Power for the Partially-Paired Randomization Design as Compared to the Unpaired Design in Ophthalmological Clinical Trials

Michele Melia and Adam Glassman for the
Diabetic Retinopathy Clinical Research Network
Jaeb Center for Health Research
Tampa, FL

Society for Clinical Trials

May 2013

Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY14229, EY018817

DRCR.net

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Eye Institute

National Eye Institute
NATIONAL INSTITUTES OF HEALTH

Unique Features of Ophthalmology Studies

- Paired organ system

- Many diseases can affect one or both eyes; frequently both eyes are affected
  - E.g. Glaucoma, cataract, diabetic retinopathy
  - Disease severity and progression may differ between eyes, but usually there is correlation between eyes

- Many treatments are delivered at the eye level rather than patient level

Choices of Design in Ophthalmology Trials

- **Unpaired design**
  - Randomize 1 eye, regardless of # eligible eyes
- **Fully-paired design**
  - Require both eyes eligible and randomize both eyes
    - Randomize both eyes to same treatment
    - Randomize eyes to different treatments
- **Partially-paired design**
  - Randomize 1 eye if 1 eye eligible and randomize both eyes if both eyes eligible
    - Randomize both eyes to same treatment
    - Randomize eyes to different treatments

Goals of Presentation

- Consider partially-paired designs with paired eyes randomized to different treatments
- Explore impact on statistical power of:
  - Proportion of subjects with 2 eyes randomized
  - Between-eye correlation in outcome within subject
- Compare to unpaired design

Specific Designs Considered

- 2 armed trial
  - 1 eye: Randomize to A and B with equal frequency
  - 2 eyes: Randomize to A(right eye) B(left eye) and B(left eye) A(right eye) with equal frequency
- 3 armed trial
  - 1 eye: Randomize to A, B, and C with equal frequency
  - 2 eyes: Subject is randomized with equal frequency to
    - A in eye with better visual acuity, B in other eye
    - B in eye with better visual acuity, A in other eye
    - A in eye with better visual acuity, C in other eye
    - C in eye with better visual acuity, A in other eye
    - One eye always gets A (control treatment)

Methods

- Simulate change in visual acuity (VA) data for 10,000 clinical trials varying:
  - Sample size (# of subjects)
  - Proportion with 2 eyes
  - Correlation in outcome between eyes within subject
  - Treatment effect(s)
- Following also are pre-specified by user (but were not varied for this presentation):
  - Mean (SD) baseline visual acuity (65 letters, 11.0)
  - Between-eye correlation in baseline VA (0.17)
  - Range for baseline visual acuity (24 - 78 letters)
  - SD for change in visual acuity (12.0)
- Pre-specified values are based on prior trials

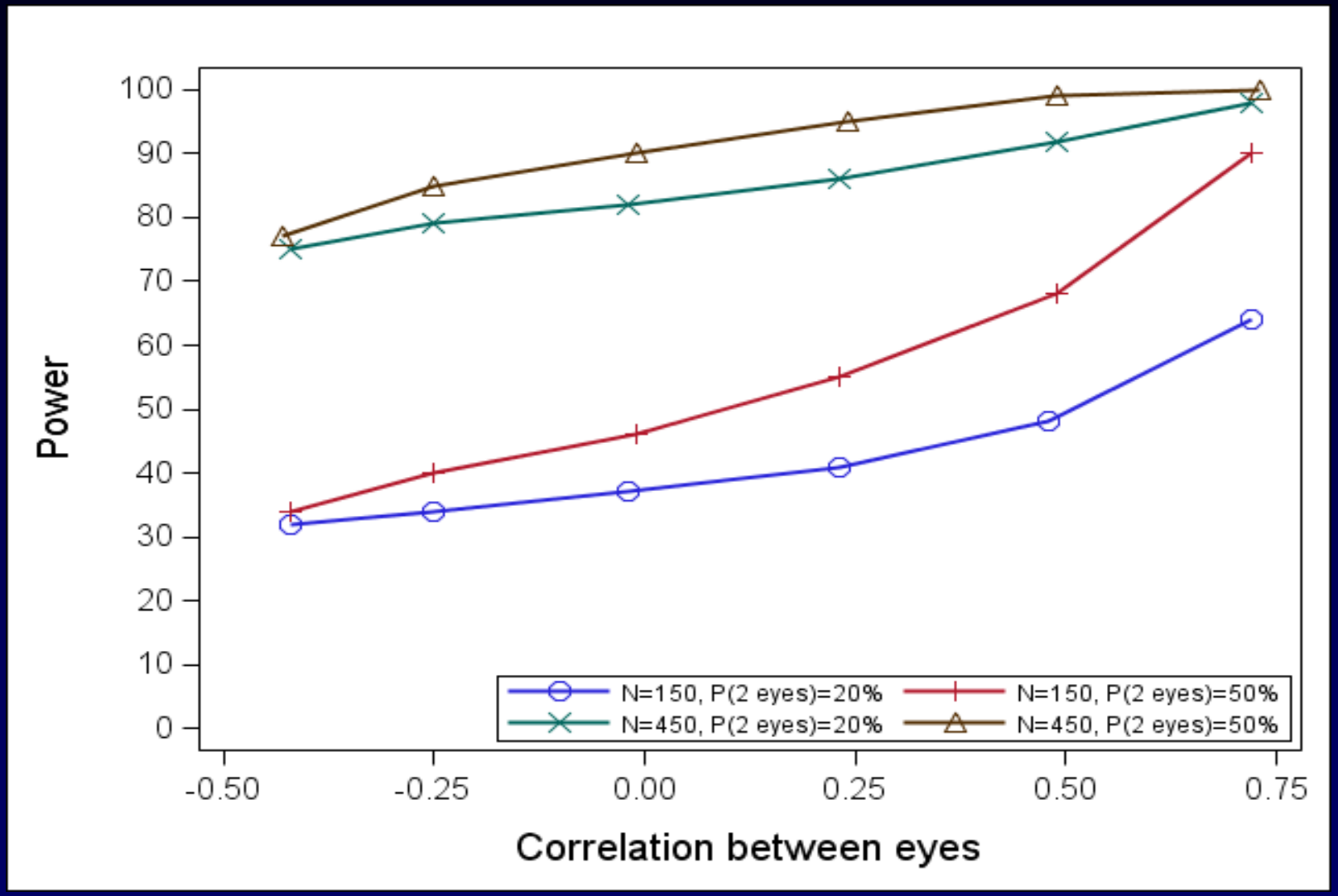
Methods

- Analyze simulated trials with linear mixed model to estimate power (proportion of comparisons for which H_o: treatment effect=0 is rejected)
  - Marginal model
  - Compound symmetry for correlation structure
  - Adjust for baseline visual acuity and number of eyes randomized

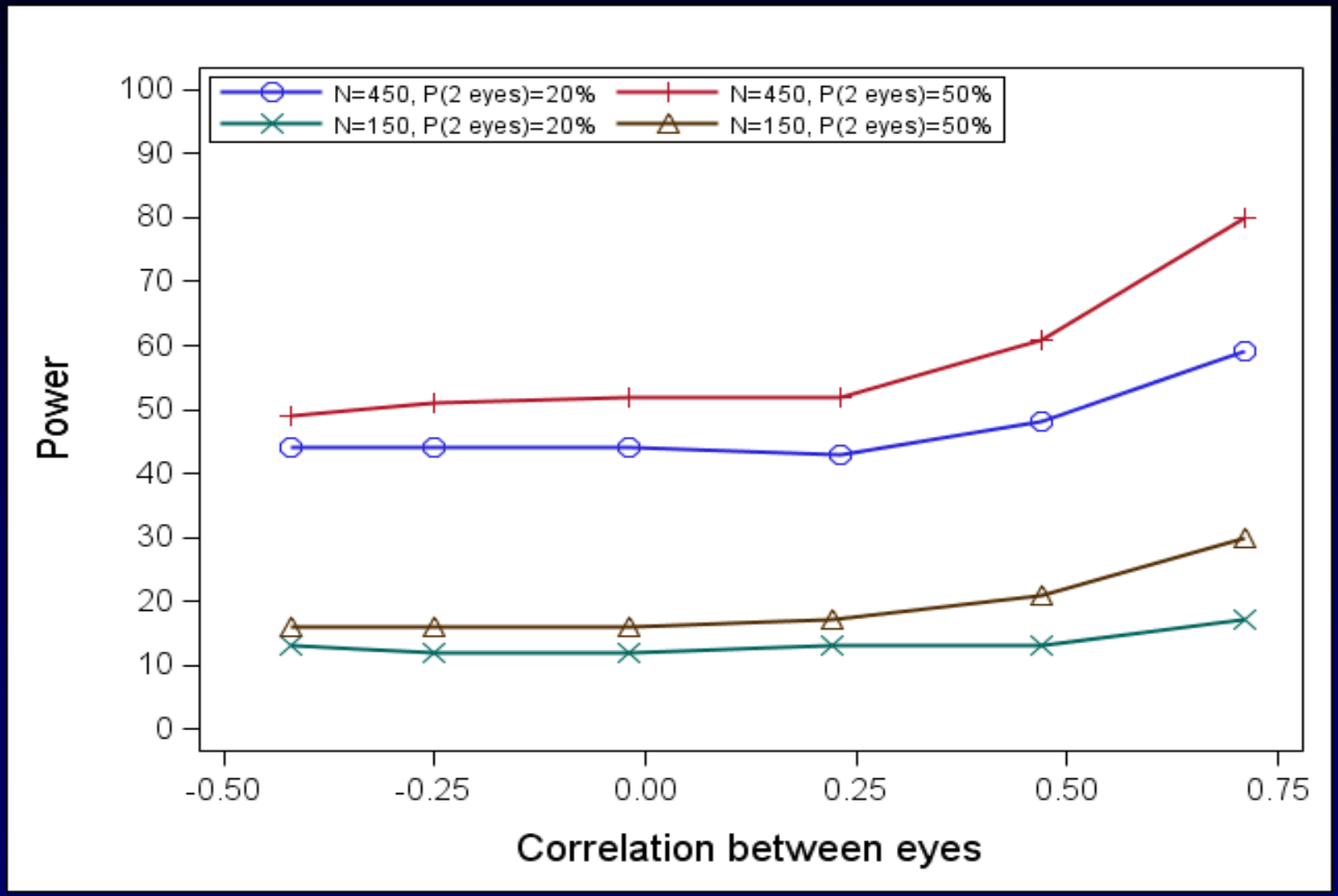
Simulation Validation

- Check that the following agree with pre-specified values when averaged across simulated trials:
  - Number randomized to each treatment group
  - Mean and SD for VA change for each treatment group
  - Mean estimated treatment effects from mixed model
  - Percent of subjects with both eyes randomized
  - Between-eye correlation in change in VA (outcome)
- Check that type I error rate is equal to pre-specified alpha when treatment effect sizes are set to 0

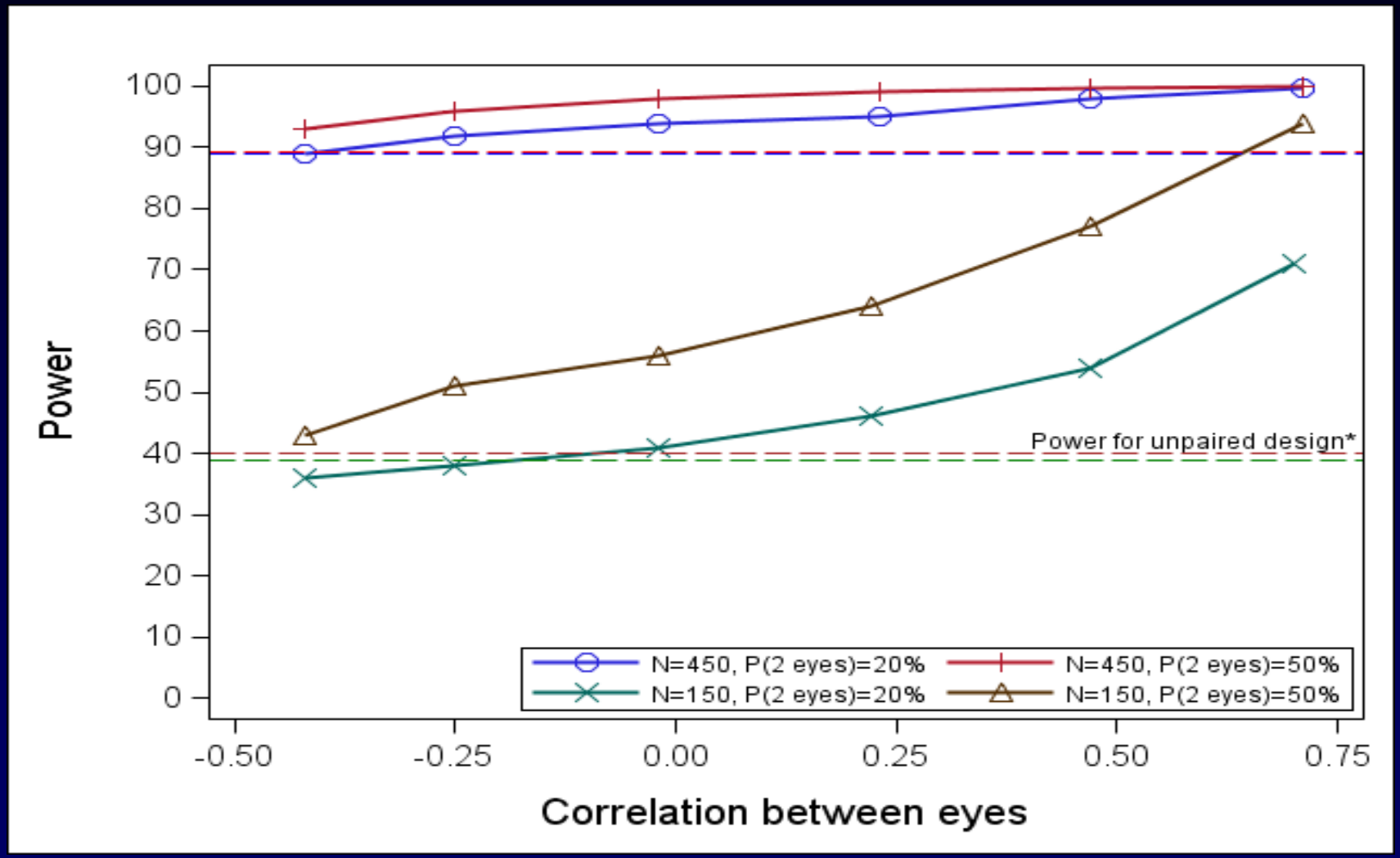
Power as a Function of Correlation Between Eyes – 2 arms, Δ=3 letters, SD=12



Power as a Function of Correlation Between Eyes – 3 arms, Δ=3 letters (B vs C), SD=12



Power as a Function of Correlation Between Eyes – 3 arms, Δ=5 letters (A vs C), SD=12



*Power for unpaired design with same # subjects and same randomization ratio.

Limitations/Further Work

- Correlations tended to fall a bit short of pre-specified values, i.e. closer to 0, especially for large negative correlations
  - Plots show correlation that was actually achieved rather than pre-specified values
  - Due to bounded VA and VA change scale?
- Mixed model did not obtain estimates for treatment differences in a small # (<0.1%) of simulated trial scenarios
  - Only happened with negative between-eye correlation and smaller total sample size
- Observed α ranged from 0.045 to 0.055 (vs expected 0.050) with one exception (α=0.037), and 0.0130 to 0.0184 (vs expected 0.0167)

Conclusions

- Reluctance to allow randomization of one ***or*** both eyes in ophthalmological trials
  - Particularly true for randomizing to different treatments due to concern over loss of power with - correlation
- Simulations used to address these concerns
  - Quantify likely impact on statistical power of between-eye correlation
  - Potentially could be used to reduce sample size
  - However, need good estimate of between-eye correlation; this frequently is lacking
  - Given uncertainty regarding correlation, and modest power benefits for low + correlation and low % with 2 eyes (usual situation in our studies), conservative approach assuming correlation=0 seems prudent