

Posterior Capsule Opacity Evaluation in Intraocular Lens Clinical Studies

Review of Clinical Protocol Issues

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1. Exclusion Criteria

The following exclusion criteria have been proposed for all patients enrolled in PCO studies: pseudoexfoliation syndrome, uveitis, non-age-related cataracts, previous intraocular surgery or laser treatment, diabetes, glaucoma, current use of systemic steroids or topical ocular medications, previous use of cytotoxic drugs or total body irradiation and previous ocular trauma. The following exclusion criteria are proposed as intraoperative exclusions: tear in the capsulorexis, zonular dehiscence, posterior capsule rupture, vitreous loss and other unexpected surgical complications that could reasonably be assumed to affect PCO development.

The first set of exclusion criteria is designed to exclude groups of patients who have a different risk of PCO than unaffected individuals. The desire to exclude these groups is presumably because there are possible different mechanisms for PCO formation in these patients or because these patients are likely to have events that will confound the ability to assess the outcome variable. Excluding such persons means that the study results may not be generalizable to these population groups. However, if the new IOL is demonstrated to be effective in the "normal" population, it is particularly likely to be used "off label" in these other high risk patient groups, some of which form a sizable proportion of the population undergoing cataract extraction.

The guidelines should not specify a fixed rule for these exclusion criteria. There may be specific reasons for including or excluding some of these groups of patients depending on the type of IOL. In general it seems reasonable to exclude groups of patients having conditions that are infrequent and that have complications that are likely to confound the outcome, such as those with previous intraocular surgery or laser treatment that might affect visual acuity, pseudoexfoliation syndrome, previous use of cytotoxic drugs or total body irradiation and previous ocular trauma.

The decision to include or exclude persons with uveitis or steroid use may be particularly difficult. Uveitis is relatively infrequent and may be confounding both in the mechanism for PCO formation and in assessing the outcome. Perhaps specific trials should be designed for these groups of patients depending on the lens type and its presumed mechanism for lower risk of PCO. The category "current use of systemic steroids or topical ocular medications" may be difficult to define and may have particular confounding issues. Is occasional use of a steroid inhaler considered steroid use? If not, how do you define "occasional." What are topical ocular medications? Perhaps they are limited to those that cannot be obtained over the counter. If these groups are to be excluded, then the definitions need to be carefully spelled at the beginning of the trial. It would seem appropriate to include persons who use non-prescription topical medications or who use steroids only on an occasional basis.

Persons who regularly use ocular or systemic steroids may have problems that would confound the treatment assessment or limit follow-up and exclusion seems appropriate for that reason (see discussion on uveitis above).

Persons with conditions that are more frequent, such as diabetes, glaucoma and non-age-related cataracts, should be considered for inclusion in PCO studies. If included, these groups can be defined and stratified at baseline. Persons with these conditions but with serious and demonstrable pathology, such as markedly enlarged optic nerve cupping, proliferative diabetic retinopathy or diabetic macular edema might be excluded, while still including the majority of patients with these conditions. If these high risk groups of patients are included in the study, it should be stated in the study design that analyses will be done with and without these groups. The study design does not need to require that adequate numbers of such patients are included to independently assess the treatment effect in the subgroup. However, if significant interactions are present, the labeling can indicate the special risks or benefits for these groups. Strong negative trends in these groups might well indicate that “off label” use should be avoided until definitive trials can be carried out. Without including these populations in the randomized trial there is a much greater risk that they will be inappropriately treated after the trial than if there is at least some randomized trial information. If these subgroups are included in the trial the sample size should be adjusted to assure that analyses excluding these subgroups have appropriate power. Such analyses will greatly improve the ability to assess whether there are special risks or benefits in these subgroups.

The intraoperative exclusion criteria are necessary because these intraocular events could confound the assessment of the capsular outcome variable or because they may make the capsular outcome impossible to assess. If randomization occurs after the surgical complication, these patients can be excluded without any additional data collection because they were never entered into the randomized clinical trial. The trial results then relate to uncomplicated cataract surgery. However, if randomization occurs prior to the surgical complication then an accounting for these patients is required. Their results can be excluded from certain analyses, but they need to be accounted for in other analyses. For example, if a new intraocular lens had characteristics that made PCO less frequent, but also had characteristics that led to more capsular rupture, it would be important to capture this information to assess the risk/benefit ratio of this new lens. The study protocol needs to assure that once a patient is randomized there will be an accounting for this patient in all analyses (for some analyses, such as proportion with PCO opacity, this would mean that the patient was accounted for as “non-assessable”). Other analyses can be performed to demonstrate any differences in complication rates between the lenses studied. There should be no opportunity for the clinician or others to exclude a patient because of a complication after randomization.

2. Time Points for PCO Assessment

The FDA guidance for IOL studies suggests scheduled follow-up at day 1, week 1, month 1, month 4-6, and years 1, 2, and 3. This schedule has worked well for IOL studies in the past and should serve as the guideline for future IOL studies. Assessing PCO at all these visits

would be superfluous. Because the overall event rate for PCO at one year is around 10%, assessment at yearly visits is appropriate. Assessment at the 4-6 month visit is likely to be worthwhile and individual investigators should consider this. If early assessment is not performed, then mechanisms must be in place to document the severity of PCO prior to any surgical intervention. Lack of documentation of PCO will lead to the presumption of possible selection bias and could make a study's results uninterpretable if there are a sizable number of such events. This is especially true if there is an imbalance by treatment group.

Long-term follow-up is desirable because most surgical interventions will occur after one year. I would think that the minimum duration for a study would be 1 year, with at least some 2-year data available.

3. Standardization of Techniques

It is critical that the surgical techniques do not differ in important ways between IOL groups. If the surgical techniques are different for "lens A" than "lens B" it will be impossible to determine if differences in results are due to the lens or to the surgical technique (including postoperative medications). Standardization within studies will be difficult; standardization across studies will be very difficult. Because of this, it seems inappropriate to compare results from one trial with historical results from other trials. There are almost certainly important confounders between trials. This includes both treatment related factors and outcome assessment factors.

Outcome assessment should be standardized and, to the extent possible, masked. Outcome measures should be reliable and reproducible so that investigators can be assured of finding a difference when one exists. Assessment of outcome measures should be appropriately masked so that reviewers can be assured that they are witnessing a difference that is due to treatment effect rather than bias.

4. Nd:YAG Capsulotomy Rate as an Outcome Variable

There is ample evidence in the literature that Nd:YAG capsulotomy rates vary considerably by surgeon and region of the country. This indicates that there is considerable room for investigator bias in the assessment of PCO severe enough to require Nd:YAG capsulotomy. If complete masking of investigators to the lens type is not possible then objective criteria for "a clinically important PCO" is critical to allow for assessment of trial results. If the study does not have such objective criteria, the investigator must be able to fully document that the trial is masked; if not, reviewers should assume that bias in outcome assessment may have affected the results. The definition of "a clinically important PCO" should include visual function assessments in addition to photographic assessments of PCO. If visual function assessments, it is important to establish a baseline for the post-operative visual function parameter. It could be defined as the better of the measurements (or the average of the measurements) for that parameter at the 1-month or 4-6 month visits. For best corrected visual acuity (with or without glare), a two-line decrease on a logMAR chart would be the minimum threshold for a clinically important decrease. Contrast sensitivity measurements and subjective assessments (such as the NEI-VFQ or an enhanced version of the

questionnaire) can be used to help document the functional effect of a photographically documented PCO, but reliable levels for clinically important decreases in these measurements are not available. Currently, there are no convincing data that lens opacity measurements alone are an adequate surrogate for either clinically important PCO or the need for Nd:YAG capsulotomy. Therefore, until there are such data, some visual function data will be necessary. These data are most likely to come from careful assessment of reduced best-corrected visual acuity, either with or without glare. Only after there is documentation of a clear association between decreased visual acuity and increased PCO, as graded or measured from red reflex photographs or other methods, can a photographic assessment serve as a surrogate. This would be a useful step for future clinical trials of PCO, because confounding of visual function with other diseases will be less of a problem. However, even if there is an agreed upon surrogate, visual function measures in all IOL trials will be necessary, both to confirm the objective finding and to help rule out unknown adverse side effects related the new IOL.



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