

Updating Bayesian Clinical Trials —A Personal Perspective

**Donald A. Berry
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Bayesian adaptive designs

- MDACC (> 300 trials)
- Device companies (> 25 PMAs)*
- Drug companies (Most of top 40; many biotechs)**

*<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm>

**<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf>

Some areas of application of Bayesian adaptive drug trials

- Oncology
- Migraine
- Rheumatoid Arthritis
- Lupus
- Sepsis
- Diabetes
- Obesity
- Stroke
- Gastroparesis
- Spinal Cord Injury
- HIV
- Hepatitis C
- Pre-term labor
- Constipation
- Overactive bladder
- Libido
- Alzheimer's
- Parkinson's

Some areas of application of Bayesian adaptive device trials

- Orthopedics
- Diagnostics
- Screening
- Stents
- Shunts
- Bronchial thermoplasty
- Ablation catheters
- PFO closure
- Left atrial appendage closure
- Contraceptives
- Defibrillators
- Neurostimulation

Two Recent High Profile Bayesian Trials

- Bayesian predictive probabilities
- Longitudinal modeling

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Adjuvant Chemotherapy in Older Women with Early-Stage Breast Cancer

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A Bayesian statistical design was used with a range in sample size from 600 to 1800 patients.

BACKGROUND

Older women with breast cancer are underrepresented in clinical trials, and data on the effects of adjuvant chemotherapy in such patients are scant. We tested for the noninferiority of capecitabine as compared with standard chemotherapy in women with breast cancer who were 65 years of age or older.

METHODS

We randomly assigned patients with stage I, II, IIIA, or IIIB breast cancer to standard chemotherapy (either cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide plus doxorubicin) or capecitabine. Endocrine therapy was recommended after chemotherapy in patients with hormone-receptor-positive tumors. A Bayesian statistical design was used with a range in sample size from 600 to 1800 patients.

The primary end point was relapse-free survival.

From the University of Vermont, Burlington (H.B.M.); the M.D. Anderson Cancer Center, Houston (D.A.B.); the Cancer and Leukemia Group B (CALGB) Statistical Center, Duke University Medical Center (C.T.C., P.A.K.) and Duke University Medical Center (H.J.C., J.D.W., A.A.M.) — both in Durham, NC; Memorial Sloan-Kettering Cancer Center, New York (M.T., L.N., C.A.H.); CALGB, Chicago (A.M.M., H.P.B.); the Dana-Farber Cancer Institute, Boston (A.B.K., A.H.P., H.J.B., E.P.W.); the University of North Carolina, Chapel Hill (L.G.D.); the North Central Cancer Treatment Group, Rochester, Minn. (A.P.); the

Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation

A Randomized Controlled Trial

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Vivek Reddy, MD

Context Antiarrhythmic drugs are commonly used for prevention of recurrent atrial fibrillation (AF) despite inconsistent efficacy and frequent adverse effects. Catheter ablation has been proposed as an alternative treatment for paroxysmal AF.

Objective To determine the efficacy of catheter ablation compared with antiarrhythmic drug therapy (ADT) in treating symptomatic paroxysmal AF.

Design, Setting, and Participants A prospective, multicenter, randomized (2:1), unblinded, Bayesian-designed study conducted at 19 hospitals of 167 patients who did not respond to at least 1 antiarrhythmic drug and who experienced at least 3 AF episodes within 6 months before randomization. Enrollment occurred between October 25, 2004, and October 11, 2007, with the last follow-up on January 19, 2009.

Intervention Catheter ablation (n=106) or ADT (n=61), with assessment for effectiveness in a comparable 9-month follow-up period.

Main Outcome Measures Time to protocol-defined treatment failure. The pro-

Design, Setting, and Participants A prospective, multicenter, randomized (2:1), unblinded, Bayesian-designed study conducted at 19 hospitals of 167 patients who

Christine Y. Liu, MPH

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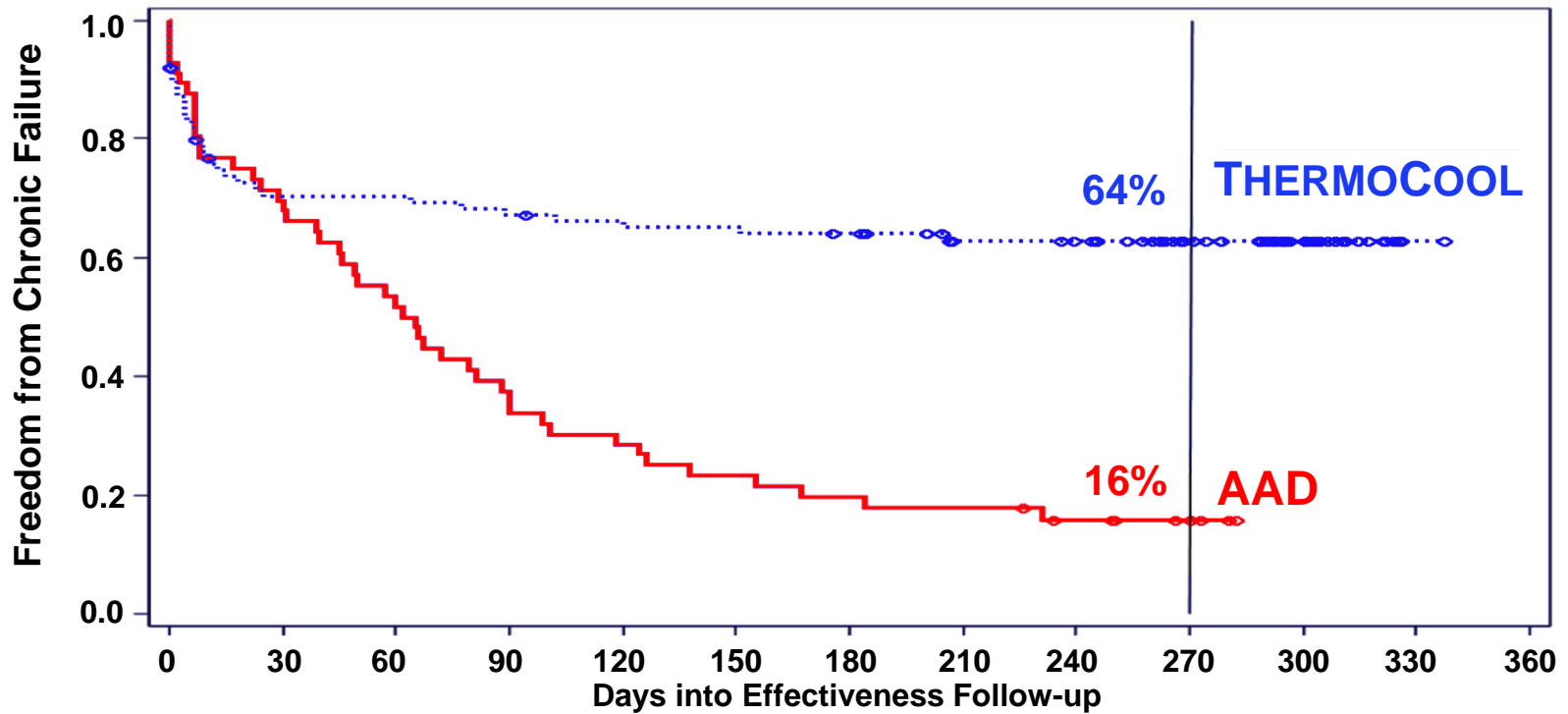
Donald A. Berry, PhD

for the ThermoCool AF Trial
Investigators

in the catheter ablation group remained free from protocol-defined treatment failure compared with 16% of patients treated with ADT. The hazard ratio of catheter ablation to ADT was 0.30 (95% confidence interval, 0.19-0.47; P<.001). Major 30-day treatment-related adverse events occurred in 5 of 57 patients (8.8%) treated with ADT and 5 of 103 patients (4.9%) treated with catheter ablation. Mean quality of life scores improved significantly in patients treated by catheter ablation compared with ADT at 3 months; improvement was maintained during the course of the study.

Conclusion Among patients with paroxysmal AF who had not responded to at least

Time to Chronic Failure by Randomization Group (Updated)



TCool	10	69	69	66	63	62	61	54	52	37	15	3	2
	3												
AAD	56	39	29	19	16	13	11	10	7	2	0	0	0

Bayes and Comparative Effectiveness Research

Bayesian Meta-analyses for Comparative Effectiveness and Informing Coverage Decisions

Scott M. Berry, PhD, K. Jack Ishak, PhD,† Bryan R. Luce, PhD,‡ and Donald A. Berry, PhD*§*

Background: Evidence-based medicine is increasingly expected in health care decision-making. The Centers for Medicare and Medicaid have initiated efforts to understand the applicability of Bayesian techniques for synthesizing evidence. As a case study, a Bayesian analysis of clinical trials of implantable cardioverter defibrillators was undertaken using patient-level data not typically available for analysis.

Purpose: Conduct Bayesian meta-analyses of the defibrillator trials using published results to demonstrate a Bayesian approach useful to

time. The Bayesian approach used in a sequential manner over time can predict results and help assess the utility of future clinical trials.

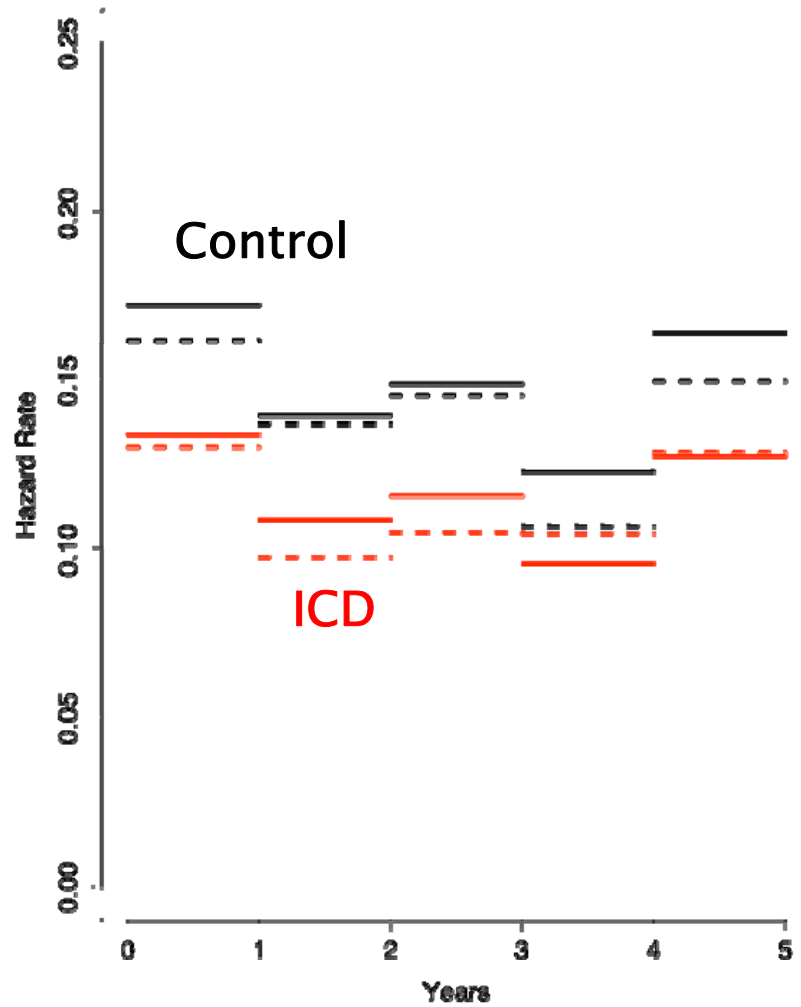
Key Words: Bayesian analysis, comparative effectiveness, meta-analysis, coverage decisions

(Med Care 2010;48: 000)

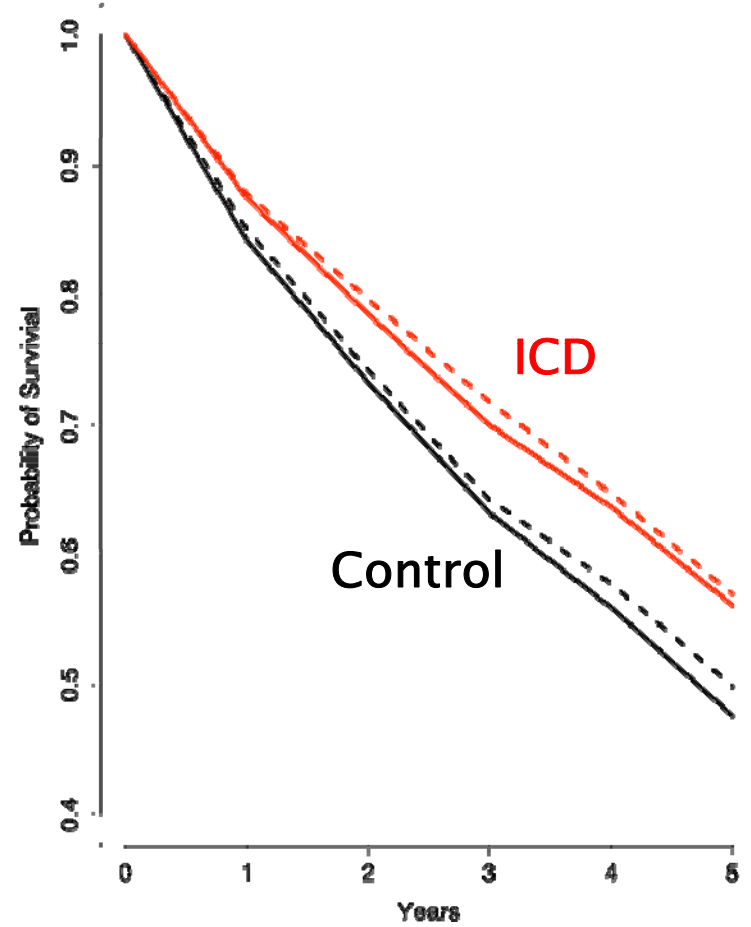
Application to Implantable Cardioverter Defibrillators

Hazard Rates & Survival: Models 1 & 2

Hazard rates

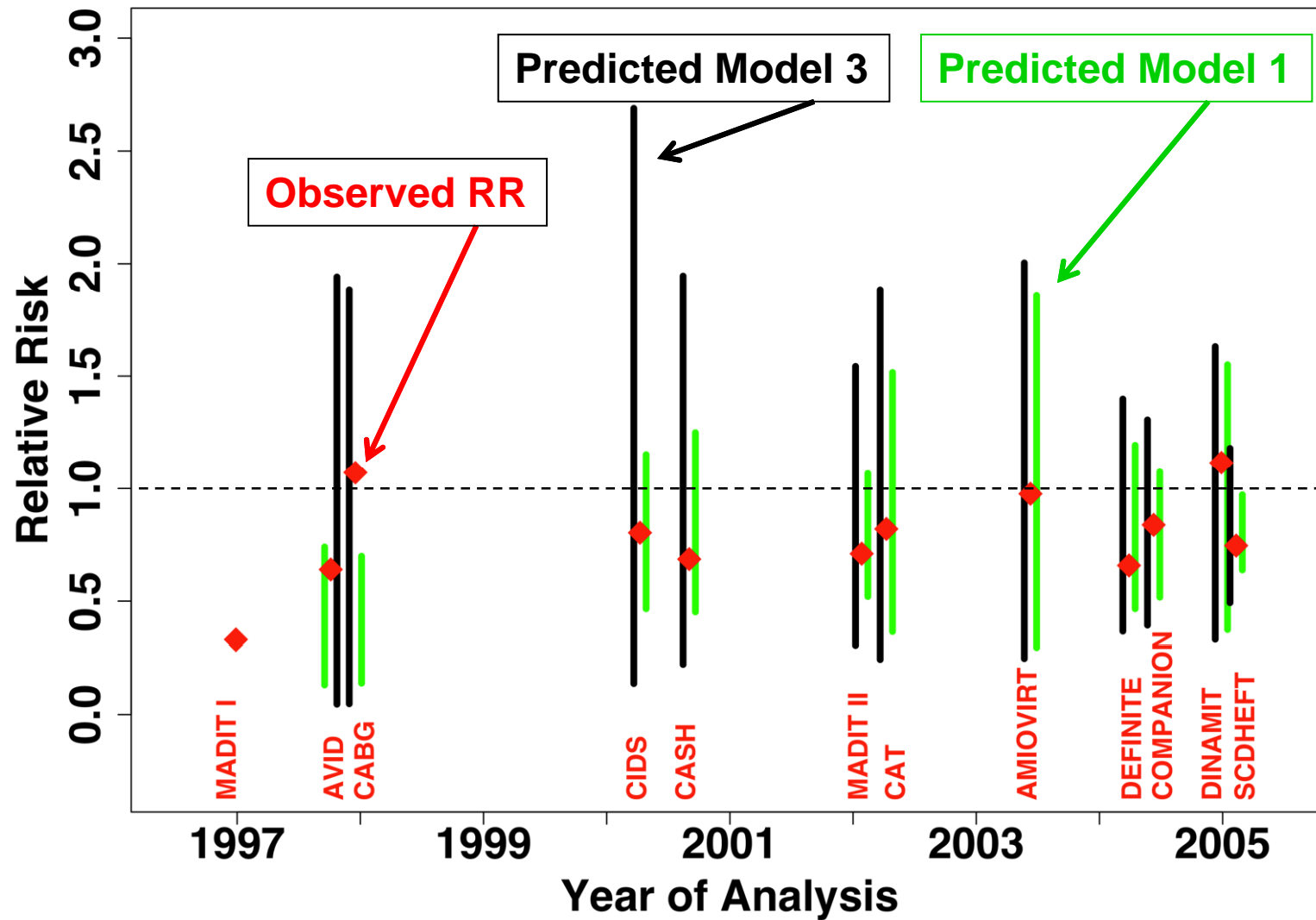


Survival probabilities



Model 1 ———
Model 2 - - - -

Predictive Probabilities over Time



FDA/NIH Grant for Bayesian Adaptive Designs in Neurology



FDA's \$25 Million Pitch for Improving Drug Regulation

by Jennifer Couzin-Frankel on 7 October 2010, 3:17 PM | [Permanent Link](#) | [0 Comments](#)

"Our current approach [to trials] is horribly inefficient, and we need to do something better," says Roger Lewis, an emergency medicine physician at Harbor-University of California, Los Angeles, Medical Center. Lewis helps advise a company called Berry Consultants ...

in conjunction with the National Institutes of Health (NIH), [it announced four sizable grants](#), totaling \$9.4 million, in regulatory science. (FDA contributed just under \$1 million and NIH gave the rest.) They include support for a heart-lung system that can test potential drugs and an effort to dramatically streamline clinical trials.

"Our current approach [to trials] is horribly inefficient, and we need to do something better," says Roger Lewis, an emergency medicine physician at Harbor-University of California, Los Angeles, Medical Center. Lewis helps advise a company called Berry Consultants founded by Donald Berry, a biostatistician at M.D. Anderson Cancer Center in Houston, Texas. He and Berry, along with emergency medicine physician William Barsan at the



*Science***Insider**

Breaking news and analysis from the world of science policy

FDA's \$25 Million Pitch for Improving Drug Regulation

by Jennifer Couzin-Frankel on 7 October 2010, 3:17 PM | [Permanent Link](#) | [0 Comments](#)

Lewis and Berry, along with emergency medicine physician William Barsan at the University of Michigan, will be studying whether "adaptive" trial designs that incorporate new information in midcourse can answer medical questions. They also want to learn what concerns researchers might have about this

approach.

regulatory science. (FDA contributed just under \$1 million and NIH gave the rest.) They include support for a human lung system that can test potential drugs and an effort to dramatically streamline clinical trials.

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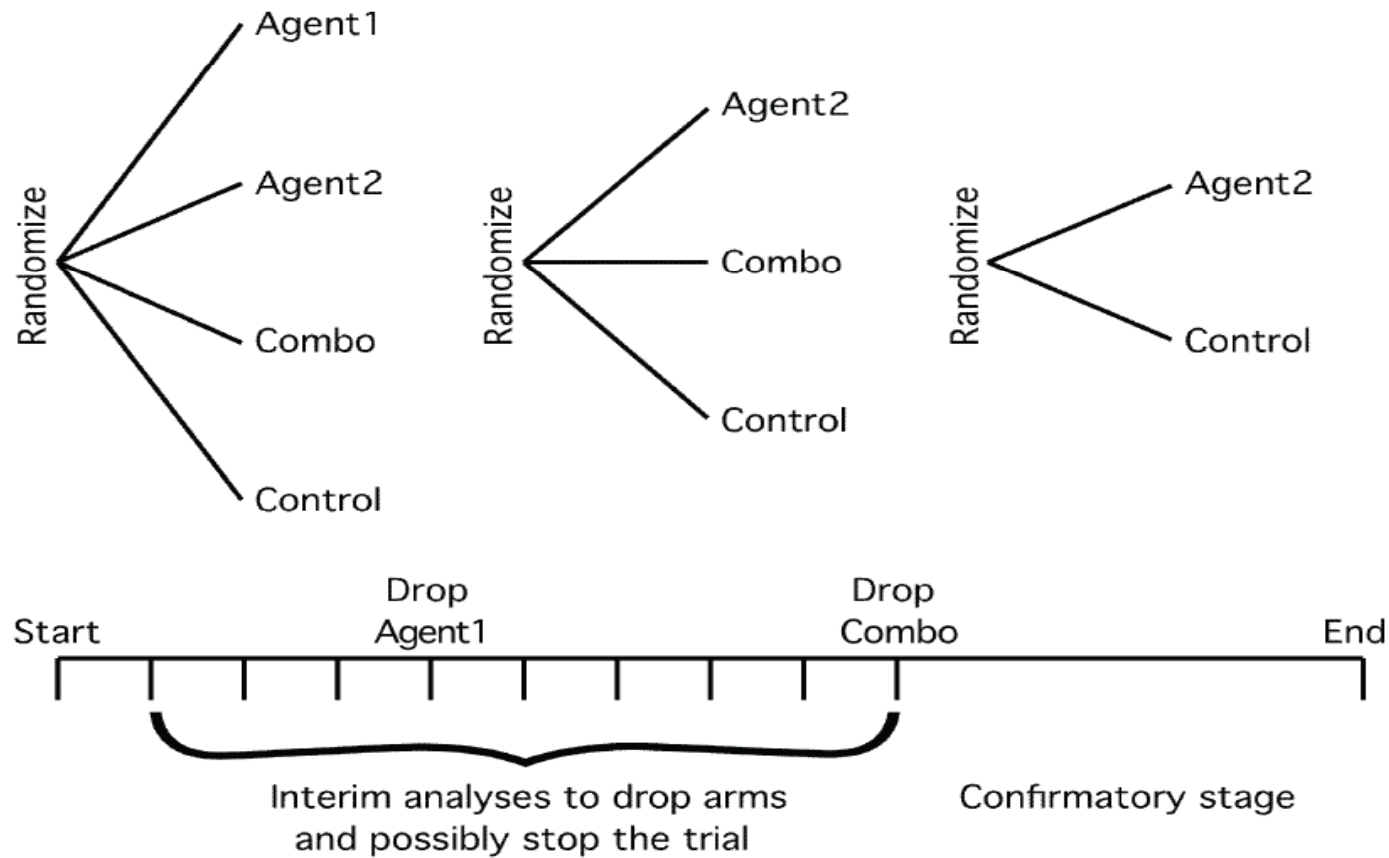
A NATIONAL CANCER CLINICAL TRIALS SYSTEM FOR THE 21ST CENTURY

Reinvigorating the NCI Cooperative Group Program

Committee on Cancer Clinical Trials and the
NCI Cooperative Group Program
Board on Health Care Services

Sharyl J. Nass, Harold L. Moses, and John Mendelsohn, *Editors*

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES



Most clinical trials are designed to employ classical “frequentist” statistical methods.²⁰ Another approach to clinical trial design and analysis is the Bayesian approach, which considers the treatment effect as a random variable with a probability distribution rather than as an unknown constant that the investigator wishes to estimate. FDA has issued draft

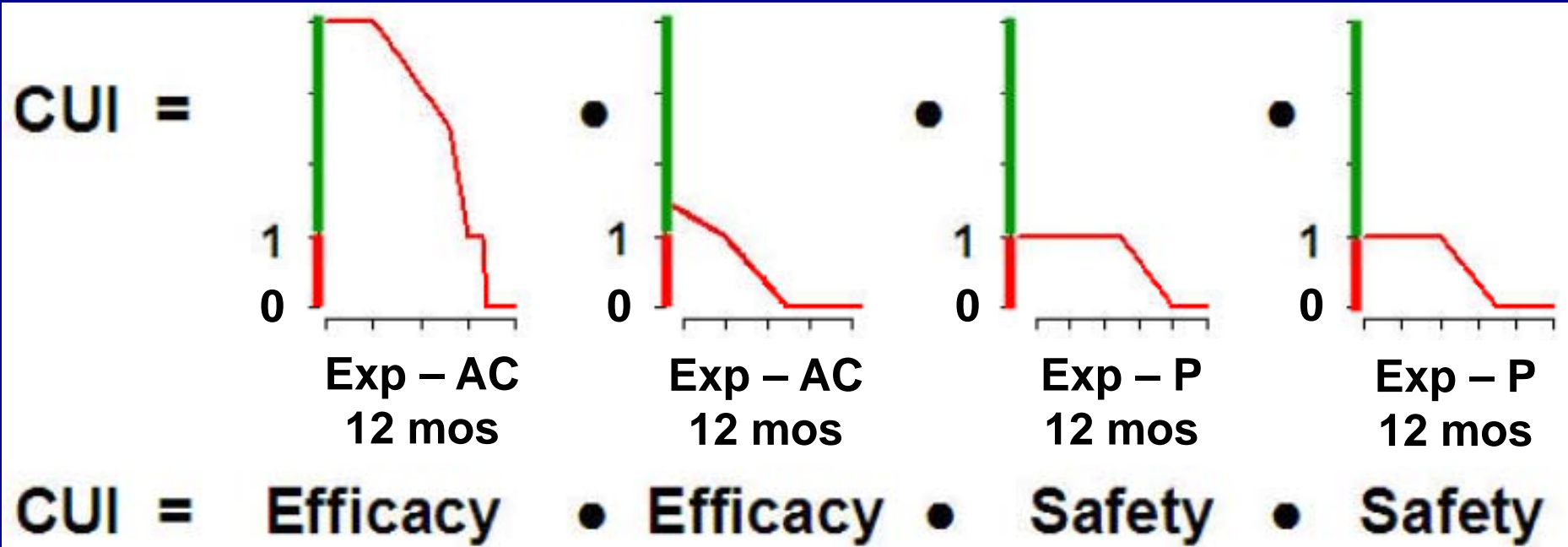
Example from BB2009

- **Type II diabetes**
- **Seamless phase II/III: dose finding plus confirmation**
- **Active comparator & placebo**
- **Primary endpoint:
clinical utility index (12 months)**

Some Details

- Longitudinal modeling
- Phase II: 7 doses experimental drug
- Phase III
 - 1 or 2 doses experimental drug
 - Sample size via predictive power considering available phase II data
 - Adaptive transition: Bayesian predictive probabilities
- Both phases driven by CUI

Clinical Utility Index



- Dose-response modeling
- Longitudinal modeling

Example from BB2009

I-SPY 2

- Neoadjuvant breast cancer
- Longitudinal modeling
- Biomarker subsets
- Many arms: adaptive randomization

A New Rx for Med

Fed up with slow drug trials, ca
treatments.

By RON WINSLOW

New trial design
Uses genetic profiles to highlight 'biomarker' differences among patients and to match drugs to patients with biomarkers that predict a benefit.

back to personalized

PERSONALIZED MEDICINE | How

1 cube = 10 patients

Traditional clinical trial

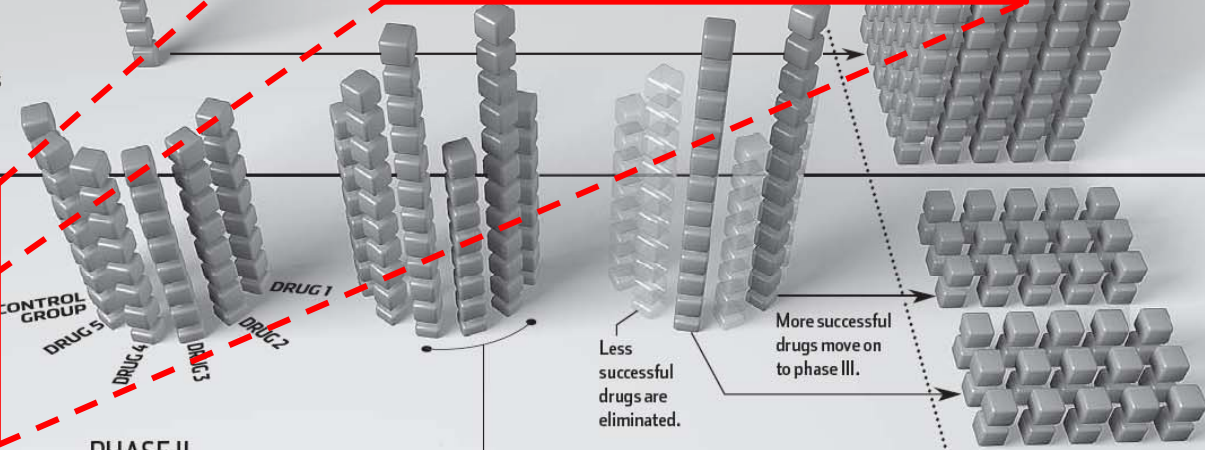
Takes essentially all patients with a disease being studied and is typically intended to eliminate differences in patient characteristics that could bias measures of drug effectiveness.

PHASE II

Randomized or non-randomized trial: about 60 patients are put in two groups: One drug and the other serves as a control group about 40 patients receive the experimental

New trial design

Uses genetic profiles to highlight 'biomarker' differences among patients and to match drugs to patients with biomarkers that predict a benefit.



PHASE II

Patients are placed in groups based on genetic profiles and are randomly assigned to either standard therapy or one of five different drugs plus standard care.

Early results increase chances that patients entering the trial later will be assigned to a drug showing benefit against tumors with their genetic profile.

It will take up to 120 patients for each drug to determine which ones graduate to phase III studies.

Drug development

PHASE III

If a drug graduates to phase III, it typically takes 3,000 patients and about three years to determine if it is safe and effective enough for approval.



HISTORIC SUCCESS RATE
30 TO 40%

PHASE III

Researchers expect that drugs graduating from I-Spy 2 to phase III can be tested with 300 patients selected according to genetic profiles found to respond to the drug in phase II. It is hoped that this will shorten the time to approval.



PROBABILITY OF SUCCESS
85%

Note: In all clinical trials, phase I consists of testing on human subjects to determine toxicity levels.

Graphic by Maryanne Murray/WSJ

Source: Donald Berry, M.D. Anderson Cancer Center

A New Rx for Medicine

Fed up with slow drug trials, cancer patients and doctors are testing a fast track to personalized treatments.

By RON WINSLOW

PERSONALIZED MEDICINE | How redesigning a clinical trial can speed drug development

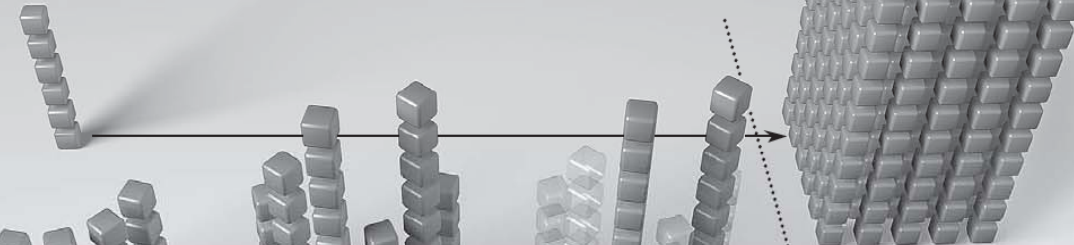
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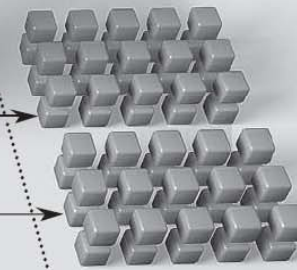
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Early results increase chances that **patients entering the trial later will be assigned to a drug showing benefit** against tumors with their genetic profile.

It will take up to 120 patients for each drug to determine which ones graduate to phase III studies.

Less successful drugs are eliminated.

More successful drugs move on to phase III.



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