

Biostatistics and Public Policy: A View from the Food and Drug Administration

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Outline

- Impact of Statistics at FDA
- Statistical Review of Premarket Submissions
- Statistics and FDA Advisory Committees
- Guidance Efforts

Why Statistics is so Important at FDA

- FDA is a science-based agency that values transparency and innovation and regulates about 25% of the GDP of U.S.
- Companies generate data on which FDA bases almost all decisions
- The watchword at FDA is pre-specification of the design and the statistical analysis plan.
- FDA reviews most of the clinical trial designs and analyses before any subjects are studied in the trial. FDA also reviews analyses of completed studies.

Why Statistics is so Important at FDA (cont.)

- Decisions are made with a clear understanding of exactly what the data are telling us, not what the company who performed the clinical trial says it says.
- Unlike academia, FDA has to make decisions, to tell a company they are approve or not.

FDA has about 300 statisticians, most of whom have Ph.D.s.

Methodologies that Come into Play in Statistical Premarket Reviews

- Survival analysis (Kaplan Meier, Cox regression)
- Group sequential trials (O'Brien-Fleming)
- Longitudinal data analysis
- Multiplicity of endpoints, analyses, etc.
- Treatment of missing data
- Non-inferiority trials
- Logistic regression
- Analysis of (co)variance
- Sampling (not so much)

Methodologies that Come into Play in Statistical Premarket Reviews

- Subgroup analysis
- Combining (disaggregating) data -- “Lumping and splitting”
- Meta-analysis
- Bayesian methods
- Methods to evaluate diagnostic medical tests
- Adaptive designs and analyses
- Methodologies for non-randomized (observational) studies and for non-compliance
- Simulation, bootstrapping

Federal Advisory Committee Act (FACA)

- About 1000 committees with a total of 69,000 members serving 54 federal agencies of the US government provide expert advice, shaping the programs and policies of the U.S. Government.
- Meetings are generally open unless there is a good reason for a closed meeting
- Meetings and committees announced in the Federal Register
- Activities are tracked by GSA: www.fido.facadatabase
- FDA has about 30 such committees, whose members serve as Special Government Employees

FDA and Advisory Committees

- Most Advisory Committees have one or more statisticians
- Two types of meetings (all with public comment and patient and industry non-voting reps)
 - Advice about a particular submission with presentations by the company and FDA
 - Advice about trial design or post-market issues
- All conflicts of participants are reviewed.
- All issues are discussed openly.

18 Panels of the FDA Medical Devices Advisory Committee

Anesthesiology and Resp. Therapy
Devices

Circulatory Syst. Devices

Clin. Chemistry and Clin.
Toxicology Devices

Dental Products

Dispute Resolution

Ear, Nose and Throat Devices

Gastroenterology and Urology
Devices

General and Plastic Surgery Devices

General Hospital and Personal Use
Devices

Hematol. and Pathol. Devices

Immunology Devices

Microbiology Devices

Molecular and Clinical Genetics

Neurological Devices

Obstetrics and Gynecology Devices

Ophthalmic Devices

Orthopaedic and Rehabilitation Devices

Radiological Devices

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FDA Statisticians and the Advisory Committees

- FDA statisticians sometimes make presentations. CDRH statisticians make an average of 12 presentations per year.
- FDA statistician provides input into official panel package and the FDA presentation
- FDA presents what it thinks the panel needs to know in terms of factual information in order to provide FDA with the best advice
- Challenge is to make statistical issues comprehensible to non-statisticians.

Recent CDRH Advisory Committees

1. Tipping point analysis panel
2. Bayesian panel
3. Propensity score analysis panel

1. Tipping Point Analysis Panel

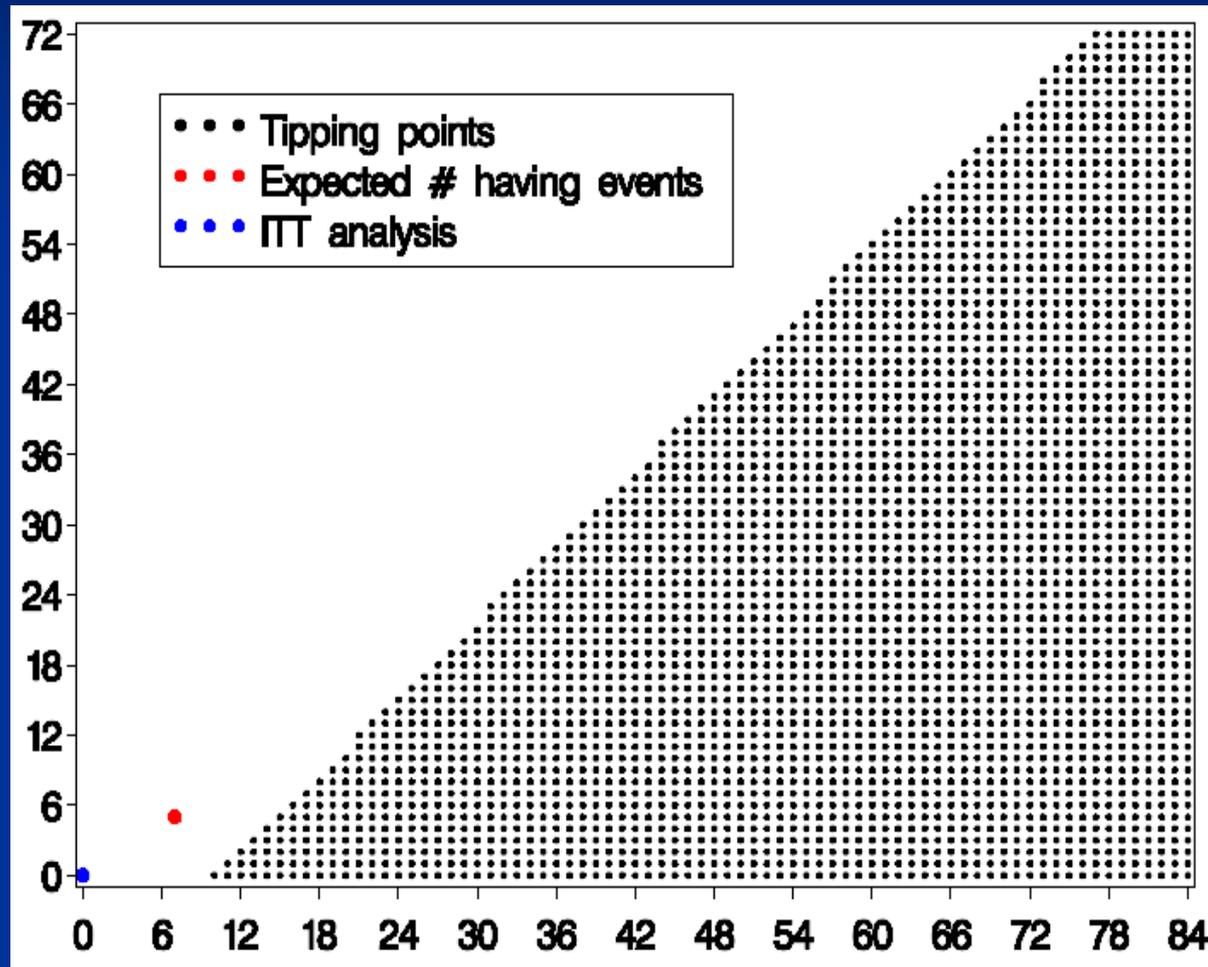
- RX Acculink Carotid Stent System by Abbott Vascular at Cir. Syst. Devices panel, Jan. 26, 2011.
- <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm248649.pdf>

1. Subjects Having Missing Values in Intention To Treat (ITT) Population

- Subjects not observed any primary endpoint event nor completing the 1-year endpoint may due to
 - Death between 31 days and 1 year
 - Withdrawal from study
 - Lost to follow-up
- In ITT, # of subjects with missing value / Total # of subjects
 - Exp. CAS: 84/1259 (6.7%) Cntrl CEA: 72/1237 (5.8%)
- Kaplan-Meier estimate may be biased if
 - the pattern of censoring is not independent of the survival times, or
 - the survival rate of censored subjects is not consistent with the rate in subjects remaining in the study.

1. Tipping Point Analysis Based on ITT Population

of subjects having events in CEA



of subjects having events in CAS

2. Bayesian Panel

- AtriCure Surgical Ablation System by AtriTech at Circ. Syst. Devices Panel, Oct. 27, 2011
- <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm277441.pdf>

2. Bayesian Panel: Study Design

- Prospective, single-arm, unblinded, multicenter trial at 9 sites
- Primary effectiveness endpoint: the proportion of subjects that are free of atrial fibrillation while off of any antiarrhythmic medication (Class I or III) at six months post procedure --- p_T

- $H_0: p_T \leq 60\%$ vs. $H_a: p_T > 60\%$

- The null hypothesis is rejected if the posterior probability that the six-month success rate p_T exceeds 60% is greater than 0.975

$$P(p_T > 60\% \mid \text{data}) \geq 0.975$$

- Prior distribution on p_T : non-informative (uniform) prior

2. Bayesian Panel: Sample Size Adaptation

- Sample size targeted between 50 and 100 subjects
- Bayesian adaptive design to determine sample size
 - First interim analysis: 50 patients enrolled, 20 patients reached 6-month endpoint
 - Repeated after every five patients were through 30 days
 - A maximum of 10 interim looks

2. Bayesian Panel: Sample Size Adaptation (Cont.)

- At each interim analysis, calculate the predictive probability of trial success for two scenarios:
 - 1) assuming enrollment stops and all currently enrolled patients are followed to six months (**for success**)
 - 2) assuming enrollment continues to the maximum sample size, 100 patients, and all are followed to six months (**for futility**)
- Trial success requires meeting both the primary effectiveness and safety endpoints.

2. Bayesian Panel: Predictive Probability

- Predictive probability was used to decide:
 - Stop enrollment, wait 6 months and do final analysis
 - Stop trial for futility
 - Continue enrollment
- Predictive probability is calculated according to pre-specified rules agreed upon between FDA and the sponsor.
- Predictive probability is only for sample size adaptation, not for making of study success decision.

2. Bayesian Panel: Predictive Probability at 55 patients

- First interim look conducted when 55 patients had been enrolled
- All 55 patients had 30-day safety outcomes
 - the primary safety endpoint was met
- The predictive probability of meeting the effectiveness endpoint with the current sample size was calculated to be 0.988
- The predictive probability of trial success is 0.988, which exceeds the threshold of 0.9, and accrual was stopped for probable success.

3. Propensity Score Panels

- Use of prospectively defined propensity score analysis for non-randomized studies.
- HeartWare Ventricular Assist System by HeartWare, Circ. Syst. Devices panel, April 25, 2012.
- CardioMEMS Circ. Syst. Devices Panel, Dec. 8, 2011.
- Berlin Heart Pediatric LVAD, Circ. Syst. Devices Panel, July 21, 2011.

FDA Guidance Documents

- Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (March, 2006).
- Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests (March, 2007).
- The Use of Bayesian Statistics in Medical Device Clinical Trials (February, 2010).

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 (CDRH) at 301-796-5750 or greg.campbell@fda.hhs.gov or the Office of Communication, Outreach and Development, (CBER) at 1-800-835-4709 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 Biologics Evaluation and Research

- Finalized February 5, 2010.
- <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm>

Pivotal Clinical Study Design Guidance

**Draft Guidance for Industry,
Clinical Investigators, and Food and
Drug Administration Staff**

**Design Considerations for Pivotal
Clinical Investigations
for Medical Devices**

This guidance document is being distributed for comment purposes only.
Document issued on: August 15, 2011

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact Gregory Campbell, PhD at (301) 796-5750 or by email at greg.campbell@fda.hhs.gov, if desired.
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Surveillance and Biometrics
Office of Device Evaluation
Office of In Vitro Diagnostics
Center for Biologic Evaluation and Research

- Finalized Nov. 7, 2013
- Discusses several concepts that are fundamental to Good Device Development Practices with respect to clinical trials.
- Some of these concepts have always been true, but have not been promulgated widely by the Agency
- http://www.fda.gov/download/medicaldevices/device_regulationandguidance/guidance_documents/UCM373766.pdf

Benefit-Risk Determinations

Guidance for Industry and Food and Drug Administration Staff

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications

Document issued on: March 28, 2012

The draft of this document was issued on August 15, 2011.

For questions about this document concerning devices regulated by CDRH, contact Ruth Fischer at 301-796-5735 or by electronic mail at Ruth.Fischer@fda.hhs.gov. For questions about this document concerning devices regulated by CBER, contact the Office of Communication, Outreach and Development (OCOD) by calling 1-800-835-4709 or 301-827-1800.



Department of Health and Human Services
Food and Drug Administration

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- Issued March 28, 2012
- <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm>
- Gastro and Uro. Dev Panel on obesity devices, May 12, 2012.

Quantitative Decision Analysis Initiative in CDRH

- How FDA makes decisions on the approval or clearance of pre-market submissions and on post-market and compliance actions
- Quantifying not only risks but also potential benefits.

Closing Remarks

- We statisticians need to be sure to communicate well with non-statisticians and educate them about statistical issues. We need to communicate not just point estimates but uncertainty (both within the model and of the model).
- We need to be able to partner well with decision-makers in many other disciplines by understanding the medicine and science.
- We can help shape public health policy.
- We statisticians can make a difference in people's lives every day!

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