Bayesian Statistics at the FDA: The Trailblazing Experience with Medical Devices

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Emerging Issues in Clinical Trials
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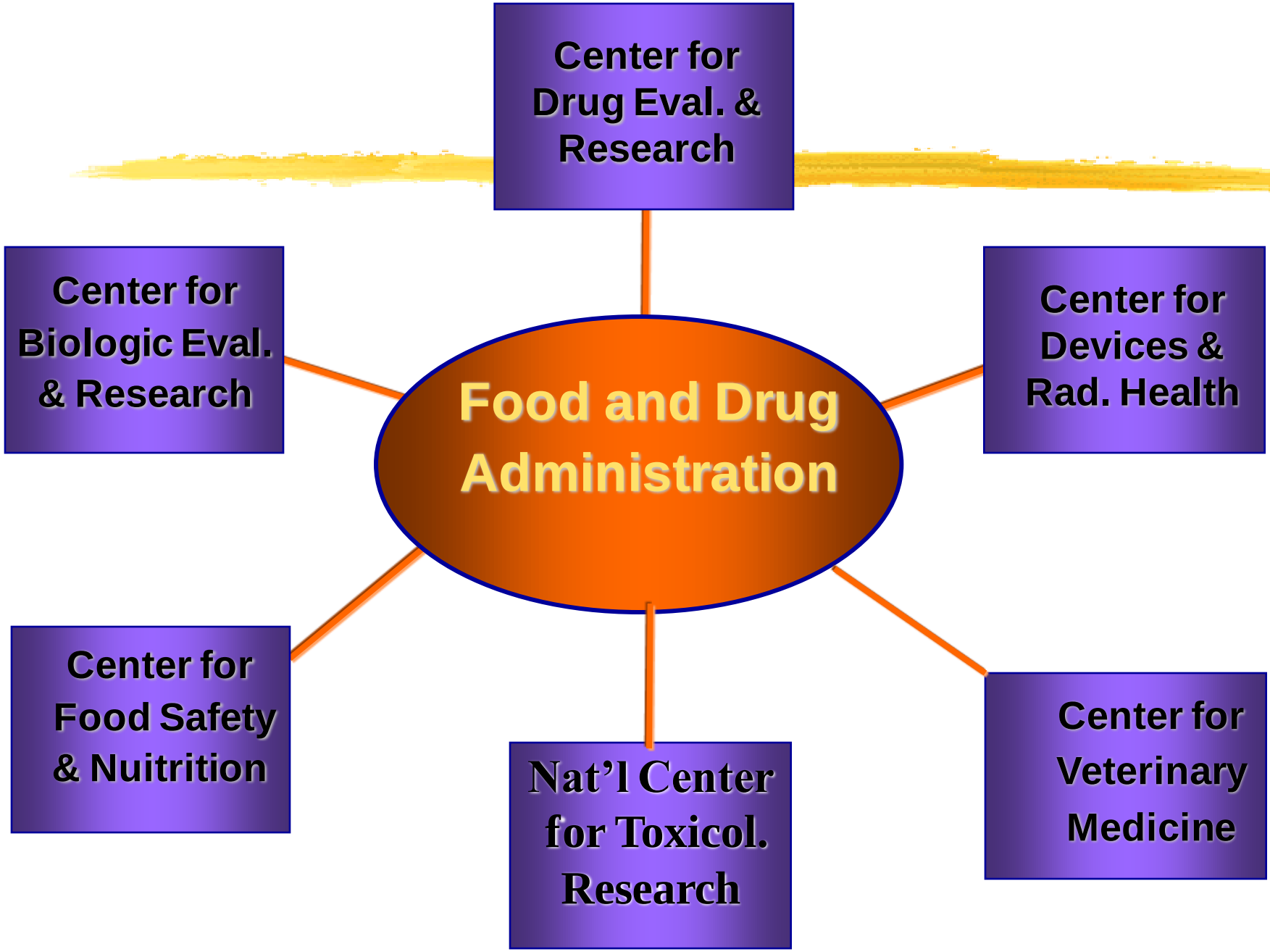
Outline

- What are devices?
- The nature of medical devices and their regulation
- Why Bayesian medical device trials?
- What has been learned and accomplished
- Some myths dispelled
- Challenges for the future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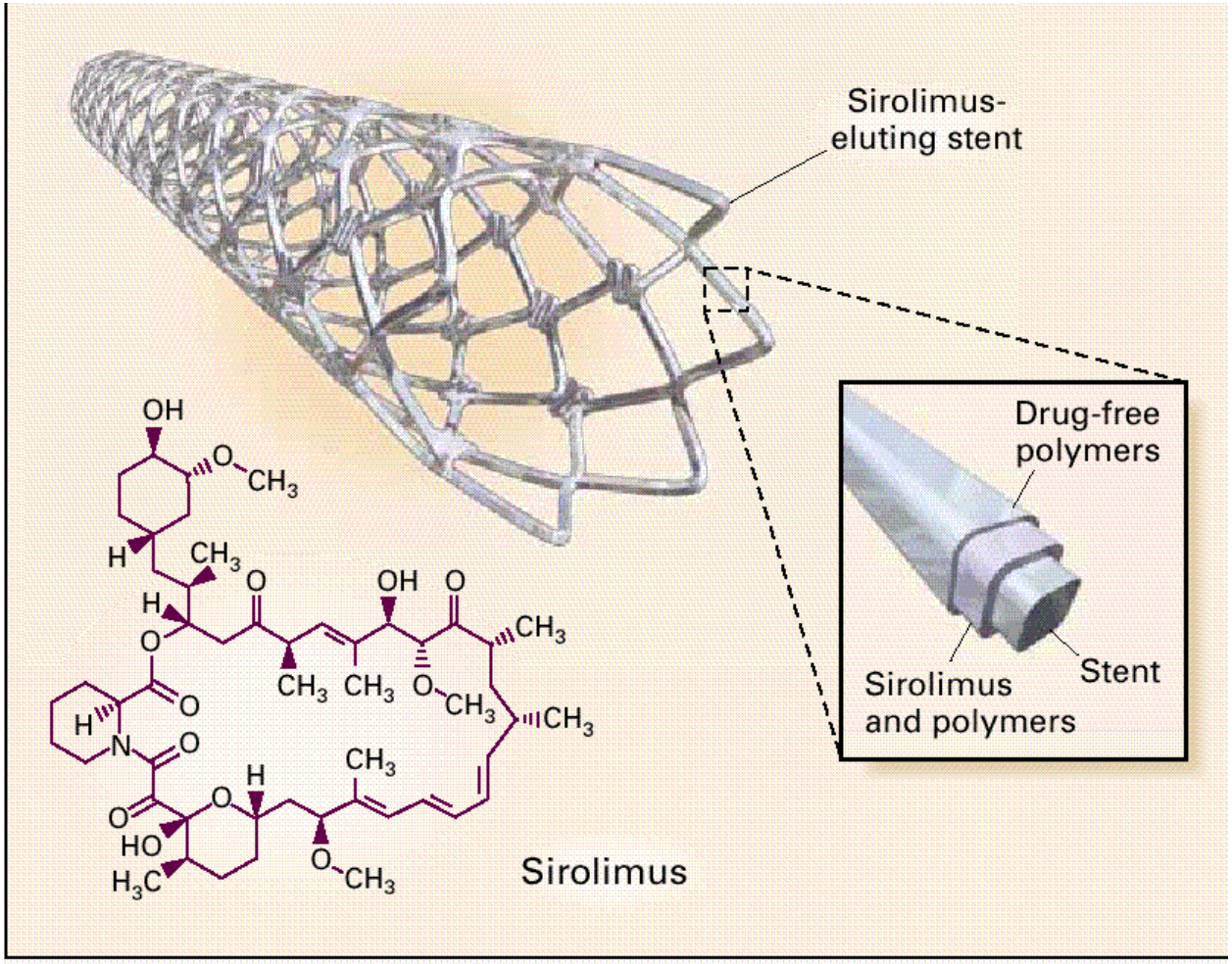
What are Medical Devices?

Definition by exclusion: any medical item for use in humans that is not a drug nor a biological product

intraocular lenses
MRI machines
breast implants
surgical instruments
thermometers
(drug-coated) stents
home kit for AIDS
diagnostic test kits
bone densitometers
artificial hips
PRK lasers
pacemakers
defibrillators
spinal fixation devices
glucometers
artificial hearts
hearing aids
latex gloves
artificial skin
software, etc

What is a Drug-Eluting Stent?

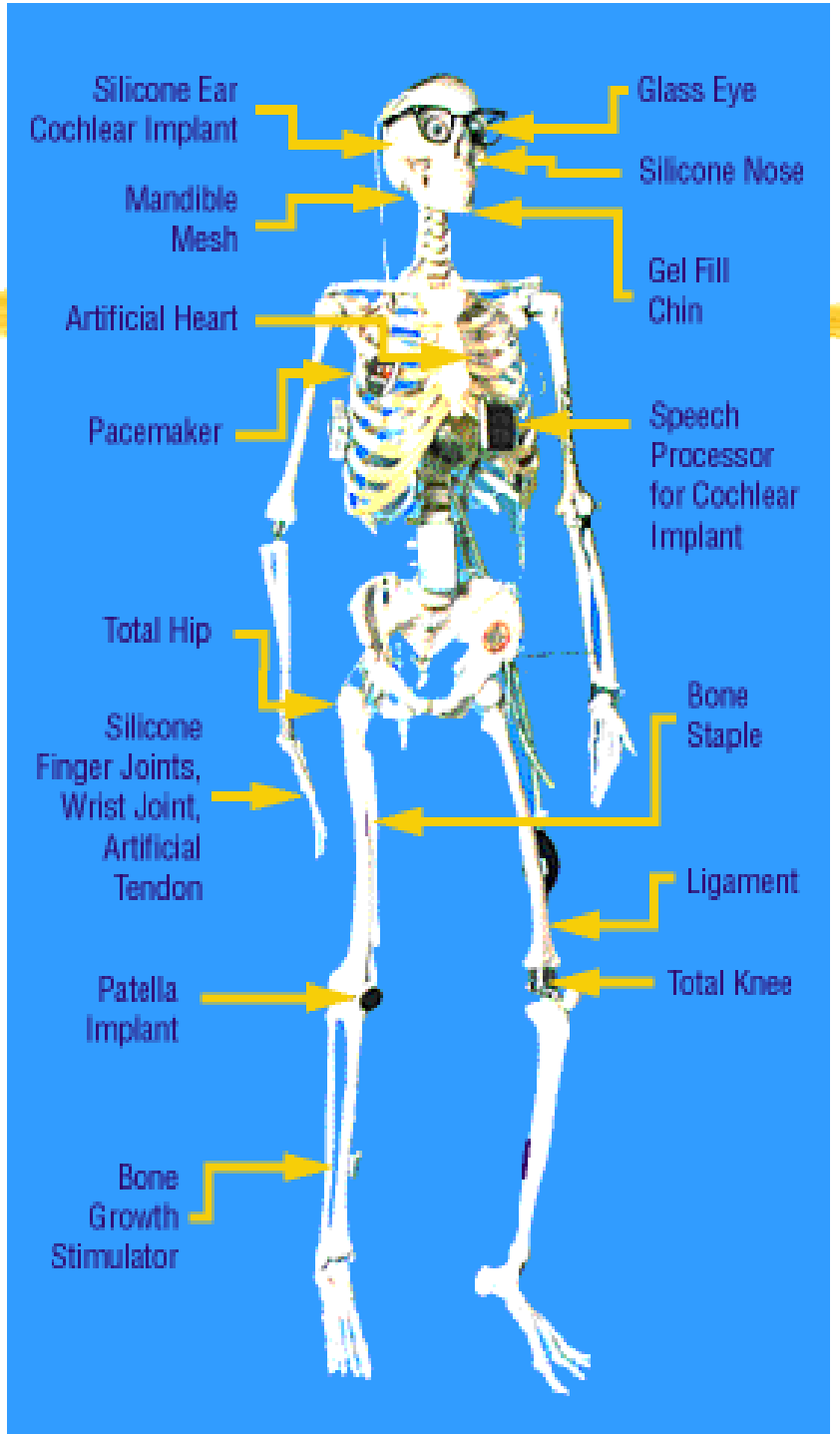
Example: **Cordis' Cypher™ Sirolimus-Eluting Coronary Stent**



Components

- Stent Platform & Delivery System
- Carrier(s)
- Drug

Meet Yorick


Silicone Ear Cochlear Implant
Glass Eye
Silicone Nose
Mandible Mesh
Gel Fill Chin
Artificial Heart
Pacemaker
Speech Processor for Cochlear Implant
Total Hip
Bone Staple
Silicone Finger Joints, Wrist Joint, Artificial Tendon
Ligament
Patella Implant
Total Knee
Bone Growth Stimulator

Devices Not Drugs -- The Differences

- Different Alphabet Soup
  IDE -- **I**nvestigational **D**evice **E**xemption
  PMA -- **P**re**M**arket **A**pproval
  510(k) -- Substantial Equivalence---not bioequivalence
- A Single Confirmatory Trial (not 2).
- A 'Sham' Control Trial may not be possible
- Masking (blinding) may be impossible for patients, health care professionals, investigators
- Usually don't use Phase I, IIA, IIB, III, IV

Devices Not Drugs -- The Differences (Cont.)

- Bench/Mechanical Testing not PK/PD
- Mechanism of Action often well understood
  - Effect tends to be localized rather than systemic, physical not pharmacokinetic
- Pre-clinical Animal Studies (not for toxicity)
- Number & Size of Device Companies
  - About 15,000 registered firms
  - Median device company size--under 50 employees (Many are new start-up companies.)
- Implants (skill dependent; learning curve)

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

FDA Premarket Review for Market Entry

- Premarket notification (510(k))
  - "Substantially equivalent" to a predicate (pre-amendments or reclassified post-amendment devices)
  - Presumes safety and effectiveness of predicate imputed from marketing experience
- Premarket approval application (PMA)
  - Class III pre-amendment devices, and transitional devices
  - Device for which there is no predicate device

“Substantial Equivalence”

- 510(k) pre-market notification process
- Comparison not to first approved device
- Danger of becoming worse than placebo (sham); this can be called predicate creep
- Change in technology could make old device obsolete
- No uniform process to set the non-inferiority margin

The Regulatory View in Devices

- Statutory directive for the FDA's CDRH:

  rely upon valid scientific evidence to determine whether there is reasonable assurance that the device is safety and effective.

- Valid scientific evidence for PMA is evidence from:
  - well controlled studies
  - partially controlled studies
  - objective trials without matched controls
  - well documented case histories
  - reports of significant human experience (21 CFR 860.7)

Why Did CDRH Launch the Bayesian Effort?

- 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.

Early Decisions We Made

- Restrict to data-based 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.
- Need to bring the industry and FDA review staff up to speed
- New decision-rules for clinical study success

Important Lessons Learned Early

- 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 CDRH. The prior information needs to be identified in advance as well as be agreed upon and legal.
- The control group cannot be used a source of prior information for the new device, especially if the objective is to show the new device is non-inferior.

Important Lessons Learned Early (cont.)

- Both the label and the Summary of Safety and Effectiveness (SS&E) of the device need to change.
- A successful company generally has a solid Bayesian statistician (or someone who really wants to learn) as an employee or consultant.
- The importance of simulation
- Entire FDA review team plays a big role

The Importance of Simulation

- We need to understand the operating characteristics of the Bayesian submissions.
- Why? The Type 1 error probability (or some analog of it) protects the US 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.

The Role of Education

- Educational Efforts are important: HIMA/FDA Workshop "Bayesian Methods in Medical Devices Clinical Trials" in 1998.
- FDA internal course "Bayesian Statistics for Medical Device Trials: What the Non-Statistician Needs to Know".
- Lots of short courses and seminars and one-on-one consults

"Can Bayesian Approaches to Studying New Treatments Improve Regulatory Decision-Making?"

- Title of a Workshop jointly sponsored and planned by FDA (CDER, CDRH, CBER) and Johns Hopkins University
- Presentations by Janet Woodcock, Bob Temple, Steve Goodman, Tom Louis, Don Berry, Greg Campbell, 3 case studies and panel discussions.
- Held May 20-21, 2004, at NIH
- August, 2005 issue of the journal *Clinical Trials* is devoted to this workshop

Legal Sources of Prior Information Based on Data

- Company's own previous studies: pilots, studies conducted overseas, very similar devices, registries
- Permission legally obtained to use another company's data
- Studies published in the literature.

For the above, summaries of previous studies may not be sufficient to formulate prior; e.g., patient-level data are often necessary.

Bayesian Statistics: Submissions to CDRH

- At least 20 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)
- A number of reviews are in process.

Areas of Bayesian Application for Medical Device Studies

- Incorporation of **data-based** prior information into a current trial, allowing the data from the current trial to "gain strength" as dictated through one of a number of methodologies.
- Prediction models based on surrogate variables
- Analysis of multi-center trials (e.g., use hierarchical models to address variability among centers)
- Bayesian subgroup analysis
- Sensitivity analysis for missing data
- Flexibility of a Bayesian design and analysis in the event of an ethically sensitive device. This could be useful in a design with a changing randomization ratio in an adaptive design (as in ECMO). An added advantage is to increase enrollment and address investigator equipoise.

FDA Draft Guidance Document

- "Draft Guidance for the Use of Bayesian Statistics in Medical Device Trials" released May, 2006
  http://www.fda.gov/cdrh/osb/guidance/1601.pdf
- Public meeting to comment on the draft was held in Rockville MD in July, 2006.

Dispelling Some Myths

- Does CDRH entertain only Bayesian submissions?

  NO, only about 5-10% of submissions are Bayesian.
- Are most of the Division of Biostatistics statisticians Bayesian?

  NO
- Do the Bayesians in CDRH do only Bayesian submissions?

  NO
- Does saying the words "Bayesian statistics" make for an incantation that leads automatically to approval?
  NO

Dispelling Some Myths (2)

- Does CDRH force companies to do Bayesian approaches?

  NO (although it may be "least burdensome"). It may be a trade for a possibly lower clinical burden but a higher statistical/computational burden

- Is there a lower success criterion for Bayesian submissions?

  NO. However, there is a different one. If a standard statistical analysis and a Bayesian analysis were to always yield the same basic conclusion, there would be no reason to consider a different approach. Often in the Bayesian approach there is prior information that is ignored in the frequentist approach.

Recent FDA Advisory Committee Panel Meetings

- One in November, 2008, that used an adaptive design with a non-informative prior and a predictive model to stop recruiting and another to stop for success or futility

  http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4393s1-00-Index.html

- One in March, 2009, that used prior information from a previous trial in a Bayesian hierarchical model

  http://www.fda.gov/ohrms/dockets/ac/09/slides/2009-4419s1-00-index.html

Decision Theory, Clinical Trials and Risk

- Use Statistical Decision theory to decide when to curtail a study, when the loss of enrolling more patients is larger than that of stopping (for either success or failure). (Lewis, 1996)
- Risk versus benefit (in public health terms).
- For FDA this would require quantitative (non-economic) measures of benefit as well as risk. Often in premarket submissions this is a balance between safety and effectiveness.
- Health outcomes researchers use QALYs (Quality Adjusted Life Years).

Conclusion

- Bayesian statistics is well established as an approach for medical device clinical trials.
- Statistical issues that confront medical devices are challenging and exciting.
- The statistical worlds of the pharmaceutical industry and the device industry are growing ever closer, with combination products such as drug eluting stents and also with combination of diagnostics and drugs in pharmacogenomics.


Center for Devices and Radiological Health
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Adaptive Trials

- Adaptive trials require meticulous planning; it is not just an attitude of changing the trial in the middle without a lot of pre-planning.
- “Adaptive by design”
- You can only adapt to the changes you could have anticipated (not the ones you can’t or don’t)
- Adaptive bandwagon

Familiar Types of Adaptive Trial Designs

- For time-to-event studies, the number of events and not the number of patients that drives the power.
- In trials with low recruitment rates, DMCs often adapt by changing the inclusion/exclusion criteria, increasing the number of sites, changes in the endpoint, other changes in the protocol, etc.
- Such changes require an IDE (or IND) amendment.
- Group sequential designs

Adaptive Approaches

- Dose-finding in Phase II drug studies
- Sample size re-estimation
- Seamless Phase II-III studies
- Dropping an arm in a study with 3 or more arms
- Response Adaptive Treatment Allocation
- Bayesian sample size
- Bayesian predictive modeling

Adaptive Treatment Allocation

- Change the randomization ratio during the course of the trial.
- Two different approaches:
  - Balance of baseline covariates in the randomization
  - Response-Adaptive Treatment Allocation.

Example: ECMO

- ExtraCorporeal Membrane Oxygenation (ECMO) for the treatment of persistent pulmonary hypertension of the newborn (PPHN)
- Univ. Michigan trial
  - Randomized Play-the-Winner
  - One baby received conventional medical therapy (B) and then 11 ECMO (R): BRRRRRRRRRRR
  - Lesson: avoid extremes with very few patients in one arm
- A more recent British demonstration trial (UK ECMO Group, 1996)
  - 1:1 randomization with sequential monitoring
  - 30 deaths of 93 in ECMO arm, 54 out of 94 in control arm (p=0.0005)

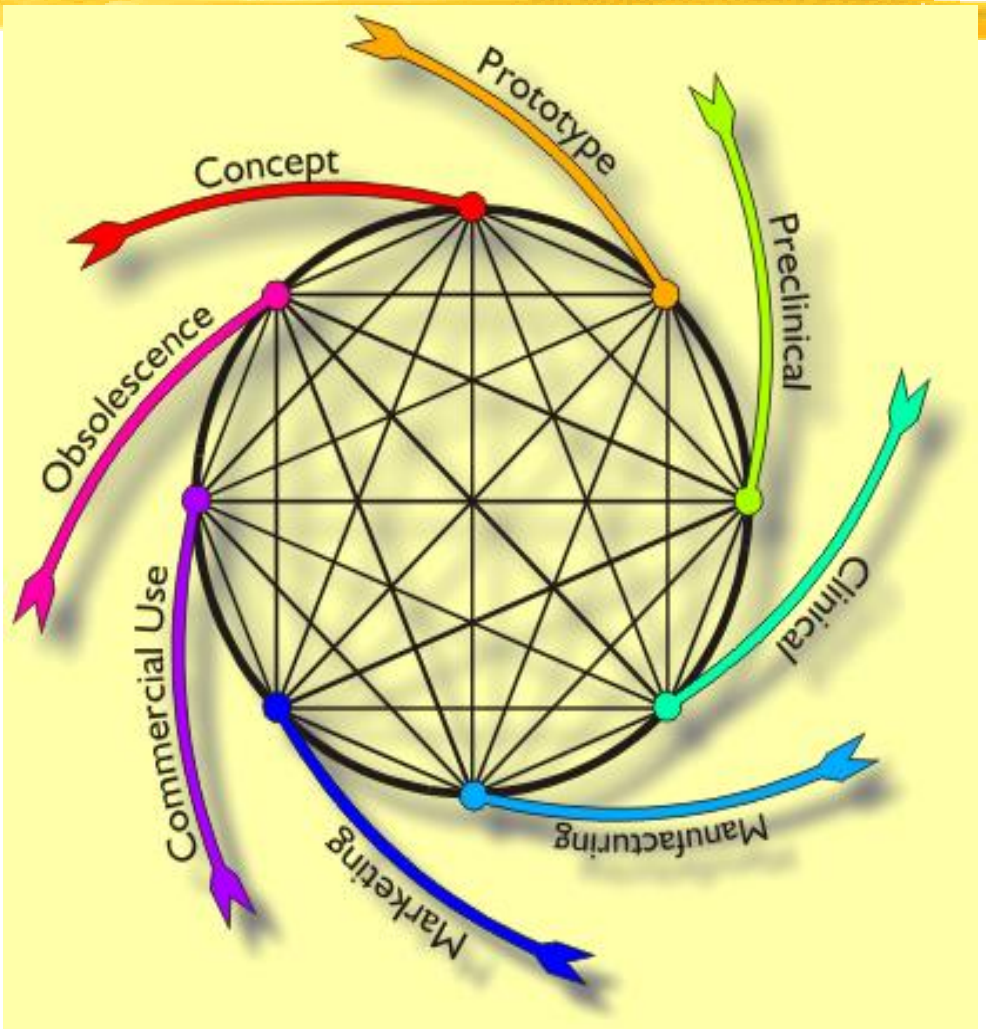
Adaptive Designs and Biomarkers

- Adapt to the expression signature and to the threshold in an adaptive drug trial. Plan to do overall analysis at alpha = 0.04. If successful, stop. If not, use the first half of the trial to develop a classifier that predicts the subset of patients most likely to benefit and test with the remaining 0.01. (Freidlin & Simon, 2005)
- Further work is continuing on selecting a threshold in an adaptive manner as well.

Are Adaptive Trials Always More Efficient or Less Risky?

- Do they always reduce risk? Not necessarily!
- What if you look all the time with a group sequential methods (Bayes or freq)? If the effect is not much larger than originally planned, it would require a larger sample and so may increase the risk.

Total Product Life Cycle (TPLC) for Devices



"Ensuring the Health of the Public Throughout the Total Product Lifecycle . . . It's Everybody's Business"

Biomarkers and Clinical Trials

- Genetic analysis could be used to tailor the dose or the schedule during a trial
- Many trials now bank genetic samples for later analysis so microarray analysis becomes retrospective
- Post hoc analysis could be used (carefully) to identify poor metabolizers or persons with adverse events

Regulatory Perspective

- Two types of genomic investigations
  - One with good scientific basis a priori, well-understood prior to collection of the data
  - One that relies on the data to suggest the hypotheses; here more of a data burden might be expected.
- The FDA will keep in mind the risk/benefit trade-off.

FDA's Critical Path Medical Device Opportunities List

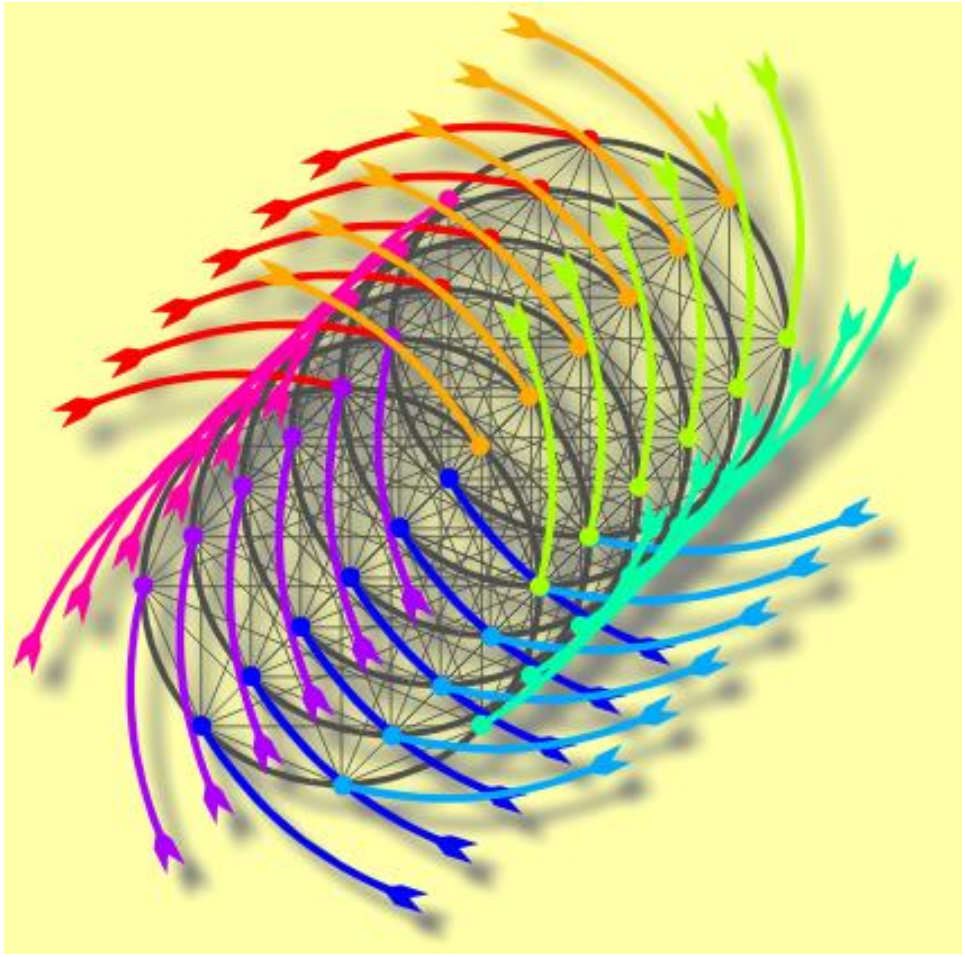
- #1 Biomarker Qualification
  - One of five questions is "What types and levels of evidence are needed to accept a biomarker as a surrogate endpoint for product efficacy?"
- #6 Surrogates Outcomes for Cardiovascular Drug Eluting Stents
- #23 Imaging Biomarkers in Cardiovascular Disease

http://www.fda.gov/oc/iniatitives/criticalpath/reports/opp_list.pdf

Practical Considerations

- It may be that the use of microarrays is primarily for exploratory and hypothesis generation.
- Right now, microrarrays are very expensive and reproducibility is questionable.
- For discovery of SNPs, it is very useful but it is much cheaper to produce the SNP test which would tend to a more targeted and reproducible test.
- However, for patterns involving many genes, microarrays hold some promise

CDRH's Vision of the Pipeline



Bayesian Medical Device Trials Outline

- Why Bayesian medical device trials?
- What CDRH learned
- What has been accomplished
- Some myths dispelled
- Secrets of success
- More challenges in the future