The DAWN Trial Design: Focus on the Unknown

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- Berry Consultants, LLC
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Selected “Unknowns”

- The “region” of the mRS disability scale over which benefit might exist
- Who benefits (vs who will do well)
  - Broad range of core infarct sizes
  - Only those with smaller core infarct sizes
- The magnitude of benefit
  - None
  - Small
  - Large
- Making an incorrect assumption could be very bad

Location of Benefit in mRS Disability

- Traditionally the mRS is dichotomized for analysis, blinding us to benefit within the ranges of 0-2 or 3-6
- Need a patient-centered approach sensitive to all important benefits: Utility Weighted mRS

mRS	0	1	2	3	4	5	6
Rivero-Arias et al	10	8.7	7.3	6.0	2.8	-0.1	0
Hong & Saver	10	9.5	7.9	6.7	3.5	0.1	0
DAWN	10	9.1	7.6	6.5	3.3	0	0

Who Benefits?

- Core infarct size thought to be most likely eligibility characteristic that might define differentially responding populations
- Strategies
  - Expansion: Start small and expand if benefit
  - Enrichment: Start broadly and restrict if necessary
- DAWN Strategy
  - Enroll up to 50 cc core infarct volume
  - Enrich by lowering upper limit (50 → 45 → 40 etc.) if that increases the likelihood of a positive trial

Magnitude of Benefit

- None
  - None at all → stop efficiently
  - None in larger core infarct sizes → stop enrolling that population
- Small but clinically important
  - Large maximum sample size (up to 500)
  - More sensitive outcome measure (uw-mRS)
- Large
  - Stop early for predicted success (as early as 200)

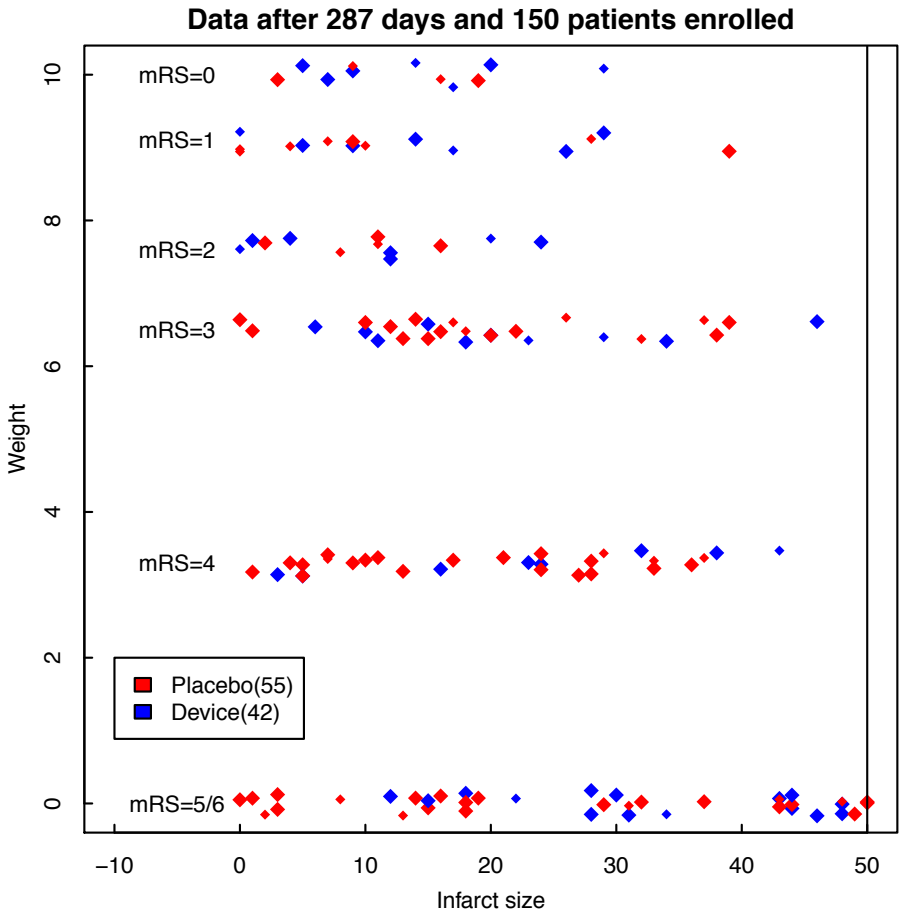
Prespecification

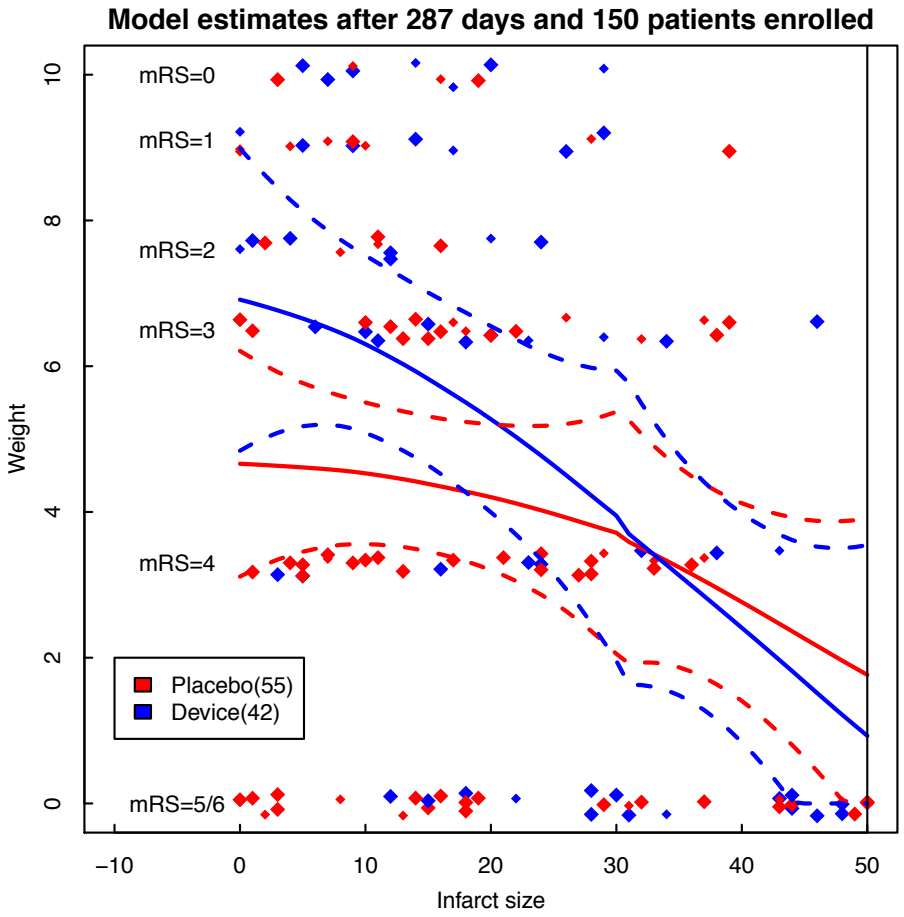
- DAWN Design used specific prespecified rules
  - Timing of interim analyses 150, 200, … , 450
  - Possible decisions, and criteria, at each analysis
  - Rules for early stopping (200, 250 …) based on probability of success > 95%, > 90%, > 85%, > 80%
  - Rules for early stopping for futility (150, 200 …) based on uniform probability of success < 10%
  - Enrichment
    - If it increases chance of positive trial by 10%
    - Eliminate populations based on core infarct size if < 40% chance of benefit in that population

Statistical Details

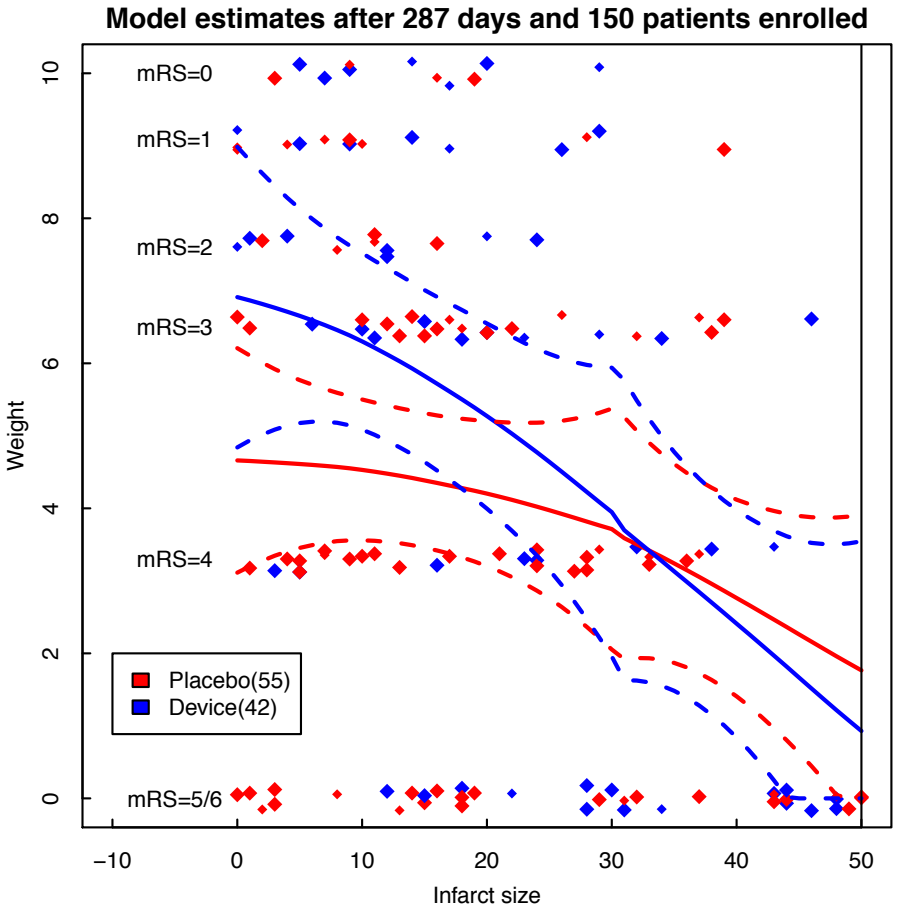
- If no enrichment, requires probability of benefit of 98.6% to be positive
- Criterion is more restrictive if enrichment occurs
- Statistical models used to “share” information across infarct-size populations
- Computer simulation used to demonstrate that is all works as intended

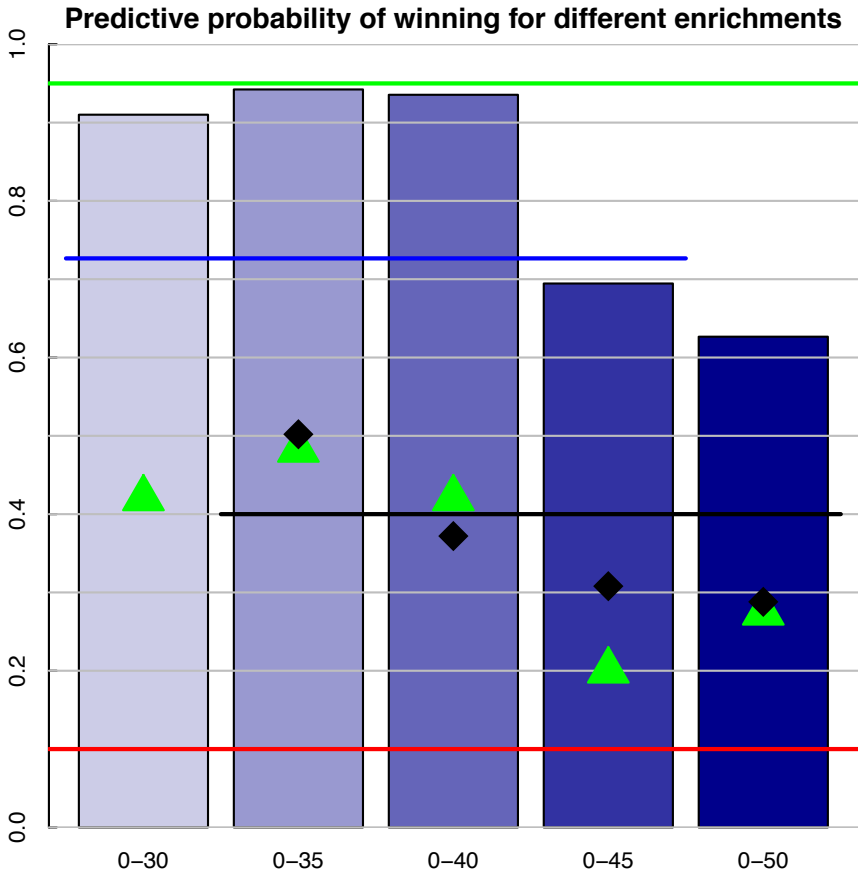
Simulation Snapshot (n = 150)



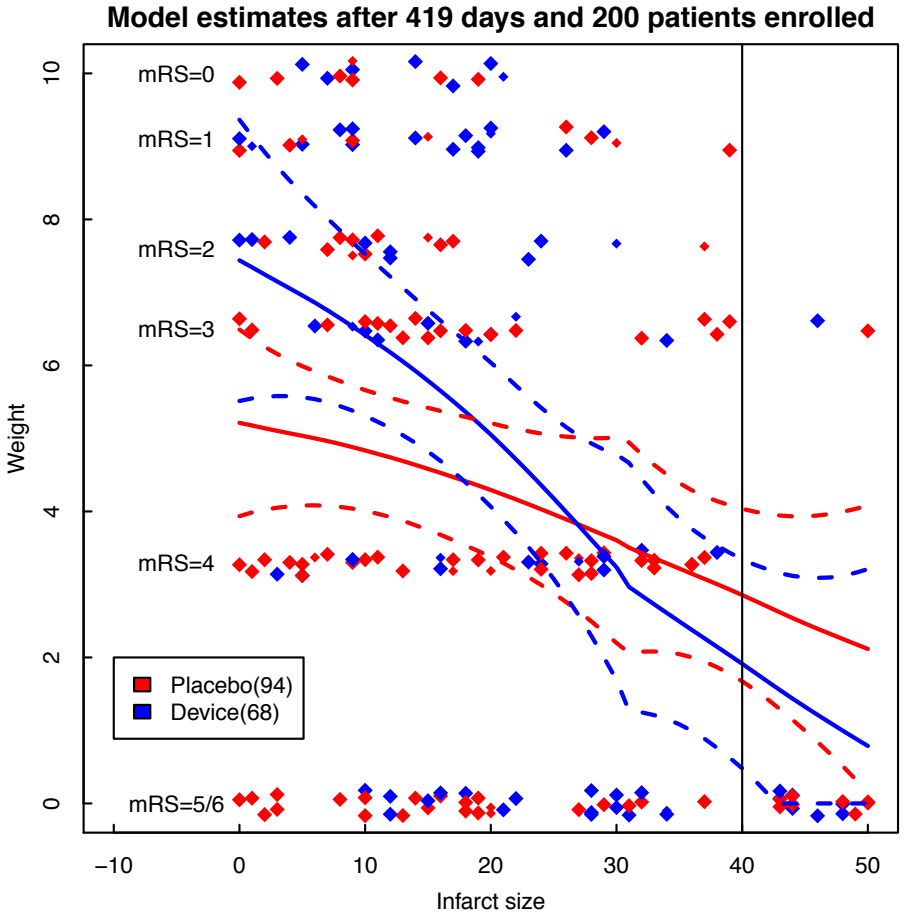


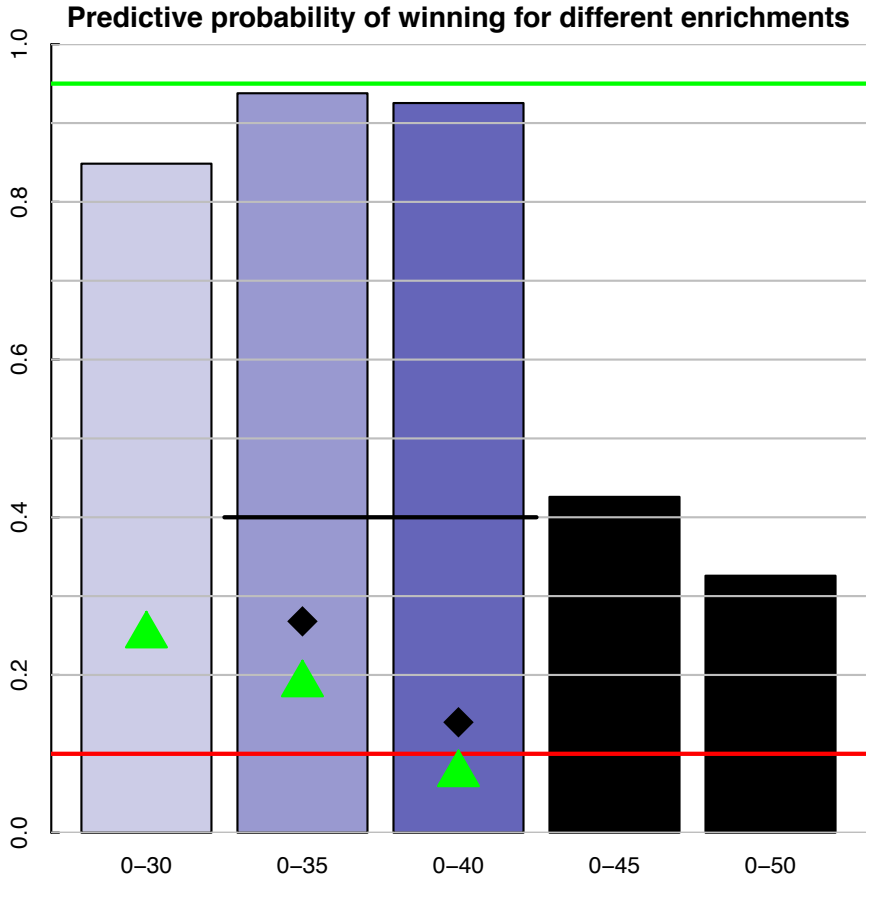
Simulation Snapshot (n = 150)





Simulation Snapshot (n = 200)





Operating Characteristics

- Many 1000s of trials simulated, to determine operating characteristics
  - Type I error risk of 0.025
  - Power
    - Complicated, depends on magnitude and pattern of benefit
  - Average required sample size

Research

International Journal of Stroke WSO

Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with Trevo (DAWN) trial methods

Tudor G Jovin[1], Jeffrey L Saver[2], Marc Ribo[3], Vitor Pereira[4], Anthony Furlan[5], Alain Bonafe[6], Blaise Baxter[7], Rishi Gupta[8], Demetrius Lopes[9], Olav Jansen[10], Wade Smith[11], Daryl Gress[12], Steven Hetts[13], Roger J Lewis[14], Ryan Shields[15], Scott M Berry[16], Todd L Graves[16], Tim Malisch[17], Ansaar Rai[18], Kevin N Sheth[19], David S Liebeskind[2] and Raul G Nogueira[20]

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Conclusions

- Enthusiasm and hope are not the same as being able to predict the future
- You never know as much about what's going to happen in a clinical trial as you think you do
- The trial design needs to work well across the range of things that might happen
  - Life is complicated and pretending it's simple is not a good research strategy