Adaptive Clinical Trials

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More info available at . . .

https://openworks.mdanderson.org/biostatistics_adventures/

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Adventures in Statistics II

Dr. Donald Berry is a pioneer and leader in Bayesian biostatistics. In this free four-part lecture series, Don will share his adventures on Bayesian statistics on a wide variety of important and interesting topics. Each session consists of a 60-minute lecture followed by 30 minutes of Q/A and discussions.

Follow

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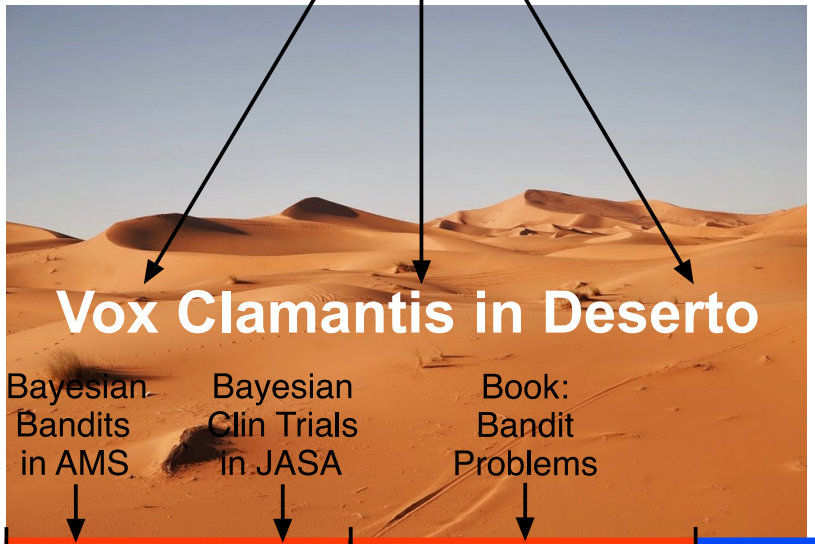
1) Adventures in Statistics I: From multi-armed bandit strategies to designs for phase 3 adaptive Bayesian platform clinical trials

Donald A. Berry PhD

This lecture was presented on September 28, 2021.

The recorded lecture and slides are available to view and download

Bayesian Adaptive Clinical Trials over Time



No Bayesian trials

Bayesian Bandits in AMS

Bayesian Clin Trials in JASA

Book: Bandit Problems

Pfizer ph 2 trial

CALGB 49907 design

First Bayesian PMA

CDRH Bayesian guidance

CPI at FDA

Adaptive trials at MDA

BATTLE at MDA

CALGB 49907 NEJM

Draft CDER adaptive guidance

I-SPY 2

ThemoCool JAMA

Lilly ph 2/3 trial

FDA/NIH innovative trials grant

GBM AGILE press conf

REMAP-CAP COVID-19

CDER guidance on CID

CDER adaptive guidance

GBM AGILE ph 3

Precision Promise ph 3

Univ. Minnesota | Duke & CALGB | M.D. Anderson

1970 1980 1990 2000 2010 2020

Computer hardware improved dramatically

Efficient Bayesian software developed

Why Bayes? Top 5 reasons

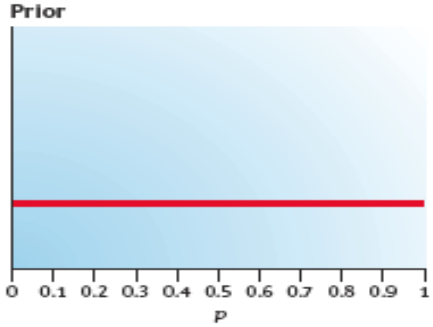
1. Continual learning/adapting
2. Predictive probabilities
3. Longitudinal modeling of disease
4. Decision analysis
5. Hierarchical modeling

De Facto Characteristics of Bayesian Adaptive

- Ask many questions in same trial:
  - What doses? duration? combination therapies?
  - For which patients?
  - What treatments work?
  - Longitudinal outcomes?
  - Go to phase 3?
- Get answers faster
- Better treatment of patients in trials
- Need for simulation

Bayesian updating

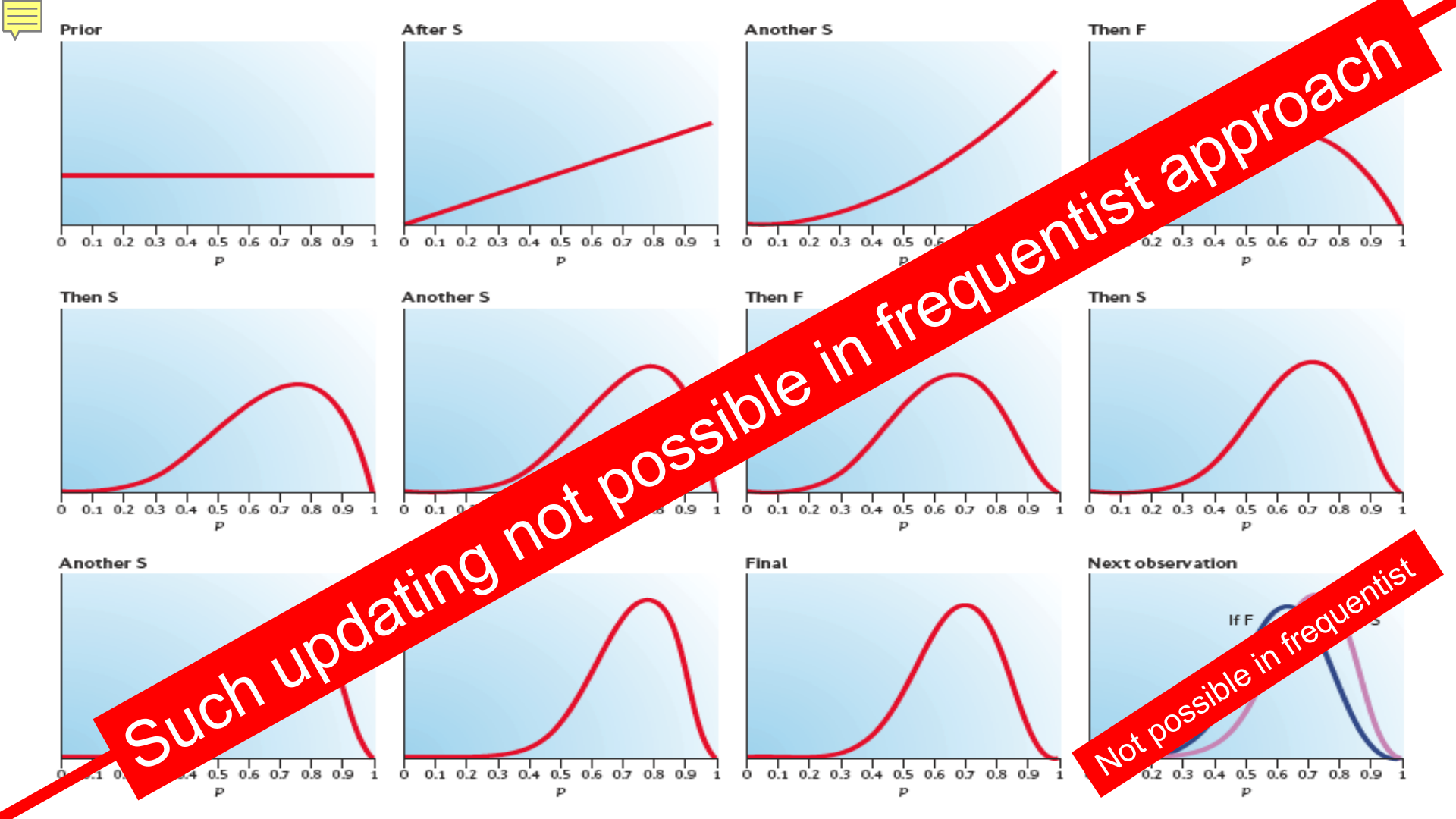
- **Paired observations, T vs C**
- **p = P(S) = P(T wins)**
- **H_0: p = 1/2**
- **Data: SSFSS FSSSF**



Prob:
2/3

Prob:
1/3

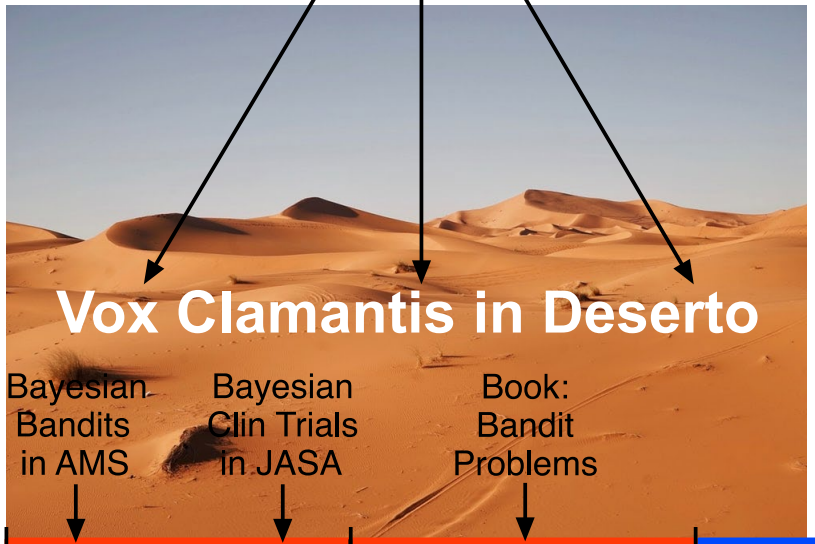
Contrast with traditional ("frequentist") approach


Prior
After S
Another S
Then F
Then S
Another S
Then F
Then S
Another S
Final
Next observation
If F
p
Such updating not possible in frequentist approach
Not possible in frequentist

Bayesian can ask, and answer, …

- **Given the available data, what is probability the therapy is effective in patient population?**
- **Given the available data, what is probability the therapy will be shown to be effective in the trial? In a subsequent phase 3 trial?**
- **Given the available data, what is probability the therapy is effective in Ms. Hernandez?**

Bayesian Adaptive Clinical Trials over Time



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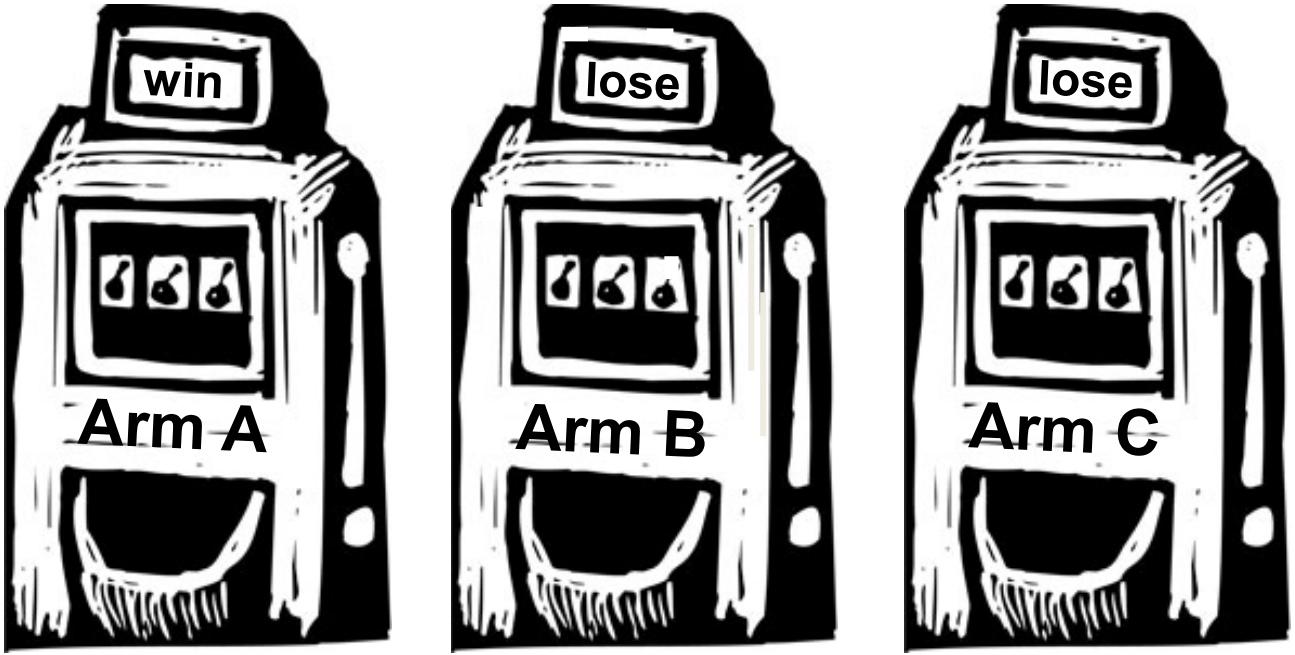
Multi-armed bandit problems



Goal of Bayesian Bandits

- **In gambling, Maximize expected winnings**
- **In clinical research, Maximize expected number of patients treated effectively**

Hal Varian, Chief Economist, Google, in 2009:

“I keep saying that the sexy job in the next 10 years will be statisticians.”

Hal Varian at RSS 2012 Conference: Statistics at Google

https://www.youtube.com/watch?v=p8R-UL6RPSg

YouTube Search

Google

Multi-armed bandits

Website Optimizer: allowed for A-B testing of web page design for users of Google Analytics
- Optimize some objective, e.g., conversions
- Experiments are expensive!
- Could not easily model features (font, colors,images,layout)

Google Analytics Content Experiments
- Multiarmed bandit
- Far more cost-effective testing
- More natural interpretation
- Can model features easily

Janet Woodcock, then Director CDER FDA

2011, NEJM: “In 2010, the [FNIH] Biomarkers Consortium [including] the NIH, the FDA, patient groups, and pharmaceutical and biotech initiated a groundbreaking trial in breast cancer to predict drug responsiveness based on the presence or absence of genetic and biological markers … I-SPY 2.”

2013: FDA will need to "turn the clinical trial paradigm on its head” to allow personalized drug therapies to get on the market faster.

2015, Press launch of GBM AGILE: “This is the future.”

Prototype Bayesian Adaptive Platform Trial: I-SPY 2

- https://www.ispytrials.org/i-spy-platform/i-spy2
- Everlasting Phase 2 trial in neoadjuvant breast cancer
- 27 experimental arms (19 pharma companies)
- Adaptively randomized
- Fixed randomization (20%) to control
- > 2000 patients randomized, 2010 – present
- 8 disease subtypes; 10 possible signatures (indications)
- 7 arms have “graduated,” in 7 different signatures

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 7, 2016 VOL. 375 NO. 1

Adaptive Randomization of Neratinib in Early Breast Cancer

J.W. Park, M.C. Liu, D. Yee, C. Yau, L.J. van 't Veer, W.F. Symmans, M. Paoloni, J. Perlmutter, N.M. Hylton, M. Hogarth, A. DeMichele, M.B. Buxton, A.J. Chien, A.M. Wallace, J.C. Boughey, T.C. Haddad, S.Y. Chui, K.A. Kemmer, H.G. Kaplan, C. Isaacs, R. Nanda, D. Tripathy, K.S. Albain, K.K. Edmiston, A.D. Elias, D.W. Northfelt, L. Pusztai, S.L. Moulder, J.E. Lang, R.K. Viscusi, D.M. Euhus, B.B. Haley, Q.J. Khan, W.C. Wood, M. Melisko, R. Schwab, T. Helsten, J. Lyandres, S.E. Davis, G.L. Hirst, A. Sanil, L.J. Esserman, and D.A. Berry, for the I-SPY 2 Investigators*

ABSTRACT

BACKGROUND

The heterogeneity of breast cancer makes identifying effective therapies challenging. The I-SPY 2 trial, a multicenter, adaptive phase 2 trial of neoadjuvant therapy for high-risk clinical stage II or III breast cancer, evaluated multiple new agents added to stan-

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Esserman at the UCSF Carol Franc Buck

EDITORIAL

I-SPY 2 — Toward More Rapid Progress in Breast Cancer Treatment

Lisa A. Carey, M.D., and Eric P. Winer, M.D.

ORIGINAL ARTICLE

Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer

H.S. Rugo, O.I. Olopade, A. DeMichele, C. Yau, L.J. van 't Veer, M.B. Buxton, M. Hogarth, N.M. Hylton, M. Paoloni, J. Perlmutter, W.F. Symmans, D. Yee, A.J. Chien, A.M. Wallace, H.G. Kaplan, J.C. Boughey, T.C. Haddad, K.S. Albain, M.C. Liu, C. Isaacs, Q.J. Khan, J.E. Lang, R.K. Viscusi, L. Pusztai, S.L. Moulder, S.Y. Chui, K.A. Kemmer, A.D. Elias, K.K. Edmiston, D.M. Euhus, B.B. Haley, R. Nanda, D.W. Northfelt, D. Tripathy, W.C. Wood, C. Ewing, R. Schwab, J. Lyandres, S.E. Davis, G.L. Hirst, A. Sanil, D.A. Berry, and L.J. Esserman, for the I-SPY 2 Investigators*

ABSTRACT

BACKGROUND

The genetic and clinical heterogeneity of breast cancer makes the identification of effective therapies challenging. We designed I-SPY 2, a phase 2, multicenter, adaptively randomized trial to screen multiple experimental regimens in combination with standard neoadjuvant chemotherapy for breast cancer. The goal is to match ex-

PERSPECTIVE

STATISTICS IN MEDICINE

I-SPY 2 — A Glimpse of the Future of Phase 2 Drug Development?

David Harrington, Ph.D., and Giovanni Parmigiani, Ph.D.

The articles by Rugo et al. (pages 23–34) and Park et al. (pages 11–22) in this issue of the *Journal* report results from the I-SPY (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Mo-

ing in larger, phase 3 trials. The value of I-SPY 2, however, may well go beyond the clinical results described in the current articles. Adaptive multigroup trials such as I-SPY 2 have the potential to answer several questions si-

good responses and, equal portant, may be useful in ing patients to avoid treat when meaningful benefit likely. The challenges, ho in identifying successful ta therapies in cancer are su

Prototype Bayesian platform trials for drug registration in cancer

- **GBM AGILE (glioblastoma)**
- **Precision Promise (pancreatic cancer)**

New & Transformative in a Phase 3 trial

1. Seamless shift, learn (phase 2) to confirm (phase 3)
2. Many arms, that enter and leave the trial
3. Common control (by patient subtype)
4. Controls include “contemporary controls” via time machine
5. Continuous learning and updating information
6. Adaptive randomization (in learn stage)
7. Identify and confirm arms’ biomarker indications, if any
8. Interpretation of Type I error
9. Decisions determined by predictive probability (PP)
10. Longitudinal model of disease burden
11. Hierarchical modeling of two control arms
12. Re-randomize patients to second-line therapy

FDA U.S. FOOD & DRUG ADMINISTRATION

March 11, 2018

Brian Alexander, M.D.
Dana-Farber Cancer Institute
Harvard Medical School
25 Shattuck Street
Boston, MA 02115

Dear Dr. Alexander,

FDA strongly supports the development of disease-specific platform trials. In particular, the agency is

We expect no increased regulatory risk to result from the innovative statistical design for GBM AGILE. Moreover, depending on the specific results, we anticipate that data from experimental arms that have "graduated" and been confirmed by GBM AGILE will be used as the foundation for new drug application (NDA) or biological drug application (BLA) submissions and registration.

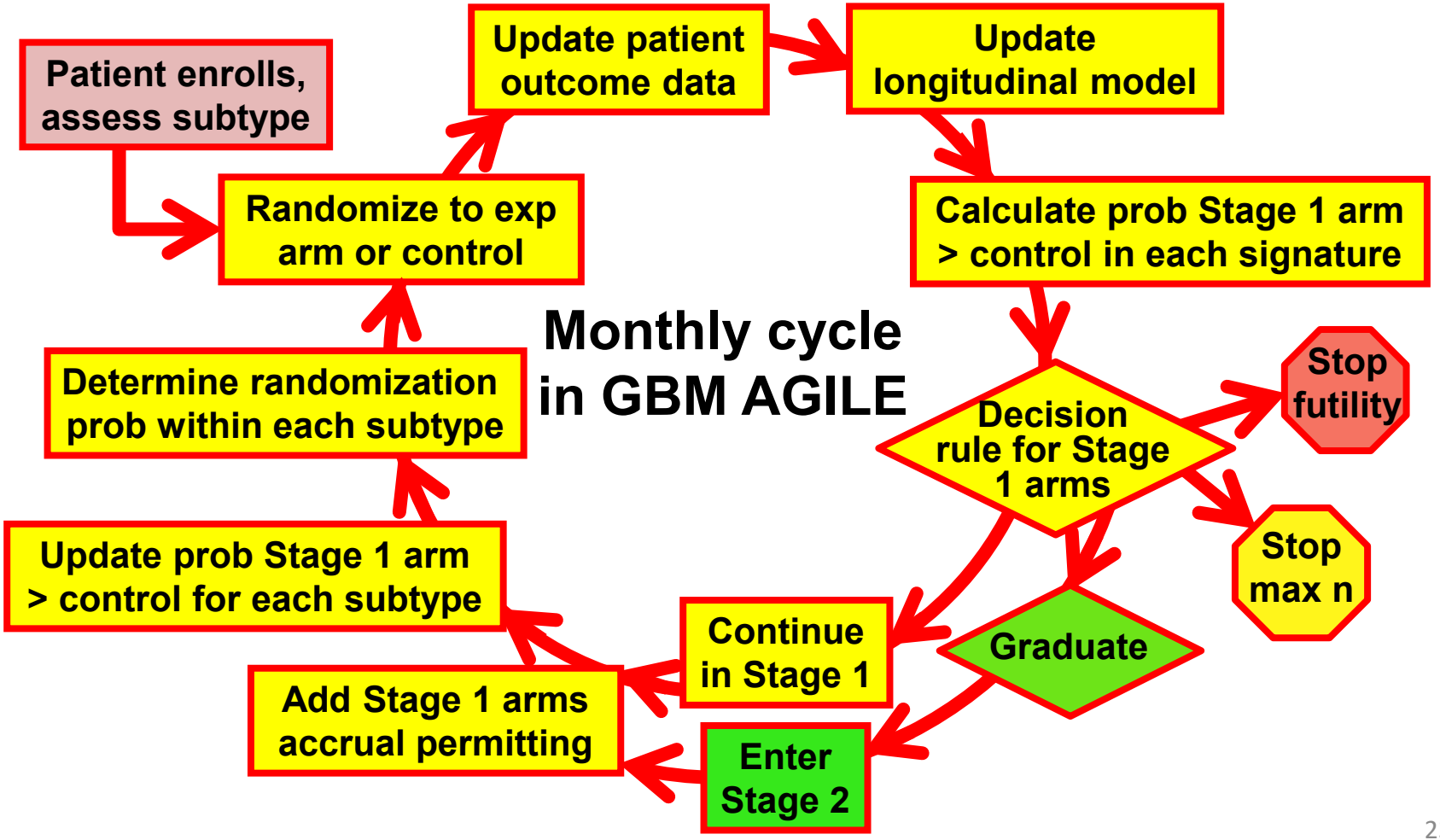
the master protocol for GBM AGILE, and there have been extensive interactions between the trial design team and FDA biostatisticians. While you can be assured that each substudy will be reviewed prospectively and we will base all regulatory decision-making on our usual high standards, we agree with and support the design and objectives of the GBM AGILE trial.

We expect no increased regulatory risk to result from the innovative statistical design for GBM AGILE. Moreover, depending on the specific results, we anticipate that data from experimental arms that have "graduated" and been confirmed by GBM AGILE will be used as the foundation for new drug application (NDA) or biological drug application (BLA) submissions and registration.

Thank you for your tireless efforts to address this debilitating, deadly disease.

Sincerely,

Janet Woodcock, M.D.
Director,
Center for Drug Evaluation and Research
U.S. Food and Drug Administration


Patient enrolls, assess subtype
Update patient outcome data
Update longitudinal model
Randomize to exp arm or control
Calculate prob Stage 1 arm > control in each signature
Monthly cycle in GBM AGILE
Determine randomization prob within each subtype
Decision rule for Stage 1 arms
Stop futility
Stop max n
Update prob Stage 1 arm > control for each subtype
Continue in Stage 1
Graduate
Add Stage 1 arms accrual permitting
Enter Stage 2

In diabetes (Trulicity)

ORIGINAL ARTICLE | Open Access

Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5)

Z. Skrivanek, B. L. Gaydos, J. Y. Chien, M. J. Geiger, M. A. Heathman, S. Berry, J. H. Anderson, T. Forst, Z. Milicevic, D. Berry

Diabetes, Obesity and Metabolism, Volume: 16, Issue: 8, Pages: 748-756, First published: 25 April 2014.

In Alzheimer's disease

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Lecanemab for Patients With Early Alzheimer Disease

Bayesian Analysis of a Phase 2b Dose-Finding Randomized Clinical Trial

Donald A. Berry, PhD; Shobha Dhadda, PhD; Michio Kanekiyo, MS; David Li, PhD; Chad J. Swanson, PhD; Michael Irizarry, MD; Lynn D. Kramer, MD; Scott M. Berry, PhD

Abstract

IMPORTANCE Bayesian clinical trial designs are increasingly common; given their promotion by the US Food and Drug Administration, the future use of the bayesian approach will only continue to increase. Innovations possible when using the bayesian approach improve the efficiency of drug development and the accuracy of clinical trials, especially in the context of substantial data missingness.

Key Points

Question The US Food and Drug Administration has promoted innovation in clinical trial design via the bayesian approach; does that make clinical trials more efficient?