Conducting Clinical Trials

Jason Connor, PhD
Berry Consultants, Austin TX
University of Central Florida College of Medicine, Orlando FL

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My task

- What levels of evidence are needed to warrant clinical use?
- What considerations are important when designing clinical trials?
- What challenges exist for developing clinical trials for non-invasive neuromodulation devices?
- How can clinical trials be conducted effectively?

Personalized Medicine & 21st Century Clinical Trials

- Personalized medicine tailors therapy to a patient, his/her disease, his/her genetic profile, etc.
  - Challenge: you don't go to CVS and wait 30 min for it
- Ideally clinical trials tailor the design to answer the most important remaining scientific questions
  - Challenge: you can't use simple off-the-shelf software

Tailoring Clinical Trials

- Involve key stakeholders early
- Involve statisticians early
- Involve patients & advocates early
- Let them talk to each other
  - to identify the key questions
  - to develop methods to efficiently & ethically answer those questions
- Then discuss with FDA & consider them a team member

Quiz

- Why & when were our current standard statistical methods invented?

Irony of Biostatistics

- Our job is to identify whether new, state-of-the-art medical therapies are better for patients
  - Therapies involving lasers, robotics, genetics, biochemistry, tailored cancer vaccines, etc.

- We insist that nothing new or better has been created in our field and rely on 50 to 100-year-old methods that may not even require a computer

FDA Critical Path Initiative

From FDA website:

> Many of the tools used today to predict and evaluate product safety and efficacy are badly outdated from a scientific perspective. We have not made a concerted effort to apply new scientific knowledge -- in areas such as gene expression, analytic methods, and bioinformatics -- to medical product development. There exists tremendous opportunities to create more effective tests and tools, if we focus on the hard work necessary to turn these innovations into reliable applied sciences.
>
> http://www.fda.gov/scienceresearch/specialtopics/criticalpathinitiative/ucm077015.htm

FDA Critical Path Initiative

From FDA website:

Inefficient clinical trial designs. Innovative clinical trial design may make it possible to develop accepted protocols for smaller but smarter trials. For example, new statistical techniques may make it possible to reduce the number of people who need to receive placebo or to adaptively change the trial based on ongoing results.

Be Creative & Solve Your Problem

- Statisticians have been too good at training MDs
- There is no single recipe
- Balancing Benefits vs. Risks is very different
  - Across diseases
  - Depending upon availability of alternative therapies
  - Depending on number of patients on the horizon
  - Depending on morbidity / mortality of the disease
  - Is the implant reversible?

Simulate Clinical Trials

- Execute the trial millions of times before it is actually run
  - Run for a variety of 'true' scenarios
  - The first time you run a trial should never be the actual time you run the trial
- Incredible learning tool / amazing diagnostic
  - Shows process to MDs & stakeholders
  - Check decisions / common sense of execution
  - Analysis code / key points in SAP already written
  - Makes you think about missing data, etc. sooner
- Valuable for fixed / standard trials too

Clinically Relevant Evidence

- Consider clinical utility
  - We can agree on utility functions
- Move away from overly simplistic one-level of evidence
  - need not have 1 efficacy & 1 safety hypothesis
  - never made sence clinically or logically
- Construct trials that can learn & adapt during the trial

Why Adapt?
The Prospective Postmortem

- Imagine you run your trial and it fails
  - Result ambiguous
  - Spawns a future trial that fails (P2 leads to failed P3)
- Imagine *why* you might have ended up there
- Imagine *what* you might have done differently
  - More doses, higher doses included
  - Studied a different patient population
  - Used a larger sample size

Why Adapt?
The Prospective Postmortem

- Consider whether any adaptations might be added to *prospectively* address *potential* regrets

- Be honest with yourself in design phase
  - We overestimate treatment effects
  - We underestimate variability
  - Because we need to justify a doable trial
  - Because we can't be honest in grant proposals

What are Possible Adaptations

- Adaptive sample sizes
  - Stop early for success or stop accrual for predicted success
  - Terminate early for futility
  - Increase maximum sample size
- Adaptive randomization
  - For statistical efficiency
  - For improved patient treatment
- Combination therapies
- Adapt to responding sub-populations
- Adaptive borrowing of information
- Seamlessly combine phases of development
  - Inferentially vs. operationally seamless

Recommendations

- Disclaimer:
  - I am not a regulator, I don't speak for FDA
  - I am a scientist, a clinical trial designer
  - I believe in decency over dogma
- Remember that current trialists were trained by people who were trained by people who had seeds as patients
- Nearly all clinical trial methods were developed without considering the balance of
  - Minimizing the probability of approving a bad device
  - Maximize the probability of identifying a good device
  - Learning efficiently
  - Treating patients in the trial optimally

Recommendations

- Involve lots of stakeholders & let them communicate
- Trials can answer multiple clinically relevant questions
- Tailor methodology to unique situation
- Can adapt to focus on remaining questions
- Borrow data from previous high quality trials
  - especially for safety or new generation of device
- CDRH is very collaborative & innovative
- Be honest in concerns
  - No trial is perfect
  - Increases your scientific credibility

Would you want to be the last patient enrolled in a clinical trial?

Or the first person treated after the trial results are published?

Should there be much difference?