A Discussion on the Role of DSMBs in Adaptive Trials

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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
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 behavior of the simple final analysis is unknown on pencil and paper.
• 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
• 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**
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

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


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www.clinicaltrialsalliance.org.au
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).

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<thead>
<tr>
<th>Table 2. Efficacy Outcomes.*</th>
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<tr>
<td><strong>Outcome</strong></td>
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<td>Primary end points</td>
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<td>Score on utility-weighted modified Rankin scale at 90 days</td>
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<td>Functional independence at 90 days — no. (%)</td>
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Precision Promise
New patient accrues; assess subtype

Randomize to exp arm or ctrl

Determine randomization prob within each subtype

Update patient outcome data

Update longitudinal model: CA19-9 & imaging

Calculate PP Stage 1 arm > ctrl in each signature

Decision rules for Stage 1 arms

Graduate (175)

Go Stage 2;

Continue in Stage 1

Add stage 1 arms accrual permitting

Stop futility

Stop N=100

Monthly Interims
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
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)

- Site 1
- Site 2
- Site 3
- Site 4
- Site 5
- Site 6

Randomization
Drug supply
Database (EDC)

Independent Statistician
Supporting DSMB

DSMB
SAC

Sponsor Representative

Australian Clinical Trials Alliance

www.clinicaltrialsalliance.org.au
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 always 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?