Randomizing 1 Eye or 2 Eyes
A Missed Opportunity

Although there are several paired organ systems in the body, the eyes are unique in that many ocular diseases can affect one eye or both eyes and many treatments are delivered ocularly, not systemically. These unique traits allow each eye to be tested and treated independently when evaluating a new treatment delivered ocularly. Since more data are generally better, why do the majority of ophthalmology clinical trials limit enrollment to 1 eye per participant ignoring the opportunity to efficiently collect more information?1

Randomizing Both Eyes
Ophthalmological clinical trial study design may include one or both eyes from the same participant. When both eyes are randomized, they may be assigned to the same treatment group or to different treatment groups. Each design has its advantages and disadvantages and appropriateness depends on study-specific circumstances.

The amount of information, or sample size, in a study plays a critical role in statistical inference when comparing 2 treatment groups. More information results in more precision, which translates to smaller confidence intervals and an increased chance of detecting treatment differences when they are present. In most practical cases, for a fixed number of participants, allowing 2 study eyes increases the total amount of information in a study. Depending on the design of the study, the amount of information gained can be more than just the increase from including an additional eye.

Standard statistical approaches assume that outcomes are independent, ie, that knowing the outcome from one eye is noninformative regarding the outcome for all other eyes. However, outcomes from 2 eyes within a participant tend to more resemble each other than outcomes from eyes of other participants. Knowing the outcome in one eye usually is informative regarding the outcome in the fellow eye because participant-level factors (both observed and unobserved) can affect ocular outcomes. The relationship between eyes of the same participant may be stronger for diseases where systemic factors are known to affect ocular outcome. For example, worse glycated hemoglobin control has been shown to result in greater chance of development or worsening of diabetic retinopathy.2 This relationship or correlation between eyes of the same participant impacts the amount of information available on the treatment group difference and violates the assumption of data independence.

How correlation between a participant’s eyes impacts the information depends on the randomization scheme. When each eye of a participant is assigned to a different group, the participant acts as their own control. This results in more information about the treatment group effect since the noise related to participant-level factors is removed from the treatment group comparison, and the possibility of confounding by a systemic factor is eliminated. Including both eyes in this scenario and accounting for the correlation will increase precision and narrow confidence intervals more than including another eye from a different participant. For example, consider a participant with 2 study eyes each receiving different treatments in a trial evaluating diabetic macular edema. The observed difference in diabetic macular edema between treatments is more likely a result of the different treatments and not the underlying systemic diabetes control. The effect of systemic control is removed as a potential confounding factor.

Alternatively, if both eyes are assigned to the same treatment group, then less information is obtained from 2 study eyes from 1 participant than from 2 participants with 1 study eye because the participant’s 2 eyes may behave similarly. Here, including the second eye provides less information about treatment effect than adding an additional participant. Consider again a diabetic macular edema study but in this case both eyes of a participant receive the same treatment. Here, the impact of systemic diabetes control cannot be separated from the treatment effect and therefore the second eye is providing less information about the treatment than an eye from another participant. However, there is still a statistical benefit of including the second eye, provided it does not replace recruitment of an additional participant.

Regardless of the design, for a fixed number of participants, the statistical power for detecting treatment differences is increased by including the second eye. The magnitude of the increase in power depends on the correlation and whether randomization is at the participant or eye level. The details of the statistical methods for correlation adjustment are reported elsewhere.3,4

The Hybrid Design
Although many ocular diseases occur bilaterally, the extent or severity of the disease may not be the same in both eyes and thus both eyes may not be eligible for study enrollment. Therefore, requiring randomization of both eyes may significantly limit recruitment potential. Some studies use a hybrid design, which allows 1 eye to be randomized if only 1 eye is eligible but allows both eyes to be randomized if both eyes are eligible.5 The Diabetic Retinopathy Clinical Research Network has used this hybrid design in several large randomized trials. Typically, approximately 25% of participants have had 2 study eyes in these

References

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trials. The hybrid approach can lead to faster recruitment and reduced costs considering the overall number of participants is reduced compared with each participant contributing 1 eye, particularly if each eye receives a different treatment.

Beyond the Statistics
From a statistical perspective, there is little reason not to permit both eyes of the same participant to be enrolled and analyzed. However, many other aspects of study design must be considered when evaluating the appropriateness of permitting 2 study eyes. Bilateral enrollment can be logistically complicated. The timing and frequency of treatments and follow-up may not be conducive to enrolling both eyes. Depending on the type of treatment, it could also be more difficult to mask the treatment groups, potentially introducing bias for subjective outcomes. Ethically, it may be more appropriate to treat each eye with a different treatment since if one intervention is better (or harmful), the participant will have received the better (or harmful) treatment in one eye.

Assessment of efficacy and safety can be adversely impacted by the decision to include both eyes in specific situations. If an appreciable amount of crossover effect of treatment in the contralateral eye is possible, it would not be advisable to allow bilateral randomization to different treatment groups. Treatment crossover will bias the results toward showing the treatments are similar. If evaluating risk of systemic adverse events by treatment group is an objective of the study, then assignment of fellow eyes to different treatment groups also would not be advisable. For example, systemic safety analyses would have been compromised in the CATT trial if an appreciable number of participants were permitted to have one eye assigned to bevacizumab and one to ranibizumab. Similarly, effect of treatment on participant-level outcomes such as quality of life cannot be evaluated with this design.

Conclusions
In ophthalmic clinical trials, careful consideration should be given to enrollment of both eyes when possible. Because of the additional information provided by the second eye, bilateral enrollment should be permitted unless there is a reason why it is not appropriate for the study. If supported by the trial design, including and analyzing both eyes from the same participant can save time and money provided that the within-participant correlation is appropriately accounted for in the sample size and analysis.

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REFERENCES