

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

	Overall	A	B	C	D
Overall (N)	854	293	187	188	186
% OU	38%	56%	30%	30%	27%

➤ 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**