Issues in Planning and Interpreting Small Trials: How To Make Their Data Meaningful

What is a Small Trial*?  
- Trial in which the number of subjects is **unavoidably** small  
- Statistical power may not be adequate by traditional standards

* IOM Report on Small Trials - 2001

When is a Small Trial Appropriate?  
- Rare disease or unusual population (e.g., astronauts, siamese twins)  
- Unusual treatment (individualized gene-based therapies)  
- Isolated populations (Antarctic research stations, submarines, etc.)

* IOM Report on Small Trials - 2001

When is a Small Trial NOT Appropriate?  
- Adequate numbers of subjects are available but the trial would be expensive or annoying to conduct  
- Investigator doesn’t want to do a traditional trial

* IOM Report on Small Trials - 2001

Pilot Studies and Small Trials  
- Pilot studies are intended to establish effect sizes and lead to larger trials  
- Small trials may never be repeated  
- Both should meet highest feasible design standards, but small trials especially

Disclosure
- No Conflicts
Small Trials

- The greatest difference between small trials and traditional trials is that small trial inferences are more uncertain.
- Both should meet highest feasible design standards, but small trials especially.

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Small Trials – Special Designs

- N-of-1 designs (multiple blinded trials of Rx in one patient)
- Adaptive designs (play the winner)
- Risk-based allocation (sicker patients more likely to get experimental Rx)

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Small Trials – Special Designs

- N-of-1 designs (multiple blinded trials of Rx in one patient)
  - Conventional & experimental treatments are applied randomly over multiple cycles until the superior one declares itself
  - Rx has to be amenable to crossover so may not be ideal for surgery

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Small Trials – Special Designs

- Adaptive designs (play the winner)
  - First subject randomized – remaining subjects accrue to that Rx until AE occurs – Next and subsequent subjects accrue to the alternate Rx until AE occurs; repeat
  - Minimizes exposure to inferior treatment

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Small Trials – Special Designs

- Risk-based allocation (sicker patients more likely to get experimental Rx)
  - Not being given “new” Rx may be unacceptable to some subjects. Changing allocation probabilities by disease severity permits in-sample Rx heterogeneity

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Conclusion?

- Small trials are not ideal and are to be avoided if possible
- Estimates from Rz trials are still incredibly valuable and represent best unbiased estimates
- Bayesian analyses may provide greatest information on probable effects