Randomizing Two Study Eyes from the Same Participant in Ophthalmic Clinical Trials

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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

- Randomize 1 eye, regardless of # eligible
- Require eligibility and randomization of both eyes
  - Randomly assign both eyes within a subject to the same treatment group
  - Randomly assign each eye within a subject to different treatment groups
- Randomize 1 eye when 1 eye is eligible and randomize both eyes when both eyes are eligible
  - Randomize both eyes to same treatment group
  - Randomize both eyes to different treatments
Goals of Presentation

- Consider the advantages and disadvantages to allowing both eyes to be randomized.

- If both eyes are allowed to be randomized, discuss whether they should be randomized to the same or different treatment group.

- Consider possible randomization schemes if both eyes are allowed to be randomized.
Advantages and Disadvantages to Allowing Both Eyes to be Randomized
Allow One Study Eye Only

Pros:
- **Logistics**
  - Timing of treatments/follow-up may not be conducive to bilateral enrollment
  - If study procedures/treatments are time-intensive, it may be too burdensome to have two study eyes
- **Safety** – may not be appropriate to treat both eyes in the study

Cons:
- **Less information from 1 eye than 2 eyes**
  - Increased number of participants needed => increased recruitment time => increased costs
Randomize Both Eyes

Pros:
- Study controls for systemic factors
- Statistical power enhanced, sample size reduced

Cons:
- Can add logistical complexities
- Potential recruitment limitations
  - Consider frequency of bilateral disease
  - Less of an issue if 2 study eyes are allowed but not required
- Statistical complexity
  - With current statistical software, complexity should not be a reason to not include 2 eyes
Eyes Randomized to Different or Same Group

➢ Eyes receiving different treatment:
  • Treatment effect in contra-lateral eye
    • Treatment could affect fellow eye and bias results
  • Systemic adverse events
    • If systemic AE is possible from both treatments
      would not be possible to attribute event to 1 treatment
  • Masking
    • Maybe more difficult to mask different groups.
    • If treatment is not masked and outcome is subjective,
      outcome could be biased
  • Quality of Life Assessments
    • Treatment group comparison of QOL cannot be assessed if eyes are randomized to different groups

➢ Eyes receiving same treatment:
  • Safety – can/should treatment be given bilaterally
Statistical Considerations

- Measurements from 2 eyes within a subject more resemble each other than measurements from other subjects
  - Based on observed and unobserved patient-level factors
  - Data from 2 eyes within a subject are likely positively correlated

- How does correlation impact results?
- Depends on study design
  - Trial where both eyes receive same treatment (or no treatment)
  - Trial where each eye receives different treatment
Correlation Impact on Results
Two eyes - same group

- If positive within subject correlation exists, less information is obtained from a subject with 2 study eyes than 2 subjects with 1 study eye.
- If data from same subject is treated as independent the assumption is that 2*N pieces of information exists when in fact there is less.
- Adjusting for correlation will appropriately decrease precision: widen confidence intervals, increase p-values.
Correlation Impact on Results
Two eyes – different groups

- Subjects act as their own control
  - Eliminates the effect of patient-level systemic factors
- If positive within subject correlation exists, more information on treatment group difference is obtained from a subject with 2 study eyes than 2 subjects with 1 study eye
- Adjusting for correlation will appropriately increase precision: decrease standard error, narrow confidence intervals, decrease p-values
Sample Size Impact

- Allowing 2 study eyes will (in all practical cases) reduce the number of subjects needed in a trial regardless of study design.

- How much of an impact depends on trial design, frequency of subjects with 2 study eyes, and correlation between eyes within subject.
Example: Anti-VEGF Injections for Proliferative Diabetic Retinopathy

- 2 Treatment groups, 2 eyes allowed (not required)
  - # eyes = 380; # participants (assumed) = 316

- Recruitment:
  - N= 380 eyes/316 participants: 10 months (actual)
  - N = 380 eyes/380 participants: 13 months (projected)

- Budget including bilateral participants:
  - N= 316 participants: $6.7 million
  - N= 380 participants: $7.9 million
Randomization Scheme
Randomization Scheme Bilateral Participants

- RCT for Diabetic Macular Edema Treatment
- 4 groups, bilateral participants receive control in one eye and one of the other 3 groups in other

Randomization Scheme (all pts receive A)
- 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
- A in eye with better visual acuity, D in other eye
- D in eye with better visual acuity, A in other eye
Randomization Scheme Bilateral Participants

4 Group Diabetic Macular Edema Study

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<th>Overall</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<td>187</td>
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<td>38%</td>
<td>56%</td>
<td>30%</td>
<td>30%</td>
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</tbody>
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➢ Is the imbalance a concern (i.e. could it be a confounder)?
  • Possibly; if having bilateral DME impacts the visual acuity outcomes then this imbalance could be a confounder
  • Note: Analyses confirmed it is not in this case
Summary

- Careful consideration should be given when designing a study where multiple measurements per participant are possible.

- If supported by the trial design, including and analyzing both eyes from the same subject is a useful tool provided that the within-subject correlation is appropriately accounted for in the analyses.