Innovation and Statistics: A Medical Device Perspective

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Outline

- Medical Device Innovation
- Innovation in Statistics
- Statistical Innovations in Devices
  1. Bayesian Statistics in Clinical Trials
  2. Adaptive Trials
  3. Propensity Score Methodology
  4. Diagnostic Test Evaluation; Companion Diagnostics
  5. Missing Data
- The Future of Innovation in Medical Devices and in Statistics
- Concluding Remarks
Top 10 Medical Innovations

- Released each year in October by Cleveland Clinic
- In the past years, half of the innovations have been medical devices or diagnostics and about 1/3 have been approved by FDA including:
  - Retinal prosthesis system
  - Genome-guided solid tumor diagnostics
  - Hand-held optical scan for melanoma
  - Digital breast tomosynthesis (3-D mammography)
  - Implantable device to treat complex brain aneurysms
  - Increasing discovery with Next Generation Sequencing
  - CT scans for early detection of lung cancer (spiral CT)
Top 10 Medical Innovations 2016

- Released last October by Cleveland Clinic
- 5 of the 10 were medical devices:
  - Cell-free fetal testing (from maternal blood)
  - Cancer screening via protein marker analysis
  - Naturally controlled artificial limbs (brain-machine)
  - Frictionless remote mentoring (skin top glucose monitor)
  - Neurovascular stent retriever (for blood clots).
Most Implanted Medical Devices in America

1. Artificial eye lenses
2. Ear tubes
3. Coronary stents
4. Artificial knees
5. Metal screws, pins, plates and rods (traumatic fracture)
6. Intra-uterine devices
7. Spinal fusion hardware
8. Breast implants
9. Heart pacemakers
10. Artificial hips
11. Implantable cardioverter defibrillators (ICDs)

The Nature of Medical Device Studies

• Whereas drugs are discovered, devices evolve; they are constantly being “improved”; life length of a device is 1-2 years.
• Rapidly changing technology
• And the medical device industry is very innovative.
Device Development: FDA Guidance

- Discusses several concepts that are fundamental to Good Device Development Practices with respect to clinical trials.

- Finalized Nov. 7, 2013

Types of Device Studies

- Clinical outcome
  - All therapeutic and aesthetic devices and some diagnostic devices
  - Controls (randomized, historical, concurrent non-randomized, patient as own control)
- Uncontrolled One-Arm Studies
  - Objective Performance Criteria and Performance Goals
- Diagnostic clinical performance
  - Some diagnostic devices including many IVDs
Statistics: An Exciting Time

- Statistical Century* (Brad Efron)
- Dream Job of the 2010s according to Hal Varian, Chief Economist at Google
- Analytics and “Big Data”
- It is an extremely data-rich world and who knows how to analyze it
- Nate Silver *The Signal and the Noise: Why So Many Predictions Fail*
- Challenge of “Big Data”

Role of the Food and Drug Administration (FDA)

- FDA – to protect and promote the public health
- FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.
- FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.
Statistical Innovations in the Device World

1. Bayesian Device Trials
2. Adaptive Trials
3. Propensity Score Methodology
4. Tipping Point Analysis for Missing Data
5. Diagnostic Tests and Companion Diagnostics
1. Bayesian Medical Device Trials—Why?

- Devices often have a great deal of prior information.
  - The mechanism of action is physical (not pharmacokinetic or pharmacodynamic) and local (not systemic)
  - Devices usually evolve in small steps whereas drugs are discovered.

- Computationally feasible due to the gigantic progress in computing hardware and algorithms

- The possibility of bringing good technology to the market in a timely manner by arriving at the same decision sooner or with less current data was of great appeal to the device industry.
Recent Bayesian Book


- Two quotes:
  - “When the facts change, I change my opinion. What do you do, sir?” John Maynard Keynes
  - “If you are not thinking like a Bayesian, perhaps you should be.” John Allen Paulos, New York Times Book Review
Early Decisions FDA Made

- Restrict to quantitative (empirical) prior information. A subjective approach is fraught with danger.

- Companies need access to good prior information to make it worth their risk.

- FDA needs to work with the companies to reach an agreement on the validity of any prior information.

- New decision rules for clinical study success
Important Lessons

- Bayesian trials need to be **prospectively designed**. (It is almost never a good idea to switch from frequentist to Bayesian or vice versa.)

- Companies need to meet early and often with FDA. The prior information needs to be identified in advance as well as be agreed upon and legal.
The Importance of Simulation

- We (FDA and industry) all need to understand the operating characteristics of the Bayesian designs.
- Why? The Type 1 error probability (or some analog of it) protects the U.S. public from approving products that are ineffective or unsafe.
- So simulate to show that Type 1 error (or some analog of it) is well-controlled.
- Simulations can also be of help in estimating the approximate size of the trial and the strategy of interim looks. Usually Bayesian studies are not a fixed size.
FDA Bayesian Guidance

Guidance for Industry and FDA Staff

Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials

Document issued on: February 5, 2010

The draft of this document was issued on 5/23/2006

For questions regarding this document, contact Dr. Greg Campbell (CDR(R)) at 301-796-5750 or greg.campbell@fda.hhs.gov or the Office of Communication, Outreach and Development, (CBER) at 1-800-255-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Division of Biostatistics
Office of Surveillance and Biometrics

Center for Biologies Evaluation and Research

- Finalized February 5, 2010.
Two Bayesian Approaches

A. Bayesian Hierarchical Modeling using data from one or more prior studies

B. Bayesian adaptive designs, usually with non-informative priors
   - Usually these designs are Bayesian group sequential
   - The BIG advantage here is to model the primary outcome in terms of intermediate endpoints.
A. Bayesian Hierarchical Modeling

- Use Bayesian Hierarchical Models to adaptively “borrow strength” using the empirical data from one or more previous studies.
- The model decides how much strength to borrow based on how similar the current data are to the previous studies.
- Often the prior for the hierarchical model is a non-informative one.
B. Bayesian Adaptive Designs Using Predictive Probability

- Predictive posterior probability was used to decide:
  - Stop enrollment, wait 6 months and do final analysis
  - Stop trial for futility
  - Continue enrollment

- Predictive posterior probability is calculated according to pre-specified rules agreed upon between FDA and the sponsor.

- Predictive posterior probability is only for sample size adaptation, not for making of study success decision.

Bayesian Statistics: Submissions to CDRH

• At least 21 Original PMAs and PMA Supplements have been approved with a Bayesian analysis as primary.
  • The Supplements include stent systems, a heart valve, and spinal cage systems.
• Many IDEs have also been approved.
• Several applications for “substantial equivalence” (510(k)s)
Rare Diseases and Pediatrics

- These populations are currently underserved by the medical products industry and the trials are difficult.
- One approach is Treatment Response Adaptive Designs, adjusting the randomization ratio according to outcomes, such as “Play the Winner”. The famous ECMO trial is one such example.
- Another is to use Bayesian statistics to “borrow strength” from
  - Other pediatric studies in U.S. and overseas
  - Other adult studies
  in either
  - Control arm
  - Experimental arm (or both)
Recent FDA Pediatric Guidance

- FDA Guidance: Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices (effective Sept. 19, 2016)


- Response to Pediatric Medical Device Safety and Improvement Act of 2007

- Appendix on Bayesian Hierarchical Modeling
2. Adaptive Clinical Study Designs for Medical Devices

- FDA has issued a final guidance for Adaptive Designs for Medical Device Clinical Studies (July 27, 2016).
- The Bayesian experience has been most helpful.
- CDRH has seen about 240 adaptive submissions from 2007 to 2013 (Yang, X. et al, 2016).
Several Key Points on Adaptive Designs

- Devices have some unique challenges for adaptive studies: diagnostic studies, one-arm studies, unblinded studies.
- Simulations are absolutely essential to understanding the operating characteristics of the design.
- The fixed sample size design is almost always a fantasy! So almost always consider sample size reassessment (recalculation).
3. Propensity Score (PS) Methodology

- Generation of the idea: In the past (more than 10 years ago) medical device companies were routinely conducting historical controlled studies. Sometimes the control was years out of date and there was a hand-wave that the populations were comparable.

- FDA began to ask for analytical demonstration that the two groups were comparable via propensity scores. These results were presented by FDA and the sponsors at FDA Advisory Committee meetings.
Propensity Score (PS) Methodology

- PS-- Replace the collection of confounding covariates with one scalar function of these covariates: the propensity score (PS).

- PS is the conditional prob. of receiving Exp. Trt. rather than Control, given a collection of observed covariates.

PS in Building Stage

- It is crucial to mask or blind the PS modeling from the outcome data.
- If the observational data does not collect all the important covariates (not just ones correlated with the outcome), the PS analysis is worthless.
- A model that improves the balance by deleting covariates in the logistic regression model cannot be correct.
PS in Building Stage
May Not Work

- Whereas it might make sense to trim many observations from the control (especially if it is large), under no circumstances should you trim (discard) observations from the new treatment arm (since this non-prospective act would make the label impossible to write).

- A PS model does not guarantee that PS will be similar OR that the covariates will be balanced; both need to be checked.
Non-Overlapping PSs
Pre-specification of PS Model

- It is important to build the propensity score model with safeguards in place so the outcome data remain masked or blinded. This can be advantageous to the sponsor in that, if the model fails, another observational dataset may be substituted.


4. Diagnostic Devices

- Can be used for
  - Diagnosis
  - Screening
  - Monitoring disease or medical condition

- Types of devices
  - *In vitro* diagnostic devices
  - Imaging systems
  - Other *in vivo* devices
Guidelines for Reporting Diagnostic Test Results

- STARD Initiative for reporting studies of diagnostic accuracy in medical journals
    Also in Ann. Int. Med. and others


http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm
Diagnostic: Analyses Using ROC Plots

- Since the Receiver Operating Characteristic (ROC) plot is a plot over all sensitivities and specificities, it gives a global assessment, a visual presentation of the entire performance.
- Very useful methodology in CDRH.
- If the data are ordinal, one can use latent variables to build the theoretical ROC curve.
- ROC methodology can be used in a variance components effort to model the variance due to readers, to cases and help plan the trial.
Types of Genetic Tests

- Single Nucleotide Polymorphisms (SNPs)
  - Basically Qualitative Assay: Is the particular sequence present or not. Examples include Factor V Leiden, HLA typing, cytochrome P-450 superfamily SNPs

- Microarrays
  - Basically quantitative, measuring gene expression
  - Two types: cDNA array and Oligonucleotide array (Affymetrix)

- Next Generation Sequencing (NGS)
  - Detect DNA changes in CFTR (cleared Nov. 2013)

IVD Companion Diagnostic Device

- An *in vitro* diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product (could be a drug, biologic or another device).

- Its use is stipulated in the instructions for use in the labeling of both the diagnostic device and the therapeutic product.
FDA Guidance

Issued jointly by CDRH, CDER and CBER on August 6, 2014.

IVD Companion
Diagnostic Device

It could be used to:

- Identify patients who are most likely to benefit from the product
- Identify patients who are likely to be at increased risk for serious adverse reactions from the product
- Monitor the response to treatment for the purposes of adjusting treatment
- Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population.
Bridging (Diagnostic) Study

- A market ready test (MRT) for companion diagnostic test (CDx) may not be available at the time of the pivotal clinical trial of the drug and so a (non-commercial) clinical trial assay (CTA) is used instead.

- So a bridging study is a supplemental agreement study of CDx and CTA. It is designed to assess the agreement between CDx and CTA and can allow for the extrapolation of CTA’s clinical data to CDx. How much should they agree?


5. Tipping Point Analyses in Missing Data

- Ask what pattern of filling in the missing data will lead to a change in the inference. For dichotomous outcomes, this defines the Tipping Point Boundary.

- This approach for dichotomous data makes almost no assumptions.

Tipping-Point Graph

### MCAR

<table>
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<th></th>
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<th>Success</th>
</tr>
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<td>18</td>
</tr>
<tr>
<td>Control</td>
<td>18</td>
<td>9</td>
</tr>
</tbody>
</table>

#### Legend
- Dark shade: significant
- Light shade: not significant

#### Case Scenarios
- **Best Case**
- **All Suc.**
- **All Fail**
- **Worst Case**
Missing Data

- Missing data issues arise in many device studies, from tipping point to propensity scores to diagnostic studies.

For More Information on These Statistical Innovations

Medical Device Innovation Consortium (MDIC)

- First Public-Private Partnership in order to advance medical device regulatory science, started in 2013
- Members include FDA, CMS, Pew Charitable Trust, PCORI, and 25 medical product firms (including J&J and Novartis)

Projects
- Computational Modeling and Simulation (Virtual Patient)
- Patient-Centered Benefit Risk Assessments
- Clinical Trial Innovation and Reform
- Case for Quality
- Clinical Diagnostics
- Application of Clinical Trial Practices
- MDIC NEST Coordinating Center
A. The Future in Medical Devices

- Artificial everything (pancreas, retina, etc); bionic humans
- Diagnostics: Decision Support Systems and smart phone apps (Star Trek tricorder)
- Less invasive implantables (RF replace wires)
- Brain and nerve stimulation
- Continued miniaturization and personalization (3-D printing) of devices
- More home health care and telemedicine
- With the genomics explosion, the new reality of personalized (not just stratified medicine) with combined companion diagnostics guiding drug therapies and not just for cancer
- Unique Device Identifiers (UDI) on all crucial medical devices
- Many more combination products, especially drug-diagnostics
B. The Future in Clinical Investigations

- Fewer clinical trials (too costly) and many more simulated ones
- Use of prior information and virtual patients
- Vastly increased involvement by patients (decision-making that takes into account their preferences of benefit/risk)
- “Big Data” in EHR and registries (use of real-world evidence); randomized registry trials
- More well-designed prospective retrospective studies
- More blurring of the pre-market and post-market
B. Innovative PostMarket Activities

- Unique Device Identifiers (UDI)
- High-Quality Registries
- National Evaluation System for health Technology (NEST)
  - http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm301912.htm
- Electronic Health Records (EHR)
- Premarket-Postmarket Balance
B. Unique Device Identifiers
C. The Future in Statistics

- More adaptive designs and less irrelevant sample size calculations
- More simulations at the design stage
- Predictive modeling (Bayesian and otherwise), not just for populations but for particular patients
- Continued methodological innovation in analysis of clinical data
- More statistical involvement in analysis techniques for “Big Data”
- More statisticians familiar with both diagnostic and therapeutic statistical techniques
Conclusion

- There is a commitment by FDA, MDIC and others to encourage medical device innovation and to improve clinical trials.
- There are a number of possible innovative clinical study designs.
- Innovations are ongoing in statistical methodology.
- It is an exciting time for the medical device community but the future is even brighter.
- We can all make a difference. Be Innovative!
Thank you!