Gaining Acceptance for Innovative Designs / Analyses in Pharmaceutical R&D

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EFSPI Recent Advances In Clinical Trial Design

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“Getting a new idea adopted, even when it has obvious advantages, is difficult. Many innovations require a lengthy period of many years from the time when they have become available to the time when they are widely adopted.”

Everett M Rogers. *Diffusion of Innovations (5th Edition).* New York: Free Press, 2003.

The Slow Pace of Translation of Methodological Development into Practice.

4 Examples

Example 1.

Timeline of an Innovation

264 years

1601

James Lancaster
Lemon Juice

1795

Navy adopts
Citrus

1865

Merchant Marine
Adopts Citrus

1747

James Lind
Citrus

1497

Vasco da Gama
lost 100/160 sailors

1932

Vitamin C identified
Charles King

1400 1500 1600 1700 1800 1900 2000 2100

Frederick Mosteller (1981). Innovation and Experimentation, Science, 211, 881-886)

Example 2.

Adaptive Ideas Are Not New

ON THE LIKELIHOOD THAT ONE UNKNOWN PROBABILITY EXCEEDS ANOTHER IN VIEW OF THE EVIDENCE OF TWO SAMPLES.

By WILLIAM R. THOMPSON. From the Department of Pathology, Yale University.

Biometrika, 1933

Thus, if, in this sense, P is the probability estimate that one *treatment* of a certain class of individuals is *better* than a second, as judged by data at present available, then we might take some monotone increasing function of P, say $f_{(P)}$, to fix the fraction of such individuals to be treated in the *first manner*, until more evidence may be utilised, where $0 \leqslant f_{(P)} \leqslant 1$; the remaining fraction of such individuals $(1 - f_{(P)})$ to be treated in the *second manner*; or we may establish a probability of treatment by the two methods of $f_{(P)}$ and $1 - f_{(P)}$, respectively. If

- Ethical Design – concentrating on delivering the best treatment to the most patients

Randomised Design

ON THE THEORY OF APPORTIONMENT.

By William R. Thompson.

Annals of Mathematics, 1935

> as in the case $k = 2$, we may apportion *individuals* among the k rival *treatments* by assigning to each T_i the portion, f_i, or making the chance of this assignment equal f_i, respectively.

Simple Idea

At some point in a trial we have the following data:

Trt A	Trt B
1	0
0	0
0	1
1	0
.	.
.	.
1	0
r_A / n_A	r_B / n_B

- If π_A and π_B are the response rates of each treatment then

$$P(\pi_A < \pi_B \mid Data)$$

- measures the "superiority" of B over A.
- Thompson proposed patients be randomised to A and B in the ratio

$$\frac{1 - P(\pi_A < \pi_B \mid Data)}{P(\pi_A < \pi_B \mid Data)}$$

2x2 Contingency Table - Posterior Inference
"Uninformative Priors" : $\alpha_A = \beta_A = \alpha_B = \beta_B = 1$

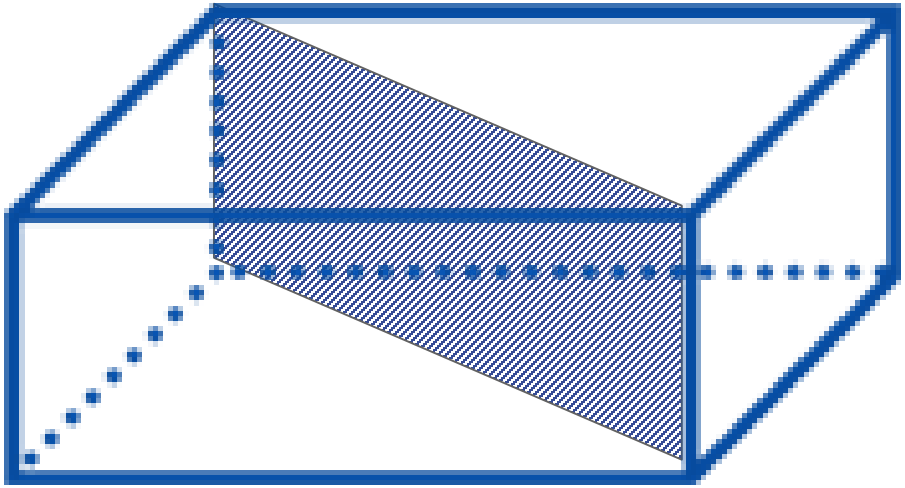
- For a uniform prior ($\alpha_1 = \alpha_2 = \beta_1 = \beta_2 = 1$ - Thompson) the probability of interest is

$$\text{Prob}(\pi_A < \pi_B \mid \text{Data}) = \sum_{k=0}^{n_1 - r_1} \frac{\binom{n_1 + n_2 - r_1 - r_2 - k}{n_2 - r_2}\binom{r_1 + r_2 + 1 + k}{r_2}}{\binom{n_1 + n_2 + 1}{n_1 + 1}} = \sum_{k=0}^{\min(b-1, W-w)} \frac{\binom{W}{w+\alpha}\binom{B}{b-1-\alpha}}{\binom{W+B}{w+b-1}}$$

- based on the cumulative hypergeometric function - as is Fisher's exact test (Altham JRSSB,1969)
- This second term is the probability under sampling without replacement from a mixture of W white balls and B black balls that we will get w white balls before b black balls

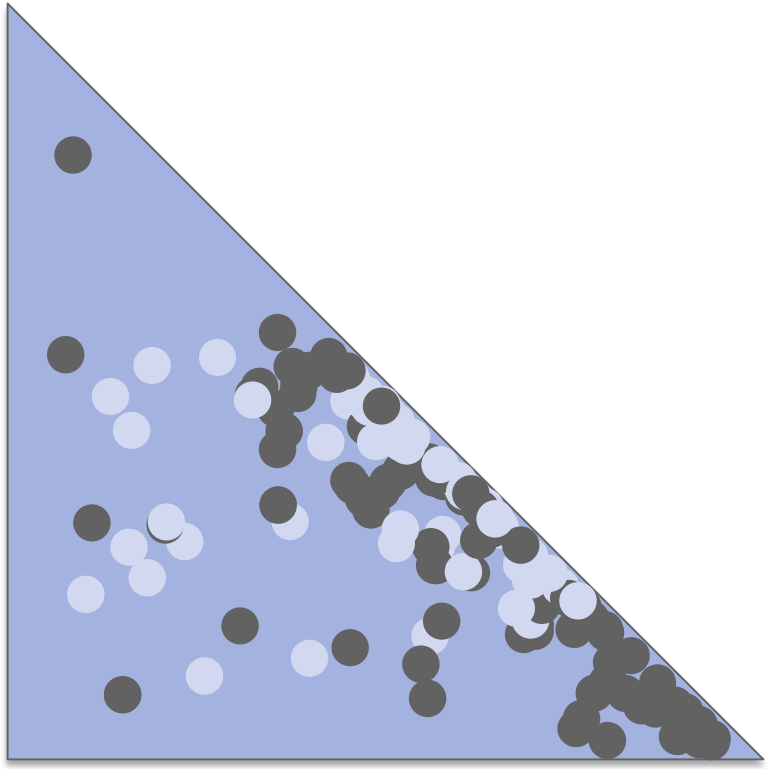
- For $W=n_1+1$, $B=n_2+1$: choose Trt A if $w=n_1-r_1+1$ white balls occur before $b=n_2-r_2+1$ black balls, else Trt B.

Thompson(1935)
Mechanical Randomisation & Simulation



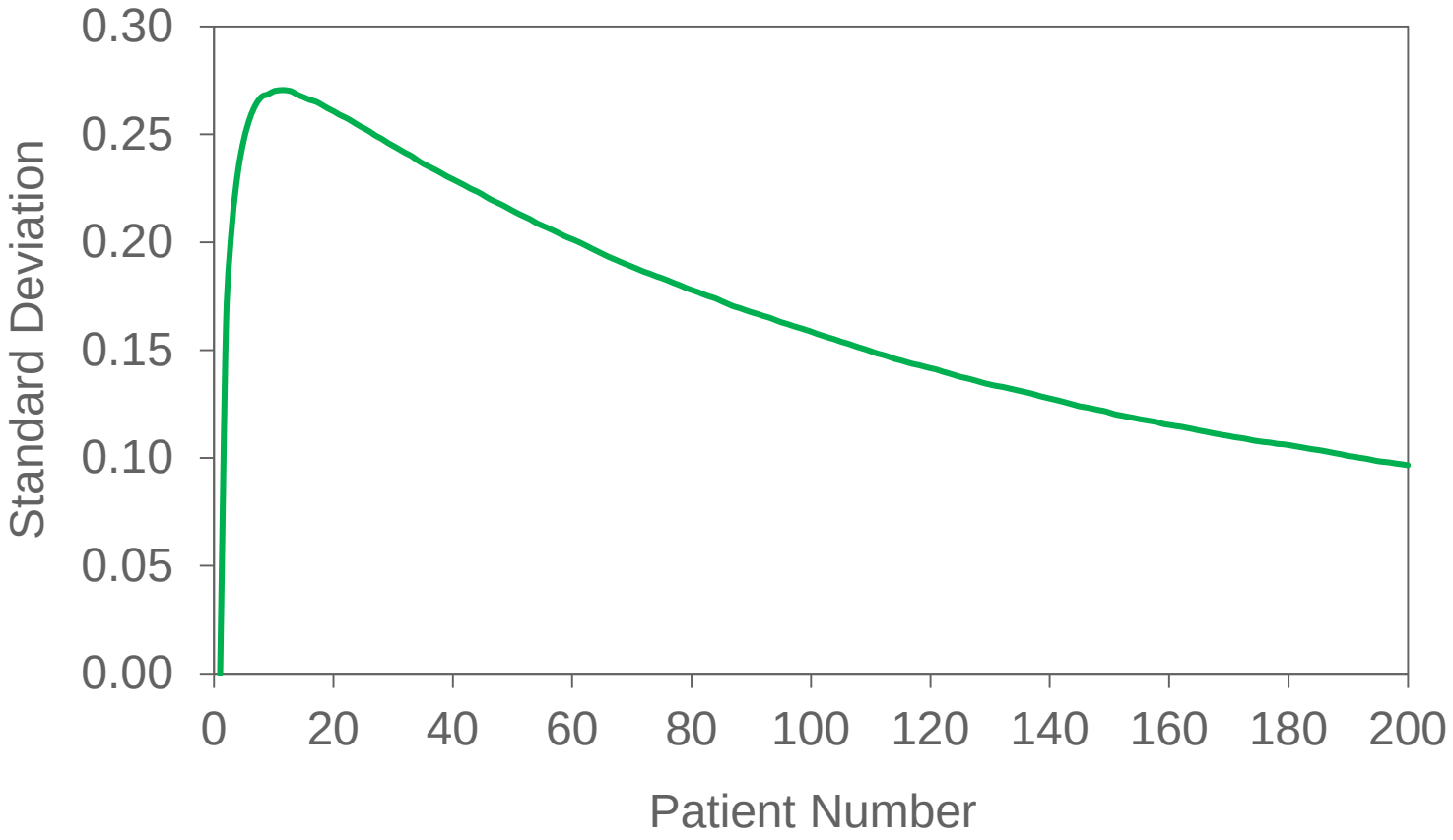
$r_1=2$, $n_1-r_1=2$, $r_2=4$, $n_2-r_2=3$

W=5, B=8, w=3, b=5



Variability of Randomisation Probabilities

π_A=0.25 , π_B=0.45



Bayesian Adaptive Randomisation
Thall and Wathen (Eur J Cancer, 2007)

- Early instability
- Thall and Wathen (2007)

$$\frac{P(\pi_A < \pi_B \mid Data)^C}{P(\pi_A < \pi_B \mid Data)^C + \left(1 - P(\pi_A < \pi_B \mid Data)\right)^C}$$

Example 3.

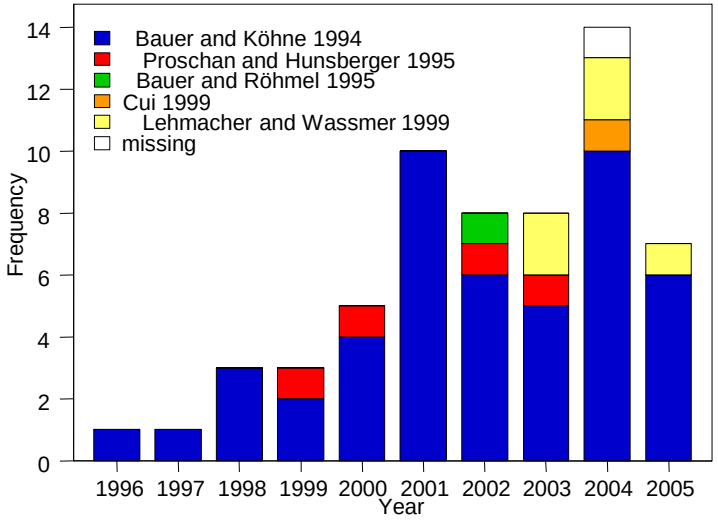
Adaptive Confirmatory Interim Designs
Bauer & Koehne (Biometrics,1994)

General Strategy - >=1 adaptive interims

- Adaptation
- reassessment of sample size
- change of follow-up time
- reallocation to treatment arms
- choice of test statistic
- dose-finding, e.g., in Phase I/II toxicity and efficacy studies
- Combining Phase II/III studies (adaptive seamless phase II/III designs)
- Selection of endpoints, study population (sub-group analysis or population enrichment designs)

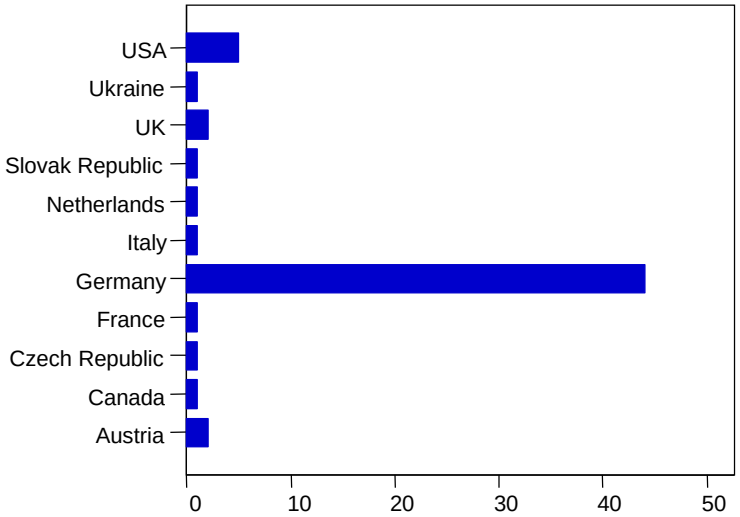
Review of Adaptive Interims
Bauer and Einfalt (Biometrical J, 2006)

- Identified 75 papers dealing with adaptive designs : 1989-2004
- combination tests
- conditional error function
- did not consider Bayesian approaches



By: year and adaptive methodology

- Searched for “applied papers” in SCI, SSCI, IAHCI referring to at least one of the 75 papers
- Identified 60 applied medical papers



By: Country of corresponding author

Adaptive Confirmatory Interim Designs

- Adaptive interims not widely used
- Methods used mainly in Germany
- Adaptations in practice are limited to sample size re-assessment
- Sophistications – dropping treatment arms, modifying endpoints etc have not entered medical literature
- Standard of presenting statistical methods poor
  - pressures on space ? (Aptiv experience)
- Mid-trial changes may impact negatively on the “persuasiveness” of the results

Example 4.

MTD Determination - 1990

The Continual Reassessment Method (CRM) was proposed by O'Quigley, Pepe and Fisher (Biometrics 1990) to address ethical and statistical concerns of phase I dose finding trials in cancer as an alternative to the 3+3 MTD-finding design

- CRM reassesses a dose-response relationship based on accrued data of the on-going trial
- which allows investigators to make decisions based on a constantly updated dose-response model

Model-Based (CRM & Progenies) vs Algorithmic (3+3 or A+B)

Due to their flexibility, Bayesian adaptive design methods based on accrued data of on-going trials have been recommended to be used for dose response trials in early clinical development by the US Food and Drug Administration's (FDA) and the European Medicines Agency (EMEA, 2002)

Market Leader Design - Algorithmic approaches

- Algorithmic designs to determine the MTD have been around for over 40 years
- Carter (1972). In *Design of Clinical Trials in Cancer Therapy* (ed. Staquet,M).
- Rogatko et al (*Journal of Clinical Oncology* , 2007) - 98% used traditional algorithmic approaches.
- Tourneau et al (*Journal of the National Cancer Institute*, 2009) - 92% used traditional algorithmic approaches.
- The predominant algorithmic design is the 3 + 3 design

The Slow Pace of Translation of Methodological Development into Practice Sylvie Chevret (SIM, 2011)

- Bayesian clinical trials have been recommended for twenty years
  - Early phase trials -> phase III
  - BUT have been reported poorly used in practice
  - Possibly due to the usual time lag of the technical innovation spread - This was confirmed in this study with only 3% of biostatistical papers reaching 25 citations after publication, as compared to 15% of reviews and 32% of clinical trial reports

- Despite advantages and recommendations, Bayesian adaptive designs have not been widely adopted in practice

- Only 20 (1.6%) of 1,235 phase I cancer trials have been reported to follow a Bayesian design by Rogatko et al. (J Clin Oncol 2007)

- This could be in agreement with the previous report from Altman and Goodman (JAMA 1994)

Altman and Goodman (JAMA 1994)
Transfer of Technology from Statistical Journals to the Biomedical Literature

Table 1.—Statistical Articles Included in This Study

Source, y	Topic
Methodological articles	
Cornfield,[3] 1951	Odds ratio
Cochran,[4] 1954	χ^2 Trend test
Woolf,[5] 1955	Combining 2×2 tables
Kaplan and Meier,[6] 1958	Survival curve
Mantel and Haenszel,[7] 1958	Stratified 2×2 table
Cohen,[8] 1960	κ Statistic
Mantel,[9] 1963	Survival analysis
Box and Cox,[10] 1964	Transformations
Mantel,[11] 1966	Survival analysis
Elston and Stewart,[12] 1971	Heredity
Peto and Peto,[13] 1972	Log rank test
Cox,[14] 1972	Proportional hazards regression
Dempster et al,[15] 1977	EM algorithm
Efron,[16] 1979	Bootstrap
Hanley and McNeil,[17] 1982	Receiver operating characteristic curve
Geman and Geman,[18] 1984	Gibbs sampling
Breiman et al,[19] 1984	Classification and regression trees
Zeger and Liang,[20] 1986	Longitudinal data
Expository articles	
Peto et al,[21] 1977	Log rank test
Bland and Altman,[22] 1986	Method comparison

Altman and Goodman (JAMA 1994)

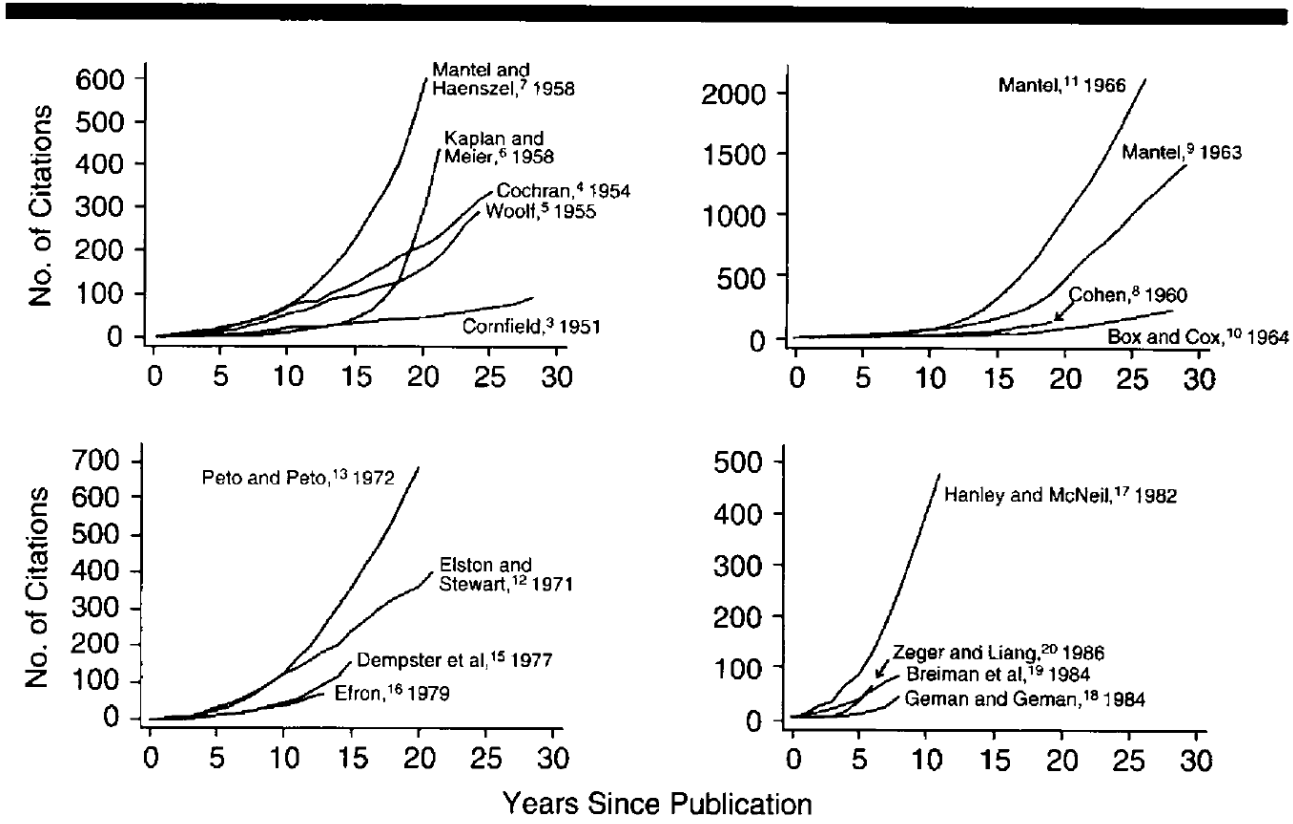


Fig 1.—Cumulative citations in medical journals for selected articles published in 1950 through 1959 (top left), 1960 through 1969 (top right), 1970 through 1979 (bottom left), and 1980 through 1989 (bottom right).

Altman and Goodman (JAMA 1994)

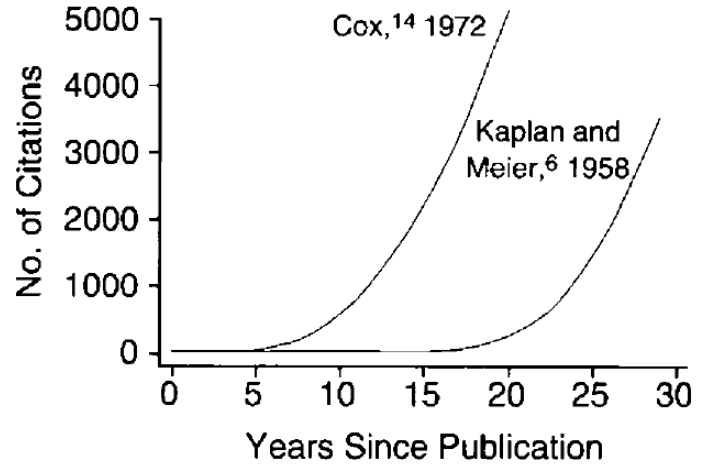


Fig 2.—Cumulative citations in medical journals for two heavily cited articles on survival analysis methods.

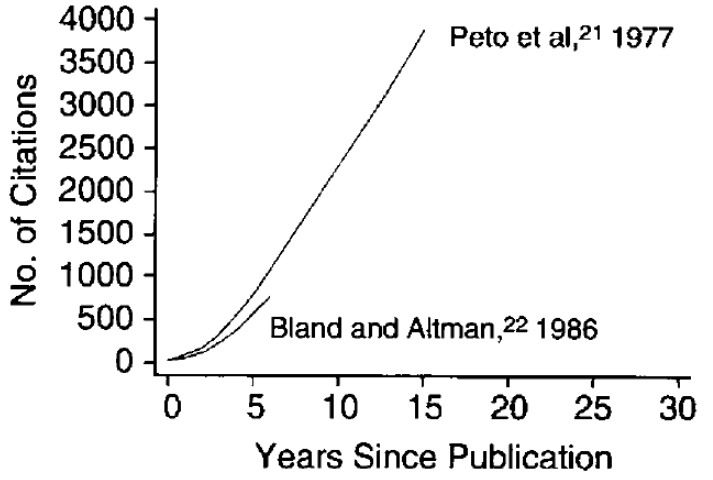


Fig 3.—Cumulative citations in medical journals for two expository articles.

« Newer technical innovations still typically take 4 to 6 years before they achieve 25 citations in the medical literature. »

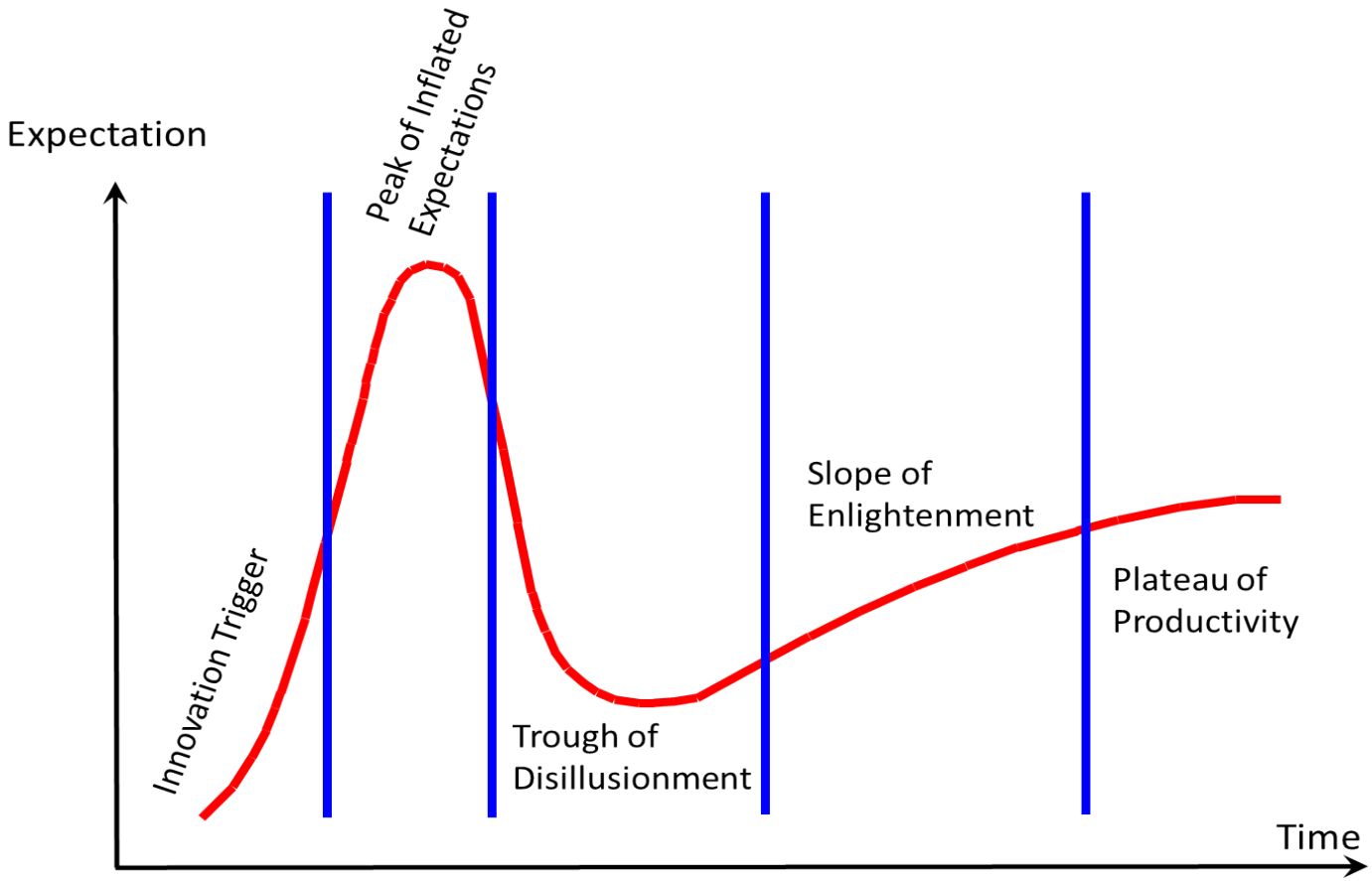
Altman and Goodman (JAMA 1994)

Newer Statistical Methods That may be Seen More Often In the Coming Years

Table 3.—Newer Statistical Methods That May Be Seen More Often in the Coming Years

Method	Description	Purpose
Bootstrap (also called resampling; related to the jackknife)[17]	Multiple new data sets are generated by random sampling "with replacement" from the original data	To calculate SEs or assess the stability of a statistical model, often when standard assumptions are unreliable or the sampling distribution is unknown
Gibbs sampling[18,34]	Random sampling from conditional distributions within a complex structure	Bayesian estimation of complex models
Generalized additive models[35]	Nonparametric smoothing of explanatory variables in regression	To replace regression when assumptions are not tenable
Classification and regression trees[19,36] (also known as recursive partitioning)	Division of a set of subjects by combinations of characteristics, to minimize the differences within groups and to maximize the differences between groups	To find combinations of variables of predictive importance
Models for longitudinal data ("general estimating equations")[20]	Modeling repeated measurements of an outcome variable while allowing for covariates	Regression for multiple assessments of outcome
Models for hierarchical data (also called multilevel models)[37]	Fitting mixed linear models to hierarchical data using iterative generalized least squares	Modeling data with more than one level of variation (eg, within and between patients)
Neural networks[38]	Nonparametric modeling of complex data	To provide nonlinear approximations to multivariable functions or for classification

Gartner Technology Hype-Cycle

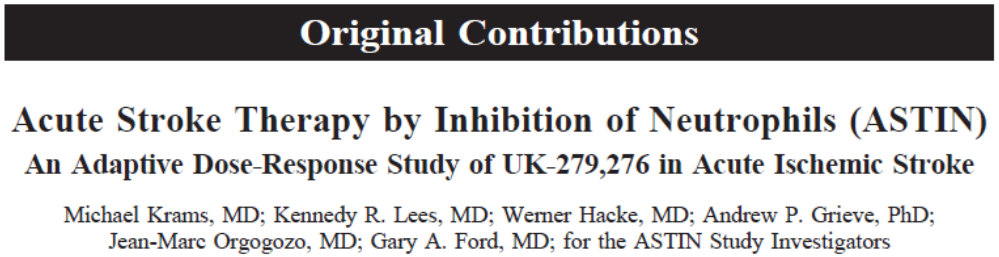


Is Innovation Always an Advantage?

> “Being first to market with a new chemical entity is commercially advantageous; being first to registration with a new statistical method may not be.”

Simon Day (2002), Changing times in pharmaceutical statistics: 2000–2020, Pharmaceutical Statistics, 1, 75-82.

The ASTIN Trial - 1997



Original Contributions

Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN)

An Adaptive Dose-Response Study of UK-279,276 in Acute Ischemic Stroke

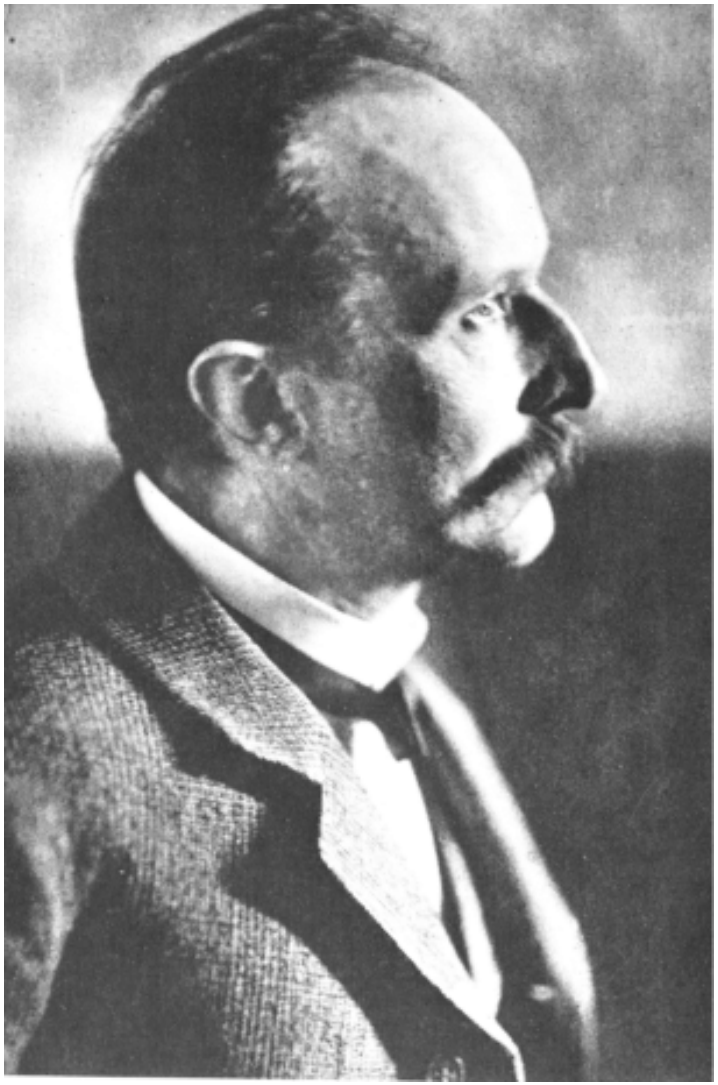
Michael Krams, MD; Kennedy R. Lees, MD; Werner Hacke, MD; Andrew P. Grieve, PhD; Jean-Marc Orgogozo, MD; Gary A. Ford, MD; for the ASTIN Study Investigators

- Met with Ellenberg & Lachenbuch to gain “preliminary support for the design”
- Dose selection, Bayesian adaptive randomisation, computer driven, 15 doses - +ve response, “neat idea”, “someone needs to pilot it”
- Visited
  - FDA
  - MCA (MHRA)
  - Bfarm
  - MPA
  - HPFB
  - EMEA
- All given a 45 minute presentation on the design, uniformly positive response

Rogers (2003) - .*Diffusion of Innovations (5th Edition).* New York: Free Press.

- Innovation
- The Relative Advantage
- Compatibility
- Complexity
- Trialability
- Observability

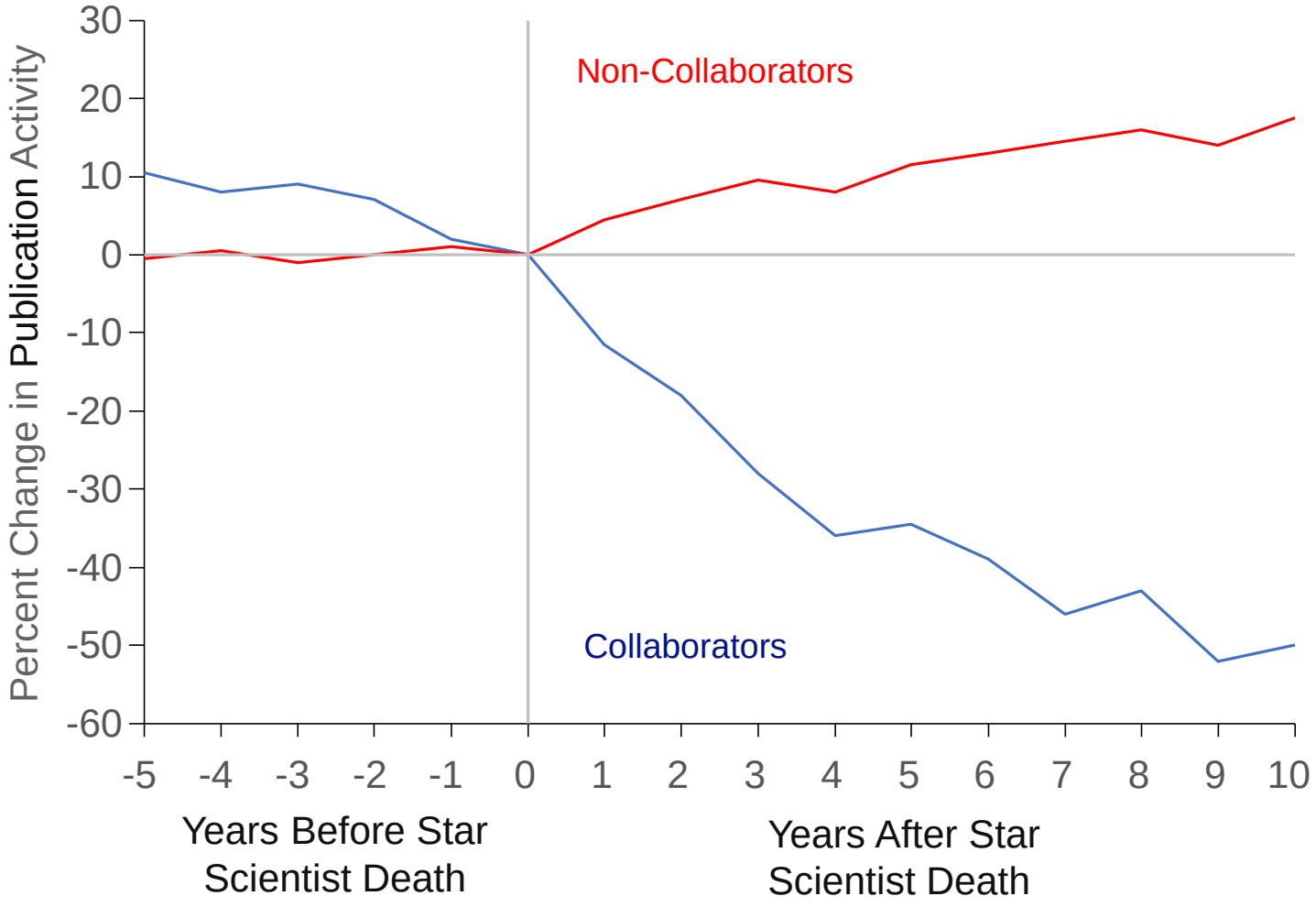
When will Change Occur



"A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die out, and a new generation grows up that is familiar with it."

Max Planck, Scientific Autobiography, 1948

The Death of a Star Scientist and Publication Activity



How is FDA being encouraged to be warm to Adaptivity and Bayes ?

- 21st Century Cures Act
- PDUFA VI

21st Century Cures Act (proposed)

Section 2061 BROADER APPLICATION OF BAYESIAN STATISTICS AND ADAPTIVE TRIAL DESIGNS

- encourages FDA to issue guidelines and policy for: ***"the use of adaptive trial designs and Bayesian methods in clinical trials, including clinical trials proposed or submitted to help to satisfy the substantial evidence standard under section 505(d) of the FD&C Act.*** "

21st Century Cures Act

SEC. 2061. BROADER APPLICATION OF BAYESIAN STATISTICS AND ADAPTIVE TRIAL DESIGNS.

- Finalize guidance on adaptive trial designs
- Draft guidance on the use of Bayesian methods in the development and regulatory review and approval
- use of adaptive trial designs and Bayesian to help to *satisfy the substantial evidence standard*
- recommended analysis methodologies
- consult with representatives of regulated industry, academia, et al in a *public meeting within 1 year*
- *Publish final guidances not later than 18 & 48 months after public meetings*

Prescription Drug User Fee Act
PDUFA VI

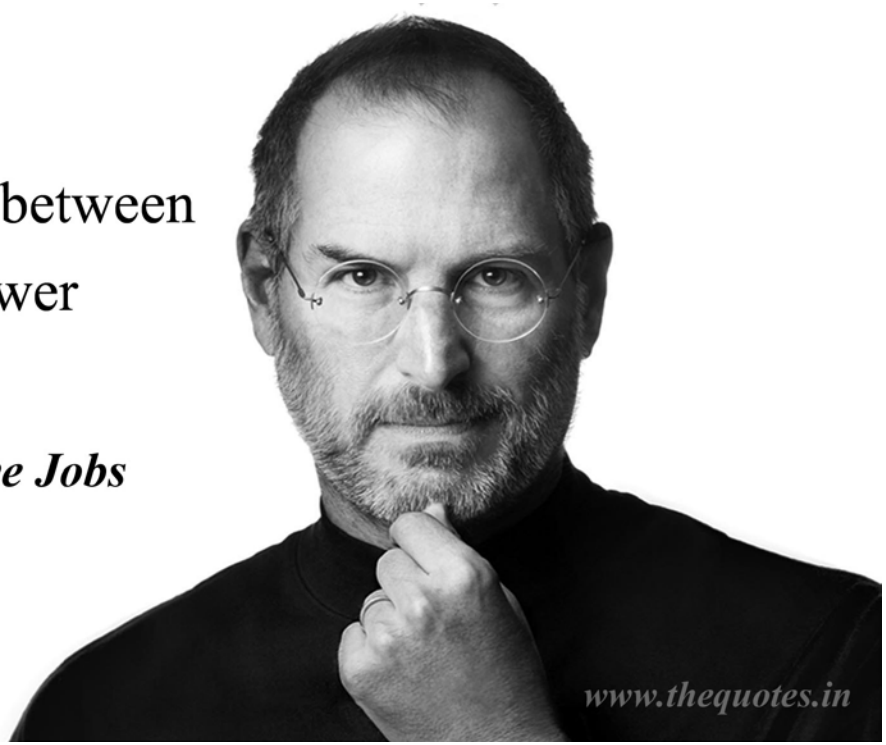
Enhance Capacity to Review Complex Designs

- develop staff capacity, Pilot Program, & 2018 public workshop to evaluate complex *adaptive, Bayesian trial designs*, which require simulations to *evaluate operating characteristics*.
- 2 meetings to provide better understanding of the agency's requirements for trial simulations
- 8 Pilot Program proposals each year, prioritized based on trial design features and high unmet need.
- trial designs to be presented in a guidance or public workshop as case studies
- 2018 publish draft guidance on complex *adaptive (including Bayesian adaptive*) trial designs.
- 2020 publish MAPPs, SOPPs and review templates to incorporate guidelines on evaluating complex clinical trial designs that rely on computer simulations to determine operating characteristics.

It is Up to Us to Lead

Innovation distinguishes between
a leader and a follower

Steve Jobs



The Benefits of the Adaptive Debate – FDA/PhRMA Adaptive Design Workshop Washington, DC Nov, 2006.

- Statisticians are not only at the table
  - They are at the forefront
  - Declan Doogan "….impressed by how much statisticians can contribute …"
  - proactive, assertive
- Statisticians need to decide to which of the following groups they belong, or want to belong
  - "Some people make things happen"
  - "Some people watch things happen"
  - "Some people ask what has happened"