Pragmatic Clinical Trials: Different Strokes for Different Folks

Bruce A. Barton, Ph.D.
September 18, 2012
Purpose

• Review/Discuss Pragmatic Clinical Trials
• Discuss two case studies
• Discuss studies where PCTs are particularly beneficial
• Discuss ways to make PCTs more efficient
Pragmatic Clinical Trials

• Four major features:
  o Clinically relevant treatments – may be hard to quantify
  o Diverse patient population
  o Heterogeneous practice settings
  o Collect data on wide range of health outcomes

• Examples from past studies: GISSI Studies (60,000 patients at time of (or immediately after AMI)) or ISIS (134,000 patients having AMI)

• Let’s explore
Past Pragmatic Clinical Trials

• GISSI Studies
  o Multiple studies conducted in 60,000+ patients from 1984-2007
  o GISSI 1: Streptokinase vs. control in 11,700 patients (1984-1985) with AMI with 12 hours of onset of symptoms – results significant in favor of SK
  o GISSI 2: Streptokinase vs. tPA in 12,490 patients (1988-1989) with/without follow-up heparin with in-hospital morality or left ventricular damage outcome – results not significant
  o GISSI 3: ACE inhibitor and nitrate (2x2 factorial design) in 19,394 patients post-AMI (1991-1993) with 6-week mortality or left ventricular damage outcome – results significant for ACE inhibitors but not for nitrates
  o GISSI Prevention and GISSI AF additional studies with 10,000+ patients in each

• Open protocols taking all comers with AMI, large number of Italian hospitals/clinics, narrow set of outcomes, but treatments were on the market and clinically relevant
Past Pragmatic Clinical Trials

• ISIS (International Studies of Infarct Survival)
  o Multiple studies conducted in 134,000 patients from 1981-1993 in 20 countries
  o ISIS-1: Beta-blocker vs. placebo in 16,027 patients (1981-1985) with AMI within 12 hours of onset of symptoms – results significant in favor of beta-blocker
  o ISIS-2: Streptokinase and aspirin (2x2 factorial design) in 17,187 patients with AMI within 24 hours of onset of symptoms (1985-1988) – results significant reduction in cardiovascular events and CVD death at 5 weeks
  o ISIS-3: Streptokinase, tPA, and anistreplase with/without heparin (3x2 factorial design) with all taking aspirin in 41,299 patients with AMI within 24 hours of onset (1988-1991) with 35-day mortality and clinical event outcome – results no significant difference between treatments and aspirin alone
  o ISIS-4: ACE inhibitor, nitrate, magnesium (2x2x2 factorial design) in 58,050 patients with AMI within 24 hours of onset (1991-1993) with 5 week mortality and clinical event outcome – results significant for ACE inhibitor
PCTs Investigation - I

• **Clinically relevant treatments**

• Active treatments – treatments that your local PCP would give you – not experimental

• Looking for moderate treatment effects

• Comparative Effectiveness Research (CER) types of studies

• Treatments may also be hard to quantify – life style interventions, CAM treatments
PCT Investigation - II

- **Diverse patient population**
- PCTs – provide information to policy/decision makers
- Recruit all types of patients – why? What does this imply?
- Type of analysis – simple or complex?
- Actually looking for different responses to treatment – why?
PCT Investigation - III

• **Recruit from heterogeneous practice setting**

• Practice settings: large, small, solo
  o Group, CHCs, hospital-based, etc.

• Looking for different levels of expertise for administration/performance

• New wrinkle – predicting prescribing patterns
PCT Investigation - IV

• Collect data on a wide range of health outcomes

• Efficacy + safety outcomes – especially interested in “rare” events in addition of major outcomes in a variety of populations, situations

• In a PCT, this could be done through various means
  o How about tapping into EMR systems?
  o At what level - practice, hospital, system?
Important distinction

• Usual RCT – experimental treatment vs. “standard”
  o Cancer treatments good example
  o Intended for researchers, FDA, regulators

• PCTs tend to be comparative effectiveness in intent – compare treatments that have already been tested in a “usual” RCT
  o Results for policy makers – like CMS, MassHealth, insurance companies
  o Not for FDA – although FDA is likely interested
# PCT vs. RCT vs. Big, Simple

<table>
<thead>
<tr>
<th>Factor</th>
<th>PCT</th>
<th>RCT</th>
<th>Big, Simple</th>
</tr>
</thead>
<tbody>
<tr>
<td>Audience</td>
<td>Policy makers</td>
<td>FDA, Researchers</td>
<td>Both?</td>
</tr>
<tr>
<td>Sample</td>
<td>Heterogeneous</td>
<td>Homogeneous</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>Sample size</td>
<td>Moderate-Large</td>
<td>Small-moderate</td>
<td>Large</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Broad</td>
<td>Focused</td>
<td>Focused</td>
</tr>
<tr>
<td>Treatments</td>
<td>Heterogeneous</td>
<td>Homogenous</td>
<td>Homogenous</td>
</tr>
<tr>
<td>Tx Group Assignment</td>
<td>Random/Cluster</td>
<td>Random/Patient</td>
<td>Random/Patient</td>
</tr>
<tr>
<td>Tx Assignment</td>
<td>MD Choice/Random</td>
<td>Random</td>
<td>Random</td>
</tr>
<tr>
<td>Analysis</td>
<td>Complex</td>
<td>Straight-forward</td>
<td>Straight-forward</td>
</tr>
<tr>
<td>Therapy</td>
<td>Approved/NA</td>
<td>Pre-approval</td>
<td>Both?</td>
</tr>
<tr>
<td>Adaptive designs</td>
<td>Bayesian/none</td>
<td>Frequentist</td>
<td>Frequentist</td>
</tr>
</tbody>
</table>
Case Study 1: Diabetes Medication

- Population: Type II diabetics already on Metformin
- Treatment:
  - Sulfonylurea
  - DDP-4 inhibitor
  - GLP-1 receptor agonist
  - Insulin
- Sample size: 6000 patients
- No. of clinical sites: 41
- Design: PCT with randomization to drug (1:1:1:1)
- Outcome: A1c levels over 5 years, clinical outcomes
- Length of study: 8 years
Case Study 1: Diabetes Medication

• Analysis plan
  o Cox regression - time to achieve A1c < 7.0
    • Predictors: drug, baseline A1c
  o Interim analysis: none

• Major problem #1: can declare one treatment(s) superior to others, but that may not be true for everyone - no attention to HTE

• Major problem #2: By the time this study is finished (8 years), these drugs will be supplanted by others and potentially even new classes of drugs - rendering this study virtually meaningless
Case Study II: Surgery vs. Endovascular Tx for CLI

- **Population**: Patients with Critical Limb Ischemia
- **Treatments**: Surgical therapy – four types of grafts with three well established surgical techniques permitted
  - Endovascular therapy – any angioplasty, stenting with any stent, and any artherectomy
- **Sample size**: 2100
- **No. of clinical sites**: 120
- **Design**: PCT with randomization to class of treatment; actual treatment chosen by MD
- **Outcome**: Major adverse limb event (MALE)
- **Length of study**: 5 years
Case Study II: Surgery vs. Endovascular Tx for CLI

• Analysis plan:
  o Primary analysis of MALE: Log rank comparing distributions of MALE-free survival between surgery and endovascular groups
  o Secondary Analysis of MALE: Cox model adjusting for covariates imbalanced at baseline and covariates known to be associated with outcome

• Major problem: Can say which general approach is “better”, but not which technique or for whom?
• What would you do for analysis?
PCT Design Strategies

• Multiple arm studies - randomization at the patient level
• Cluster randomized study – randomization at the cluster level (i.e., practice, NH, ILF)
• Two arm study with multiple treatments possible – randomization at the patient → arm level
• Remember – PCTs are not just surveillance studies
• Term “Trial” indicates that you are testing something
PCT Analysis Strategies

• Clearly, much more subgroup analysis to get at the HTE issue
• In depth investigation of treatment effect – latent class analysis to identify particularly effective (or not) treatments in subgroups of patients
• Approach – look at response of individual patients with interest in grouping into similar response groups
• Techniques that allow the modeling (and eventual grouping) of individual patient responses
PCT Analysis Strategies

• Specific approaches
• Mixed effect models for continuous outcomes to model individual trajectories
• Non-linear mixed effect models for binary or categorical outcomes to model response probabilities
• Survival analysis: start with Cox models, but then move into frailty models – essentially Cox models with random effects included, ideal for looking at response of individual patients/groups of patients
## Types of Studies Suited for PCTs

<table>
<thead>
<tr>
<th>Studies in Elderly</th>
<th>Clinically Relevant Treatments</th>
<th>Diverse Patient Population</th>
<th>Varied Practice Settings</th>
<th>Range of Health Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meds, LSI, Psych</td>
<td>60-90</td>
<td>PCP, OP, ILF</td>
<td>Pain, Clinical Measures, Depression</td>
<td></td>
</tr>
<tr>
<td>Exercise / LSI</td>
<td>Aerobic, resistance</td>
<td>All comers</td>
<td>PCP, Home</td>
<td>Pain, CM, Depression</td>
</tr>
<tr>
<td>Tai-Chi / CAM</td>
<td>Aerobic, herbal</td>
<td>All comers</td>
<td>PCP, Home</td>
<td>BP, CM, Depression</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Meds, LSI</td>
<td>Type 2</td>
<td>PCP, OP</td>
<td>A1c, CM</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Meds, LSI</td>
<td>All ↑ BP</td>
<td>PCP, OP</td>
<td>BP, CM</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Meds, LSI</td>
<td>Range of disorder/sev</td>
<td>Psych</td>
<td>Depression, symptoms</td>
</tr>
<tr>
<td>Cardiology</td>
<td>Meds, LSI</td>
<td>All ↑ symp</td>
<td>Cardio</td>
<td>CM</td>
</tr>
</tbody>
</table>
Beyond PCTs

• So far, straight-forward discussion of where we are in the development of PCTs
• But what is next?
• How can we make PCTs more effective, more efficient, and more meaningful?
• Can we incorporate prior information into our current results to provide for better prediction?
• Potentially, Bayesian approaches/statistics can help
Bayesian Statistics - Definition

• As opposed to the point estimators (means, variances) used by classical (frequentist) statistics, Bayesian statistics are concerned with generating the posterior distribution of the unknown parameters (say, treatment effect) given both the current, observed data and some prior density for these parameters. As such, Bayesian statistics provide a much more complete picture of the uncertainty in the estimation of the unknown parameters.
History of Bayesian Statistics

- Thomas Bayes (1702–1761), English mathematician and Presbyterian minister
- In the early eighteenth century, many problems concerning the probability of certain events were solved
- For example, given a specified number of white and black balls in an urn, what is the probability of drawing a black ball?
- Attention turned to the converse: given that one or more balls has been drawn, what can be said about the number of white and black balls in the urn?
- Bayes' solution was published posthumously (1763) in An Essay towards solving a Problem in the Doctrine of Chances
- This essay contains a statement of a special case of Bayes’ Theorem
History of Bayesian Statistics

• Pierre-Simon Laplace (1749–1827) introduced a general version of the theorem and applied it to celestial movements, medical statistics, and reliability.

• When insufficient knowledge was available to specify an informed prior, Laplace used uniform priors, according to his “principle of insufficient reason.”

• This early Bayesian inference was called “inverse probability” because it infers backwards from observations to parameters, or from effects to causes.)
History of Bayesian Statistics

- After the 1920s, inverse probability was largely supplanted by a collection of methods that were developed by R. A. Fisher, Jerzy Neyman, and Egon Pearson dealing with sampling theory.
- Their methods came to be called frequentist statistics.
- Fisher initially rejected the Bayesian view, but, later, expressed greater respect for the essay of Bayes, which Fisher believed anticipated his own approach to probability.
- Neyman started out as a "quasi-Bayesian", but subsequently developed confidence intervals because "the whole theory would look nicer if it were built from the start without reference to Bayesianism and priors.”
- The word Bayesian appeared in the 1930s, and by the 1960s was in widespread use.
Closet Bayesians?

• Are we all closet Bayesians?

• Maybe – consider a typical research paper reporting results from an RCT:
  o Introduction = qualitative statement of prior probabilities
  o Methods = still description of methods of conduct of the study
  o Results = report of the results of the current study – typically frequentist methods
  o Discussion = qualitative Bayesian analysis – statement of the posterior probabilities

• A Bayesian analysis “just” takes these qualitative statements and makes them quantitative
Closet Bayesians?

• Also consider how frequentists put together prior studies and combine them with the current study
• We combine the summary statistics from relevant studies into a weighted analysis of past data
• We call it meta-analysis
• Really, not very far removed from a Bayesian analysis
PCT/RCT Evolution

• Next step in evolution of clinical trials in general is to incorporate Bayesian approaches to analysis and monitoring

• We currently perform interim analyses and adaptive designs in RCTs (and PCTs) using frequentist measures

• Much easier to implement using Bayesian approaches – while avoiding the statistical penalties of current interim analytic approaches
  o Alpha- and beta-spending functions, monitoring bounds (O’Brien-Fleming, Pocock, etc.), and the whole industry that supports it (EAST software)
PCT/RCT Evolution

• How do we avoid the usual statistical price from repeated looks at the data?
• Remember that Bayesian statistics produce posteriors distributions – so there is no “right” or “wrong” answer – there is no alpha or beta error – only the distribution of probabilities
• Thus, it is easy to change study design (i.e., add new treatments or drop old treatments) without affecting the other treatments
FDA Stance

• Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials
• Released in February, 2010
• Covers many areas of interest:
  o What are Bayesian Statistics
  o Outcomes for Bayesian clinical trials (BCTs)
  o Design of BCTs
  o Analysis of BCTs
  o Bayesian principles in post-marketing surveillance

• Also mentioned in Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics
Applications - RCTs

• Highly adaptive study designs such as I-SPY 2
• I-SPY 2 (investigation of serial studies to predict your therapeutic response with imaging and molecular analysis 2) is a process targeting the rapid, focused clinical development of paired oncologic therapies and biomarkers
• The framework is a hyper-adaptive phase II clinical trial design in the neoadjuvant setting for women with locally advanced breast cancer
• Design allows new therapeutic arms to be added and non-effective arms dropped “easily” without paying a statistical price
Applications - PCTs

• Using highly adaptive study designs such as I-SPY 2, PCTs can continually evolve with the changing market to add new treatments (or any/all types) while dropping non-effective treatments.

• In the current research arena where new treatments are continually evolving – and even “old” therapies are being repurposed and repositioned – this flexibility is essential.

• Case in point – previous Diabetes case study.
Applications - HSR

• In HSR, what are the implications and applications?
• Beyond PCTs, which are definitely part of HSR, primary impact in predictive modeling
• Questions such as “What patients have the highest expenditures in Medicaid” – are clearly predictive in intent
• Rather than give a set answer from, say, the previous year, can we construct a set of prior probabilities to better predict future expenditures – and generate the posterior distribution of expenditure probabilities?
\textbf{Next “Concrete” Steps}

- More scholarship/training in Bayesian approaches, especially in the analysis of randomized – and pragmatic – clinical trials
- Better understanding of monitoring of study results while data accumulates through a clinical trial
- More experimentation/workshops in Bayesian approaches to predictive modeling
- Drawbacks? Sure
- World is not ready to drop all p-values
- Also need good education program for clinicians – and even reviewers – to understand this process
Conclusions

• PCTs take RCTs to the next step
• PCTs are evolving to reflect changes in the medical care “marketplace”
• Innovation (efficiency, delivery) and implementation (moving research into practice) are the new order
• Efforts underway to set the standards for progression from research to CER to implementation
• Evaluation of Bayesian approaches for RCTs/PCTs
• Better PCT design and analysis
Questions?