Innovating the Clinical Trial: Adaptive and Platform

Scott M. Berry

Jan 15, 2020

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Austin Bradford Hill

- Credited with designing the first randomized clinical trial in humans

- Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. BMJ. 1948; 2:769-782.

Born	8 July 1897
Died	18 April 1991 (aged 93)
Nationality	United Kingdom
Occupation	Epidemiologist statistician
Known for	"Bradford Hill" criteria
Awards	Guy Medal (Gold, 1953)

- Traditional looking Table 1 and Table 2
- Streptomycin very effective!
- "typo" (4/55 = 7.3%)

- The clinical trial didn't change much for the next 60 years…

- The clinical trial is now the 'science' being innovated!

Table I.–*Condition on Admission*

General Condition	S Group	C Group	Max. Evening Temp. in First Week*	S Group	C Group	Sedimentation Rate	S Group	C Group
Good .	8	8	98-98·9° F. (36·7-37·15° C.)	3	4	0-10	0	0
Fair ..	17	20	99-99·9° F. (37·2-37·75° C.)	13	12	11-20	3	2
Poor ..	30	24	100-100·9° F. (37·8-38·25° C.)	15	17	21-50	16	20
			101° F (38·3° C.) +	24	19	51+	36	29
Total	55	52	Total	55	52	Total	55	51†

* Temperature by mouth in all but six cases.

† Examination not done in one case.

Table II.–*Assessment of Radiological Appearance at Six Months as Compared with Appearance on Admission*

Radiological Assessment	Streptomycin Group		Control Group	
Considerable improvement ..	28	51%	4	8%
Moderate or slight improvement	10	18%	13	25%
No material change	2	4%	3	6%
Moderate or slight deterioration	5	9%	12	23%
Considerable deterioration ..	6	11%	6	11%
Deaths	4	27%	14	27%
Total	55	100%	52	100%

Outline

- Some comments on FDA Adaptive Design Guidance and FDA draft Guidance on CID
- Couple quick examples of complex adaptive designs
- Moving to platform trials
- And beyond?

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Two Key Guidances

Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2019
Biostatistics

Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

Draft Guidance for Industry

Additional copies of this guidance are available from:

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO71, Room 3128
Silver Spring, MD 20993
Phone: 800-835-4709 or 240-402-8010
E-mail: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

or

Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993
Phone: 301-796-3400 or 855-543-3784; Fax: 301-431-6353
E-mail: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

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Discussion of Guidances

- Assuming you all have read them…. I'll react to several important aspects of them
- Existence may be the most important thing
- They are in NO way limiting
- Completely opens this concept of adaptive designs and complex trials as "good"
- They are forward looking and do not restrict tomorrow's innovation of the trial design

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Snippets of AD Guidance (I added color)

- In still other cases, such as many Bayesian adaptive designs (section VI.B.), it may be critical to use simulations (section VI.A.) to evaluate the chance of an erroneous conclusion.
- The choice of scale is relatively unimportant as long as the operating characteristics of the designs are adequately evaluated.

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Snippets of AD Guidance (I added color)

- The second type is response-adaptive randomization, an adaptive feature in which the chance of a newly-enrolled subject being assigned to a treatment arm varies over the course of the trial based on accumulating outcome data for subjects previously enrolled….
- Response-adaptive randomization alone does not generally increase the Type I error probability of a trial when used with appropriate statistical analysis techniques.

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Snippets of AD Guidance (I added color)

- In almost all cases, there are an infinite number of scenarios potentially compatible with the null hypothesis. Identifying which scenarios should be considered when estimating Type I error probability can be challenging and may rely on a combination of medical and mathematical considerations.
- It is common to perform simulations on a grid of plausible values and argue based on the totality of the evidence from the simulations that maximal Type I error probability likely does not exceed a desired level across the range covered by the grid.
- However, with any approach, the evaluation at the end of the trial should consider whether the statistical inference is appropriate and the conclusions are justified in light of the accumulated information about the nuisance parameters. In the example, if the observed placebo mortality rate was unexpectedly 50 percent, additional simulations would be required. "POST-SIMULATION"

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Snippets of AD Guidance (I added color)

- In general, the same principles apply to Bayesian adaptive designs as to adaptive designs without Bayesian features. Trial designs that use Bayesian adaptive features may rely on frequentist or Bayesian inferential procedures to support conclusions of drug effectiveness.

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Snippets of CID Guidance (I added color)

- Although CID has been referred to as complex adaptive, Bayesian, and other novel clinical trial designs, there is no fixed definition of CID because what is considered innovative or novel can change over time. For the purposes of this guidance, CID includes trial designs that have rarely or never been used to date to provide substantial evidence of effectiveness in new drug applications or biologics license applications.
- A common feature of many CIDs is the need for simulations rather than mathematical formulae to estimate trial operating characteristics
- A simulation report if simulations are used to evaluate study operating characteristics.

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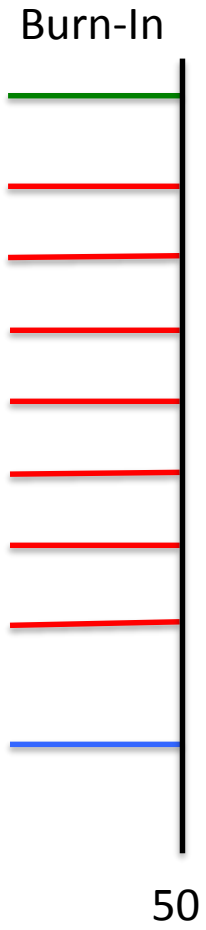
Diabetes II/III Seamless

- 7 doses + PBO + Active Control



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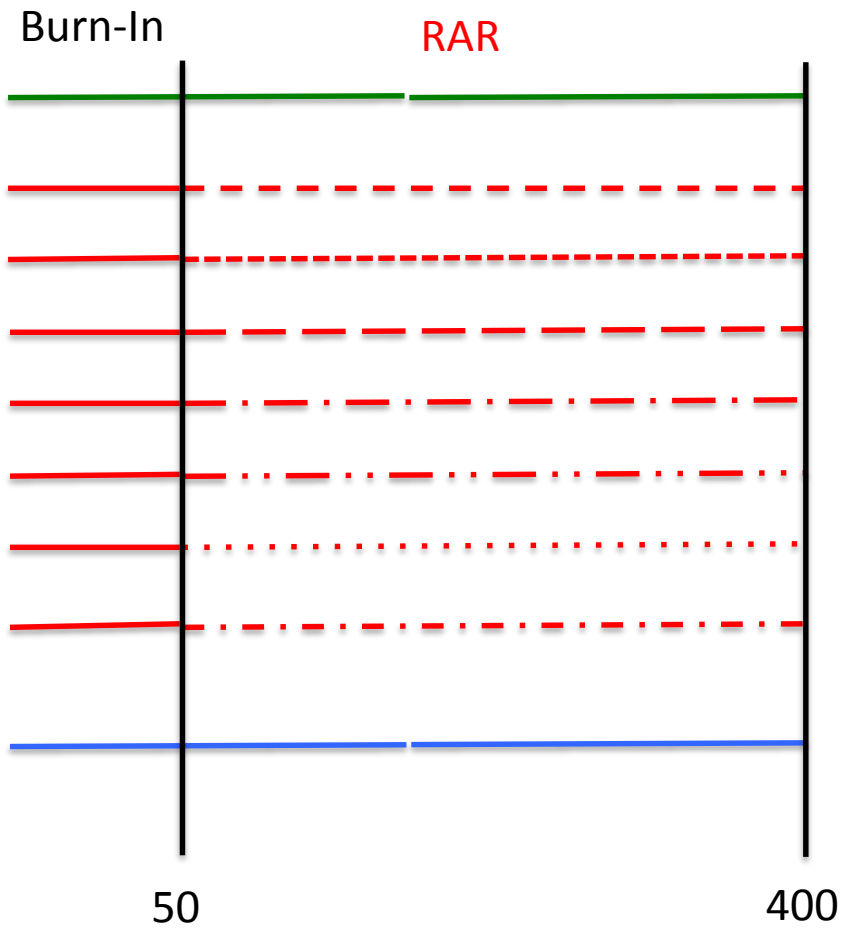
Diabetes II/III Seamless

- 7 doses + PBO + Active Control
  - Interims every 2 weeks
  - RAR based on 4 endpoints
    - HbA1c, Weight Loss, DBP, HR with utility function



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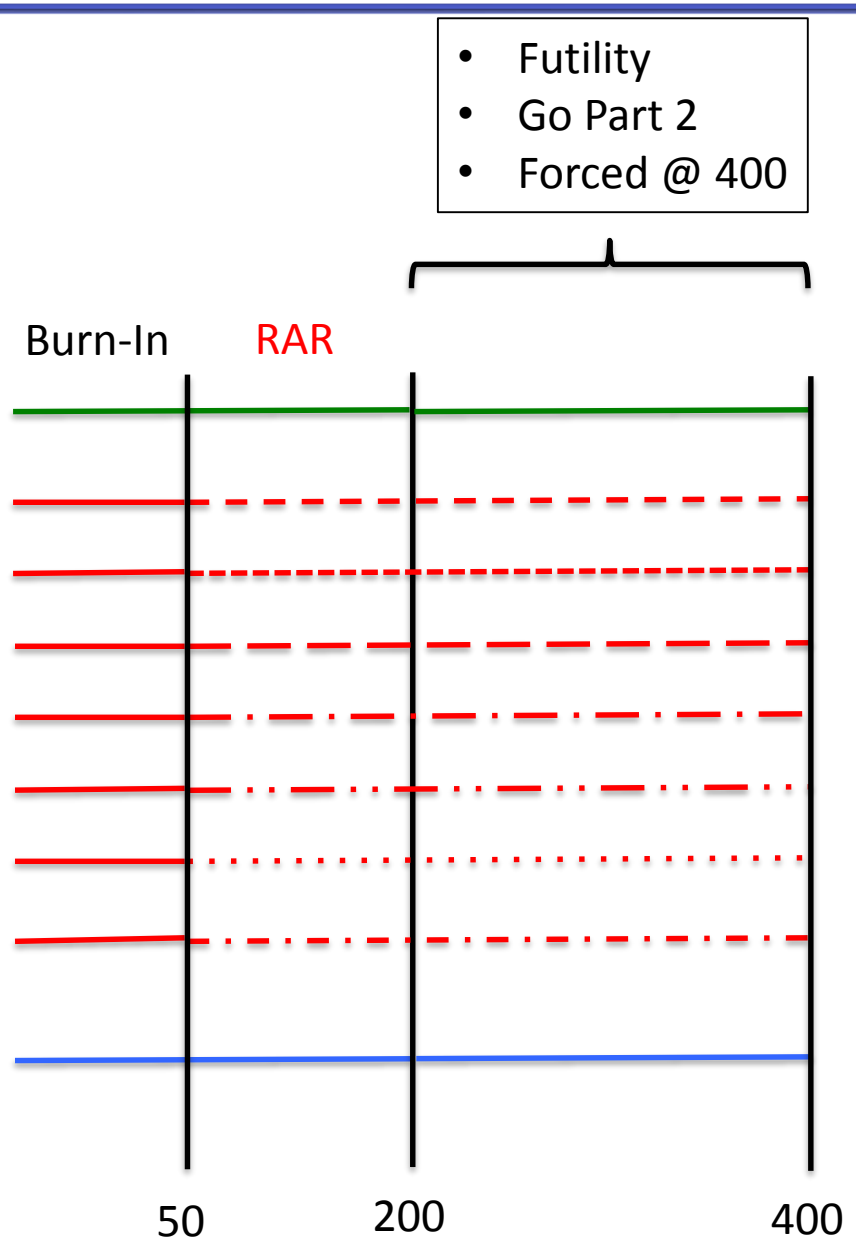
Diabetes II/III Seamless

- 7 doses + PBO + Active Control
  - Interims every 2 weeks
  - RAR based on 4 endpoints
    - HbA1c, Weight Loss, DBP, HR with utility function
  - 200-400 make decision:
    - Go to Phase III (pick 1 or 2 doses); spawn other phase III
    - Stop futility



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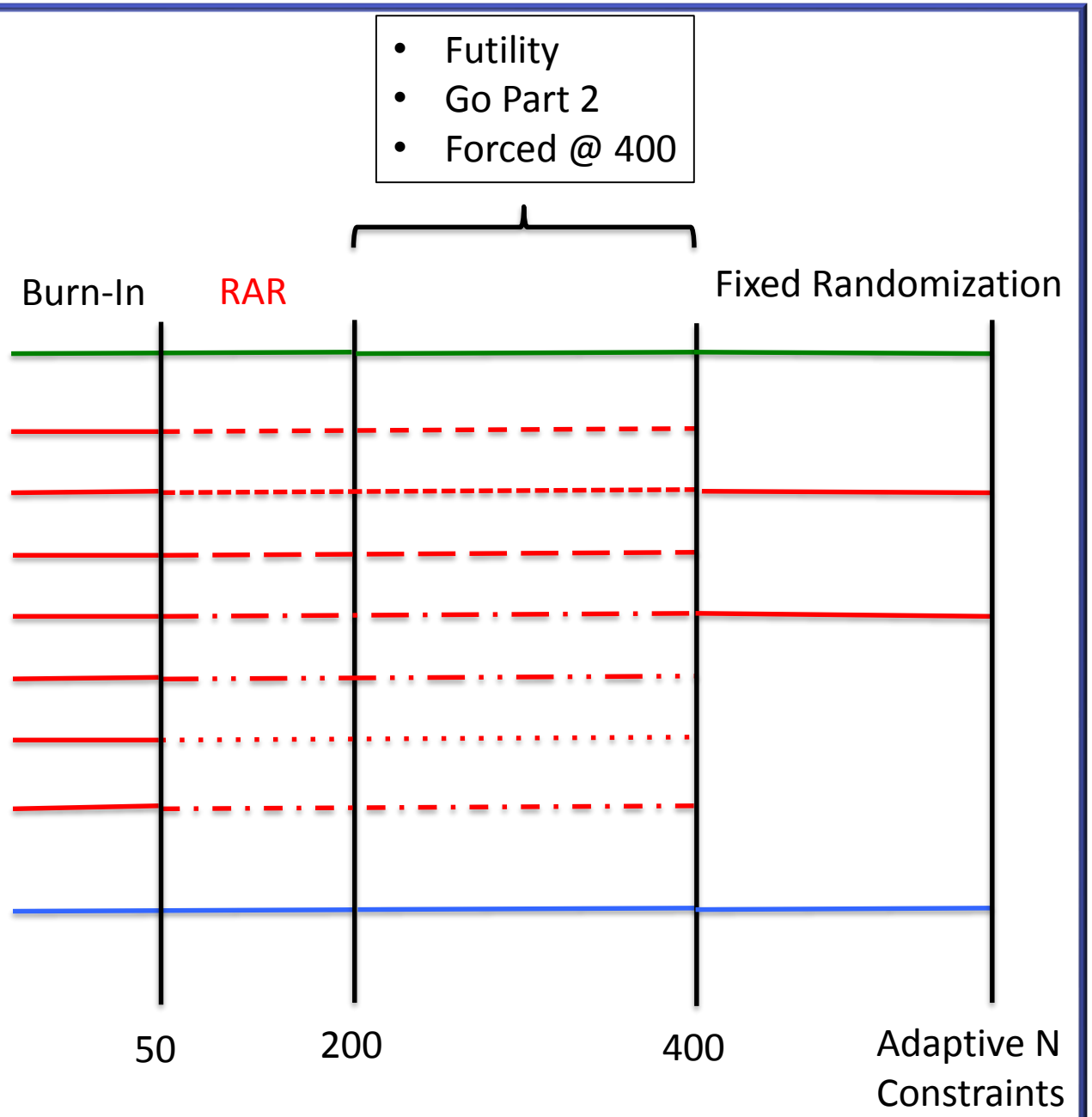
    - Stop futility
  - Phase III part powered by phase II



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Diabetes II/III Seamless

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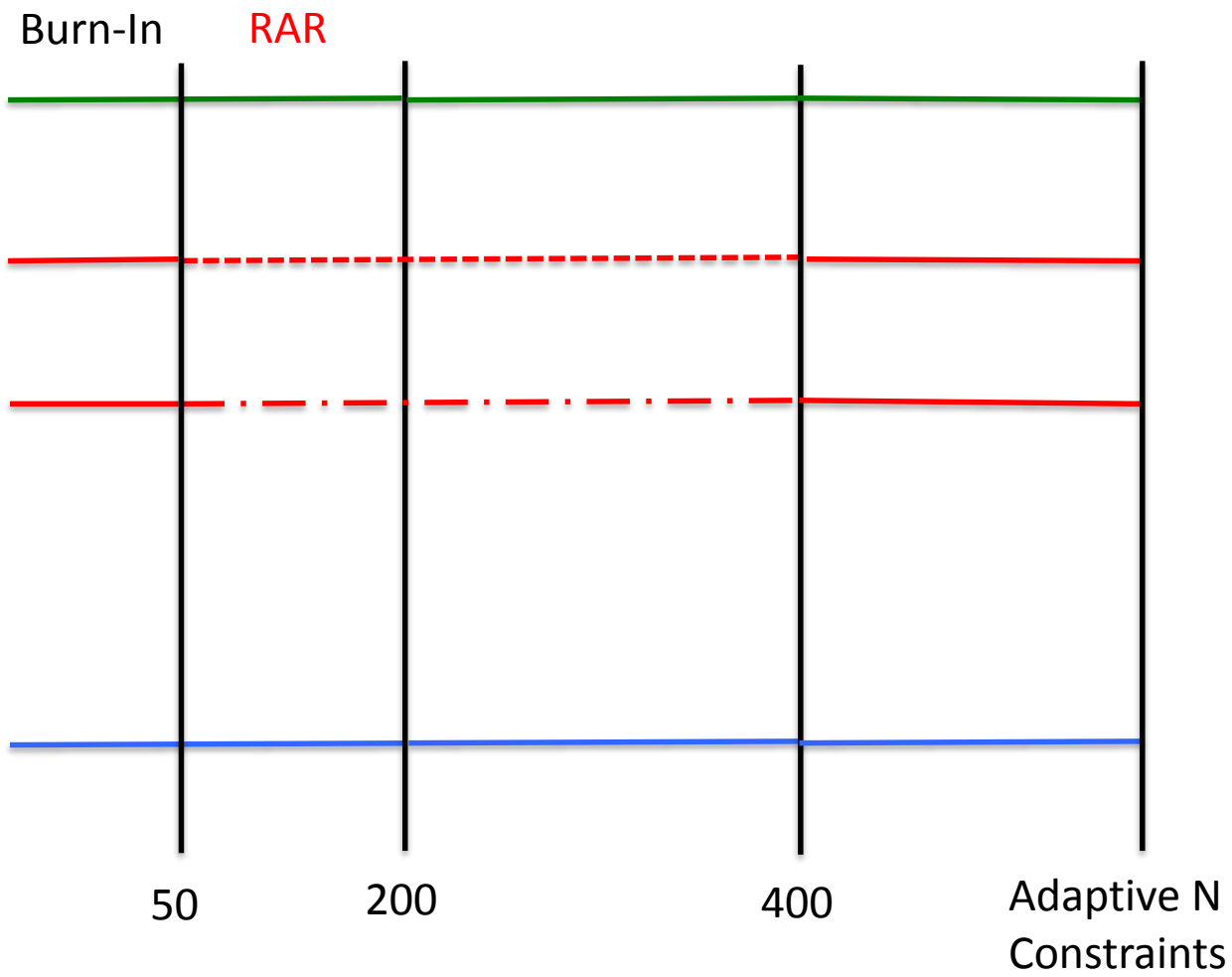
  - 200-400 make decision:
    - Go to Phase III (pick 1 or 2 doses); open more phase III
    - Stop futility
  - Phase III part powered by phase II
  - Final Analysis includes all on arms continue (0.020 ANCOVA)



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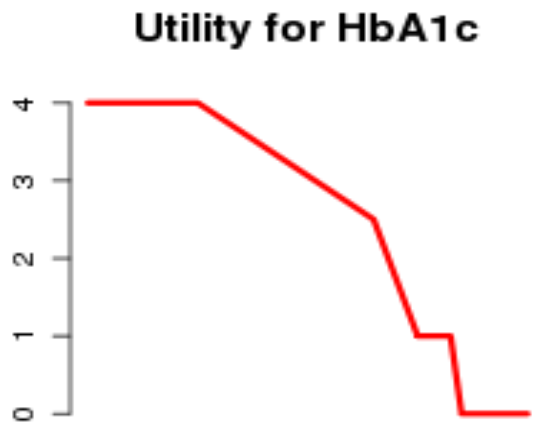
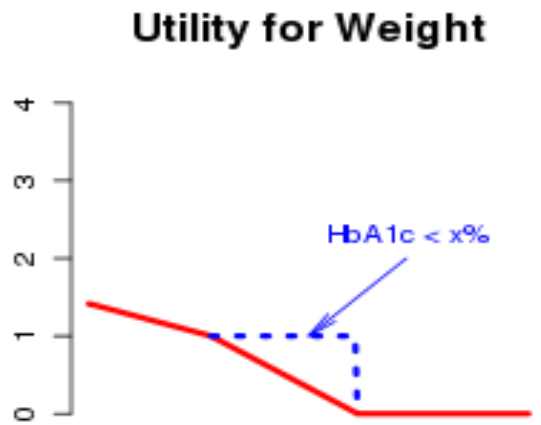
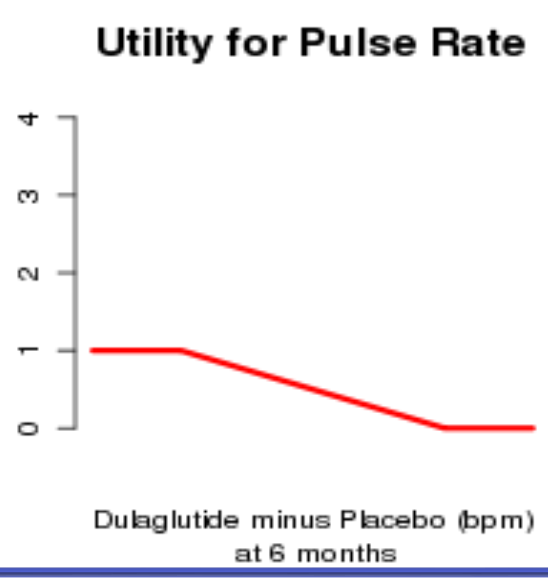
Modeling

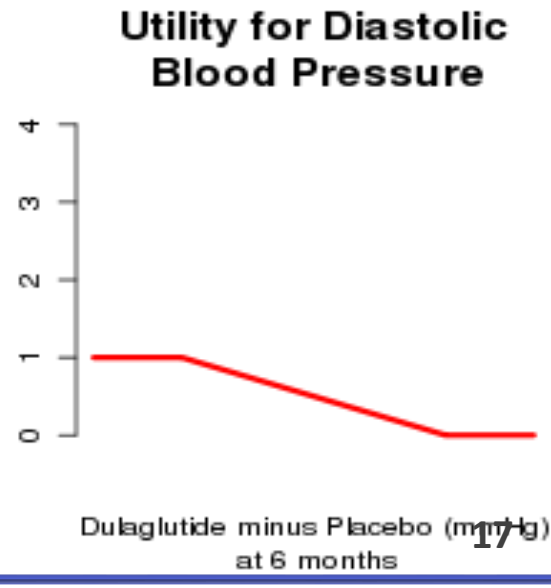
- Bayesian repeated measures & dose-response models for four endpoints
- Single utility function connecting 4 endpoints on one scale
- Predictive probability of statistical success

Utility of Drug?









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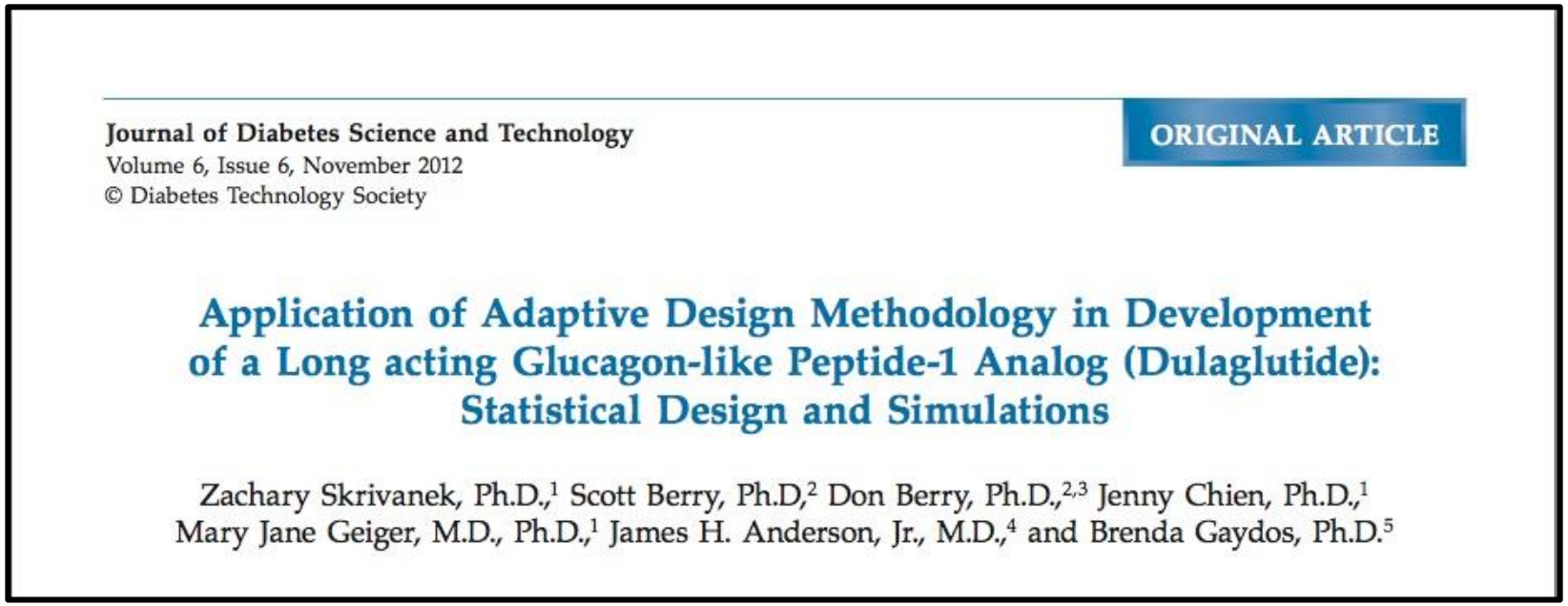
Diabetes II/III Seamless

- Trial ran (for 3,467,321st time!)
- Shifted at 200 -- very successful!
  - Ran *exactly* as planned, spawned other phase III
  - Selected 0.75mg and 1.5mg doses



Journal of Diabetes Science and Technology
Volume 6, Issue 6, November 2012

ORIGINAL ARTICLE

Application of Adaptive Design Methodology in Development of a Long acting Glucagon-like Peptide-1 Analog (Dulaglutide): Statistical Design and Simulations

Zachary Skrivanek, Ph.D.,[1] Scott Berry, Ph.D,[2] Don Berry, Ph.D.,[2,3] Jenny Chien, Ph.D.,[1]
Mary Jane Geiger, M.D., Ph.D.,[1] James H. Anderson, Jr., M.D.,[4] and Brenda Gaydos, Ph.D.[5]

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FierceBiotech
THE BIOTECH INDUSTRY'S DAILY MONITOR

NEWS TOPICS ANALYSIS FEATUR

UPDATED: FDA hands Eli Lilly a big win, OKs dulaglutide for diabetes

September 18, 2014 | By John Carroll

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An embattled Eli Lilly ($LLY) won a major battle today, gaining the FDA's approval to market dulaglutide for

Lilly Diabetes President

"Projecting $1.3 billion in 2020"

With Novo Nordisk ($NVO) already digging in to defend its position around Victoza, the once-weekly treatment has been widely billed as a likely blockbuster. The Phase III program has long represented Eli Lilly's best shot at opening a major new market, though many analysts are

Peak sales projections for dulaglutide are all over the map. Cowen has pegged the potential at $700 million, with Bernstein's Tim Anderson now projecting $1.3 billion in 2020. That's not enough to make up for the patent losses, but it would go a long way to providing some credibility for an R&D group that is drawing an increasing amount of critical scrutiny.

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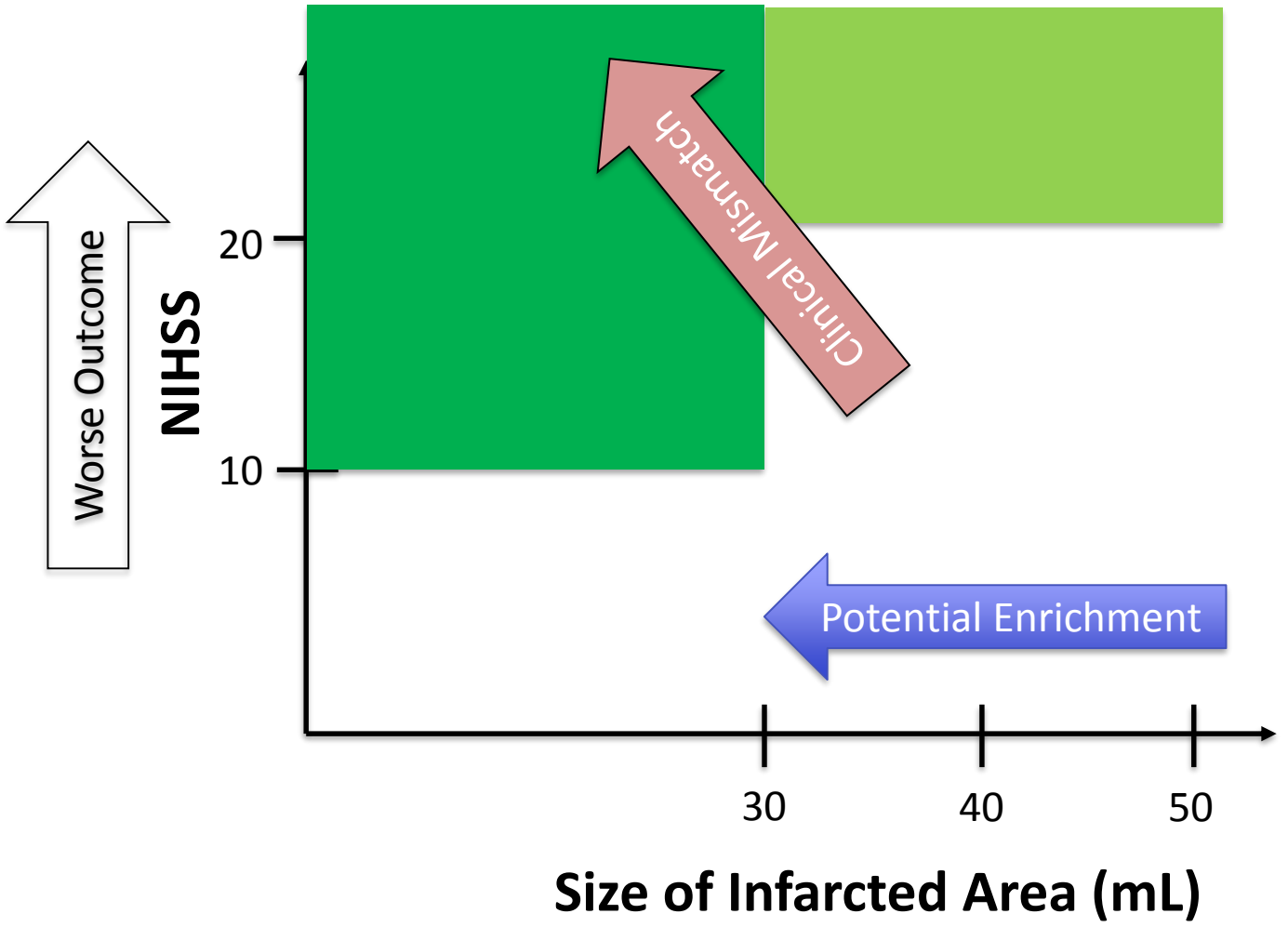
(Dollars in millions)	Fourth Quarter			Year-to-Date		
Established Pharma Products	2018	2017	% Change	2018	2017	% Change
Humalog®	$ 770.4	$ 782.2	(2)%	$ 2,996.5	$ 2,865.2	5%
Alimta	556.9	525.2	6%	2,132.9	2,062.5	3%
Cialis	350.7	597.4	(41)%	1,851.8	2,323.1	(20)%
Forteo	437.1	513.2	(15)%	1,575.6	1,749.0	(10)%
Humulin®	337.4	362.6	(7)%	1,331.4	1,335.4	(0)%
Cymbalta®	184.5	192.8	(4)%	708.0	757.2	(6)%
Erbitux®	159.8	168.9	(5)%	635.3	645.9	(2)%
Trajenta®[(a)]	156.2	129.7	20%	574.7	537.9	7%
Zyprexa®	110.8	152.2	(27)%	471.3	581.2	(19)%
Strattera	107.2	98.3	9%	450.8	618.2	(27)%
Select Products Launched Since 2014						
Trulicity	924.7	649.0	42%	3,199.1	2,029.8	58%
Taltz	307.0	172.5	78%	937.5	559.2	68%
Cyramza®	220.6	204.8	8%	821.4	758.3	8%
Basaglar	232.2	153.8	51%	801.2	432.1	85%
Jardiance[(b)]	193.2	143.2	35%	658.3	447.5	47%
Lartruvo	83.5	59.0	41%	304.7	203.0	50%
Verzenio	83.1	21.0	NM	255.0	21.0	NM
Olumiant	70.1	23.0	NM	202.5	45.9	NM
Emgality	4.9	—	NM	4.9	—	NM
Subtotal	2,119.4	1,426.3	49%	7,184.7	4,496.7	60%
Animal Health	816.5	790.9	3%	3,142.5	3,085.6	2%
Total Revenue	6,438.6	6,160.7	5%	24,555.7	22,871.3	7%

$3.2 Billion in 2018

DAWN

- Endovascular Thrombectomy for ischemic stroke (approved ≤ 8 hours)
- New trial enrolling 6-24 hours since last seen well
- “Clinical Mismatch”



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Adaptive Enrichment Design

- Interims at 150, 200, 250, 300, 350, 400, … max of 500
- At 150, …, 400 can “enrich” to smaller entry criterion
  - Infarct size of 0-30; 0-35; 0-40; 0-45
  - Restrict final analysis to the ‘restricted group’
  - Adjust CV for ‘cherry picking’
- Could Stop for Expected Success (at 200+ interims)
- Could Stop for Futility

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DAWN Result

- At the 150-interim there was *no enrichment*
  - no futility
  - No expected success possible
- At 200-interim PP > 0.9999; no enrichment; stop for expected success
- Followed for 90 days; success at full data primary analysis (posterior probability superiority greater than 0.986)

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The NEW ENGLAND JOURNAL of MEDICINE

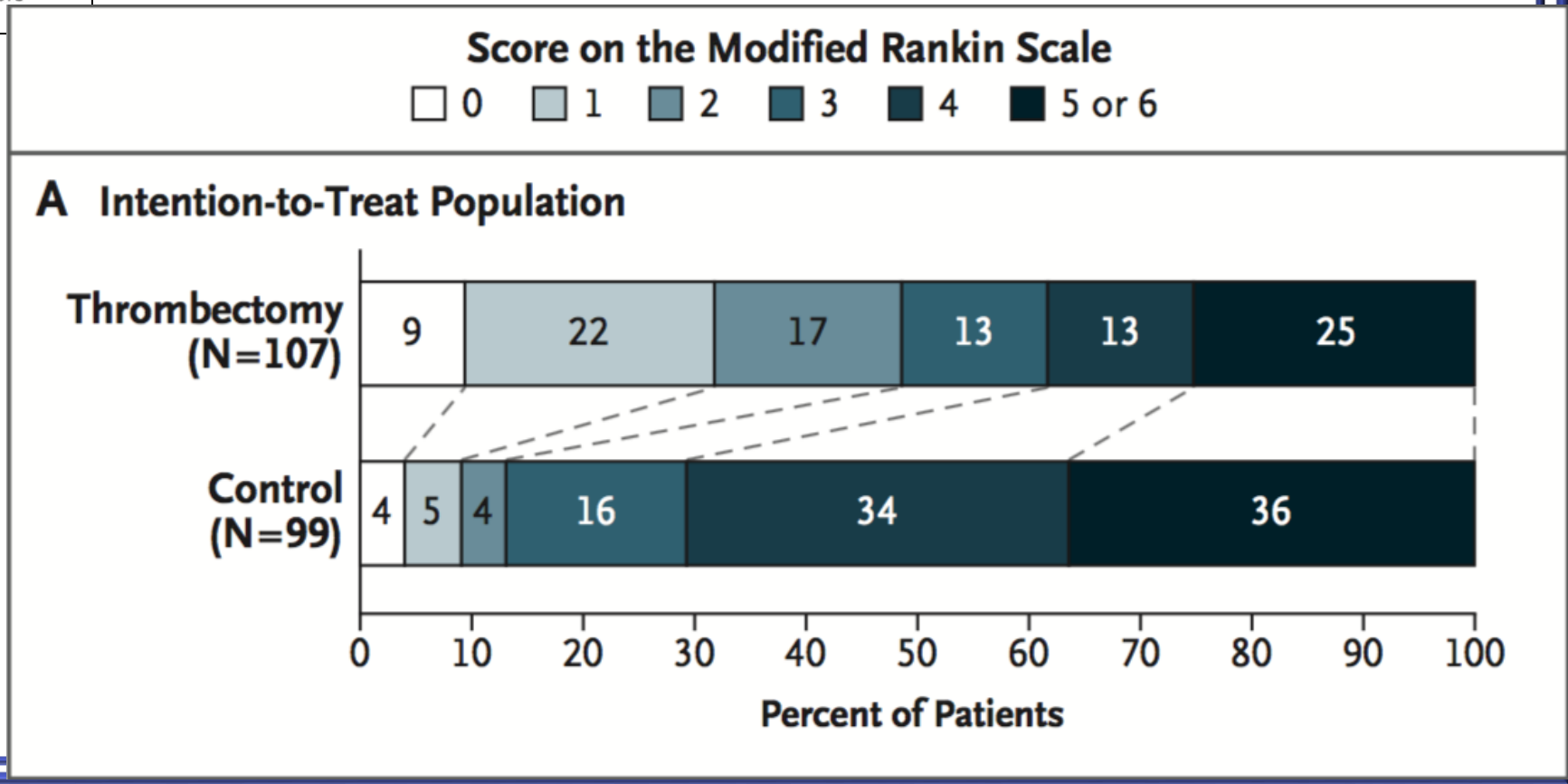
ORIGINAL ARTICLE

Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

R.G. Nogueira, A.P. Jadhav, D.C. Haussen, A. Bonafe, R.F. Budzik, P. Bhuva, D.R. Yavagal, M. Ribo, C. Cognard, R.A. Hanel, C.A. Sila, A.E. Hassan, M. Millan, E.I. Levy, P. Mitchell, M. Chen, J.D. English, Q.A. Shah, F.L. Silver, V.M. Pereira, B.P. Mehta, B.W. Baxter, M.G. Abraham, P. Cardona, E. Veznedaroglu, F.R. Hellinger, L. Feng, J.F. Kirmani, D.K. Lopes, B.T. Jankowitz, M.R. Frankel, V. Costalat, N.A. Vora, A.J. Yoo, A.M. Malik, A.J. Furlan, M. Rubiera, A. Aghaebrahim, J.-M. Olivot, W.G. Tekle, R. Shields, T. Graves, R.J. Lewis, W.S. Smith, D.S. Liebeskind, J.L. Saver, and T.G. Jovin, for the DAWN Trial Investigators*

This article was published on November 11, 2017, at NEJM.org.

DOI: 10.1056/NEJMoa1706442



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RESULTS

A total of 206 patients were enrolled; 107 were assigned to the thrombectomy group and 99 to the control group. At 31 months, enrollment in the trial was stopped because of the results of a prespecified interim analysis. The mean score on the utility-weighted modified Rankin scale at 90 days was 5.5 in the thrombectomy group as compared with 3.4 in the control group (adjusted difference [Bayesian analysis], 2.0 points; 95% credible interval, 1.1 to 3.0; posterior probability of superiority, >0.999), and the rate of functional independence at 90 days was 49% in the thrombectomy group as compared with 13% in the control group (adjusted difference, 33 percentage points; 95% credible interval, 24 to 44; posterior probability of superiority, >0.999). The rate of symptomatic intracranial hemorrhage did not differ significantly between the two groups (6% in the thrombectomy group and 3% in the control group, P=0.50), nor did 90-day mortality (19% and 18%, respectively; P=1.00).

Table 2. Efficacy Outcomes.*

Outcome	Thrombectomy Group (N=107)	Control Group (N=99)	Absolute Difference (95% CI)†	Adjusted Difference (95% Credible Interval)‡	Posterior Probability of Superiority
Primary end points					
Score on utility-weighted modified Rankin scale at 90 days§	5.5±3.8	3.4±3.1	2.1 (1.2–3.1)	2.0 (1.1–3.0)	>0.999
Functional independence at 90 days — no. (%)¶	52 (49)	13 (13)	36 (24–47)	33 (21–44)	>0.999

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Snippet of AD Guidance

- A special case of adaptive treatment arm selection occurs in the context of an adaptive *platform trial* designed to compare more than one experimental treatment against an appropriate control for a disease (e.g., Woodcock and LaVange 2017).

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Confluence

Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2019
Biostatistics

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Lee Pai-Scherf at 301-796-3400 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2018
Procedural

22257542dft.docx
8/20/2018

Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

Draft Guidance for Industry

Additional copies of this guidance are available from:

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO71, Room 3128
Silver Spring, MD 20993
Phone: 800-835-4709 or 240-402-8010
E-mail: ocod@fda.hhs.gov
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or

Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993
Phone: 301-796-3400 or 855-543-3784; Fax: 301-431-6353
E-mail: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

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NOVEMBER 25, 2016

RULES COMMITTEE PRINT 114-67

Subtitle C—Modern Trial Design and Evidence Development

SEC. 3021. NOVEL CLINICAL TRIAL DESIGNS.

(a) PROPOSALS FOR USE OF NOVEL CLINICAL TRIAL DESIGNS FOR DRUGS AND BIOLOGICAL PRODUCTS.—For purposes of assisting sponsors in incorporating complex

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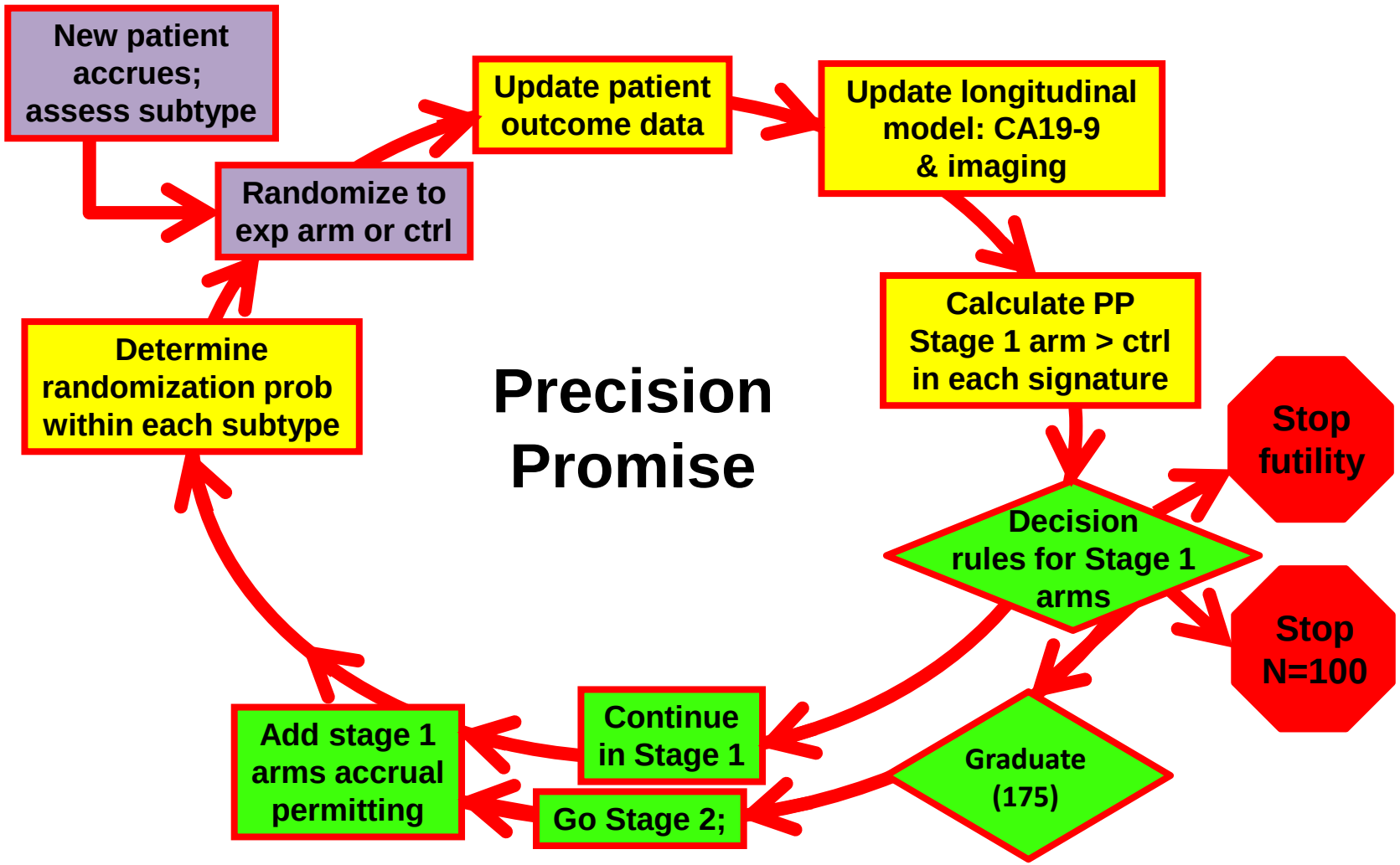

Precision Promise

Monthly Interims

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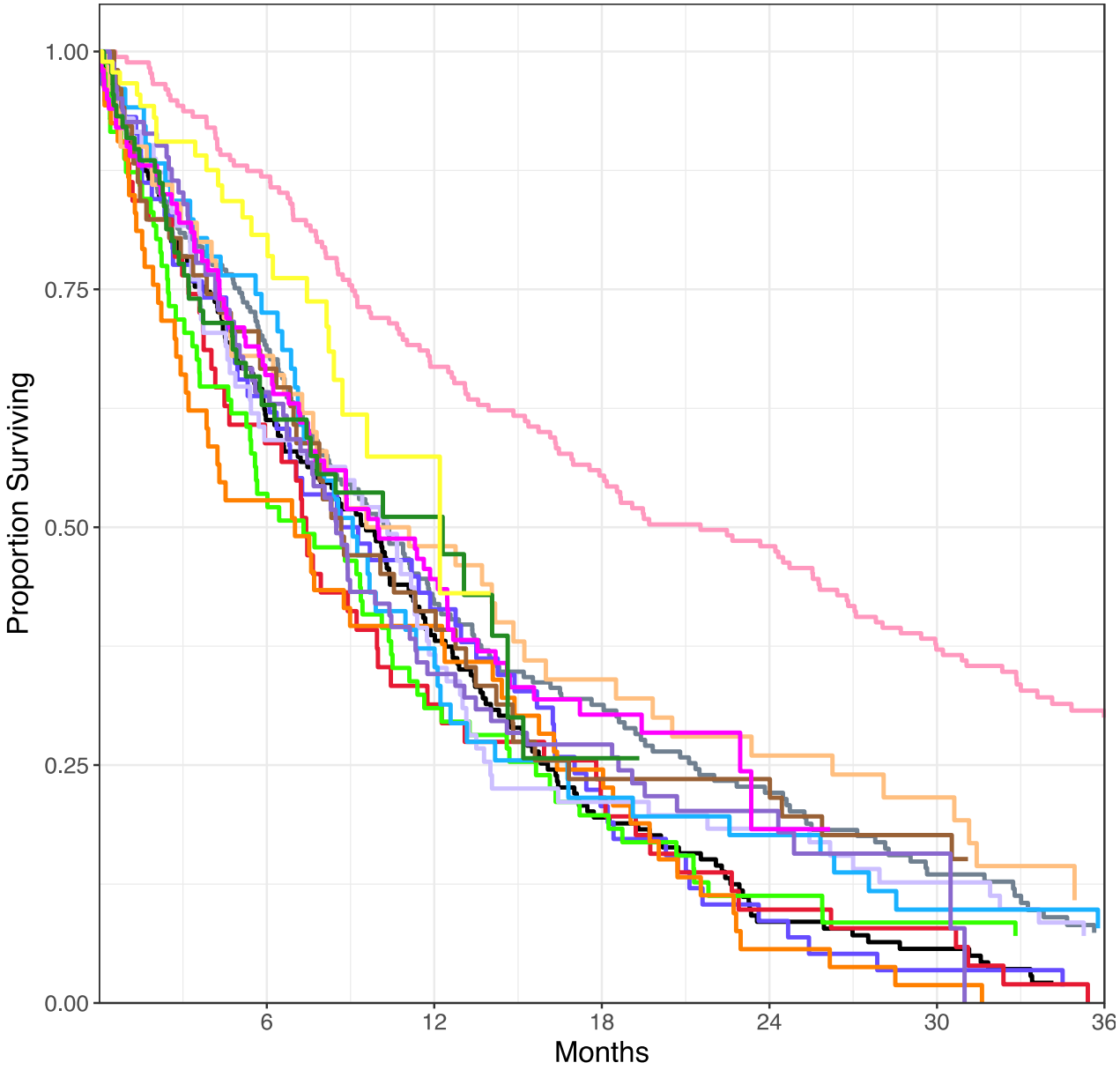
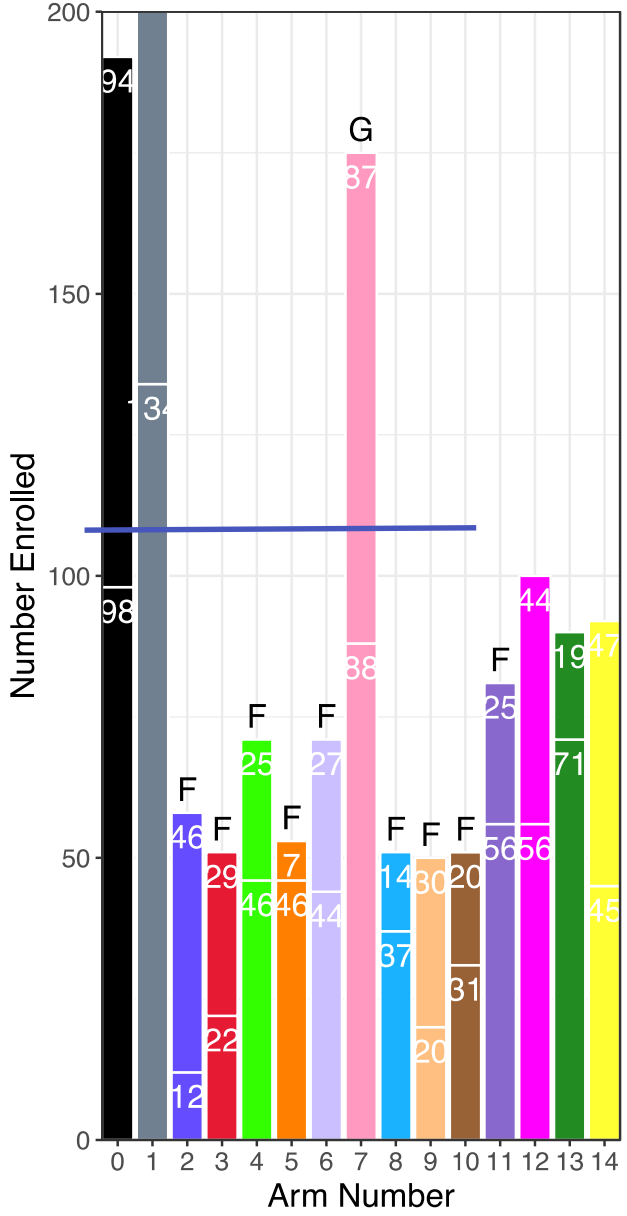
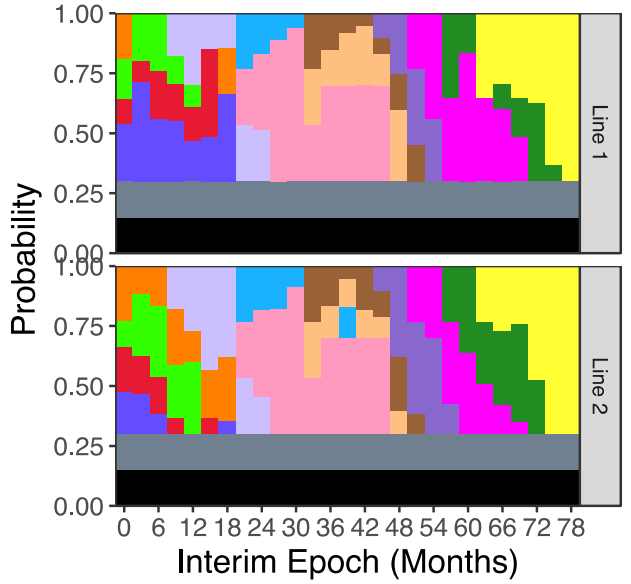
Overall Survival: All Patients. 81 Months After Trial Start



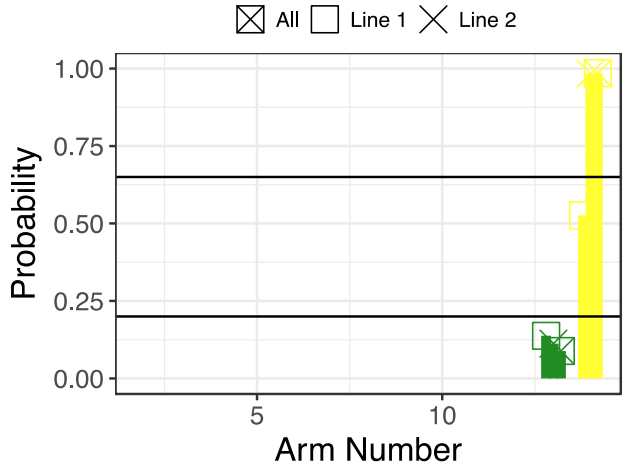
Sample Size



Randomization Probabilities



Predictive Probabilities for These Signatures



Adaptation By Arm: Stage 1

Stage 1

- Potential Enrichment biomarker for an arm
- Adaptive Randomization across subtypes and arms
- Sample size between 50 and 100
- Stop enrolling (phase 2 trial) up until n=100

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Stage 1 -> Stage 2 Transition

Stage 1 

- Graduates at n=100 if predictive probability success at end of Stage 2 ≥ 0.65 in at least one signature (collection of an arms subtypes)

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Stage 2

- Fixed randomization within graduating signature
- N=+75 in Stage 2
- Final analysis 1 year after last patient enrolled and on all Stage 1 and Stage 2 patients
- Comparison to all relevant shared controls (before and during era of an arm)

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Adaptations for Patients

- Each patient is a member of a trial subtype
  - 1st line; 2nd line; potential biomarker group
  - Randomized 30% to control(s); 70% to experimental
  - The 70% of experimental broken up by RAR for arms by subtype and 40% Stage 2 arms (if applicable)
- Upon progression a patient is re-randomized as part of the platform (potentially a second experimental arm)

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Statistical/Scientific Aspects (CID)

- Primary endpoint is overall survival
- Modeling partitions effect of 1st/2nd line therapies
- Common controls; effects of time modeled within the trial
- Single model estimate of effects of all arms
- RAR by subtype
- Potential graduation by signatures (model potential differential effects across subtypes)
- Simulation of type I error; interpretation of type I error

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The Future?

- Embedded platform trials?
  - Merging clinical care and learning

- The beauty is that the future of innovation in trial design is awesome and restricted only by our imaginations…
- Tomorrow is here…

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