Australian Clinical Trials Alliance

A Discussion on the Role of DSMBs in Adaptive Trials

Berry Consultants
Statistical Innovation

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April 3, 2020

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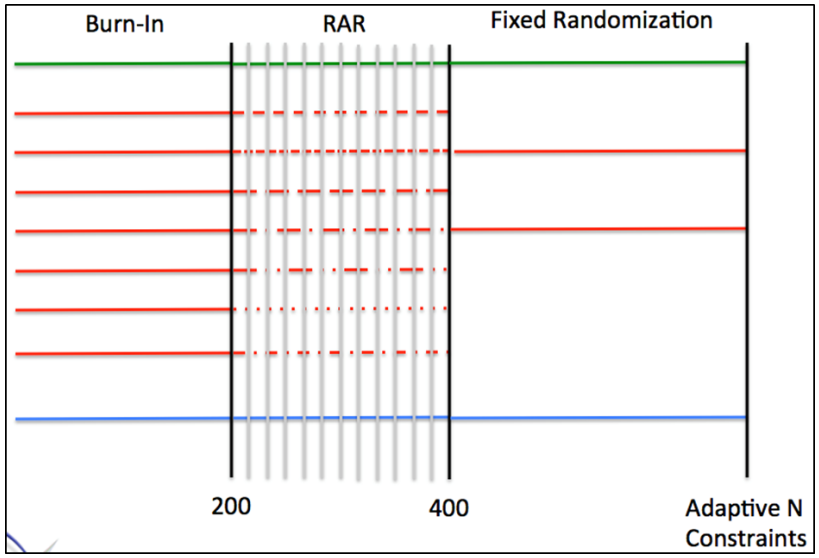
Outline

- Several examples of “complex” adaptive trials
- Role of Data and Safety Monitoring Board (DSMB) in adaptive trials
- Structure
- Best practices
- Discussion

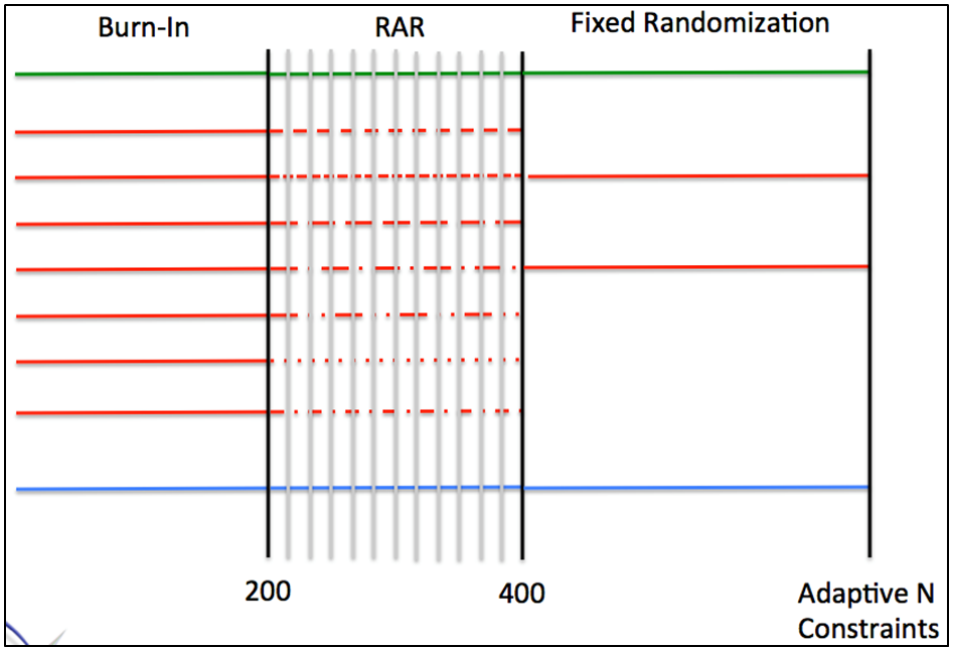
Trulicity Trial: Design

- 7 dose + 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); open more phase III
    - Stop futility
  - Phase III part powered by phase II
  - Entirely prospectively planned
    - Algorithms, Rules, Decisions, Analyses



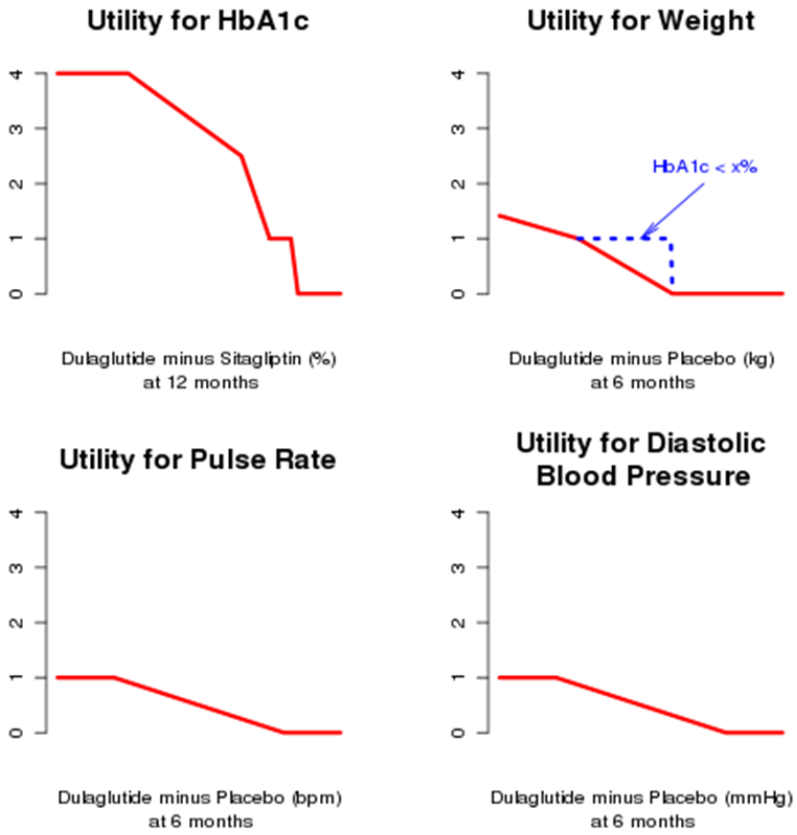
Trulicity Trial: Modeling

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



Trulicity Trial: Utility

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



Trulicity Trial: Final Analysis

- Final Analysis is an ANCOVA model for the high dose compared to control for NI using all patients on each arm
  - Nominal Alpha = 0.020
- The design dictates the the behavior of the simple final analysis is unknown on pencil and paper

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

Slide title

- Trial ran (for ~33,467,321st time!)
- Shifted at 200 -- very successful!
  - Ran *exactly* as planned, spawned other phase III
  - Selected 0.75mg and 1.5mg doses

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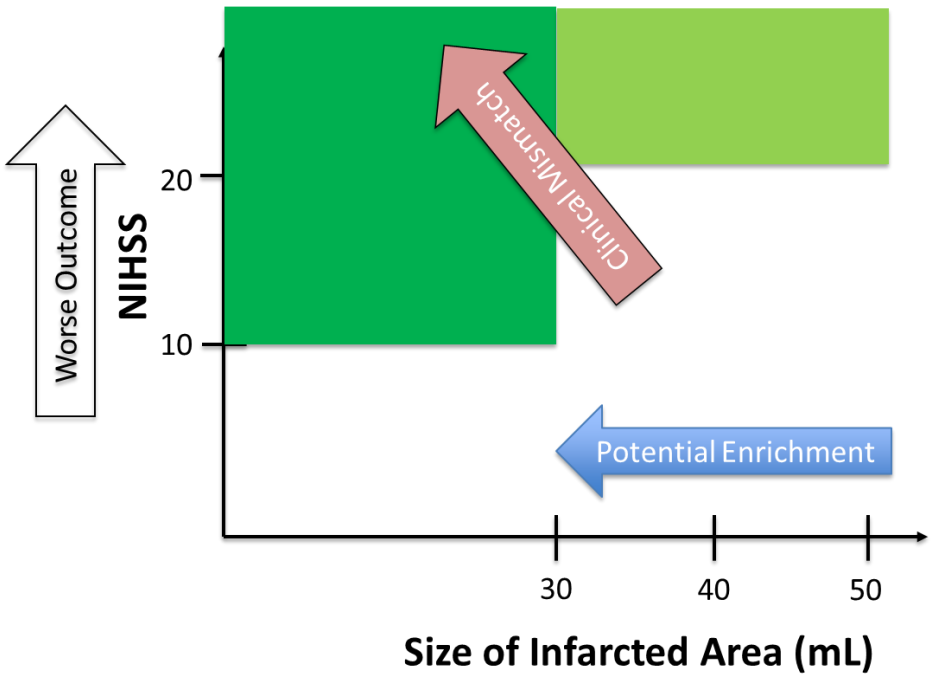
DAWN

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



DAWN: 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

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)

DAWN: Result

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.

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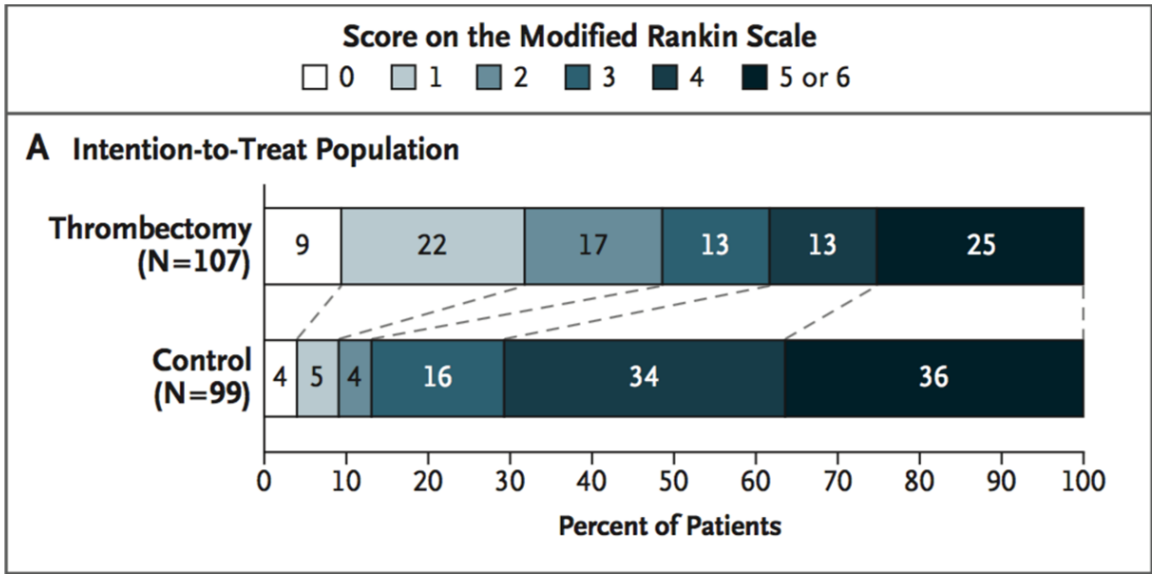

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DAWN: Result

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

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

2225754Gdft.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
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NOVEMBER 25, 2016
RULES COMMITTEE PRINT 114-67
TEXT OF HOUSE AMENDMENT TO THE SENATE

21 **Subtitle C—Modern Trial Design**
22 **and Evidence Development**
23 **SEC. 3021. NOVEL CLINICAL TRIAL DESIGNS.**
24 (a) PROPOSALS FOR USE OF NOVEL CLINICAL TRIAL
25 DESIGNS FOR DRUGS AND BIOLOGICAL PRODUCTS.—For
26 purposes of assisting sponsors in incorporating complex

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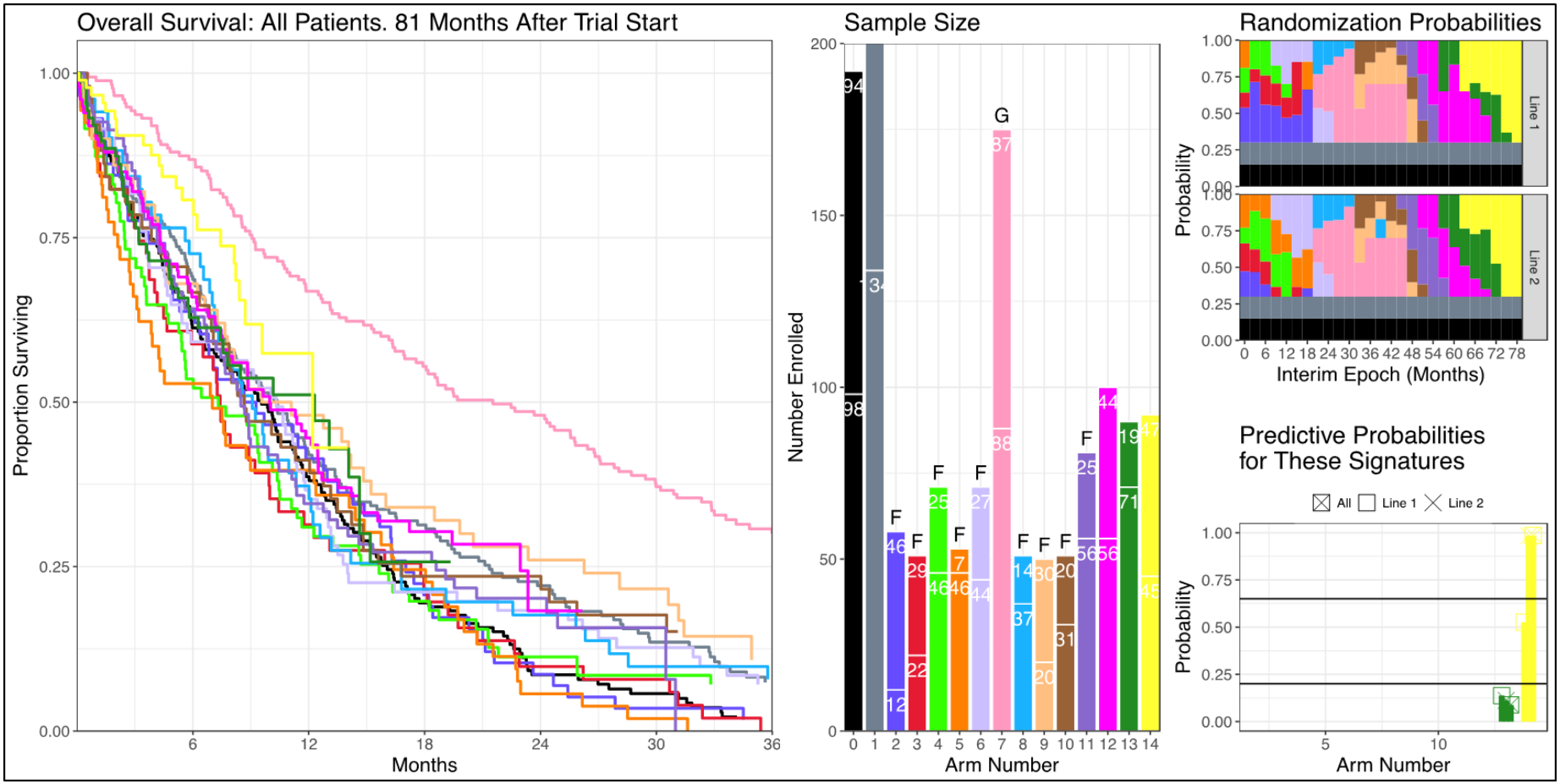
Precision Promise



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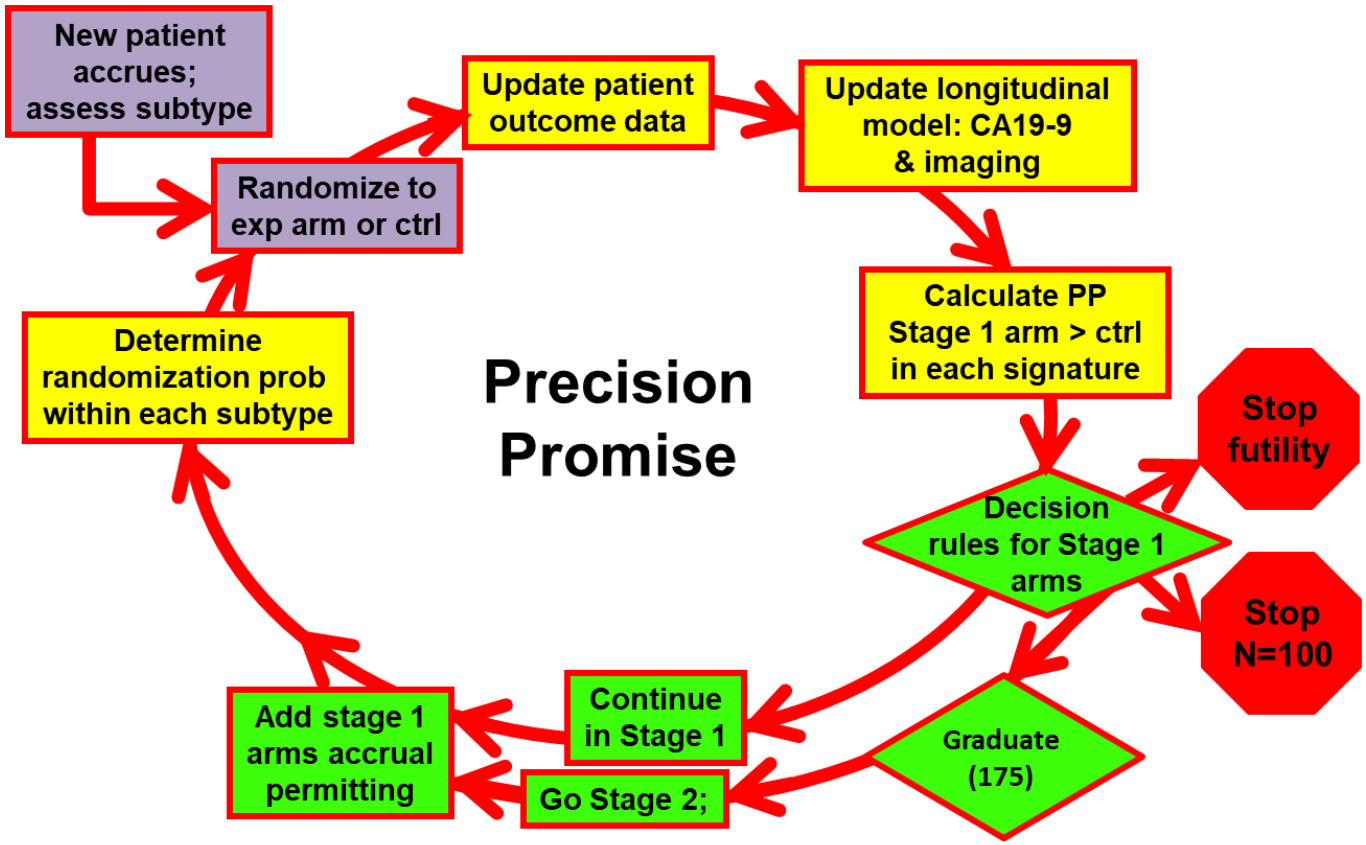

Monthly Interims

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DSMB Role

- Usual role to ensure:
  - Protection of human subjects
  - Proper conduct of the trial
  - Ongoing scientific validity, integrity, and clinical and scientific relevance of the study

- Review of standard unblinded DSMB report prepared by independent statistician

DSMB Role

- Monitoring trial conduct now includes ensuring adaptations are implemented *as specified in protocol*
- Must be unblinded to treatment assignment
- Must be allowed to review all trial data including outcomes

DSMB Role - Additional Considerations

- DSMB must understand design and what trial is supposed to do so they can:
  - Assess if something is going wrong (with help of Statistical Analysis Committee)
  - Assess if trial's prespecified actions are no longer appropriate
  - Recognize the potential negative impact on trial validity of making design change recommendations after they've seen unblinded data

DSMB Member Preparation

- Kickoff meeting is a key activity
  - Should occur before enrollment begins
  - Usual DSMB training
  - Also train DSMB on adaptive design
  - Need adequate time for design team to describe design and show example trials

DSMB Role in Interim Analyses

- Review interim analysis reports
  - Prepared by Statistical Analysis Committee (SAC)
  - Provided to DSMB for informational purposes
  - Supplemental to usual full DSMB report

- Interim analyses are prespecified
- Deliberations should be guided by trial design
- Note – trial is adaptive, DSMB is not adaptive

DSMB Role in Interim Analyses

- Some DSMB members consider trial adaptations, e.g. stopping boundaries, as guidelines, not rules
- If DSMB recommends to deviate from design:
  - Design is no longer prespecified
  - Trial operating characteristics (Type I error and power) no longer known
  - Decision likely introduces bias because of knowledge of unblinded data, bias is unable to be quantified
  - Trial integrity may be questioned

DSMB Role in Interim Analyses

- May recommend deviations from design based on patient safety
- Non-safety recommendations to deviate are technically protocol deviations and may have consequences
- Allow DSMB to talk to regulatory authorities before recommending deviations
- FDA Adaptive Design Guidance:
  - *"When completely unforeseen circumstances arise, we recommend discussing any potential design changes with FDA as soon as possible. "*

DSMB Meeting Timing

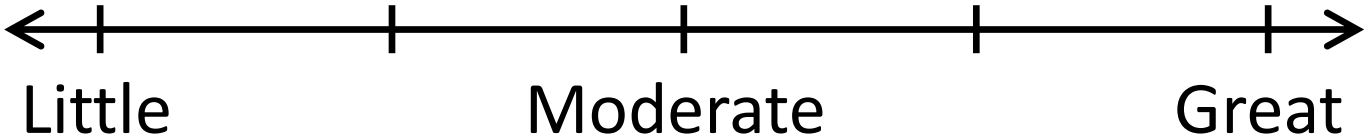
- Do DSMBs need to meet at each interim analysis?
- Examples:
  - Response adaptive randomization
    - Do not need to approve updated probabilities, part of protocol
    - But need to know results in case need to make safety recommendation
  - Major stopping decisions
    - May require a DSMB review, before actions transmitted, to allow DSMB to add recommendations if desired
- DSMB must be nimble—review, meet, and react quickly

DSMB Member Selection

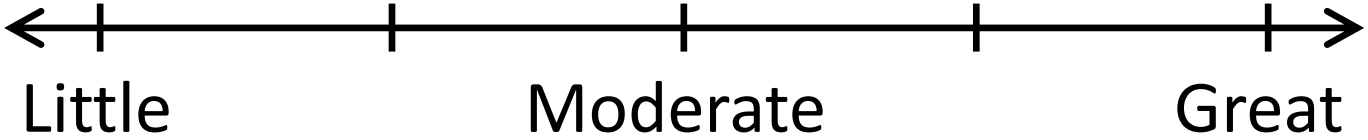
- DSMB members must be nimble and able to react quickly – KOLs may have limited time
- Experience in adaptive designs is key
- No pre-formed opinions regarding intervention or design
- Balance necessary expertise with conflict of interest requirements

Member Expertise and Conflicts of Interest

Expertise



Conflict of Interest



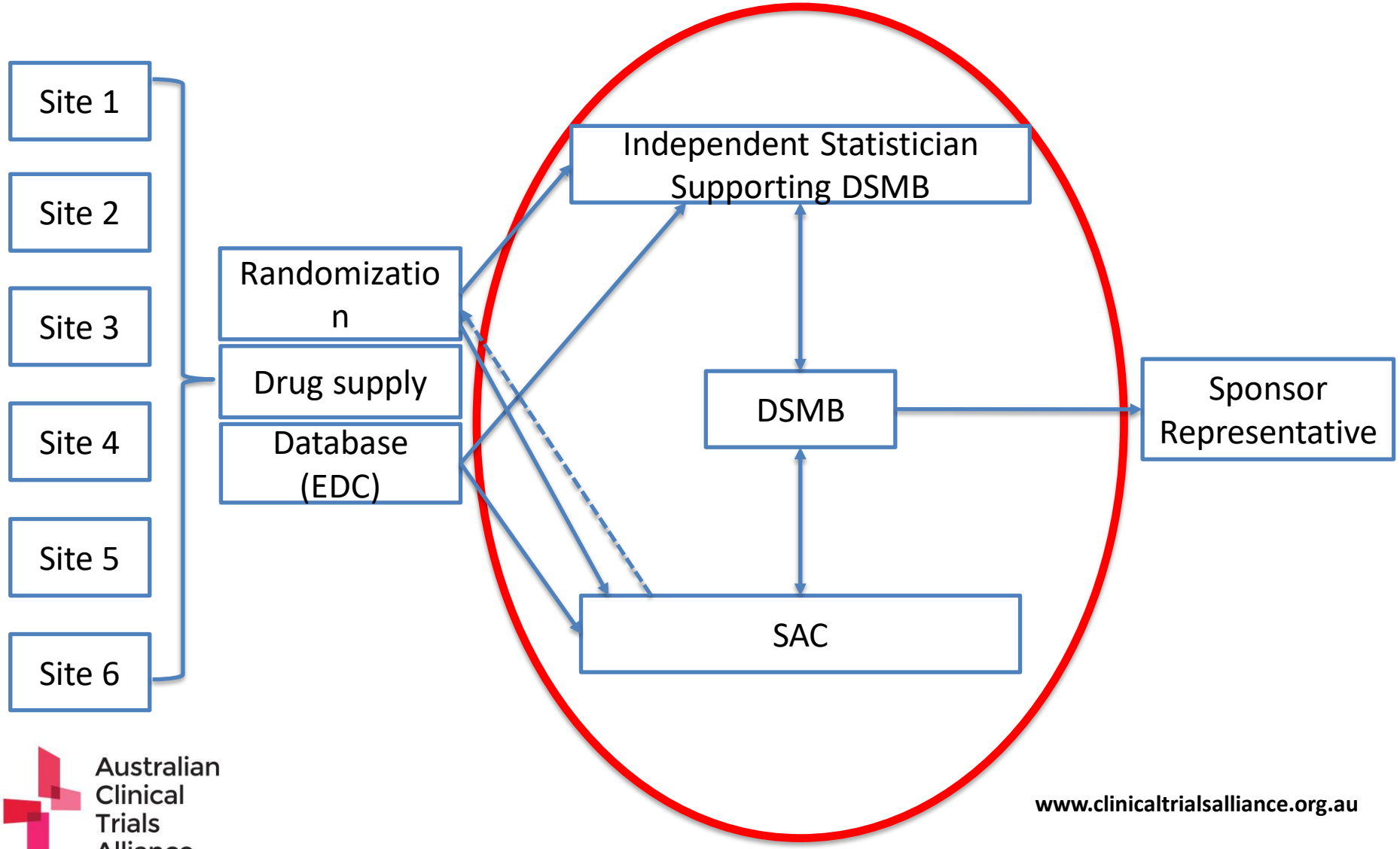
Statistical Analysis Committee (SAC)

- Also known as:
  - Statistical Monitoring Committee (SMC)
  - Independent Statistical Analysis Committee (ISAC)
- Small unblinded team of 2-4 statisticians, (platform trial teams are the larger teams)
- Experienced in adaptive design and relevant statistical methodology
- Overlap with design team is preferable

Statistical Analysis Committee Role

- Performs interim analyses as specified in protocol
  - No secondary or safety analyses
- Receives limited data—only data directly used in interim analyses and subject disposition
- Prepares interim analysis summary report
- Interacts with DSMB
- Sometimes has separate charter

Sphere of Confidentiality (unblinded)



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Restrict Access to Interim Analysis Results

- Operational bias results when information from ongoing trial causes changes to participants enrolled, investigator behavior, or other clinical aspects in such a way so that conclusions are biased
- Key concern for innovative adaptive trials
- Requires planning and documentation

Data Access Plan: Who Knows What When

- Who are the unblinded personnel
- How access will be controlled? Firewalls?
- How adaptive decisions will be made
  - Prespecified in protocol
- Type of information disseminated and to whom
- Details may be in protocol, SAP, DSMB and SAC charters
- Submit to regulatory bodies during design stage

DSMB Sponsor Communication Contact

- Receives high level result of interim analysis
- Separate from study team
- Not involved in day to day trial activities
- Able to receive limited unblinding information
- Seniority to make decisions
- Transmits resulting action to study team

DSMB Communication Plan

- ONLY high level results (continue, stop for futility, stop for expected success) transmitted to sponsor contact
- Interim analysis high level results may be:
  - Sent to DSMB to communicate to sponsor contact
  - Sent directly to sponsor contact with a copy to DSMB
- Procedure detailed in DSMB charter and SAC charter (if applicable)
- DSMB <u>always</u> sees all interim analysis reports regardless of communication plan

DSMB Communication Letters

- ONLY high level results (continue, stop for futility, stop for expected success) transmitted to sponsor contact
- Recommendations need to be carefully constructed to contain minimal amount of information necessary
- Rationale may or may not be given in order to maintain the scientific integrity of the trial

SAC Interactions with DSMB

- Participate in DSMB closed sessions (interim analyses timepoints) to explain results and answer questions
- Respond to DSMB requests for additional analyses specific to adaptations
- DSMB recommendations to deviate from prespecified design should be discussed with SAC to understand implications
  - Process should be outlined in DSMB charter

Logistical Considerations

- Will interims coincide with DSMB meetings?
- Does there need to be a DSMB safety report with each interim analysis report?
  - Full report
  - Abbreviated safety report
- How to align data cuts for interim analysis reports and full DSMB reports

Summary

- Require additional considerations including member expertise, availability, and training
- Conduct analyses as specified in protocol and understand trial integrity consequences of not following prespecified design
- Maintain confidentiality of comparative interim results and preserve trial integrity

Questions?