American Course on Drug Development and Regulatory Sciences

Substantial Evidence in 21st Century Regulatory Science

Borrowing Strength from Accumulating Data

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University of California, San Francisco
Schools of Pharmacy and Medicine
Department of Bioengineering
and Therapeutic Sciences

Regulatory Perspective on the Value of Bayesian Methods

Presentation Developed By…

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Disclosures, Affiliations, and Acknowledgements

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Disclosures

This talk reflects my views and represent my own best judgement. These comments do not bind or obligate FDA

Outline

1. The use of prior information to power clinical trials
2. Bayesian adaptive designs
3. Simulations of clinical trials
4. Predictive distributions
5. Decision analysis: Benefit-Risk

1. The use of prior information

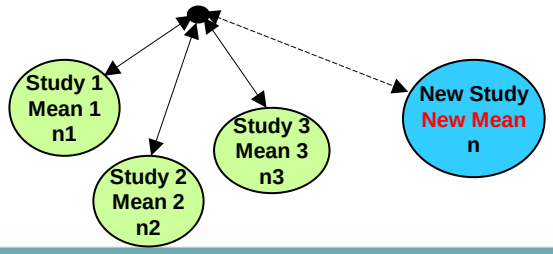
- When prior information is available, it could be used to increase the power of clinical trials
- It can reduce the size and length of trial: same decision reached faster
- Sources:
  - clinical trials conducted overseas
  - sponsor's own previous studies
  - legally available data on same or similar products
  - data registries
  - prior information on control groups
  - adult prior information extrapolated for pediatric population

Regulatory Perspective

- Agreement to be reached in advance between sponsor and FDA (exchangeability; suitability of the prior)
- CBER approval: Xyntha – prior on safety data from a previous version of the product (described in the label)
- Other cases under IND

Priors may be too informative: Remedies

- discount the prior distribution in some way
- increase the stringency of the success criterion
- increase the sample size of the pivotal trial
- Bayesian hierarchical models



Regulatory Perspective

- Subjectivity
  - How to choose the prior? Whose prior?
  - How to discount the prior?
  - Hierarchical models: how to choose the hyper parameters?
  - Selection bias: unfavorable prior information may have been omitted or selected (control group)
  - Will future regulators or advisory panel members agree with current regulators?
- Legal: prior information may not be legally available
- Need to control type I error rates; significance level fixed at traditional values: 5% or 2.5%
  - If tradition cannot be relaxed, all prior information is discounted ➔ no gains in using the prior information
  - Agree to increase the traditional value to a higher level

Promising areas for use of prior information

- Pediatric trials: extrapolation from adult population
  - Pediatric draft guidance - 2015

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM444591.pdf

- Safety
- Rare diseases or Small populations
- Unmet medical need for life threatening or irreversible debilitating diseases
- Expedited Access Program (EAP) (CDRH and CBER)
  - EAP guidance - 2015

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf

If control of type I error is required, the significance level needs to be set at a higher level (see two-phase studies in the EAP guidance) so prior information can be used

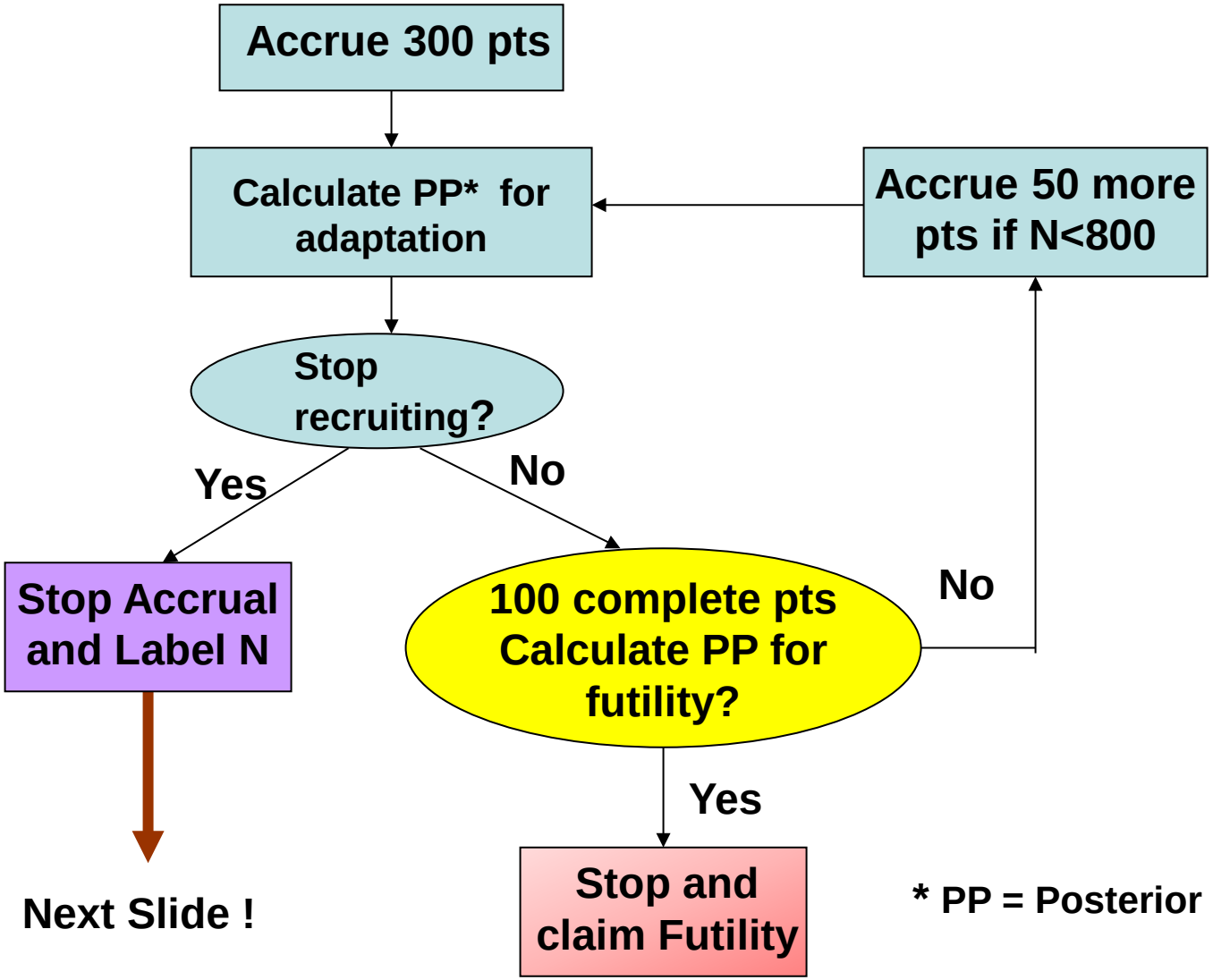
2. Bayesian Adaptive Designs

- Inherent to the Bayesian approach
- Can reduce the size (length) of a trial ➔ faster decision
- Can increase the size (length) of a trial. If it happens, **it is needed**
- Interim analyses for decisions on stopping or continuing **recruiting** based on predictive distributions ➔ sample size decided and optimized during the trial ➔ *"Goldilocks" trials*
- Modeling: results at early follow-up times predict results at the final follow-up. Model refined at interim looks when all follow-up results from patients recruited early are available.
- Adaptive randomization
  - ➢ Probability of assignment to a treatment depends on data obtained thus far
  - ➢ Ethically appealing: allocates more patients to the best treatments

Example: Bayesian adaptive design

- Treatment vs. Control: Success or Failure at 24 months
- Follow-up times: 3, 6, 12 and 24 months
- Interim looks
  - For sample size adaptation
  - For effectiveness
  - For futility
- Constant or varying accrual rate
- Model: earlier visits are used to predict 24-month results of patients that have not yet reached the 24-month follow-up
- Exchangeability among patients recruited early and later in the trial

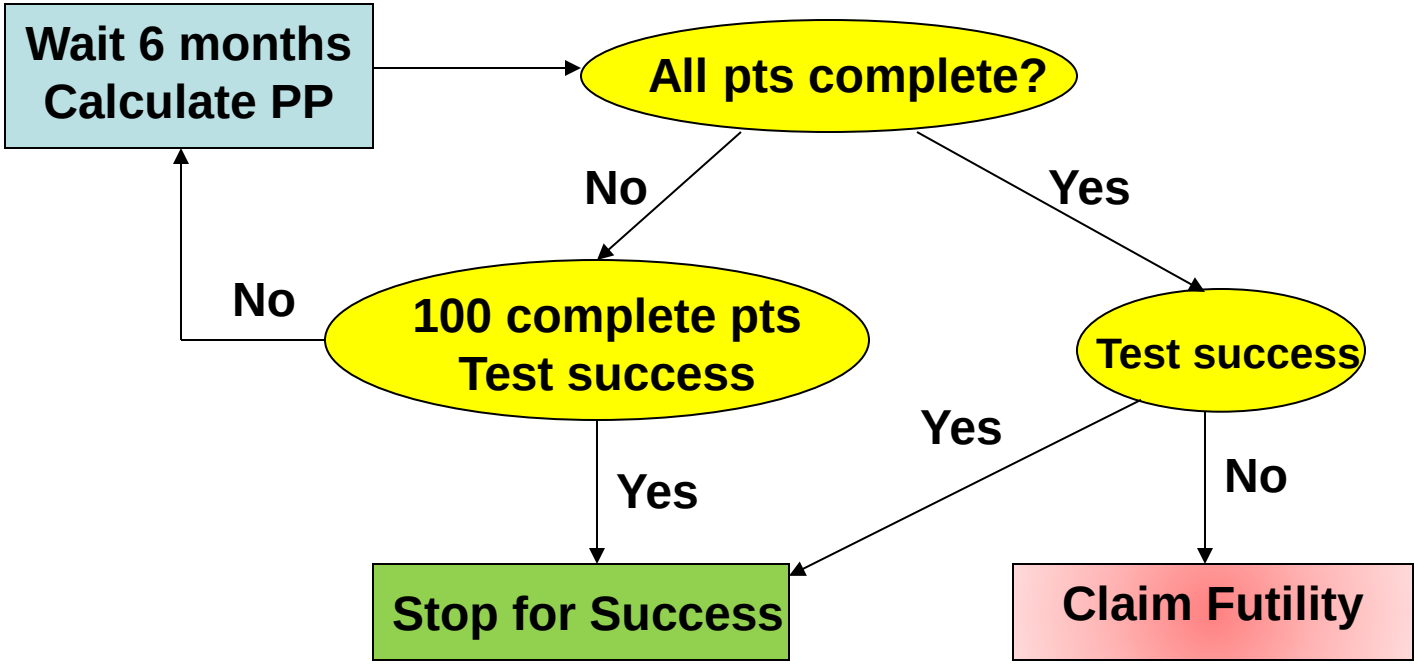
Interim Looks for Sample Size Adaptation



Interim Looks for Effectiveness

N is now fixed

Four interim looks at 0, 6, 12 and 18 months



Regulatory Perspective

- Increase the probability of trial success (insurance)
- Achieve optimal sample size
- Advantageous when there is no prior information
- Crucial when using prior information (hierarchical model): amount of strength to be borrowed is uncertain ➔ avoid failure for lack of power
- Adaptive randomization
  - ethically attractive: better overall patient outcomes
  - Increases statistical power

Regulatory Perspective

- Very advantageous when Bayesian modeling is used to predict an endpoint from earlier follow up visits – savings in sample size
- Stopping early occurs when surprises arise:
  - Treatment is better (success) or worse (futility) than predicted
  - Sample variability is smaller than predicted
  - Bayesian model makes good predictions (correlation among follow up times is high)
- Simulations are used to assess operating characteristics of the trial design - control type I error rates and power (no mathematical formulas for Bayesian adaptive designs)

3. Simulations

Simulate the trial thousands of times making assumptions about the true value of the endpoints and look at the average performance:

How often does it get the right answer?

- Calculate error rates for Bayesian trial designs
- Increase trial predictability and help sponsors prepare and budget for different scenarios and surprises
- Readily understood by clinicians who can observe what will happen under various scenarios
- Provide ability to "look into the future" to avoid "anticipated regret": if the trial were to fail, what would we do differently in retrospect?

"When you do the real trial, it is not the first time you are doing it, it is 1,000,001th!"

Regulatory Perspective

- Simulations are conducted at the design stage
- Devise a comprehensive number of scenarios to generate data
- Make assumptions to generate data
- Assess and control error rates (type I and type II error rates) under “all possible scenarios and assumptions”
- It may be more difficult for the FDA to review the simulations
- It may take more effort to reach agreement with the FDA at the design stage
- Sponsor’s documentation including the simulation code are useful to facilitate the review

Simulations are essential to strategize trial design

- Choose design type:
  - Adaptive or not?
  - Bayesian or frequentist?
  - Will prediction be used?
  - Sophisticated adaptation or just sample size re-estimation?
- Calculate probabilities of success under different scenarios
- Calculate expected trial duration and expected trial cost
- Optimize clinical trial design features

Design features to be optimized

- Stopping rules for success and futility
- Number and timing of interim analyses
- Prior probabilities; hierarchical model parameters; discount factors
- Predictive model
- Minimum sample size (*should also consider safety*)
- Maximum sample size
- Randomization ratio
- Accrual rate (not too fast and not too slow)
- Dose/treatment selection
- Number of centers
- Use of covariates (subgroup analysis)

4. Predictive probabilities

- Probability of future events given observed data
- Probability of results for a future patient in the trial
- Probability of results for missing patients
- Help to decide when to stop a trial
- Help to decide whether to stop or to continue recruiting
- Help physicians and patients make decisions about the use of a treatment (labeling)
- Predict a clinical outcome from a valid surrogate (modeling)
- Adjust trial results for missing data

Prediction in Labeling

- For a new patient receiving “Treatment”, the chance (predictive probability) of overall success would be 57%. Given the variability of the results in the study, there is 95% probability that this chance ranges from 49% to 65%.
- For a new patient receiving “Control”, the chance (predictive probability) of overall success would be 52%. Given variability of the results in the study, there is 95% probability that this chance ranges from 48% to 56%.”

5. Decision Analysis: Benefit-Risk Determinations

Postmarket Surveillance

Prophylactic Use of Inferior Vena Cava (IVC) Filters

Inferior Vena Cava (IVC) filters: prevent Pulmonary Embolism (PE) especially when anticoagulation is contraindicated or ineffective

Question

When is the optimal time to remove the IVC filter after implantation?

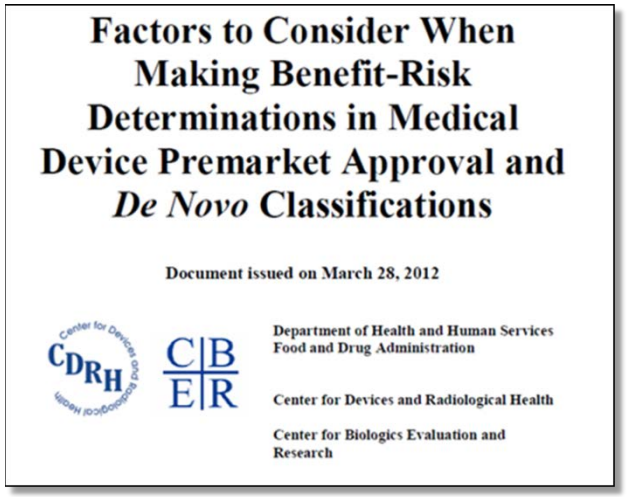
Public Health Notification

Recommendation

Remove IVC filters between 1 and 6 months post-implantation

*"Decision analysis of retrievable inferior vena cava filters in patients without pulmonary embolism", **Journal of Vascular Surgery,** 2013; J. P. Morales, X. Li, T. Z. Irony, N. G. Ibrahim, M. Moynahan, K. J. Cavanaugh, CDRH, FDA*

Benefit - Risk guidance for medical devices



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

Document issued on March 28, 2012

Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf

CDER-CBER Benefit – Risk framework for drugs and biologics

- Focus on qualitative approaches
- Slightly different factors

Factors for Benefit Risk Determination

- Benefits: type, magnitude, probability, duration
- Risks: severities, types, probabilities, duration, risk of false positives and false negatives for diagnostic devices

Additional Factors: Context

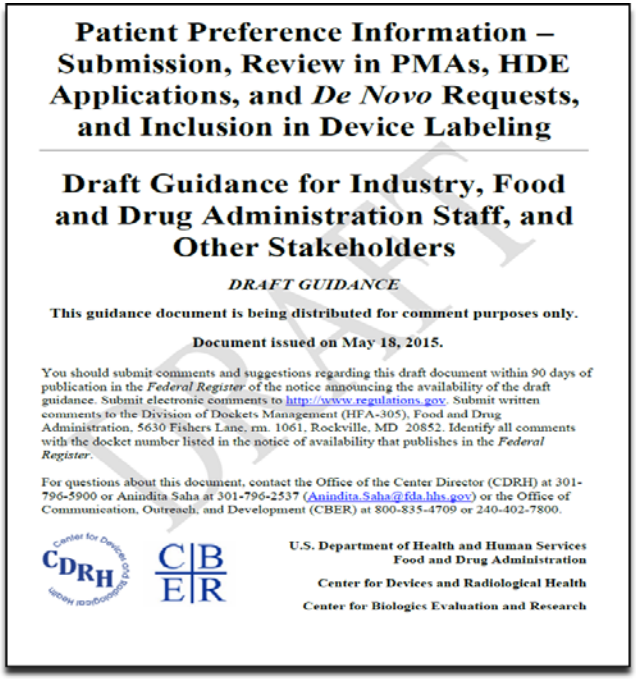
- Uncertainty
- Severity and chronicity of the disease
- *Patient tolerance for risk and perspective on benefit*
- Availability of alternative treatments
- Risk mitigation
- Post-market information
- Novel technology for unmet medical need

Patient tolerance for risk and perspective on benefit

"Risk tolerance will vary among patients, and this will affect individual patient decisions as to whether the risks are acceptable in exchange for a probable benefit. … FDA would consider evidence relating to patients' perspective of what constitutes a meaningful benefit."

The CDRH - CBER Benefit-Risk guidance document for medical devices did not say how to submit Patient Preference Information to the Center

Patient Preference Information



Patient Preference Information – Submission, Review in PMAs, HDE Applications, and *De Novo* Requests, and Inclusion in Device Labeling

Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Document issued on May 18, 2015.

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 electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Office of the Center Director (CDRH) at 301-796-5900 or Anindita Saha at 301-796-2537 (Anindita.Saha@fda.hhs.gov) or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-7800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
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http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf

"Incorporating patient-preference evidence into regulatory decision making", *Surgical Endoscopy*, M Ho, JM Gonzalez, H Lerner, C Neuland, J Whang, M. McMurry Heath, A. Hauber, T. Irony (2015)

The Medical Device Innovation Consortium Patient-Centered Benefit-Risk Assessment Framework Report and Catalog (http://mdic.org/pcbr/)

Thank you