Adaptive Clinical Trial Designs

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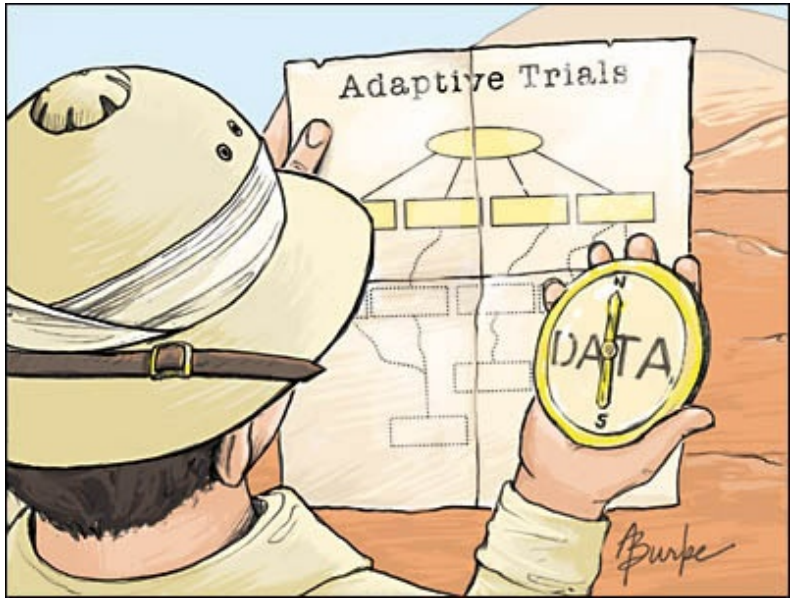
Outline

- What are adaptive designs?
- Can adaptive designs improve the ability to enroll, treat, and learn about treatments for older adults?

Adaptive Designs

- What is an adaptive design?
  - A design that has pre-specified dynamic aspects that are determined by the accruing information
  - Adaptive … “By Design”



JAMA 2006; 296:1955-1957

Adaptive Promise

- During the course of the trial things are learned that – *had you known before the trial started* – you would have changed the design.
  - Learned: It is important that the trial learn about the important aspects, and efficiently.
    - Dose-response models, Longitudinal models, prediction, imputation, biomarkers,…
  - Change: The dynamically moving aspects of the trial: prospective changes

DAWN

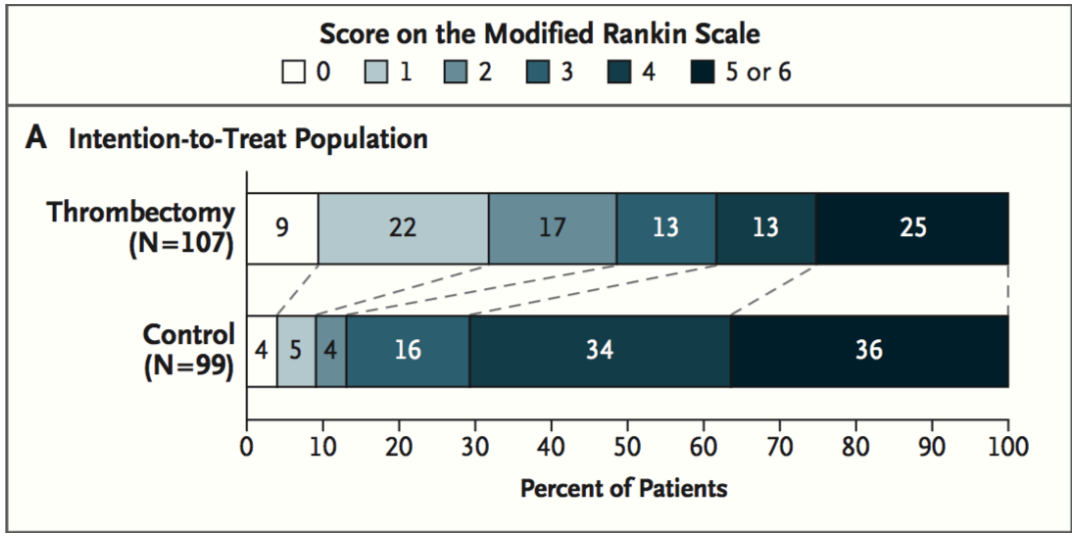
- Enrichment design of thrombectomy vs. SOC
- Could enrich to smaller stroke sizes (infarcted region mL)
- Started at 50, could go down to 45, 40, 35, or 30 based on accruing data
- Pivotal trial (adaptive sample size of 200 to 500)

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*



ICECAP

- https://siren.network/clinical-trials/icecap
- ClinicalTrials.gov: NCT04217551
- Hypothermia after cardiac arrest: Improve neurological status?
- 10 different durations: 6, 12, 18, 24, 30, 36, 42, 48, 60, 72
- 1800 patient trial, interim analyses every 50 patients
- Adaptive randomization, separately by rhythm type (shockable and non-shockable)
- Different conclusions, durations optimal by subgroup

REMAP-CAP

- Enrolling hospitalized patients with COVID-19
- Response adaptive randomization across multiple ”domains” of therapy
  - Anti-virals, immune modulation, steroids, anti-coagulation, CP, vitamin C, anti-platelet …
- The RAR varies by subgroup: moderate (non organ support) and severe (on organ support).
- One domain has RAR vary by d-dimer levels
- https://www.remapcap.org

Potential Ideas

- Are there aspects of the accruing data that would allow the enrollment of older adults? Improve the treatment of older adults? Remove barriers?
- A trial design that starts enrolling younger adults but has a predefined trigger for enrolling older adults if safety is met
- A trial that does adaptive randomization across arms specifically within older adults
- Enrichment trial that specifically models efficacy in older adults that allows success or failure within that group differently
  - Potentially borrowing efficacy/safety across subgroups (ages)