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STATISTICAL SOFTWARE & SERVICES

Bayesian Designs for Device Clinical Trials

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What is Bayesian Statistics?

- Statistical methodology built on Bayes theorem (published in 1763)
- Limited use in applications until about 1990 when breakthrough algorithms (Markov Chain Monte Carlo) for Bayesian computation were developed.
- Bayesian statistics is a rigorous approach for learning from evidence as it accumulates.
- In clinical trials, traditional methods informally use information from previous studies only at the design stage.
  The Bayesian idea considers the prior information and the trial results as part of a continual data stream, in which knowledge is updated as new data becomes available.

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A taste of Bayes…

- Two identical looking coins:
  - Fair coin (F) with probability of heads =1/2
  - Magician's coin (M) with probability of heads =3/4

  You choose one coin. You have to say if it is the fair coin or not. Since they look alike you have a 50% of picking the fair coin

- Suppose we flip the chosen coin 5 times and get 1 head.

  In the light of this information how should you update your assessment of the chance that the coin you chose is the fair coin?

- Bayes Theorem gives us the machinery to update our 'prior' belief of 50% to the 'posterior' belief that the chance now is 91%

- Suppose you see 2 heads in another 5 flips, the new updated posterior chances are now 97%

Appeal of the Bayesian Approach

- Scientifically valid way of combining previous information with current data
- Intuitive, appeals to common sense: Adjusts to changing levels of evidence
- Science is about updating information in the light of evidence accumulated to date. Today's posterior becomes tomorrow's prior
- Advantages for clinical trials:
    - Possibly fewer subjects and shorter duration
    - More information can be used in design and decisions

Another taste : A clinical trial application

- Two arm trial comparing new device to standard. Aim is to claim difference of effect size is 0.6 units (std. dev.=1)
- Traditional design with1:1 randomization ratio and 90% power requires sample size of 118 subjects (59 subjects per arm)
- Consider a Bayesian design with the same sample size but with one interim look when responses have been observed for 60 subjects (30/arm)
- Using the data at the interim we predict probability that data from remaining subjects will lead to showing significance of new device. If this probability exceeds 95% we will stop the trial and claim success.
- We specify a similar rule for success if we continue beyond the interim look to the end of the trial.

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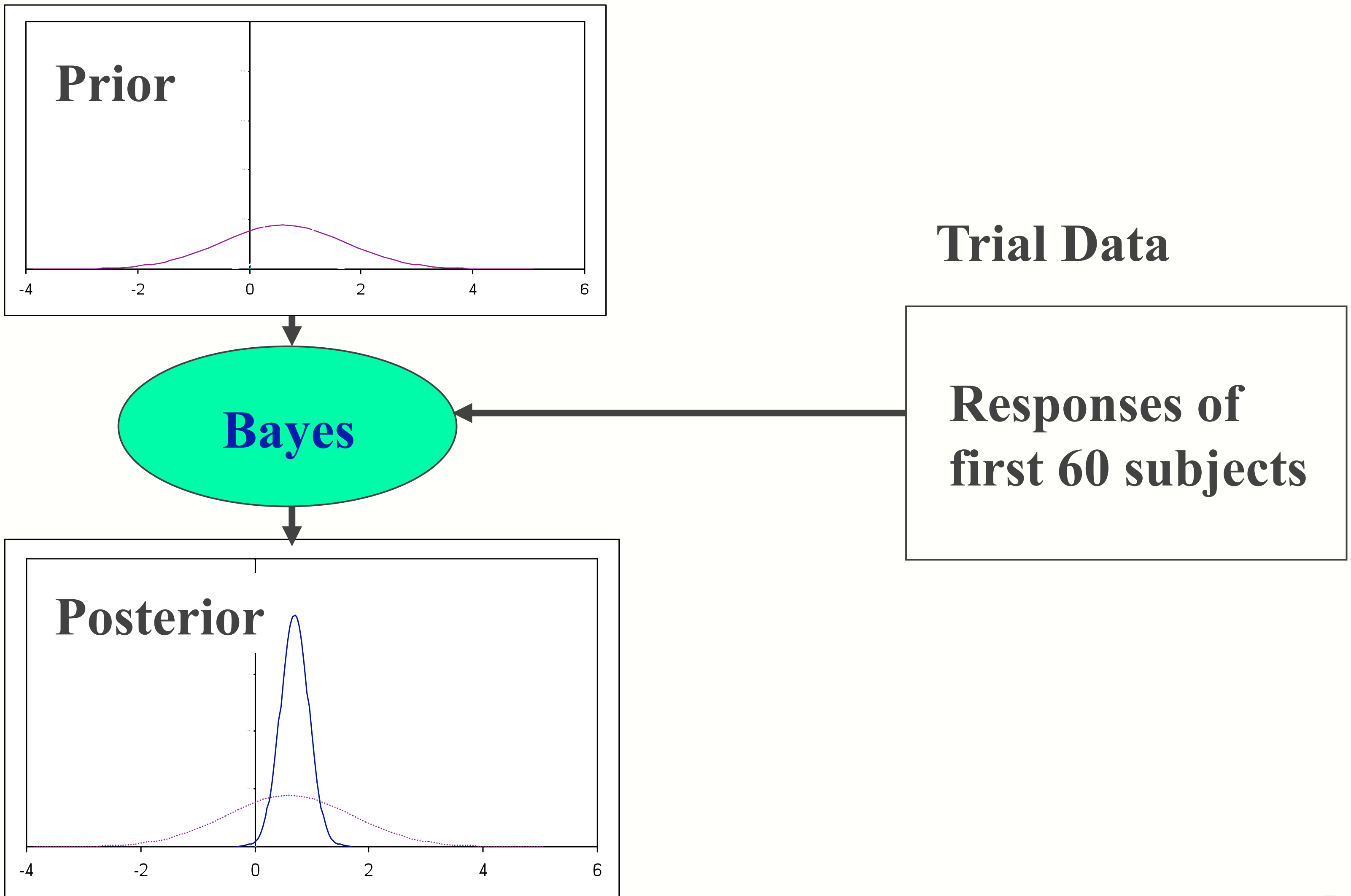
Interim Analysis



Trial results

- Prior for difference in effect size is flat over range of likely values of effect size difference between new device and standard with mean = 0.6 and std dev = 1.4
- At interim we observe average effect difference over 60 subjects to be 0.7
- Posterior has mean = 0.69 and std dev =0.25
- Then probability that data from remaining subjects will lead to showing significance of new device is 0.99 so we will stop the trial and claim success.
- We see that in this case there is a substantial reduction in trial cost and, even more important, in time to launch of the new device.
- **In practice one has to do extensive simulations and analysis to come up with a good design.**

Bayesian designs can use priors that reflect available information

Good prior information is often available for medical devices.

- Clinical trials conducted overseas
- Company's own previous studies
- Previous generations of the same device
- Data registries
- Data on very similar products that are available to the public
- Pilots

Bayesian statistics in clinical trials

- Bayesian approach is more intuitive than traditional frequentist approach (e.g. interpretation of p-values vs probabilities of different effect sizes, confidence intervals)
- Bayesian trials enable design of adaptive trials with decision rules that are intuitive (e.g. interim analyses, change to sample size, changes to randomization ratios)
- Bayesian designs enable incorporation of prior information in a scientific way
- Bayesian designs can be based on decision analysis (e.g. using financial implications in design)

Challenges

- More effort up front, requires time and cross-functional team work

- Sample size calculations require custom programming for simulations

- CDRH needs time to accept design, check programs and verify simulation results at time of design to ensure Type I error (false positive) is controlled

- Interim analysis requires
  - rapid access to data
  - tighter security against unblinding
  - Bayesian updating computation
  - more elaborate audit trail

CDRH and Bayesian Trials

- CDRH pioneered regulatory acceptance of Bayesian designs: first approved device using Bayesian design in 1999, following FDA Modernization Act of 1997
- CDRH encourages sponsors to use innovative Bayesian trials because they are often more efficient in using fewer subjects and resources than traditional designs
- Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials: Document issued on February 5, 2010
- Cytel and CDRH have an agreement to do collaborative research (CRADA) to develop 'Software for Bayesian Clinical Trials'

Software is a Bottleneck

- No validated, commercial Bayesian design software package is available today
- Burdens CDRH statisticians as they need to write special programs for each Bayesian trial submission instead of focusing on statistical aspects which is their expertise. They have to spend time on programming tasks like debugging and tabulating results that can be extensive
- Absence of commercial software also inhibits use of Bayesian designs as it places considerable burden on sponsors
- Industrial strength software would streamline discussions between CDRH and sponsors about the design

CRADA Plan

- Aim is to develop comprehensive software that becomes industry standard (e.g. East in CDER and CBER)

- First step is to jointly develop software for one of the most common and effective Bayesian designs
  – Two-arm trials with binary endpoint and repeated measurements at different time-points
  – Adaptive selection of sample size and early stopping for efficacy or futility

- Second Step is to extend the software to include other popular Bayesian designs for devices in collaboration with sponsors and consultants interested in Bayesian designs

Recent Bayesian Trial

FDA Press Release on February 6, 2009

"The U.S. Food and Drug Administration today approved the first ablation catheters for the treatment of atrial fibrillation (uncoordinated contractions of the upperheart chambers), one of the most common types of arrhythmias—or abnormal heart rhythms—affecting more than two million Americans.

The devices approved today, the NaviStar ThermoCool saline irrigated radio-frequency ablation catheter and the EZ Steer ThermoCool Nav, can be used to create small, strategically placed scars in heart tissue to block irregular electrical waves that cause atrial fibrillation. …"

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Navistar ThermoCool Catheter Trial

- Endpoint: 9 months failure free
- Superiority: Chances of 9 months failure free for catheter exceeding that for drug has 98% probability
- Interims when 150, 175, 200 subjects enrolled, max enrolment = 230 subjects.
- Stop accrual if predicted probability of successful trial > 0.9
- Submit early for success if predicted probability of successful trial > 0.99
- Stop for futility if predicted probability of successful trial < 0.05

- In July 2007, first analysis at 150 subjects, predicted probability of successful trial >0.99 and PMA was filed

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- Details in:
  - Wilber D. et. al., Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA 2010, 303, 333-340.

    Berry S. et.al., 'Bayesian Adaptive Methods for Clinical Trials' CRC Press, 2011

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Summary

- The recent guidance and past experience at CDRH on Bayesian trials shows that Bayesian designs can reduce costs and increase effectiveness of device trials
- Two situations where Bayesian trials are worth considering are:
  - when there is uncertainty about key design assumptions in traditional designs
  - when good prior information that is relevant to the trial is available
- Bayesian trials require
  - More up-front planning and care in trial execution
  - A key facilitator is a specialized Bayesian design tool
    - Cytel is working with CDRH to develop such a tool
    - We are seeking participation from the device industry to support and shape our efforts. If you are interested, please contact us.

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Acknowledgements

Slides prepared by the following were very helpful in developing my presentation today

Telba Irony, FDA, CDRH

Roman Torgovitsky, Cytel Inc.

Vickie (Yuanye) Zhang, U. of Connecticut

Thank you

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