Classical" RCT

- ▶ Assumptions underlying sample size calculation may be wrong
  - ▶ Conservative assumptions may yield trial that is unnecessarily large
- ▶ Accumulating evidence during trial may shift equipoise
- ▶ Sample size requirements may be infeasible
  - ▶ The bar may be set too high
  - ▶ May exceed recruitment population
- ▶ Interests of subjects sacrificed to greater good

# Adaptive Randomization

- ▶ Randomization probabilities adapt over trial to favour the winning therapy
- ▶ Works best if primary outcome discovered quickly
  - ▶ Play the winner = PTW
  - ▶ urn or biased coin methods for randomization
- ▶ More subjects treated with the best therapy
- ▶ Reduction in expected number of failures
  - ▶ Though reductions are not typically "large"
- ▶ Sample size requirements differ little from standard approach

Barriers to acceptance - ECMO trial

# Sequential Trials

- ▶ Multiple interim analyses facilitates early stopping
- ▶ Analysis may be performed at every step or in chunks (group sequential designs)
- ▶ Final statistical report must adjust for the stopping rule
- ▶ Sample sizes variable may exceed fixed design requirements
- ▶ Failure reduction not as great as adaptive randomization

# Bayesian Inference

- ▶ Intuitive method for incorporating data in decision making
- ▶ Same logic as diagnostic test interpretation
  - ▶ Prior probability of disease +
  - ▶ Test Result
  - ▶ yields Post-test probability
- ▶ Classical methods "disdain" use of prior probabilities
- ▶ In typical cases, results are relatively insensitive to specification of prior

# Bayesian Adaptive Randomization

- ▶ Seamless integration of adaptive, sequential and Bayesian concepts
- ▶  $P_C$  = success probability for control therapy
- ▶  $P_E$  = success probability for experimental
- ▶ Primary criterion for inference:  $Prob\{P_E > P_C\}$
- ▶ Begin with prior specification for  $Prob\{P_E > P_C\}$
- ▶ Successive observations lead to updating of  $Prob\{P_E > P_C\}$  via Bayes rule
- ▶ Randomization probability (E vs C) is calculated from  $Prob\{P_E > P_C\}$
- ▶ Trial stops when  $Prob\{P_E > P_C\}$  is sufficiently large or small.

# Pros and Cons

## Pros:

- ▶ Sample size requirements are smaller
- ▶ Bayesian framework is flexible
  - ▶ Particularly good for 3+ Arm trials, allows early dropping of arms
  - ▶ Allowance can be made for for dynamics of therapy e.g time horizon to further advances
  - ▶ Prior knowledge can be incorporated into inferences
  - ▶ Combination of evidence from study phases is "easy"
- ▶ Futility and safety monitoring rules natural in sequential framework
- ▶ Bayesian outputs are more directly interpretable (unlike P-values)

## Cons:

- ▶ Choice of "prior probabilities" may be prone to debate
- ▶ Bayesian methods unfamiliar to many clinicians.

# Hybrid Approach

A compromise:

- ▶ Approach accounts for type I error and power values, see:
  - ▶ Berry, Bayesian clinical trials, Nature Reviews Drug Discovery 5, 27-36 (2006)
  - ▶ Scott & Baker, Overhauling clinical trials, Nature Biotechnology 25, 287-292 (2007)
  - ▶ Thall & Wathen, Practical Bayesian adaptive randomisation in clinical trials , European Journal of Cancer Volume 43(5) 859866 (2007)

Design software from M.D. Anderson biostats group