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Intraocular Lenses for the Treatment of Age-Related Cataracts

An Evidence-Based Analysis

Presented to the Ontario Health Technology Advisory Committee in June, 2009

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practising medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

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Table of Contents

List of Tables & Figures

List of Abbreviations

AUC	Area under the curve
BCDVA	Best corrected distance visual acuity
BCNVA	Best corrected near visual acuity
BCVA	Best corrected visual acuity
BDCUNVA	Best distance corrected unaided near visual acuity
CI	Confidence interval(s)
DCNVA	Distance corrected near visual acuity
HRQL	Health related quality of life
IOL	Intraocular lens
MAS	Medical Advisory Secretariat
Nd:YAG	Neodymium:yttrium-aluminum-garnet
PCO	Posterior capsule opacification
PMMA	Polymethyl methacrylate
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SROC	Summary receiver operating characteristic
UCVA	Uncorrected visual acuity
VA	Visual acuity

Executive Summary

Objective

The objective of the report is to examine the comparative effectiveness and cost-effectiveness of various intraocular lenses (IOLs) for the treatment of age-related cataracts.

Clinical Need: Target Population and Condition

A cataract is a hardening and clouding of the normally transparent crystalline lens that may result in a progressive loss of vision depending on its size, location and density. The condition is typically bilateral, seriously compromises visual acuity and contrast sensitivity and increases glare. Cataracts can also affect people at any age, however, they usually occur as a part of the natural aging process. The occurrence of cataracts increases with age from about 12% at age 50 years, to 60% at age 70. In general, approximately 50% of people 65 year of age or older have cataracts. Mild cataracts can be treated with a change in prescription glasses, while more serious symptoms are treated by surgical removal of the cataract and implantation of an IOL.

In Ontario, the estimated prevalence of cataracts increased from 697,000 in 1992 to 947,000 in 2004 (35.9% increase, 2.4% annual increase). The number of cataract surgeries per 1,000 individuals at risk of cataract increased from 64.6 in 1992 to 140.4 in 1997 (61.9% increase, 10.1% annual increase) and continued to steadily increase to 115.7 in 2004 (10.7% increase, 5.2% increase per year).

Description of Technology/Therapy

IOLs are classified either as monofocal, multifocal, or accommodative. Traditionally, monofocal (i.e.. fixed focusing power) IOLs are available as replacement lenses but their implantation can cause a loss of the eye's accommodative capability (which allows variable focusing). Patients thus usually require eyeglasses after surgery for reading and near vision tasks. Multifocal IOLs aim to improve near and distant vision and obviate the need for glasses. Potential disadvantages include reduced contrast sensitivity, halos around lights and glare. Accommodating IOLs are designed to move with ciliary body contraction during accommodation and, therefore, offer a continuous range of vision (i.e. near, intermediate and distant vision) without the need for glasses. Purported advantages over multifocal IOLs include the avoidance of haloes and no reduction in contrast sensitivity.

Polymethyl methacrylate (PMMA) was the first material used in the fabrication of IOLs and has inherent ultraviolet blocking abilities. PMMA IOLs are inflexible, however, and require a larger incision for implantation compared with newer foldable silicone (hydrophobic) and acrylic (hydrophobic or hydrophilic) lenses. IOLs can be further sub-classified as being either aspheric or spheric, blue/violet filtered or non-filtered or 1- or 3-piece.

Methods of Evidence-Based Analysis

A literature search was conducted from January 2003 to January 2009 that included OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), The Cochrane Library, and the International Agency for Health Technology Assessment/Centre for Review and Dissemination.

Inclusion Criteria

- adult patients with age-related cataracts
- systematic reviews, randomized controlled trials (RCTs)
- primary outcomes: distance visual acuity (best corrected distance visual acuity), near visual acuity (best distance corrected near visual acuity)
- secondary outcomes: contrast sensitivity, depth of field, glare, quality of life, visual function, spectacle dependence, posterior capsule opacification.

Exclusion Criteria

- studies with fewer than 20 eyes
- IOLs for non-age related cataracts
- IOLs for presbyopia
- studies with a mean follow-up <6months
- studies reporting insufficient data for analysis

Comparisons of Interest

The primary comparison of interest was accommodative vs. multifocal vs. monofocal lenses.

Secondary comparisons of interest included:

- tinted vs. non-tinted lenses
- aspheric vs. spheric lenses
- multipiece vs. single piece lenses
- biomaterial A (e.g. acrylic) vs. biomaterial B (e.g. silicone) lenses
- sharp vs. round edged lenses

The quality of the studies was examined according to the GRADE Working Group criteria for grading quality of evidence for interventional procedures.

Summary of Findings

The conclusions of the systematic review of IOLs for age-related cataracts are summarized in Executive Summary Table 1.

Considerations for the Ontario Health System

- Procedures for crystalline lens removal and IOL insertion are insured and listed in the Ontario Schedule of Benefits.
- If a particular lens is determined to be medically necessary for a patient, the cost of the lens is covered by the hospital budget. If the patient chooses a lens that has enhanced features, then the hospital may choose to charge an additional amount above the cost of the usual lens offered.
- An IOL manufacturer stated that monofocal lenses comprise approximately 95% of IOL sales in Ontario and premium lenses (e.g., multifocal/accomodative) consist of about 5% of IOL sales.
- A medical consultant stated that all types of lenses are currently being used in Ontario (e.g., multifocal, monofocal, accommodative, tinted, nontinted, spheric, and aspheric). Nonfoldable lenses, rarely used in routine cases, are primarily used for complicated cataract implantation situations.

ES Table 1: Conclusions for the Systematic Review of IOLs for Age-Related Cataracts

Comparison	Conclusion	GRADE Quality
Multifocal vs. monofocal	<u>Objective Outcomes</u>	
	Significant improvement in BDCUNVA	moderate
	No significant difference in BCDVA	moderate
	Inconclusive evidence for contrast sensitivity	low
	Inconclusive evidence for glare	very low
	<u>Subjective Outcomes</u>	
	Inconclusive evidence for visual satisfaction	low
	Significant increase in glare/halos	low/moderate
	Significant increase in freedom from spectacles	low/moderate
Accommodative vs. multifocal/ monofocal	Inconclusive due to Insufficient limited evidence for any effectiveness outcome	very low
Hydrophilic acrylic vs. other materials (hydrophobic acrylic, silicone)	Significant increase in PCO score	Low
Sharp edged compared to round edged	Significant reduction in PCO score	Low
One piece compared to three piece	No significant difference in PCO score	low
Hydrophobic acrylic compared to silicone	No significant difference in PCO score	moderate
Aspherical modified prolate anterior surface compared to spherical	No significant difference in VA	very low
	Significant reduction in contrast sensitivity	very low
Blue light filtering compared to non blue-light filtering	No significant difference in BCDVA	low
	No significant difference in contrast sensitivity	low
	No significant difference in HRQL	high/moderate

BCDVA refers to best corrected distance visual acuity; BDCUNVA, best distance corrected unaided near visual acuity; HRQL, health related quality of life; PCO, posterior capsule opacification; VA, visual acuity.

Background

Objective of Analysis

The objective of the report is to examine the comparative effectiveness and cost-effectiveness of various intraocular lenses (IOLs) for the treatment of age-related cataracts.

Clinical Need and Target Population

A cataract is a hardening and clouding of the normally transparent crystalline lens that may result in a progressive loss of vision depending on its size, location and density. The condition is typically bilateral, seriously compromises visual acuity and contrast sensitivity and increases glare. (1) Cataracts can also affect people at any age, however, they usually occur as a part of the natural aging process. The occurrence of cataracts increases with age from about 12% at age 50 years, to 60% at age 70. (1) In general, approximately 50% of people 65 year of age or older have cataracts. Mild cataracts can be treated with a change in prescription glasses, while more serious symptoms are treated by surgical removal of the cataract and implantation of an IOL. The most common cataract procedure is an extracapsular lens removal with implantation of a posterior chamber (behind the iris) IOL within the capsular bag.

In Ontario, the estimated prevalence of cataracts increased from 697,000 in 1992 to 947,000 in 2004 (35.9% increase, 2.4% annual increase). (2) The number of cataract surgeries per 1,000 individuals at risk of cataract increased from 64.6 in 1992 to 140.4 in 1997 (61.9% increase, 10.1% annual increase) and continued to steadily increase to 115.7 in 2004 (10.7% increase, 5.2% increase per year). (2) Another Ontario study showed that the number of cataract surgeries performed on patients over 65 more than doubled from 44,000 to 90,000 over a 10 year period (1994 to 2005), accounting for approximately 81% of all cataract surgeries in Ontario. For 2004 to 2005, rates including all cataract surgeries ranged from 4,300 to 6,600 cataract surgeries per 100,000 residents aged 65 or older. (3)

IOLs

IOL implants restore optical focusing power lost by removal of the clouded natural crystalline lens. The devices can be classified as monofocal, multifocal or accommodative. (4) Traditionally, monofocal (e.g., fixed focusing power) IOLs are available as replacement lenses but their implantation can cause a loss of the eye's accommodative capability (which allows variable focusing). Patients thus usually require eyeglasses after surgery for reading and near vision tasks. (4) Multifocal IOLs aim to improve near and distant vision and obviate the need for glasses. Potential disadvantages include reduced contrast sensitivity, halos around lights and glare. Accommodating IOLs are designed to move with ciliary body contraction during accommodation and, therefore, offer a continuous range of vision (i.e. near, intermediate and distant vision) without the need for glasses. Purported advantages over multifocal IOLs include the avoidance of haloes and no reduction in contrast sensitivity. (5)

Accommodative lenses can be ***single*** optic or ***dual*** optic (6): ***Single optic*** lenses have one focal point, but they act as if they were multifocal. They were designed with a hinge similar to the mechanics of the eye's natural lens. Using the eye's muscles, the single focal point of an accommodative IOL can shift to bring objects at varying distances into focus. ***Dual optic*** devices have a fixed anterior optic and a second posterior lens that moves anteriorly towards the anterior lens.

Monovision is also an option for some patients requiring IOLs. Patients receive an IOL where one eye is fitted for distance vision and the other eye is fitted for near vision. Patients who have in the past had monovision contact lenses (one eye for distance and one eye for near) may prefer these.

Materials and Design

Polymethyl methacrylate (PMMA) was the first material was used in the fabrication of IOLs and has inherent ultraviolet blocking abilities. (7) PMMA IOLs are inflexible, however, and require a larger incision for implantation (5-7 mm requiring sutures) compared with newer foldable silicone (hydrophobic) and acrylic (hydrophobic or hydrophilic) lenses (2.8-3.5 mm and not requiring sutures). IOLs can be further subclassified as being either aspheric or spheric, blue/violet filtered, or non-filtered. Tables 1 and 2 summarize the subclassifications of IOLs.

Table 1: Classification of IOLs for Cataracts

Classification	Description	Material
Rigid	Large incision requiring sutures.	PMMA
Foldable	Smaller incision, no sutures required. Potentially less early postoperative inflammation and reduced surgically induced astigmatism. Implanted using either forceps or an injector.	Silicone (hydrophobic) Hydrophobic acrylic Hydrophilic acrylic (hydrogel) Collagen/hydroxyl ethyl methacrylate copolymer

Table 2: Subclassifications of IOLs for Cataracts

Subclassification	Description
Blue or violet filtering	May protect against macular toxicity and provide retinal protection.
Spherical or aspherical	Traditional spheric design induces spherical aberration that when added to positive corneal spherical aberration can reduce contrast sensitivity. Aspheric IOLs with negative spherical aberration may improve contrast sensitivity and quality of vision (including night driving). Aspheric lenses currently available each correct or reduce a different amount of spherical aberration. Optimal amount unclear.
1 or 3 piece lens	1 piece lens is manufactured from a single piece of material. 3 piece is made of the optic (either silicone or acrylic) and 2 attached haptics (the arms of the lens, often made of prolene)

Complications

An 'after cataract', also called a posterior capsular opacification (PCO), is a cloudy membrane that sometimes forms on the membrane behind the IOL after cataract surgery. Although the membrane is untouched during the surgery, afterward lens epithelial cells may migrate along the posterior capsule leading to opacification. Symptoms of an after cataract include blurred vision and are similar to those of a normal cataract. Patients may also see streaks of light, halos, or excessive glare. Through the 1980s and 1990s, the 5 year incidence of PCO had been reported to be 28.4% (8), however, this rate has varied considerably with suggestions that the incidence has now decreased. (9)

Neodymium:yttrium-aluminum-garnet (ND:YAG) laser treatment for PCO involves cutting open the clouded posterior capsule allowing light to transmit normally. (7) This treatment can produce complications such as an increase in intraocular pressure, damage to the IOLs, ocular inflammation, cystoid macular edema, and retinal detachment.

Goals of IOL Insertion

In a population-based, cross-sectional study of people ≥65 years, the Salisbury Eye Evaluation (SEE) study indicated that visual acuity, contrast sensitivity, glare sensitivity, bilateral acuity and visual fields were risk factors for self-reported difficulty with everyday activities. (10) Though the study did not necessarily focus on patients with cataracts, it provides insight into outcomes that are important to an elderly population. In a separate study to determine the visual measures most predictive of falls in community-dwelling seniors, Lord et al. (11) found that multiple fallers had impaired depth perception, contrast sensitivity and low contrast visual acuity. Thus, although there is no single outcome measure that summarizes the effectiveness of an IOL, visual acuity and contrast sensitivity, are amongst the most commonly reported.

Visual Acuity

Visual acuity is a quantitative measure of the ability to resolve fine detail and the most common clinical measurement of visual function because it is easy to assess (i.e. using the Snellen chart) and because even small amounts of refractive error produce marked declines in acuity test performance. (10) The test also corresponds well with the normal daily activities that a person can handle and can evaluate their ability to do them. It should be noted, however, that those people with colour blindness, reduced contrast sensitivity or an inability to track fast moving objects, may still have 'normal visual acuity' as this does not necessarily correspond to 'normal vision'.

There are different classifications of visual acuity with the following outcomes being commonly reported:

1. Best corrected near visual acuity: near visual acuity with the aid of spectacles.
2. Uncorrected near visual acuity: near visual acuity without the aid of any spectacles.
3. Best corrected distance visual acuity: distance visual acuity with the aid of spectacles.
4. Uncorrected distance visual acuity: distance visual acuity without the aid of any spectacles.
5. Best distance corrected near visual acuity: near vision that would be obtained without the use of any additional reading spectacles when any distance refractive error is corrected.

According to an expert whom the Medical Advisory Secretariat consulted, best distance corrected unaided near visual acuity (BDCUNVA) is an important outcome when measuring the effectiveness of multifocal lenses. This outcome is the near vision obtained, after correcting any distance refractive error, without the use of any additional reading spectacles. However, since monofocal IOLs do not correct for near vision, best corrected distance acuity (BCDA) is the best overall measure of visual outcome. Uncorrected acuity would be heavily dependent on preoperative biometric accuracy as well as individual patient preference. For example, some life long myopic patients prefer to continue to wear distance spectacles postoperatively and not use spectacles for reading. Also, in unilateral cataract cases, it is preferred to keep both eyes with similar postoperative refractions.

Contrast sensitivity

Contrast sensitivity determines the lowest contrast level that can be detected by a patient for a given size target. It varies between individuals and usually peaks at age 20, then declining with age. Normally, a range of targets is used to assess contrast sensitivity, but unlike acuity which measures size alone, contrast sensitivity measures size and contrast.

Typically, there is a decrease in contrast sensitivity for intermediate and high spatial frequencies that becomes more pronounced with age. (12) For example, with advancing age, increased contrast is needed to discriminate faces. (13) Owsley et al. found that age differences in contrast sensitivity were not eliminated when young subjects viewed objects under conditions of simulated ocular aging. (12) These results indicated that the age difference in contrast sensitivity represented an age-related change in the neural rather than optical characteristics of the visual process.

A person with poor contrast sensitivity (e.g. due to cataracts) may have vision difficulties such as:

- Trouble seeing in rain, fog or at dusk/night.
- Missing facial gestures
- Tripping when using stairs or walking over curbs
- Inability to discriminate objects in a cluttered environment

Ontario Schedule of Benefits

Procedures for crystalline lens removal and IOL insertion are insured and are listed in the Ontario Schedule of Benefits. (14) If a particular lens is determined to be medically necessary for a patient, the cost of the lens is covered by the hospital budget. If the patient chooses a lens with enhanced features, then hospitals may choose to charge an additional amount above the cost of the usual lens offered.

Regulatory Status

At least 38 IOLs are licensed by Health Canada for the treatment of cataracts. These include monofocal, multifocal, and accommodating lenses with the various subclassifications summarized in Table 2 (page 12).

Existing Guidelines

Currently existing guidelines for the use of IOLs in the treatment of age-related cataracts are limited to those issued by the American Academy of Ophthalmology, which state:

"The surgeon should have access to a variety of lens styles to select an appropriate IOL for an individual patient. Variations in the preoperative state of the eye, the surgical technique, patient expectation and surgeon experience and preference affect the decision." (9)

"Whether the improvement in near unaided acuity outweighs the adverse effects of multifocal IOLs will vary among the patients, with motivation to achieve spectacle independence likely to be the definitive factor." (9)

Evidence-Based Analysis (Methods)

Research Question(s)

What is the comparative effectiveness and cost-effectiveness of using the various IOLs for the treatment of age-related cataracts?

Literature Search

A literature search was conducted from January 2003 to January 2009 that included OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), The Cochrane Library, and the International Agency for Health Technology Assessment/Centre for Review and Dissemination. Details of the literature search strategy can be found in Appendix 1.

Inclusion Criteria

- adult patients with age-related cataracts
- systematic reviews, randomized controlled trials (RCTs)
- primary outcomes: distance visual acuity (best corrected distance visual acuity), near visual acuity (best distance corrected near visual acuity)
- secondary outcomes: contrast sensitivity, depth of field, glare, quality of life, visual function, spectacle dependence, posterior capsule opacification.

Exclusion Criteria

- studies with fewer than 20 eyes tested
- IOLs for non-age related cataracts
- IOLs for presbyopia
- studies with a mean follow-up of <6 months
- studies reporting insufficient data for analysis

Comparisons of Interest

The primary comparison of interest is accommodative vs. multifocal vs. monofocal lenses.

Secondary comparisons of interest include:

- tinted vs. nontinted
- aspheric vs. spheric
- multipiece vs. single piece
- biomaterial A (e.g. acrylic) vs. biomaterial B (e.g. silicone)
- sharp vs. round edged

Assessment of Quality of Evidence

The quality of the studies was examined according to the GRADE Working Group criteria for interventions. (15)

Results of Evidence-Based Analysis

The literature search identified 739 citations, of which 3 were systematic reviews and nine were studies that were published after the literature search cut-off dates in the systematic reviews. The quality of the literature is presented below in Table 3.

Table 3: Quality of Evidence of Included Studies

Study Design	Level of Evidence*	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	3 systematic reviews 8 RCTs
Large RCT unpublished but reported to an international scientific meeting	1(g)†	0
Small RCT	2	1
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

g refers to grey literature; RCT, randomized controlled trial.

*For each included study, levels of evidence were assigned according to a ranking system based on a hierarchy proposed by Goodman. (16) An additional designation “g” was added for preliminary reports of studies that have been presented at international scientific meetings.

Summary of Existing Evidence

Descriptive Systematic Reviews from International Health Technology Assessment (HTA) Organizations

Three descriptive systematic reviews from Canada, Australia and the United Kingdom on accommodative lenses were identified in the literature search. (6;17;18) Table 4 summarizes the systematic reviews by date, country, organization, and overall conclusion.

Table 4: Conclusions of Descriptive Systematic Reviews from International HTA Organizations

Publication Date	Country	Organization	Overall Conclusion
August 2004	Australia	Australia and New Zealand Horizon Scanning Network (17)	▪ Limited case series evidence available for accommodative lenses and the reported results lack standardization.
August 2006	Canada	Canadian Agency for Drugs and Technologies in Health (6)	▪ Limited evidence suggests accommodative IOLs provide better near vision than monofocal IOLs, but not better than multifocal IOLs.
February 2007	United Kingdom	National Institute for Health and Clinical Excellence (18)	▪ Evidence of short-term efficacy in correcting visual acuity but, inadequate evidence that the procedure achieves accommodation. ▪ Procedure should not be used without special arrangement s for consent and for audit or research. ▪ No major safety concerns associated with accommodating lenses.

Meta-Analyses

IOL Materials and Design

Three meta-analyses (7;19;20) of the effect of IOLs on the development of PCO were identified (details of each are supplied in Appendix 2). The most recent systematic review from July 2007 on PCO was a Cochrane review by Findl et al. (19) As there were different types of PCO scores used in the primary studies within this review, Findl et al. converted the values to a 'common score' between 0 (no PCO) to 100 (maximum PCO score) in order to compare the values in forest plots. Further details of the scoring system were not included in their report.

Summary statistics were calculated, but there was statistical heterogeneity or 'no studies available' for analysis in many subgroups (e.g. hydrophilic acrylic lenses vs. silicone lenses).

The main findings of the Cochrane review (19) showed:

- There was a significantly higher PCO score (mean difference 12.39; 95% CI 9.82 to 14.95), and Nd:YAG capsulotomy rate (OR 8.37; 95% CI 3.74 to 20.36) in hydrophilic acrylic IOLs compared to other materials (see Table 5); however, some studies compared sharp edge to round edge IOLs.
- There was a significantly lower PCO score (mean difference -8.65; 95% CI -10.72 to -6.59; statistically significant heterogeneity) and Nd:YAG rate (OR 0.19; 95% CI 0.11 to 0.35) in sharp edged IOLs compared to round edged IOLs of any material (see Table 6).
- There was no significant difference in PCO scores or Nd:YAG rates between 1 piece and 3 piece IOLs (see Table 7); however, data was limited to acrylic and PMMA IOLs

Table 5: Meta-Analytic Results for Comparisons of IOL Materials from Findl et al.

	PMMA vs. Silicone	PMMA vs. Acrylic	PMMA vs. Hydrophilic Acrylic	Acrylic vs. Silicone	Acrylic vs. Hydrophilic Acrylic	Silicone vs. Hydrophilic Acrylic	Hydrophilic Acrylic vs. All Other Materials
BCDVA*	-0.11 (-0.16 to -0.06)	No study	0.06 (-0.02 to 0.14)	2 studies‡	0.10 (0.05 to 0.16)	No study	-0.09 (-0.13 to -0.06)
	1 study		1 study		3 studies		4 studies
PCO score*	4 studies‡	3 studies‡	-17.0 (-27.69 to -6.31)	0.00 (-0.06 to 0.05)	2 studies‡	No study	12.39 (9.82 to 14.95)
			2 studies	5 studies			5 studies
Nd:YAG rate†	6 studies‡	7.19 (2.72 to 18.96)	0.43 (0.11 to 1.69)	0.56 (0.25 to 1.28)	0.18 (0.02 to 1.38)	No study	8.37 (3.74 to 20.36)
		2 studies	1 study	7 studies	4 studies		4 studies

* Mean difference (95% CI)

† Odds ratio (95% CI)

‡ Significant statistical heterogeneity

Table 6: Meta-Analytic Results for Comparisons of IOL Designs (Round and Sharp Edges) from Findl et al.

	Sharp vs. Round Edge PMMA	Sharp vs. Round Edge Acrylic	Sharp vs. Round Edge Silicone	Sharp vs. Round Edge Any Material
BCDVA*	-0.05 (-0.18 to 0.08)	0.06 (0.01 to 0.12)	2 studies‡	7 studies‡
	1 study	2 studies		
PCO score*	-28.3 (-40.95 to -15.65)	3 studies‡	5 studies‡	12 studies‡
	1 study			
Nd:YAG rate†	0.24 (0.07 to 0.85)	0.07 (0.02 to 0.32)	0.18 (0.04 to 0.72)	0.19 (0.11 to 0.35)
	1 study	2 studies	4 studies	11 studies

* Mean difference (95% CI)

† Odds ratio (95% CI)

‡ Significant statistical heterogeneity

Table 7: Meta-Analytic Results for Comparisons of IOL Designs (One and Three Piece) from the Cochrane Systematic Review by Findl et al.

	1 Piece vs. 3 Piece Acrylic	1 Piece vs. 3 Piece PMMA	1 Piece vs. 3 Piece Silicone
BCDVA*	0.00 (-0.04 to 0.04)	No study	No study
	2 studies		
PCO score*	Not reported	No study	No study
	5 studies		
Nd:YAG rate†	0.48 (0.02 to 10.24)	0.94 (0.59 to 1.51)	No study
	3 studies	1 study	

* Mean difference (95% CI)
† Odds ratio (95% CI) ‡ Significant statistical heterogeneity

Multifocal vs. Monofocal IOLs

The only systematic review examining the efficacy of multifocal versus monofocal IOLs was a Cochrane review by Leyland and Pringle in which ten trials were identified. (21) The primary outcomes were distance and near visual acuity and spectacle dependence. Overall, there was significant heterogeneity in how outcomes were reported.

Distance Visual Acuity

- ***Best corrected distance visual acuity*** was similar between multifocal and monofocal IOLs (SMD 0.15; 95% CI -0.01 to 0.31).

Near Visual Acuity

- ***Best distance corrected unaided near visual acuity*** is an important outcome in the assessment of multifocal efficacy, but it was reported in a manner that made comparison between studies difficult.
- For studies, reading distances differed and it is unclear whether the reported print size had been corrected for reading distance to allow near acuity to be calculated.
- Two studies explicitly calculated ***best distance corrected unaided near visual acuity*** after bilateral multifocal versus monofocal implantation. (22;23) Both studies used logMAR reading charts, calculated acuity with a correction for reading distance and had a high Jadad score of methodological quality (5 out of 5). The first study (23) reported significantly improved unaided near visual acuity with multifocal IOLs while the other study (22) found no significant difference. The latter, however, by Leyland et al. (22) did not accrue the number of patients stipulated in the sample size calculation, thereby allowing the possibility of a type 2 error. Furthermore, the study included people ≥18 years of age and thus not all included patients had age-related cataracts.
- Javitt et al. (23) found a significant difference in ***best distance corrected unaided near visual acuity*** between patients who had received multifocal IOLs compared to monofocal IOLs [mean visual acuity 0.14 (SD: 0.14) logMAR versus 0.35 (SD: 0.18) logMAR; p=0.0001].

Depth of Field (Defocus Test)

- Four of the 10 studies measured depth of field. A meta-analysis was not conducted since the outcomes and methods were not similar across studies.

- All studies described better acuity with lens defocus from the distance correction with the multifocal IOL.
- Statistical (or clinical) significance was not discussed in the Cochrane review.

Contrast Sensitivity

- Seven studies reported this outcome with data presented differently in each (e.g. visual acuity at different contrast levels; difference between high contrast and lower contrast acuity), precluding meta-analysis.
- All seven studies reported lower contrast sensitivity with the multifocal IOL.
- Statistical (or clinical) significance was not discussed in the Cochrane review.

Glare

- Two studies reported numerical results for glare using a Brightness Acuity Tester.
- One study found that acuity decreased as glare increased, but there was no significant difference between the lenses. (24) The other study found no significant decrease in acuity with glare for either type of lens. (22)
- Subjective outcomes (satisfaction with vision, glare and spectacle dependence) were also reported in the Cochrane review.

Satisfaction with Vision

- Seven of the 10 included studies involved patients with surgery in one eye only. Unilateral studies allow measurement on uni-ocular outcomes such as visual acuity but are of limited use when attempting to measure the effect of multifocal IOLs on quality of life, especially where the fellow eye has good vision.
- Overall, the studies could not be combined for meta-analysis.
- Validated instruments were used by four studies, of which two (assessing bilateral outcomes) used the same questionnaire.
  - Javitt et al. (23) found a small but statistically significant increase in overall visual satisfaction with the multifocal (mean score 8.4) compared to the monofocal lens (mean score 7.9). Mean overall visual satisfaction ranged from 0 to 10; 0 being worst and 10 being best.
  - Leyland et al. (22) found no difference in overall subjective satisfaction between groups (median score for both groups was 8); however, since the study was not powered to examine this outcome, the non-significant result may be a type 2 error.

Spectacle Dependence

In all 10 studies, most multifocal IOL patients still used spectacles for some tasks (e.g. small print).

- Independence from spectacles was found in:
  - 26% to 47% of multifocal IOL patients
  - 1% to 11% of monofocal IOL patients
- A summary statistic was calculated for eight studies. Independence of spectacles was achieved more frequently with multifocal than monofocal IOLs (OR: 0.17; 95% CI 0.12 to 0.24).

Glare

- Four studies reported the proportion of patients with glare and halos.
- Symptoms were significantly less frequent in the monofocal group (OR 3.55; 95% CI 2.11 to 5.96).

Complications

- Complications are expected to be similar for multifocal and monofocal IOLs as they are similar in all but the design of the optics and require no modifications to surgical technique.
- Pre- and post-operative complications were reported in five studies. The incidence of complications was reported to be low and similar in the multifocal and monofocal IOL groups.

Accommodating IOLs

Findl and Leydolt (25) reviewed studies that reported visual acuity after accommodating lens implantation. Of the three types of accommodative lenses included in the review, only the AT-45 Cyrstalens is licensed by Health Canada; therefore, only results pertaining to that IOL are discussed. No RCTs were identified by Findl and Leydolt. (25) The results of six nonrandomized studies (26-31) included in the review by Findl and Leydolt are shown in Appendix 2. Overall, Findl and Leydolt concluded that there were large discrepancies in VA data.

The overall limitation to the review by Findl and Leydolt was a lack of stringent inclusion criteria. For example, the objective of one of the study by Alio et al. (27) was to "investigate potential for near vision restoration using three IOL models (two multifocal and an accommodative) after presbyopic lens exchange." Patients did not require cataracts for IOL implantation. Furthermore, some patients in each study group had laser in situ keratomileusis (LASIK) 6 months after IOL implantation. VA results were reported up to 1 year. Alio et al. did not report sample size calculations. A summary of the limitations of the individual studies included in the review by Findl and Leydolt is displayed in Table 8.

Studies Published After Literature Search Cut-off Dates in Systematic Reviews

IOL Materials and Design

Four prospective randomized studies that had posterior capsule opacification as the primary endpoint were identified (32-35), of which two (and possibly three) were updates of studies that were included in the Cochrane review. (19) Detailed results of the four studies are supplied in Appendix 3.

Posterior opacification was the primary outcome for one study (32) comparing hydrophilic versus hydrophobic sharp edged IOLs; one study (33) comparing acrylic versus silicone IOLs of the same optic design and haptics; and two studies (34;35) comparing 1- and 3-piece haptic hydrophobic acrylic IOLs (the results of each are shown in Table 9). Overall, results were consistent with the previous Cochrane review. There was significantly less PCO for hydrophobic compared to hydrophilic sharp edged IOLs, but no significant difference in PCO between 1- and 3- piece IOLs. One study compared acrylic versus silicone IOLs of the same optic and haptic designs and found no significant difference in PCO.

Table 8: Limitations of Studies Included in Findl and Leydolt, 2007

Study	Objective	Limitation
Alio et al. (27)	▪ To investigate potential for near vision restoration using 3 IOL models (2 multifocal IOLs and 1 accommodative IOL) after presbyopic lens exchange.	▪ Patients did not require cataracts for IOL implantation. ▪ Some patients in each study group had laser *in situ* keratomileusis (LASIK) 6 months after IOL implantation. ▪ No sample size calculation reported.
Cumming et al. (28)	▪ To evaluate clinical outcomes in cataract patients after implantation of an accommodating IOL.	▪ Non-comparative case series feasibility study. ▪ Follow-up to 6 months.
Cumming et al. (29)	▪ To evaluate 12 month US phase 2 clinical trial results of the AT-45 accommodative lens in patients having cataract extraction.	▪ Conducted a substudy to determine: 1) whether the accommodative lens is associated with any decrease in contrast sensitivity or increase in glare and 2) uncorrected near VA when compared with a standard monofocal IOL. ▪ VA results indicated that the difference between the lens groups for percentage of eyes that were 20/40 or better was nonsignificant (p=0.05). The study was not designed or statistically powered to assess VA.
Koeppl et al. (26)	▪ To measure the shift of an accommodating plate haptic IOL along the visual axis induced by ciliary muscle contraction after application of pilocarpine.	▪ Study powered to assess pilocarpine induced IOL movement in 'polished' versus 'unpolished' anterior capsules.
Marchini et al. (30)	▪ To document ciliary body constriction and movement with the AT-45 accommodative IOL using ultrasound biomicroscopy.	▪ Not all patients specifically had age-related cataracts. ▪ Non-comparative case series.
Buratto et al. (31)	▪ To compare uncorrected near and distance visual acuity in 2 types of accommodative IOLs (including AT-45).	▪ No sample size calculation. ▪ Not specifically age related-cataracts. ▪ Analysis limited to descriptive statistics.

Table 9: Studies Comparing IOL Material and Design with PCO as the Primary Outcome (Published after Cochrane Review)

Comparison	Results	Comments
Hydrophobic vs. hydrophilic sharp edged IOL (32) Update of study in Cochrane review	▪ At 2 years, significantly less PCO (% area and severity score) for hydrophobic compared to hydrophilic sharp edged IOLs. ▪ Significant difference in BCVA.	▪ PCO area and severity calculated using POCOman software ▪ No sample size calculation. ▪ Clinical significance not discussed. ▪ Not reported if near or distant VA was assessed.
Acrylic vs. silicone IOL of same optic and haptic designs (33)	▪ At 3 years, no significant difference in PCO (or BCVA – unclear if near or distant).	▪ PCO measured using Scheimpflug videophotography. ▪ Post hoc power calculation showed 99% power to detect clinically meaningful PCO difference. ▪ Not reported if near or distant VA was assessed.
1-piece vs. 3-piece hydrophobic acrylic IOL (34) Update of study in Cochrane review	▪ At 5 years, no significant difference in mean PCO score (or BCDVA).	▪ PCO score (0 to 10) measured using image analysis software developed by the authors. ▪ Post hoc power calculation showed that a clinically relevant difference of PCO score of 1 (i.e., 10%) could be calculated with a 90% power. ▪ Results by Sacu et al. showed a slight but significant difference with more PCO in 1-piece compared with 3-piece IOL eyes 1 year after surgery. This was not seen 2 and 5 years after surgery.
1 piece vs. 3 piece hydrophobic acrylic IOL (35) Update of study in Cochrane review	▪ At 2 years, no significant difference in PCO density score (or BCVA).	▪ PCO measured using a photographic image analysis system (EPCO 2000 program) developed by one of the authors. ▪ No sample size or post-hoc power calculation. ▪ Not reported if near or distant VA was assessed. ▪ Results in 2004 showed a slight but significant difference with more PCO in 1-piece vs. 3-piece IOL eyes 1 year after surgery. This was not seen at 2 years after surgery.

Modified Prolate Anterior Surface IOLs

One prospective randomized trial was identified in which a modified prolate anterior surface IOL was compared to a spherical non-blue light filtering IOL and a spherical blue-light filtering IOL. (36) The primary endpoint was contrast sensitivity at 6 months post-implantation (detailed results of the study are found in Appendix 3). Compared with the spherical non-blue light filtering IOL, the modified prolate IOL showed significantly better results at 1 and 12 cycles per degree in photopic conditions; at 3, 12, and 18 cycles per degree, in photopic with glare; at 3, 12, and 18 cycles per degree in mesopic and at 12 and 18 cycles per degree in mesopic with glare. Compared with the spherical blue light filtering IOL, the modified prolate IOL provided significantly better contrast sensitivity at almost all spatial frequencies in any lighting condition.

The clinical significance of the contrast sensitivity results was not discussed by the authors. In a young eye, positive spherical aberration in the cornea is a partially compensated by the negative spherical aberration of the youthful lens. Positive spherical aberration of the cornea changes little with age, however, the lens changes from negative to positive spherical aberration, leading to a gradual loss of contrast sensitivity in elderly eyes.

The rationale behind the modified prolate anterior surface IOL is to compensate for corneal spherical aberration by creating a modified prolate front surface (flatter curve in the periphery of the IOL), which, in theory, provides better contrast sensitivity than a spherical IOL. It is claimed that the modified prolate produces an amount of negative spherical aberration similar to that of a young natural crystalline lens and "approximates the optical system of a youthful eye". (36)

There was no significant difference in BCVA between the study groups. It was not reported if BCVA referred to near or distant VA. Limitations to the study included:

- A lack of comparisons to aspherical IOLs that do not have a modified prolate anterior surface. Comparisons were only made with spherical IOLs.
- No reported blinding of the patient or the examiner
- No sample size calculation and no information about drop outs or if consecutive patients were randomized.
- Three different lenses were examined with differing numbers of pieces and blue-light filtering.

Blue-Light Filtering IOLs

The importance of having an IOL that closely mimics the protection afforded by the natural crystalline lens led some researchers to suggest adding a yellow chromophore to IOLs (to block blue light). (37) Their rationale for this included:

- Blue light has the highest amount of energy in the visible light spectrum.
- The ability of the lens to filter blue light decreases with age.
- Some experimental cell culture studies showed that exposure to blue light damaged retinal pigment epithelial cells. (37)
- Epidemiologic studies are inconclusive regarding a correlation between exposure to phototoxic levels of blue light after cataract surgery (and the insertion of a non blue light filtering IOL) and the development of age-related macular degeneration. (37)
- Filtering out short wavelength of visible light (up to 480 nm) eliminates intraocular scatter and enhances contrast sensitivity. (38)

It has been reported that the concentration of yellow chromophore in a blue filtering IOL results in a transmission curve that better resembles that of a 25 year old natural crystalline lens. (39) Others claim a transmission of light that mimics the natural lens of a 53-year old person without a cataract. (38)

Four prospective randomized trials (38-41) were identified in which blue-light filtering IOLs were compare to non-blue light filtering IOLs (detailed results of these studies are provided in Appendix 3). Overall, there was no significant difference between blue light filtering and non-blue light filtering IOLs in terms of contrast sensitivity and visual acuity (results shown in Table 10). Only one of the trials reported a sample size calculation, therefore there is the possibility of type 2 errors occurring in the other three studies. To date, there are no published clinical trials comparing the long-term effect of blue light filtering IOLs compared to non-blue light filtering IOLs on macular toxicity.

Quality of the Evidence

Tables 11 to 19 show the quality of evidence for the studies published concerning the use of IOL for the treatment of age-related cataracts according to the GRADE quality-of-evidence criteria.

Table 10: Studies Comparing Blue Light Filtering to Non-Blue Light Filtering IOLs.

Comparison	Results	Comments
Blue light filtering IOL vs. regular single piece IOL. (39)	▪ At 6 months after implantation, no significant difference in BCDVA, contrast sensitivity or PCO.	▪ No sample size calculation. ▪ Possible type 2 error. ▪ "Further research is needed to show clinically any potential advantages of this lens for long-term retinal health."
Blue light filtering IOL vs. conventional non-blue light filtering IOL. (40)	▪ At 6 months after implantation, no significant difference in UCVA, BCVA or Nd:YAG rate.	▪ No sample size calculation. ▪ Possible type 2 error. ▪ Poor evidence-based reporting and interpretation: "Since we are not satisfied with age-related macular degeneration treatments, we should try to prevent the disease. Blue light is surely not the only risk factor for age-related macular degeneration, but we can assume that blue light filtering IOLs may reduce risk of this disease". ▪ Follow-up was too short to reach any such conclusion. Unclear if NVA or DVA was examined.
Blue light filtering IOL vs. regular IOL. (38)	▪ At 18 months after implantation, no significant difference in BCDVA, contrast sensitivity or colour vision.	▪ No reporting if patients consecutively randomized. ▪ No sample size calculation or explicit primary outcome. ▪ Possible type 2 error. ▪ Numerous intra- and inter-group comparisons between study group and a healthy control group.
Blue light filtering IOL vs. regular single piece IOL. (41)	▪ At 6 months after implantation, no significant difference in Visual Functioning Questionnaire composite score, colour vision, driving scales, or Short Form Health Survey-12 physical and mental component.	▪ Explicit sample size calculation reported. ▪ Patient and data collectors masked. ▪ Last observation carried forward analysis.

Table 11: GRADE Quality of Evidence for Interventions – Multifocal vs. Monofocal Lenses Objective Endpoints

Outcome	Quality Assessment					Summary of Findings (Objective Endpoints)	
	Design	Quality	Consistency	Directness	Other	Effect	Quality
Best distance corrected unaided near visual acuity	RCT	High	Inconsistent (1 study)	Direct	<6 months follow-up (3 months)	Multi: mean 0.14 [0.14] logMAR (Snellen equivalent 20/28) Mono: mean 0.35 [0.18] logMAR (Snellen equivalent 20/45) P=0.0001	Moderate*
Best corrected distance visual acuity	RCT	High	Consistent with Cochrane review	Direct	<6 months follow-up (3 months)	Multi: mean 8.40 [0.97] Regan lines (Snellen equivalent 20/18) Mono: mean 8.46 [0.94] Regan lines (Snellen equivalent 20/18) P=0.60	Moderate†
Contrast sensitivity	Cochrane systematic review	Low/ Moderate	Consistent (7 studies)	Direct	Precluded combined analysis. Data described as "contrast sensitivity" using different charts; visual acuity at different contrast levels; and difference between high contrast and lower contrast acuity.	All 7 studies reported lower contrast sensitivity with multifocal IOL. Statistical significance not reported in 6 studies. Clinical significance not addressed.	Low‡
Glare	Cochrane systematic review	Low/ Moderate	Inconsistent (2 studies)	Direct	Variability in how outcomes reported.	*Leyland: Effect on acuity (logMAR)* Multi: -0.02 (0.06) logMAR Mono: -0.02 (0.06) logMAR Significance between lenses not reported. *Steibert: Effect on acuity (Regan lines)* Multi: -5.67 (SD 2.23) at high glare Mono: -6.42 (SD2.43) at high glare No significant difference between lenses.	Very Low§

* Downgraded due to inability to determine consistency and < 6 months follow-up. Unlikely to be important uncertainty.

† Downgraded due to < 6 months follow-up. Unlikely to be important uncertainty.

‡ Downgraded due to quality (3 out of the 10 studies included in the Cochrane review were double masked; 7 studies reported withdrawals; 5 reported method of randomization) and heterogeneity in how outcomes reported.

§ Downgraded due to quality, inconsistency and heterogeneity in how outcomes reported.

Table 12: GRADE Quality of Evidence for Interventions – Multifocal vs. Monofocal Lenses Subjective Endpoints

Outcome	Quality Assessment					Summary of Findings (Subjective Endpoints)	
	Design	Quality	Consistency	Directness	Other	Effect	Quality
Patient Satisfaction	Cochrane review	Low/ Moderate	Inconsistent (4 studies)	Direct	▪ Validated instruments used by 4 studies	▪ Precluded combined analysis and outcomes reported differently (e.g. mean or median overall visual satisfaction, mean change preop and postop, percentage with improved score). ▪ 2 studies found significant differences, 2 studies did not.	Low*
Glare and Halos	Cochrane review	Low/ Moderate	Consistent (4 studies)	Direct	▪ None	▪ Significant increase in glare/halos in multifocal group. ▪ OR 3.55 (95% CI 2.11 to 5.96)	Low/ Moderate
Spectacle dependence	Cochrane review	Low/ Moderate	Consistent (8 studies)	Direct	▪ None	▪ In general, total freedom from spectacles achieved more with multifocal lenses. ▪ Spectacle dependence OR 0.17 (0.12 to 0.24)	Low/ Moderate

* Downgraded due to inconsistency and heterogeneity in how outcomes reported.

Table 13: GRADE Quality of Evidence for Interventions – Accommodating IOLs

Outcome	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other	Effect	Quality
Best distance corrected unaided near visual acuity	Systematic review of observational studies	Low*	Inconsistent†	Indirect‡	▪ Only 1 of the 3 types of accommodative IOLs included in the review was licensed by Health Canada. ▪ Studies did not compare accommodative IOL to a multifocal or monofocal IOL (i.e., non-comparative or compared to another type of accommodative IOL).	No summary statistic	Very low
Best corrected near visual acuity	Same systematic review of observational studies	Low*	Inconsistent†	Indirect‡	▪ Same as above.	No summary statistic	Very low

* Downgraded due to study design (overall, lack of stringent inclusion criteria; for individual studies, no explanation how sample sizes arrived at, confounding)
† Downgraded due to variability of reported outcomes and how reported. ‡ Downgraded due to mixing of patient indications (e.g., presbyopia, non-age related cataracts).

Table 14: GRADE Quality of Evidence for Interventions – Hydrophilic Acrylic Compared to All Other Materials

Outcome	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other	Effect	Quality
PCO	Cochrane systematic review	Moderate*	Consistent (5 studies)	Direct	▪ Varying follow-up but all >12 months. PCO methods varied so a "common scoring" system was used to enable summary statistics. Details not provided. ▪ Some studies compared round with sharp edge IOLs.	12.39 (9.82 to 14.95) Mean difference (95% CI)	Low†
BCDVA	Cochrane systematic review	Moderate*	Consistent (4 studies)	Direct	▪ Some studies compared round with sharp edge IOLs.	-0.09 (-0.13 to -0.06) Mean difference (95% CI)	Low†
Nd:YAG rate	Cochrane systematic review	Moderate*	Consistent (4 studies)	Direct	▪ Some studies compared round with sharp edge IOLs.	8.37 (3.74 to 20.36) Odds ratio (95% CI)	Low†

* Downgraded due to study design (lack of details about randomization/blinding)
† Downgraded due to mixing of round and sharp edge IOLs.

Table 15: GRADE Quality of Evidence for Interventions – Sharp Edged Compared to Round Edged IOLs Regardless of Lens Material

Outcome	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other	Effect	Quality
PCO	Cochrane systematic review	Moderate*	Consistent (11 studies)	Direct	▪ Varying follow-up but all >12 months. PCO methods varied so a "common scoring" system was used to enable summary statistics. Details not provided. † ▪ Significant statistical heterogeneity ▪ All studies favoured sharp edged IOLs.	No summary statistic	Low†
BCDVA	Cochrane systematic review	Moderate*	Inconsistent (7 studies)	Direct	▪ Significant statistical heterogeneity‡	No summary statistic	Low†
Nd:YAG rate	Cochrane systematic review	Moderate*	Consistent (11 studies)	Direct	▪ None	0.19 (0.11 to 0.35) Odds ratio (95% CI)	Moderate

* Downgraded due to study design (lack of details about randomization/blinding)

† Downgraded due to significant heterogeneity.

Table 16: GRADE Quality of Evidence for Interventions – 1-Piece Compared to-3 Piece IOLs

Outcome	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other	Effect	Quality
PCO	Cochrane systematic review	Moderate*	Consistency (5 studies)	Direct	▪ Varying follow-up but all >12 months. PCO methods varied so a "common scoring" system was used to enable summary statistics. Details not provided. ▪ Results only for acrylic.	Results omitted from systematic review but 2 studies continued and reported 2 and 5 year outcomes after systematic review: Leydolt et al. (mean PCO score ±standard deviation at 5 year outcome) 1.7±1.7; vs. 1.3±1.4; p=0.30 Zemaitiene et al. (mean PCO score ±standard deviation at 2 year outcome) 0.15 ±0.19 vs. 0.14±0.22; p=0.18	Low†
BCDVA	Cochrane systematic review	Moderate*	Consistent (2 studies)	Direct	▪ Results only for acrylic.	0.00 (-0.04 to 0.04) Mean difference (95% CI)	Low†
Nd:YAG rate	Cochrane systematic review	Moderate*	Consistent (3 studies)	Direct	▪ Results for acrylic and PMMA	0.48 (0.02 to 10.24) acrylic 0.94 (0.59 to 1.51) PMMA Odds ratio (95% CI)	Low†

* Downgraded due to study design (lack of details about randomization/blinding)

† Downgraded due to limited number of materials (e.g., no silicone or acrylic only).

Table 17: GRADE Quality of Evidence for Interventions – Acrylic Compared to Silicone (Same Optic Design and Haptics)

Outcome	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other	Effect	Quality
PCO	RCT	High	Consistent (1 study; consistent with Cochrane systematic review)	Direct	▪ Post hoc power calculation showed 99% power to detect PCO difference (primary outcome). ▪ Actual data not reported (comparisons in figures only)	No significant difference P=0.96	Moderate*
BCDVA	Same RCT	High	Consistent (1 study; consistent with Cochrane systematic review)	Direct	▪ Actual data not reported (comparisons in figures only)	No significant difference No p value reported	Low/Moderate*†
Nd:YAG rate	Same RCT	High	Consistent (1 study; consistent with Cochrane systematic review)	Direct	▪ Actual data not reported (comparisons in figures only) †	No significant difference P=0.19	Low/Moderate*†

* Downgraded due to lack of explicit data and no a priori same size calculation
† Uncertainty since not primary outcome; possible type 2 error.

Table 18: GRADE Quality of Evidence for Interventions – Modified Prolate Anterior Surface IOLs

Outcome	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other	Effect	Quality
Contrast Sensitivity	RCT	Moderate*	Uncertainty (1 study)	Direct	▪ No sample size calculation. ▪ No information about dropouts or if consecutive patients randomized. ▪ 3 IOLs compared with multiple variations in design. ▪ No explicit primary objective.	▪ Compared with spherical IOL, aspherical modified prolate IOL showed significantly better contrast sensitivity at 1 and 12 cycles per degree (photopic conditions). ▪ Compared with spherical blue light filtering IOL, aspherical modified prolate IOL showed significantly better contrast sensitivity at most frequencies (photopic conditions). ▪ Clinical significance of results not addressed by authors.	Very Low†
BCVA	Same RCT	Moderate*	Uncertainty (1 study)	Direct	▪ Same as above. ▪ Not explicit if near or distant VA examined.	<u>No significant difference</u> Aspherical modified prolate 1.00±0.13 Spherical 0.97±0.12 Spherical blue light filtering 0.99±0.13	Very Low†

* Downgraded due to study design (lack of details about randomization/blinding).
† Downgraded due to uncertainty with methodological issues.

Table 19: GRADE Quality of Evidence for Interventions – Blue Light Filtering IOLs

Outcome	Quality Assessment					Summary of Findings	
	Design	Quality	Consistency	Directness	Other	Effect	Quality
Contrast Sensitivity	RCTs	Moderate*	Consistent (2 studies)	Direct	▪ No primary outcome reported in any of the trials. ▪ No sample size calculation reported; possible type 2 error.	1. No clinically significant differences (≥0.3 long units at ≥2 spatial frequencies) (p=0.62). 2. No significant difference between groups (p=0.26).	Low†
BCVA	RCTs	Moderate*	Consistent (3 studies)	Direct	▪ No primary outcome reported in any of the trials. ▪ No sample size calculation reported; possible type 2 error.	1. No significant difference in achieving BCDVA 20/40 or better (100% in blue blocking; 99.0% in regular IOL) (no p value reported). 2. All patients achieved BCVA better than 0.8 (20/25) (no p value reported). 3. Blue filter IOL: 12/13 eyes improved to 20/20 BCDVA; regular IOL: improved to 20/20 BCDVA in 13/13 eyes.	Low†
HRQL	RCT	High	Inconsistent (1 study)	Direct	▪ None	No significant difference in: ▪ National Eye Institute's Visual Functioning Questionnaire composite score ▪ Colour vision ▪ Driving scales ▪ Short Form Health Survey physical and mental component.	High/ Moderate‡

* Downgraded due to study design (lack of details about randomization/blinding).

† Downgraded due to uncertainty with methodological issues.

‡ Downgraded due to uncertainty in consistency.

Conclusions

Table 20 shows conclusions for the systematic review of IOLs for age-related cataracts.

Table 20: Conclusions for the Systematic Review of IOLs for Age-Related Cataracts

Comparison	Conclusion	GRADE Quality
Multifocal vs. monofocal	Objective Outcomes	
	Significant improvement in BDCUNVA	moderate
	No significant difference in BCDVA	moderate
	Inconclusive evidence for contrast sensitivity	low
	Inconclusive evidence for glare	very low
	Subjective Outcomes	
	Inconclusive evidence for visual satisfaction	low
	Significant increase in glare/halos	low/moderate
	Significant incr0ease in freedom from spectacles	low/moderate
Accommodative vs. multifocal/ monofocal	Inconclusive due to Insufficient limited evidence for any effectiveness outcome	very low
Hydrophilic acrylic vs. other materials (hydrophobic acrylic, silicone)	Significant increase in PCO score	low
Sharp edged compared to round edged	Significant reduction in PCO score	low
One piece compared to three piece	No significant difference in PCO score	low
Hydrophobic acrylic compared to silicone	No significant difference in PCO score	moderate
Aspherical modified prolate anterior surface compared to spherical	No significant difference in VA	very low
	Significant reduction in contrast sensitivity	very low
Blue light filtering compared to non blue-light filtering	No significant difference in BCDVA	low
	No significant difference in contrast sensitivity	low
	No significant difference in HRQL	high/moderate

Economic Analysis

Disclaimer: The Medical Advisory Secretariat uses a standardized costing methodology for all of its economic analyses of technologies. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative cost data are used for all in-hospital stay costs for the designated International Classification of Diseases-10 (ICD-10) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may need to be made to ensure the relevant case mix group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits for physician fees, laboratory fees from the Ontario Laboratory Schedule of Fees, device costs from the perspective of local health care institutions, and drug costs from the Ontario Drug Benefit formulary list price.

Discounting: For all cost-effectiveness analyses, a discount rate of 5% is used as per the Canadian Agency for Drugs and Technologies in Health.

Downstream costs: All costs reported are based on assumptions of utilization, care patterns, funding, and other factors. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature. In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the assumptions, and the revised approach. The economic analysis represents an estimate only, based on assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied for the purpose of developing implementation plans for the technology.

Literature Review

A broad range of studies assessing cost-effectiveness, economic evaluations, modelling studies and analysis of administrative data were considered in this systematic review. (42-58) The items were identified based on the current review of clinical effectiveness of IOL implantation for the treatment of age-related cataracts. All chosen studies contained Cost-Utility Analyses (CUAs) and compared multifocal and/or monofocal IOLs for cataracts.

In general, IOL implantation for cataracts was found to be cost-effective. In a 2004 study by Baltussen et al. (42), extracapsular cataract extraction (ECCE) procedures using posterior chamber IOL implantation were shown to be cost-effective (specifically when compared to intracapsular cataract extraction (ICCE) in various countries around the world including Canada. In 2007, Lansingh et al. (43) also reported cost-effectiveness of IOLs for cataract surgery for both ECCE and small incision phacoemulsification procedures across various global jurisdictions. Although there was a large range of cost-effectiveness ratios in cost per quality adjusted life years (QALY) and cost per disability adjusted life years (DALY) found among the studies reviewed, each ratio showed the procedure(s) to be cost-effective in the respective country of analysis.

Cost utility analyses (CUAs) of IOL implants for cataracts undertaken by Busbee et al. (United States) and Kobelt et al. (Sweden) also showed cost-effectiveness in terms of an increase in utility and QALY linked to an improvement in post-operative visual acuity. (44;45) It was unclear, however, whether visual

outcomes were assessed using tests for best spectacle-corrected or uncorrected visual acuity. It is important to note that the utility of cataract surgery and IOL implantation was positively correlated with visual acuity of the better-seeing eye. (43-45)

Specific evaluation of multifocal versus monofocal IOLs for cataracts was performed in several studies that valued improvement in outcomes such as spectacle independence (i.e. no need of glasses for near or far vision). Maxwell et al. performed a cost-benefit analysis (CBA) of apodized, diffractive, presbyopia-correcting IOLs in 2008, which reported a greater net benefit (11,670 USD) of implanting multifocal over monofocal IOLs for cataract patients. (44) The data used in the decision-tree analysis reported an average age of 69 for cataract patients with a life expectancy of 14 years based on the general US population of age 70. In the study done by Orme et al. in 2002, the total direct medical care costs (hospital, physician, drug) of patients receiving multifocal and monofocal IOLs was similar, but multifocal IOLs were found to be more cost-effective for spectacle-free patients than monofocal IOLs. (45) In addition, cost per patient without overall limitation in vision-related function and cost per patient without limited night vision were found to be similar for both the multifocal and monofocal IOL patient groups.

Cost-effectiveness and Modelling of Multifocal versus Monofocal IOL

The current review of effectiveness of IOLs for age-related cataract patients was used to inform the selection of strategies and target population below. In particular, complications rates following IOL implantation (e.g. raised intraocular pressure, endophthalmitis, cystoid macular edema) were found to be similar between multifocal and monofocal IOLs, as no modifications to surgical technique were required for the different lenses. (19) The rate of PCO, however, was found to differ among lens materials used and was incorporated into the model for evaluation of the effect of lens material. (32;46) Furthermore, as PCO complications were treated using Nd-YAG laser capsulotomy, retinal detachment was also included in the model following Nd-YAG laser treatment. Note that this complication was both the best documented adverse event of Nd-YAG treatment of PCO and the most costly with an incidence rate of approximately 1.2%. (47)

Target Population

The target population of interest in the current cost-effectiveness analysis consisted of cataract patients of age ≥65 years for whom IOL implantation (phacoemulsification) was performed after cataract extraction. As the population would have surgery indicated for age-related cataracts, patients with other ocular comorbidities or complicating conditions, such as diabetes or glaucoma, were not considered in the analysis.

Evaluation Strategies

Strategies that were evaluated in this CEA were based on ‘design’ and ‘material’ factors of currently manufactured IOLs. The first strategy (Strategy 1) evaluated the IOL design and compared multifocal and monofocal lenses, both made of hydrophobic acrylic material and foldable in form. The second strategy (Strategy 2) evaluated the choice of material of the implanted lens, comparing hydrophobic acrylic lenses with silicone lenses, specifically for multifocal (foldable) lenses.

Perspective

The analytic perspective taken of the current cost-effectiveness evaluation was that of the MOHLTC. It is important to note that while the cost-utility model incorporated the requirement of eyeglasses for near and far vision correction after IOL implantation, the associated costs were omitted in the economic analysis. Both direct and indirect health care costs (for hospital costs) were included in the analysis.

Model Overview: Base Case, Time Horizon and Discounting

A cost-utility analysis was performed focusing on whether eyeglasses were required for near and far vision correction after IOL implantation. A Markov model was then developed and used to evaluate both Strategies 1 and 2. The cycle length of the model was 1 year and a time horizon of 14 years was used, corresponding to the average life expectancy of the base case.

The base case used in this analysis consisted of an age-related cataract patient of age 65 years or older (average age of 70) without pre-existing eye disease or ocular comorbidities, who had cataract surgery with IOL implantation. These patients did not experience any complications from the cataract surgery itself, but may have had a PCO complication as a result of the IOL procedure. Costs and outcomes were discounted at a 5% annual rate as recommended by CADTH guidelines. (48)

Health states

The Markov model was designed with ten health states, as shown in Figure 1. Five health states were defined with no PCO complication after IOL implantation and five health states were associated with the existence of a PCO complication, with corresponding Nd-YAG laser capsulotomy. Each set of five health states incorporated the requirement of correction for near and far vision (if applicable) as follows:

1) 'No glasses' (near vision normal, far vision normal);
2) 'Distance glasses' (near vision normal, far vision glasses);
3) 'Reading glasses' (near vision glasses, far vision normal);
4) 'Both glasses' (near vision and far vision glasses); and
5) 'Bifocal glasses' (near vision / far vision glasses).

The difference between health states 4 and 5 was defined as patients having two separate pairs of glasses for reading and distance vision, and a pair of bifocal glasses, respectively. Health states 4 and 5 were used in the model to represent the cost difference of having two pairs of glasses versus one pair. However, this distinction had no effect on the cost-effectiveness of the evaluated strategies given the MOHLTC perspective defined above.

Although not shown in Figure 1, it should be noted that transition to the absorbing health state 'death' could be made from any of the 10 states. Transitions between health states (excluding death) occurred based on the need for near and/or far vision correction, represented by arrows in Figure 1. Arrows with dashed lines represented transitions from non-PCO health states to corresponding PCO health states that could only occur if a PCO complication was experienced by the patient. The occurrence of PCO necessarily implied the additional use of Nd-YAG laser capsulotomy for the treatment of PCO and an additional cost due (potentially) to retinal detachment. It is important to note the one-time cost associated with PCO and Nd-YAG laser treatment and retinal detachment was the only functional difference between the non-PCO and PCO-specific health states in the model.

An overview of the Markov model used in the CUA evaluation of strategies 1 and 2 is shown in Figure 2. The decision trees located at each of the non-PCO-related health states were structured similarly to the branches shown under 'No glasses'. Likewise, the decision trees located at each of the PCO-related health states were structured similarly to the expanded branches for health state 'PCO- No glasses'. The decision node labelled intraocular lens for cataracts' was designed to evaluate Strategies 1 and 2, with corresponding branches for each of the options in those strategies: 'Multifocal- hydrophobic acrylic' versus 'Monofocal- hydrophobic acrylic' for Strategy 1, and 'Multifocal- silicone' versus 'Multifocal- hydrophobic acrylic' for strategy 2. Note that evaluating the strategy 'Multifocal- silicone' versus 'Monofocal- silicone' would yield similar results to Strategy 1, and 'Monofocal- silicone' versus 'Monofocal- hydrophobic acrylic' would produce similar results to Strategy 2.

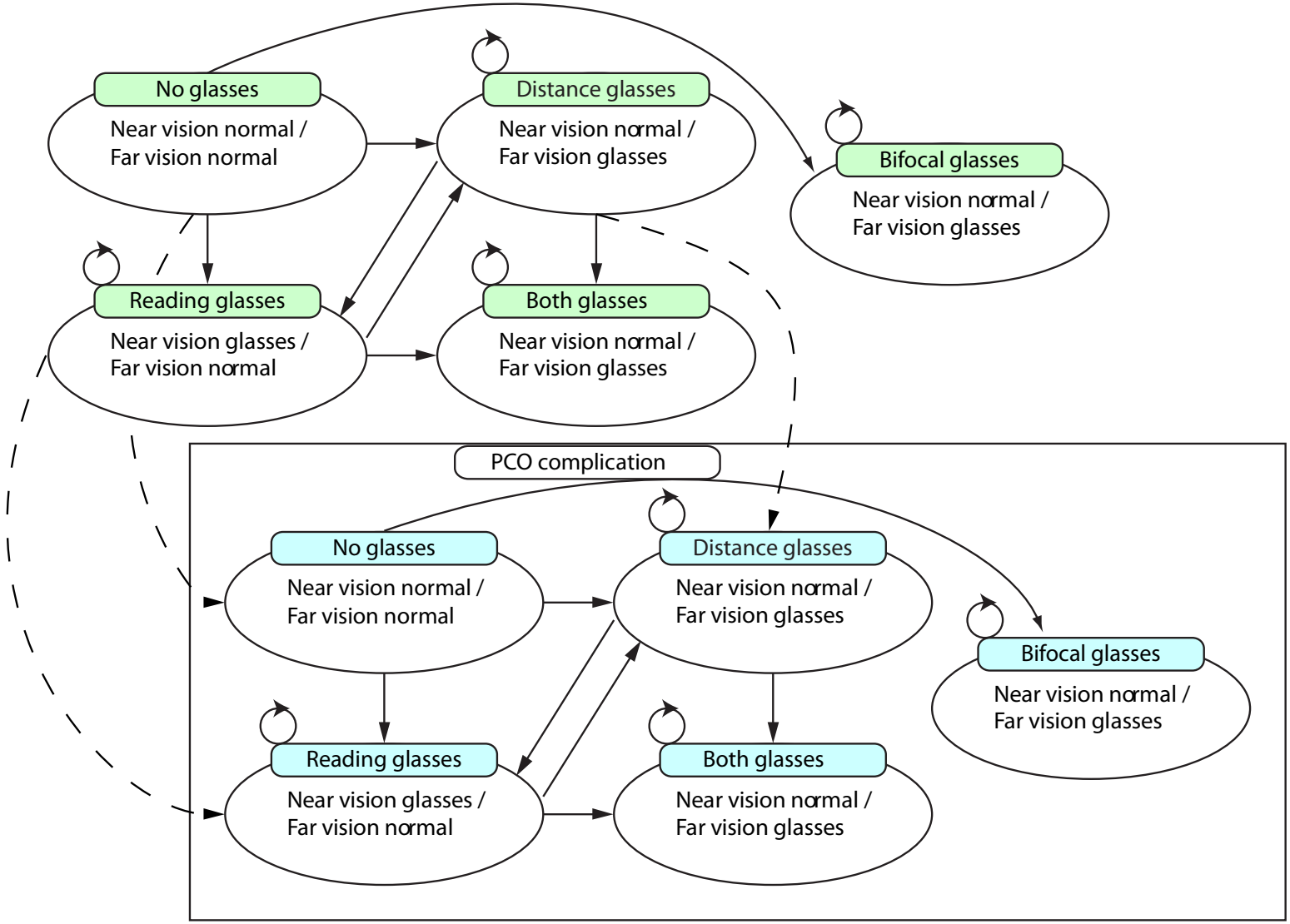

Figure 1: Markov health states for the evaluation of IOL strategies for age-related cataracts

Note: The health state 'death' is present but not shown.

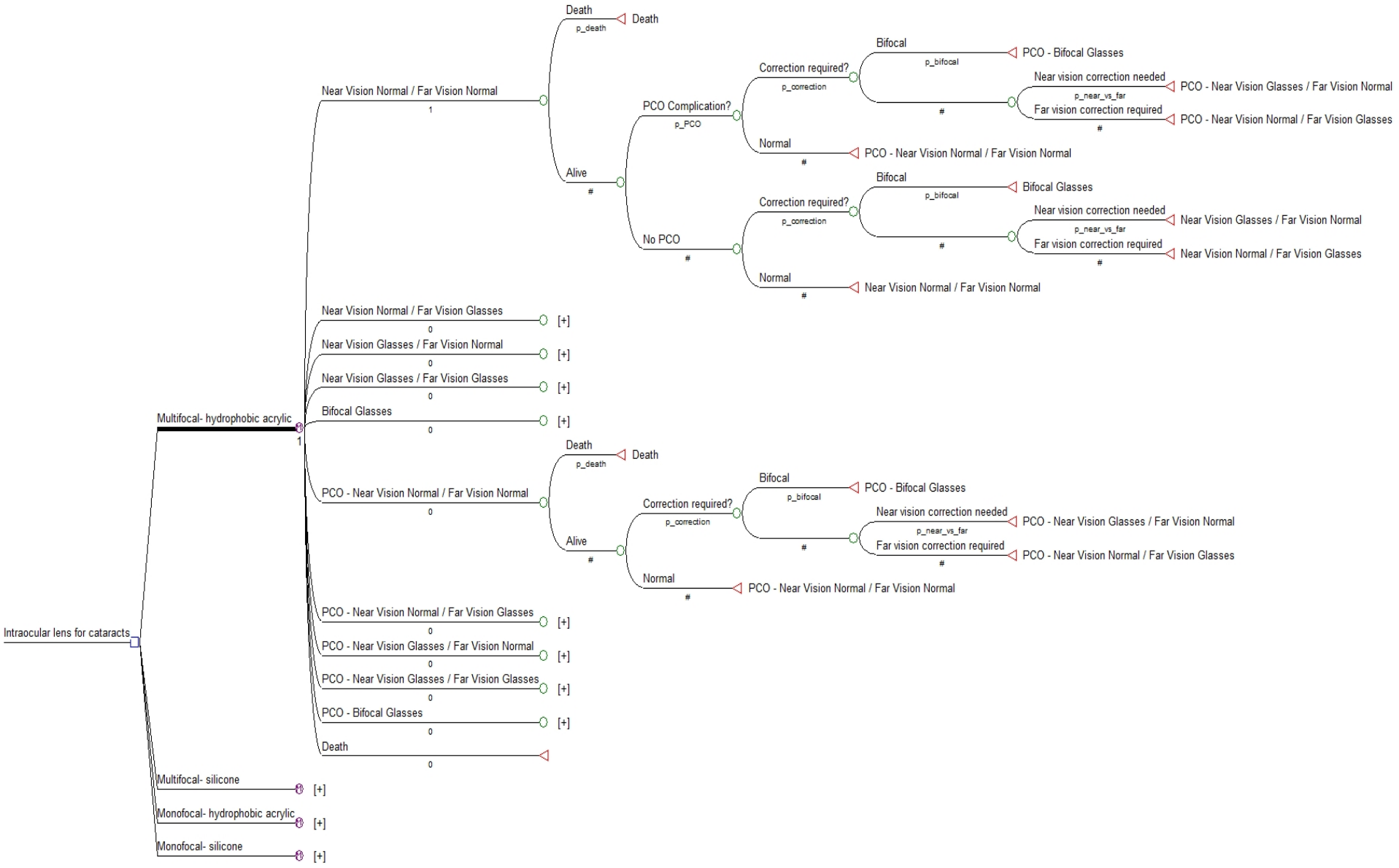

Figure 2: Markov model for CUA evaluating Strategies 1 and 2 for IOL implants for age-related cataracts

Model Assumptions

Certain simplifying assumptions were made to the model, which are summarized below:

- IOL implantation occurred in only one eye; bilateral IOL implantation was not included
- Only PCO complication after cataract extraction and IOL implantation was incorporated into the model, as the importance of this complication has been studied in detail (49;50)
- Costs of cataract surgery (hospital, physician) and associated complications (excluding PCO) were not included, as the costs of surgery were identical and differed only in IOL device costs
- Differences in PCO complication rates associated with round-edged or sharp-edged IOLs were not modelled; an overall PCO rate was used from observational data combining both types of lenses (47)
- Conditional costs of retinal detachment were incorporated directly into the costs associated with PCO and were not modelled separately; the probability of retinal detachment given a PCO complication was used to distribute the additional cost among all patients with PCO
- If PCO occurred as a complication of IOL implantation, it was assumed to occur in the first four years after cataract surgery; an average of four years was chosen due to the large variation in PCO incidence rates (46)

Costs

Total hospital costs (direct and indirect), physician costs and device costs were estimated for IOL devices and PCO complications, including retinal detachment and Nd-YAG laser capsulotomy for age-related cataracts. In the current CUA, costs for cataract surgery and cataract complications were not included, as the strategies evaluated had identical costs for surgery and IOL implantation. That is, the only cost difference between multifocal and monofocal IOLs (Strategy 1) was found to be in the cost of the device itself, given the MOHLTC perspective employed in the analysis. Similarly, the cost difference in Strategy 2 was in lens material (silicone versus hydrophobic acrylic) and costs associated with lens material-dependent PCO complication rates. The costs summarized in Table 1 are in 2009 Canadian dollars; the additional cost of silicone versus hydrophobic acrylic was estimated and 2009 Euros converted using the Bank of Canada rate. (51)

The cost of retinal detachment was also included in the model as an important potential complication of Nd-YAG laser capsulotomy and as a conditional cost of PCO complication. (46;52) In order to simplify the Markov model, the conditional probability of retinal detachment given a PCO complication (44) was used to distribute the additional cost of vitrectomy among all patients with PCO. Hospital and physician costs of vitrectomy for retinal detachment were estimated and amounted to the addition of an average of $10 for patients developing a PCO complication in the model.

Table 21: Costs used in the CUA evaluation associated with IOL devices and PCO complications

Type of Cost	Description	Cost (CAD)	Reference
Hospital	PCO complication (retinal detachment-vitrectomy)	$2,294	CCI code 1.CM.89 (OCCI 2007-08)
	PCO complication (Nd-YAG laser capsulotomy)	$58	CCI code 1.CL.59.LA-AG (OCCI 2007-08)
Physician	PCO complication (retinal detachment-vitrectomy)	$830	ON Schedule of Benefits fee code E142 (50)
	PCO complication (Nd-YAG laser capsulotomy)	$104	BC Payment Schedule fee code 22115 (49)
IOL Device	Multifocal lens (hydrophobic acrylic material)	$950	Correspondence with IOL lens manufacturers
	Monofocal lens (hydrophobic acrylic material)	$250	Correspondence with IOL lens manufacturers
	Additional cost of silicone versus hydrophobic acrylic material (multifocal design)	$8	Correspondence with IOL lens manufacturers

Treatment effects

The measure of effect used in the Markov model was visual acuity in terms of needing glasses for near or far vision correction after cataract extraction and IOL implantation. A disutility of -0.03 was assigned to health states where glasses were necessary for vision correction, based on average time trade-off (TTO) and standard gamble (SG) values from studies reporting the (dis)utility of wearing glasses. (53;54) Disutilities were also associated with IOL complications related to PCO. A disutility of -0.0004 was assigned to the conditional probability of retinal detachment based on values from the literature. (55;56) This (dis)utility was distributed among all patients with PCO in a similar fashion to how additional costs associated with vitrectomy were distributed among patients for PCO costs.

The above decrements in utility were applied to base case values derived from the literature, which were based on average utility values of cataract patients in Canada. (57) The relative improvement in utility of having surgery for cataracts (and IOL implantation) was estimated as being 21%. (55;56) This utility increase was applied to age-specific utilities of 0.77 for patients of age 60 to 69 years, 0.79 for patients of age 70 to 79 years, and 0.73 for patients of age 80 to 89 years, which provided base case utility values of 0.93, 0.96 and 0.88 for the model, respectively.

Transition rates and the probabilities of requiring reading, distance and bifocal eyeglasses were based on (retrospective) observational data. The proportion of cataract patients requiring vision correction (reading, distance, bifocal glasses) after IOL implantation was used from two studies: Javitt et al. 2000 and Maxwell et al. 2008. (23;44) Specifically, the proportion of 'wearing glasses' for near and far vision correction were based on observational data from Javitt et al., taken from the patients enrolled in that RCT, and from Maxwell et al. from a study of patients who underwent IOL implantation in a non-randomized trial. The proportion of patients requiring glasses was interpreted as the corresponding probability of requiring vision correction and, in the case of Maxwell et al., was re-weighted to derive a mutually exclusive probability of requiring near vision compared to far or distant vision correction. Note that the probability of 'requiring vision correction' remained constant over time, with the same probabilities used in each cycle of the Markov model (see Table 22).

Table 22: Probabilities of requiring near or far/distance vision correction after IOL implantation

Probability description	Multifocal IOL	Monofocal IOL	Reference
Requiring vision correction (either near or far vision)	0.201	0.923	Maxwell 2008
Requiring bifocal glasses	0.271	0.386	Maxwell 2008
Requiring near vision correction (versus far vision correction)	0.882	0.722	Maxwell 2008
Requiring far vision correction	0.250	0.400	Javitt 2000
Requiring near vision correction	0.670	0.890	Javitt 2000

The CUA and Markov model also made use of retrospective chart review data in order to estimate the rates of PCO complication. Smith et al. performed a chart review of patients with IOLs implanted in 1996 or 1997 in Europe (France, Italy, Germany, Spain) and analyzed the occurrence of PCO three years after surgery. Differences were found in the rate of PCO among different IOL materials and were incorporated into the model as follows: a rate of 8.9% for hydrophobic acrylic IOLs and 21.6% for silicone-based IOLs, for either multifocal or monofocal design. (47)

Mortality rates

Probabilities associated with transitions to the Markov state 'death' were estimated from tables summarizing deaths by age (and sex) and by province based on the Statistics Canada death database. (52) An average annual (fiscal year) rate was used for Ontario deaths combining sex-specific death rates in 2006-07.

Cost-effectiveness results

Both strategies evaluated in the current cost-utility analysis were found to be cost-effective. For hydrophobic acrylic, one of materials with the lowest rate of PCO complication, the multifocal IOL implantation for age-related cataracts (strategy 1) was found to have an ICER of about $8,000/QALY. As a result, using the commonly accepted threshold of $50,000/QALY implied cost-effectiveness of multifocal IOLs. For the second strategy, hydrophobic acrylic material was found to be the dominant strategy: it saved costs and improved quality of life (QALY) of patients receiving multifocal IOLs. Results are shown in Table 3 and Table 4.

One-way sensitivity analysis was performed on the Markov model used in the current CUA. The factors having the greatest impact on the ICER for strategy 1 were the device cost of the multifocal and the proportion of patients requiring glasses. If the lens device cost increased to $4,500, multifocal IOLs were no longer considered cost-effective, with resulting ICERs exceeding the threshold of $50,000/QALY. Likewise, if the proportion of patients requiring visual correction was increased from 20% to 63%, multifocal IOLs were not considered cost-effective.

For strategy 2 evaluating lens materials for multifocal IOLs, the factors having the greatest impact on the ICER were the difference in cost between silicone and hydrophobic acrylic and the rate of PCO complication. According to the model developed, the cost of silicone IOLs must be reduced by at least $60 for hydrophobic acrylic not to be found cost-effective. Also, the rate of PCO complication associated with hydrophobic acrylic must increase from about 9% to 24% for this material not to produce cost savings.

Table 23: Cost-effectiveness of Strategy 1 (multifocal vs. monofocal IOL made of hydrophobic acrylic)

Design	Cost	Incremental Cost	Effect (QALY)	Incremental Effect	Cost per QALY
Multifocal	$755.46	$700.00	8.902779	0.083536	$8,380
Monofocal	$55.46		8.819243		

Table 24: Cost-effectiveness of Strategy 2 (hydrophobic acrylic vs. silicone for multifocal IOLs)

Material	Cost	Incremental Cost	Effect (QALY)	Incremental Effect	
Hydrophobic acrylic	$755.46	-$59.81	8.902779	0.000125	Dominant
Silicone	$815.27		8.902654		

Discussion

Both strategies evaluated in the current cost-utility analysis were found to be cost-effective. For age-related cataract patients with IOL implantation, Strategy 1 of using multifocal lenses made of hydrophobic acrylic (low PCO rate) was found to be cost-effective with an ICER of about $8,000/QALY. In Strategy 2 the use of hydrophobic acrylic material was found to be dominant: the material saved costs and improved the quality of life (QALY) of patients receiving multifocal IOLs (compared to silicone material). Further examination of the model used in the CUA suggested Strategy 1 was sensitive to increased cost of the multifocal lens and to the increased proportion of patients required near or far vision correction after IOL implantation. The associated cost and probability parameters, however, would need to be increased 3- to 5-fold in order to change the cost-effectiveness of Strategy 1. In a similar way, factors found to influence the cost-effectiveness of Strategy 2 were the cost difference between silicone and hydrophobic acrylic lens material and the rate of PCO complications. These parameters would need to be increased 3- to 7-fold to change the cost-effectiveness of Strategy 2.

In Ontario, the total cost of providing monofocal or multifocal IOL to patients with age-related cataracts would be approximately $27.4 million for monofocal and $113.2 million for multifocal lenses. These estimates were based on 90,183 cataract surgeries performed in Ontario in 2005 (3), with an average cost per patient of $304 for monofocal and $1255 for multifocal IOLs (Markov model estimates), both made of hydrophobic acrylic material.

The CUA and Markov model used to evaluate the two IOL strategies made use of observational data and patient chart reviews. The low quality evidence currently available in these areas suggests further research is needed to develop more accurate models evaluating multifocal IOLs and the type of material used in the manufacturing process.

Ontario Health System Impact Analysis

Considerations and Implications

Ontario

- Procedures for crystalline lens removal and IOL insertion are insured and are listed in the Ontario Schedule of Benefits.
- If a particular lens is determined to be medically necessary for a patient, the cost of the lens is covered by the hospital budget. If the patient chooses a lens that has enhanced features then the hospital may elect to charge an additional amount above the cost of the usual lens offered.
- An IOL manufacturer stated that monofocal lenses comprise approximately 95% of IOL sales in Ontario and premium lenses (e.g. multifocal/accomodative) make up the remaining 5%.
- A medical consultant stated that all types of lenses are currently being used in Ontario (e.g. multifocal, monofocal, accommodative, tinted, nontinted, spheric, and aspheric). Nonfoldable lenses, rarely used in routine cases, are primarily used in complicated cataract implantation situations.

Diffusion: International

United States

Aetna (September 2008)

- Aetna considers standard fixed monofocal posterior chamber IOL medically necessary for aphakia.
- Accommodating posterior chamber IOLs (e.g., Crystalens, Eyeonics Inc., Aliso Viejo, CA), apodized diffractive optic IOLs (e.g., AcrySof ReSTOR, Alcon, Inc., Fort Worth, TX), ultraviolet absorbing lenses (e.g., AcrySof Natural blue-light filtering IOL, Alcon, Inc., Fort Worth, TX, and C-flex IOL model 570C, Rayner Surgical Inc., Los Angeles, CA), multifocal posterior chamber IOLs, and other new technology lenses (e.g., the Sofport LI61AO aberration-neutral IOL, Bausch & Lomb, San Dimas, CA) are considered non-covered deluxe items.
- Given that multifocal IOLs, accommodating IOLs, and apodized diffractive optic IOLs are intended to obviate the need for reading glasses post-surgery, these IOLs are considered convenience items.
- For members who elect non-covered new technology IOLs, cataract removal and lens implantation would be considered medically necessary if the criteria for cataract surgery outlined above are met. The new technology lens itself would not be covered.

Cigna (December 2008)

- CIGNA covers a standard monofocal or multifocal IOL implant as medically necessity for replacement of the crystalline lens as part of cataract surgery.
- CIGNA does not cover an accommodating IOL implant (e.g. Crystalens Model AT-45) for the treatment of cataracts because they are considered experimental, investigational or unproven.
- CIGNA does not cover IOL implants (clear lens extraction [CLE]) for the correction of presbyopia because the procedure is performed to correct refractive errors and is not medically necessary.

Centers for Medicare and Medicaid Services (May 2005)

- One pair of conventional eyeglasses or contact lenses furnished subsequent to each cataract surgery with insertion of an IOL is covered.

- A single presbyopia-correcting IOL essentially provides what is otherwise achieved by two separate items: an implantable conventional IOL (one that is not presbyopia-correcting) and eyeglasses or contact lenses. Although presbyobia-correcting IOLs may serve the same function as eyeglasses or contact lenses furnished following cataract surgery, IOLs are neither eyeglasses nor contact lenses.

  Therefore, the presbyopia-correcting functionality of an IOL does not fall into the benefit category and is not covered. Any additional provider or physician services required to insert or monitor a patient receiving a presbyopia correcting IOL are also not covered. For example, eye examinations performed to determine the refractive state of the eyes following insertion of a presbyopia-correcting IOL are not covered.

United Kingdom

National Institute for Health and Clinical Excellence (February 2007)

Current evidence suggests that there are no major safety concerns associated with the implantation of accommodating lenses for cataracts. There is evidence of short-term efficacy in correcting visual acuity but there is inadequate evidence that the procedure achieves accommodation. Therefore, the procedure should not be used without special arrangements for consent and for audit or research.
Clinicians wishing to undertake implantation of accommodating lenses should take the following actions.

1. Ensure that patients understand the uncertainty about the procedure's efficacy, and provide them with clear written information.
2. Audit and review clinical outcomes of all patients having implantation of accommodating lenses.

Publication of long-term efficacy outcomes of the procedure will be useful, particularly on the effects on accommodation. The Institute will review the procedure in due course.

It was noted that the evidence reviewed on this procedure relates to the treatment of cataract and not to the correction of presbyopia. It was also noted that accommodating lenses are at a relatively early stage of development and that the technology is evolving rapidly.

Glossary (optional)

Aphakic eye	An eye that does not have a new lens after cataract extraction
Contrast sensitivity	The ability to perceive differences between an object and its background
Depth of field	The range of distances over which the eye cannot detect any change in focus
Mesopic	Intermediate levels of light
Night vision disturbances	Vision quality defects apparent in low light or darkness; the best-known examples are starbursts and haloes.
Photopic	Full level of light.
Pseudophakic eye	The substitution of the natural crystalline lens with a synthetic lens.
Regeneratory posterior capsule opacification	Also referred to as 'after cataract', it's the most common long-term complication of IOL implantation surgery for cataracts. It's the result of migration of lens epithelial cells along the posterior capsule behind the IOL. These cells proliferate to form layers of lens material that leading to opacification and reduced visual function.
Visual acuity	The ability of the visual system to discern fine detail, as measured by printed or projected visual stimuli

Appendices

Appendix 1: Literature Search Strategies

Databases searched: MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Cochrane Library (all via OVID); CRD/INAHTA

Database: Ovid MEDLINE(R) <1996 to January Week 3 2009>
Search Strategy:

1 exp Lens Implantation, Intraocular/ or exp Lenses, Intraocular/ (7114)
2 ((implant* or intraocular) adj2 lens*).mp. (7878)
3 (iol or iols).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3550)
4 (Tek-Clear or Tetraflex or SmartLens or SmartIOL or FlexOptic or (Array adj3 lens*) or AcriTec or ReStor or ReZoom or Crystalens or Synchrony or Tecnis or SofPort or Acrysof).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3594)
5 exp Pseudophakia/ (769)
6 pseudophak*.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1391)
7 or/1-6 (11750)
8 exp Cataract Extraction/ or exp Cataract/ (14261)
9 (Pseudoaphaki* or cataract*).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (17315)
10 (lens* adj (opacity or opacities or opacification)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (788)
11 or/8-10 (18998)
12 7 and 11 (6241)
13 limit 12 to (english language and humans and yr="2003 - 2009") (2643)
14 limit 13 to (controlled clinical trial or meta analysis or randomized controlled trial) (346)
15 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ (35585)
16 (health technology adj2 assess$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (650)
17 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (67644)
18 exp Random Allocation/ or random$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (380904)
19 exp Double-Blind Method/ (54040)
20 exp Control Groups/ (823)
21 exp Placebos/ (9446)
22 (RCT or placebo? or sham?).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (96228)
23 or/14-22 (490457)
24 23 and 13 (438)
25 limit 24 to "all child (0 to 18 years)" (25)
26 24 not 25 (413)

Database: EMBASE <1980 to 2009 Week 05>
Search Strategy:

1 exp lens implant/ (9976)
2 exp Lens Implantation/ (2309)
3 ((implantable or intraocular) adj2 lens*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (8514)
4 (iol or iols).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (4809)
5 (Tek-Clear or Tetraflex or SmartLens or SmartIOL or FlexOptic or (Array adj3 lens*) or AcriTec or ReStor or ReZoom or Crystalens or Synchrony or Tecnis or SofPort or Acrysof).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (4509)
6 Pseudophakia/ (2508)
7 pseudophak*.mp. (3160)
8 or/1-7 (18259)
9 exp Cataract Extraction/ or exp Cataract/ (33442)
10 (Pseudoaphakia or cataract*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (36058)

11 (lens* adj (opacity or opacities or opacification)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1327)
12 or/9-11 (38013)
13 8 and 12 (10019)
14 limit 13 to (human and english language and yr="2003 - 2009") (2654)
15 Randomized Controlled Trial/ (165071)
16 exp Randomization/ (26467)
17 exp RANDOM SAMPLE/ (1395)
18 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (297798)
19 (health technology adj2 assess$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (670)
20 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (64531)
21 Double Blind Procedure/ (71178)
22 exp Triple Blind Procedure/ (12)
23 exp Control Group/ (2779)
24 exp PLACEBO/ or placebo$.mp. or sham$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (212600)
25 (random$ or RCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (429709)
26 (control$ adj2 clinical trial$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (282757)
27 or/15-26 (795016)
28 27 and 14 (510)
29 limit 28 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (32)
30 28 not 29 (478)

Appendix 2: Results of Published Meta-Analyses

A2: Results of Published Meta-Analyses

Author & Pub. Year	Objective, Method & Outcomes	Results	Comment
Findl et al. (19) 2007 Lit. search cut-off date: Jan. 2007	To determine the effect of IOL material and shape on PCO. Method: Meta-analysis *Outcomes:* *Primary:* BCVA *Secondary:* PCO rates Nd:YAG rate ≥12 months follow-up.	**Materials** ▪ Meta-analyses showed significantly higher PCO rates in hydrogel IOLs than in other IOL materials. ▪ No significant difference between other IOL materials; caveat: some studies compared vs. sharp edge IOLs. **PMMA vs. Silicone** **BCDVA (1 study, 53 eyes):** Favoured silicone (mean difference -0.11; 95% CI -0.16 to -0.06) **PCO score (9 studies, 652 eyes):** SD values missing in 5 studies. No forest plot analysis reported due to statistical heterogeneity; result inconclusive. Mean difference in remaining 4 studies favoured silicone 5.69 (95% CI -1.50 to 12.88). **Nd:YAG rate (6 studies, 478 eyes):** No forest plot analysis reported due to statistical heterogeneity; result inconclusive. Favoured silicone (OR 1.69; 95% CI 0.58 to 4.91) **PMMA vs. Hydrogel** **BCDVA (1 study, 53 eyes):** No significant difference; mean diff: 0.06 (95% CI -0.02 to 0.14). **PCO score (2 studies, 105 eyes):** Favored PMMA ; mean diff: -17.0; 95% CI -27.69 to -6.31 **Nd:YAG rate (1 study, 53 eyes):** No significant difference (OR 0.43; 95% CI 0.11 to 1.69) **PMMA vs. Acrylic** **BCDVA:** No study identified. **PCO score (5 studies, 449 eyes):** SD values missing in 2 studies. No forest plot summary analysis reported due to statistical heterogeneity; result inconclusive. Mean difference in remaining 3 studies favoured acrylic IOLs 6.55 (95% CI 1.18 to 11.91). All studies compared sharp acrylic with round PMMA. **Nd:YAG rate (2 studies, 229 eyes):** Favoured acrylic (OR 7.19, 95% CI 2.72 to 18.96). All studies compared sharp acrylic vs. round PMMA. **Acrylic vs. Hydrogel** **BCDVA (3 studies, 324 eyes):** Favoured acrylic (mean diff: 0.10; 95% CI 0.05 to 0.16). **PCO score (4 studies, 440 eyes):** Favoured acrylic. SD values not reported in 2 studies. No forest plot summary analysis reported due to statistical heterogeneity; result inconclusive. Mean difference of remaining 2 studies (both comparing sharp acrylic vs. round hydrogel) was -24.71 (95% CI -53.08 to 3.67). **Nd:YAG rate (4 studies, 440 eyes):** Favoured acrylic (OR 0.18; 95% CI 0.02 to 1.38). **Hydrogel vs. All Other Materials** **BCDVA (4 studies, 377 eyes):** Favoured all other materials (mean difference -0.09; 95% CI -0.13 to -0.06). **PCO score (5 studies, 429 eyes):** Significantly higher in hydrogel group (mean dif: 12.39; 95% CI 9.82 to 14.95). **Nd:YAG rate (4 studies, 387 eyes):** More cases in hydrogel group (OR 8.37; 95% CI 3.74 to 20.36). **Heparin surface modified PMMA vs. PMMA** **BCDVA:** No study identified. **PCO score:** No study identified. **Nd:YAG rate (1 study, 250 eyes):** Significantly lower capsulotomy rate in heparin surface modified PMMA (OR 0.26; 95% CI 0.15 to 0.45). **Silicone vs. Hydrogel:** No studies identified.	VA chosen as primary outcome since authors expected more studies reporting VA than PCO scores, and VA would be easier to compare than different types of PCO. PCO scoring systems varied largely among studies (subjective, objective or both). Findl et al. converted PCO results to a "common PCO score" ranging from 0 (no PCO) to 100 (maximum PCO score) in order to calculate the overall effect (mean difference). Different follow-up periods were used in the included studies (had to have follow-up of at least 12 months). Apart from PCO score and Ng:YAG capsulotomy rates, little evidence on patient oriented outcomes (visual acuity, contrast sensitivity, general vision related quality of life).

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Findl et al. (19) 2007 *Continued*		**Acrylic vs. Silicone** **BCDVA (2 studies, 107 eyes):** No forest plot summary analysis reported due to statistical heterogeneity; result inconclusive. No significant difference (mean difference -0.04; 95% CI -0.10 to 0.02). **PCO score (10 studies, 842 eyes):** SD values missing in 5 studies. Mean difference in remaining 5 studies did not show significant difference (0.00; 95% CI -0.06 to 0.05). **Nd:YAG rate (8 studies, 681eyes):** SD values not reported in 1 study. Remaining 7 studies did not show significant difference (OR 0.56; 95% CI 0.25 to 1.28). When looking only at 5 studies (459 eyes) that compared sharp edge acrylic vs. sharp edge silicone, overall effect was 0.57 (95% CI 0.21 to 1.60). **Optic Design** ▪ Significantly less PCO in sharp edge than in round edge IOLs of the same optic material. ▪ Pooled results of all studies comparing sharp vs. round edges (irrespective of the optic material) showed a clear difference between the edge designs in terms of BCDVA, PCO rates and Nd:YAG rate. No clear evidence for a significant effect of a laser ridge in PMMA IOLs on development of PCO. **Sharp vs. Round Edges in PMMA IOLs** **BCDVA (1 study, 64 eyes):** No significant difference (mean diff: -0.05; 95% CI -0.18 to 0.08) **PCO score (1 study, 64 eyes):** Significantly higher PCO score in round edge IOLs (mean diff: -28.3; 95% CI -40.95 to -15.65). **Nd:YAG rate (1study, 64 eyes):** Significantly higher rate in round edge IOLs (OR 0.24; 95% CI 0.07 to 0.85). **Sharp vs. Round Edges in Acrylic IOLs** **BCDVA (2 studies, 200 eyes):** Favoured sharp edge (mean diff: 0.06; 95% CI 0.01 to 0.12). **PCO score (3 studies, 334 eyes):** Favoured sharp edge. No forest plot summary analysis reported due to statistical heterogeneity; result inconclusive. Mean difference was -10.47; (95% CI -17.23 to -3.72). **Nd:YAG rate (2 studies, 200 eyes):** Favoured sharp edge (OR 0.07; 95% CI 0.02 to 0.32). **Sharp vs. Round in Silicone IOLs** **BCDVA (2 studies, 196 eyes):** Sharp significantly better in 1 study; no significant difference in second study. No forest plot summary analysis reported due to statistical heterogeneity; result inconclusive. Mean difference 0.06 (95% CI 0.00 to 0.12). **PCO score (5 studies, 462 eyes):** Favoured sharp edge. No forest plot summary analysis reported due to statistical heterogeneity; result inconclusive. Mean difference -8.24 (95% CI -14.04 to -2.44). **Nd:YAG rate (4 studies, 390 eyes):** Favoured sharp edge (OR 0.18; 95% CI 0.04 to 0.72). **Sharp vs. Round in Any IOL Material** **BCDVA (7 studies, 692 eyes):** Favoured sharp edge. No forest plot summary analysis reported due to statistical heterogeneity; result inconclusive. Mean difference 0.09 (95% CI 0.02 to 0.15). **PCO score (15 studies, 1,451 eyes):** Favoured sharp edge. SD values not reported in 3 studies. No forest plot summary analysis reported due to statistical heterogeneity; result inconclusive. Mean difference of remaining 12 studies was -8.65 (95% CI -10.72 to -6.59). **Nd:YAG rate (11 studies, 1,078 eyes):** Favoured sharp edge (OR 0.19; 95% CI 0.11 to 0.35). No significant difference. SD not reported in 1 study. Mean diff of 2 remaining studies 0.0 (95% CI -0.04 to 0.04). **PCO score (6 studies, 943 eyes):** No significant difference. SD not reported in 1 study. Mean difference of remaining 5 studies was 0.48 (95% CI 0.02 to 10.24). **Nd:YAG rate (3 studies, 755 eyes):** No significant difference (OR 0.48; 95% CI 0.02 to 10.24). **1 Piece vs. 3 Piece PMMA IOLs** **BCDVA:** No studies identified. **PCO score:** No studies identified. **Nd:YAG rate (1 study, 314 eyes):** No significant difference (OR 0.94; 95% CI 0.59 to 1.51).	

Author & Pub. Year	Objective, Method & Outcomes	Results	Comment
Li et al. (7) 2008 Lit. search cutoff date: June 2006	Examine effect of sharp edge hydrophobic acrylic IOL on development of PCO compared to silicone or PMMA IOLs. Method: Meta-analysis of RCTs Outcomes: PCO score Nd:YAG capsulotomy rate % having BCVA 0.5 or better	10 RCTs with 1,202 eyes **Quality** 1 double blind; 2 single blind; 1 open; 6 unclear No trials conducted intent to treat 1 reported sample size calculation 9 reported dropouts/withdrawals **PCO Score** Acrylic vs. round silicone (SMD -0.25; 95% CI -0.42 to -0.08; p=0.003) Acrylic vs. sharp silicone (SMD 0.48; 95% CI0.29 to 0.68; p<0.00001) Acrylic vs. round PMMA (SMD -1.07; 95% CI -1.29 to -0.85; p<0.00001) **Nd:YAG Capsulatory Rate** Acrylic vs. round silicone (OR 0.29; 95% CI 0.14 to 0.62; p=0.001) Acrylic vs. sharp silicone (OR 1.72; 95% CI 0.23 to 13.13; p=0.60) Acrylic vs. round PMMA (OR 0.09; 95% CI 0.04 to 0.20; p<0.00001) **BCVA** Acrylic vs. round silicone (OR 2.28; 95% CI 0.66 to 7.82; p=0.19) Acrylic vs. round PMMA (OR 3.20; 95% CI 0.78 to 13.16; p=0.11)	Poor study quality overall. Very limited information about quality reported in the primary studies. Variable systems for analysis of PCO. Not all are objective or have limited evidence for validity. Variable lengths of follow-up. No change in VA was documented between IOL groups. The patients who underwent an Nd:YAG capsulotomy usually were excluded from the BCVA analysis. Visual acuity after cataract surgery with IOL implantation can be reduced by many factors other than PCO, and therefore may not be suitable as a sole measure of PCO grading.
Cheng et al. (20) 2007 Lit. search cut-off date: Oct. 2006	Examine effect of different IOL materials and optic edge design in preventing PCO. Methods: Meta-analysis of RCTs Conventional considered: PMMA and round edge Hydrogel is hydrophilic acrylic Outcomes: PCO Score Nd:YAG capsulotomy rate	23 trials included **Nd:YAG capsulotomy rate (pooled risk difference [95% CI])** Acrylic vs. PMMA (5 trials; n=987 eyes) -24% (-29% to -20%) Silicone vs. PMMA (8 trials; n=826 eyes) -9% (-17% to -1%) Silicone vs. Acrylic (7 trials; n=939 eyes) 4% (-2% to 10%) Hydrogel vs. PMMA (1 trial; n=53 eyes) 14% (-8% to 36%) Hydrogel vs. Acrylic (3 trials; n=332 eyes) 19% (8% to 30%) Hydrogel vs. Silicone (1trial; n=50 eyes) 28% (10% to 46%) **Sharp vs. Round Edge** PMMA (1 trial; 34 eyes) -47% (-77% to -17%) Acrylic (2 trials; 200 eyes) -22% (-47% to 2%) Silicone (5 trials; 587 eyes) -9% (-17% to 0%) **PCO rate (pooled risk difference [95% CI])** Acrylic vs. PMMA (1 trial; n=530 eyes) -39% (-47% to -31%) Silicone vs. PMMA *Not reported* Silicone vs. Acrylic (3 trials; n=236 eyes) -14% (-29% to 0%) Hydrogel vs. PMMA *Not reported* Hydrogel vs. Acrylic (3 trials; n=238 eyes) 56% (36% to 75%) Hydrogel vs. Silicone (1 trial; n=102 eyes) 48% (31% to 64%) **Sharp vs. Round Edge** PMMA *Not reported* Acrylic (1 trial; 53 eyes) -28% (-50% to -7%) Silicone (4 trials; 222 eyes) -37% (-46% to -27%)	Follow-up ranged from 12 to 62.5 months. Quality scores indicated studies were fair to good quality. Several methods for measuring PCO and numerous ways to report PCO. Assessment criteria for performing Nd:YAG varied (e.g., eye lost ≥2 decimal lines of acuity or eye had visual acuity of ≤ 20/25 or patient reported blurred vision). Analysis of materials did not account for edge designs.

Author & Pub. Year	Objective, Method & Outcomes	Results	Comment
Leyland et al. (21) 2006 (Literature search cut-off July 2006)	Assess visual effects of multifocal compared to standard monofocal IOLs. Method: Meta-analysis of RCTs. Outcomes: *Primary:* Distance and near visual acuity Spectacle dependence *Secondary:* Depth of field Contrast sensitivity Glare Quality of life/visual function	10 RCTs included **Overall quality poor/fair** 3 were double masked 7 reported withdrawals 5 reported method of randomization 3 reported method of masking ***Objective Results*** **Distance visual acuity (multifocal vs. monofocal)** Unaided Proportion achieving < 6/6: OR 1.05 (95%CI, 0.67 to 1.63) (I^2=0%) Mean distance acuity: SMD 0.03 (95%CI, -0.13 to 0.19) (I^2=42%) Best corrected Proportion achieving < 6/6: OR 1.04 (95%CI, 0.75 to 1.46) (I^2=66%) Mean distance acuity: SMD 0.15 (95%CI, -0.01 to 0.31) (I^2=37%) **Near vision (multifocal vs. monofocal)** Heterogeneity (p=0.0006) and poor methodological data collection: variable outcome measures 2 studies "explicitly" reported near acuity: 1 study reported significantly improved acuity with multifocal IOLs while the other study found no significant difference. (Both used logMAR reading charts with acuity calculate corrected for reading distance). All studies found improvement with use of multifocals **Depth of field** 4 studies reported better acuity (amount of defocus consistent with retention of useful acuity) with multifocal IOLs **Contrast sensitivity** 7 studies variably described methods and outcomes precluding combined analysis (e.g., contrast sensitivity; visual acuity at different contrast levels; difference between high and lower contrast acuity) All studies reported lower contrast sensitivity with multifocal IOLs. **Glare** 3 studies reported results precluding combined analysis. All reported no significant differences between multifocal and monofocal lenses. ***Subjective Results*** **Satisfaction with vision** Validated instruments used by 4 studies. Data could not be combined for meta-analysis. 2 studies found significant differences and 2 studies did not. **Glare and halos** 4 studies reported proportion of patients with glare and halos significantly less frequent in the monofocal group: OR 3.55 (95%CI, 2.11 to 5.96) **Spectacle dependence** In all studies, the majority of multifocal patients still used spectacles for some tasks, usually small print. Spectacle independence achieved more with multifocal IOLs: OR 0.17 (95%CI, 0.12 to 0.24) **Complications** Incidence of complications was low and similar in multifocal and monofocal groups.	8 studies involved patients with surgery in one eye only. Unilateral studies are of limited use when trying to measure effect of multifocal IOLs on quality of life, especially when the fellow eye has good vision. Unaided near vision critical to assessment of multifocal efficacy but reported in a manner that made comparison between studies difficult. Reading distances differed and unclear whether reported print size read had been corrected for reading distance to allow a near acuity to be calculated. Jaeger cards not standardized between manufacturers so J3 from one study cannot be assumed to be the same as J3 from another. In no study did more than 50% of the multifocal IOL patients achieve spectacle independence.

<table>
<tr><th>Author & Pub. Year</th><th>Objective, Method & Outcomes</th><th>Results</th><th>Comment</th></tr>
<tr><td>Findl and Leydolt (25) 2007

Lit. search cut-off date: Oct. 2006</td><td>Assess visual acuity after implantation of accommodative IOLs.

<u>Outcomes:</u>
Distance corrected near VA

BCNVA</td><td>Visual acuity data were variably reported (details below). No RCTs were identified.

<table>
<tr><th>Author</th><th>N</th><th>Follow-up</th><th>Reading Chart</th></tr>
<tr><td>Koeppl et al.</td><td>21</td><td>3 mo</td><td>Jaeger chart at 33 cm</td></tr>
<tr><td>Alio et al.</td><td>24</td><td>1 y</td><td>Snellen chart at 40 cm</td></tr>
<tr><td>Cumming et al.</td><td>48</td><td>1 mo</td><td>Rosenbaum chart at 14 inches</td></tr>
<tr><td>Marchini et al.</td><td>20</td><td>6 mo</td><td>Jaeger chart at 30 cm</td></tr>
<tr><td>Buratto et al.</td><td>69</td><td>1 y</td><td>Jaeger chart at 35 cm</td></tr>
<tr><td>Cumming et al.</td><td>246</td><td>1 y</td><td>MN Read acuity chart at 16 inches</td></tr>
</table>

<table>
<tr><th>Author</th><th>DCNVA Accommodating</th><th>DCNVA Control</th><th>BCNVA Accommodating</th><th>BCNVA Control</th></tr>
<tr><td>Koeppl et al.</td><td>J4 (median)</td><td>-</td><td>J1</td><td>-</td></tr>
<tr><td>Alio et al.</td><td>0.8 ±0.2</td><td>-</td><td>1.0±0.0</td><td>-</td></tr>
<tr><td>Cumming et al.</td><td>96% J3 or better; 100% J5 or better</td><td>-</td><td>100% J3 or better</td><td>-</td></tr>
<tr><td>Marchini et al.</td><td>J7.3±2.1</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Buratto et al.</td><td>13% J1 or better; 55% J3 or better</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Cumming et al.</td><td>24.8% J1 or better; 90.1% J3 or better</td><td>-</td><td>96% J1 or better; 100% J3 or better</td><td>-</td></tr>
</table>
</td><td>Of the 3 types of accommodative lenses included in their review, only AT-45 Cyrstalens is currently licensed by Health Canada, therefore only results pertaining to that IOL are discussed.

No RCTs were identified.
6 nonrandomized studies included.

Limitations included lack of stringent inclusion criteria, e.g. the objective of Alio et al. was to “investigate potential for near vision restoration using 3 IOL models (multifocal and accommodative) after presbyopic lens exchange (PRELEX).” Patients did not have to have cataracts. Furthermore, some patients in both groups had LASIK 6 months after IOL implantation. VA results were reported up to 1 year.

Authors concluded that there were large discrepancies in near VA data.</td></tr>
</table>

BCDVA refers to best corrected distance visual acuity; BCNVA, best corrected near visual acuity; BCVA, best corrected visual acuity; CI, confidence interval; DCNVA , distance corrected near visual acuity; I^2, to heterogeneity; J, Jaeger chart; logMAR, logarithm of the minimum angle of resolution (score of 0 equals 6/6 or 20/20 vision); Mo, month; Nd:YAG, neodymium:yttrium-aluminum-garnet laser treatment; OR, odds ratio; PCO, posterior capsule opacification; PMMA, polymethyl methacrylate; SD, standard deviation; Y, year.

Appendix 3: Results of Studies Published After the Meta-Analyses

A3(1): Results of Studies on Posterior Opacification

Author & Pub. Year	Objective	Method	Outcomes	Results	Comment
Kugelberg et al. (32) 2008	Evaluate PCO 2 years after cataract surgery following implantation of a **hydrophilic or hydrophobic sharp edged IOL.** Follow-up of study included in PCO Cochrane review (Kugelberg et al. (58))	N=120 patients Surgery performed in 1 eye per patient. Prospectively randomized. 2 year follow-up	1° outcome: PCO 2° outcome: logMAR VA (2.5% and 100% contrast) glare disability	Hydrophobic (n=58 patients) vs. Hydrophilic (n=57 patients) median (range) PCO area (%) 4.5 (0 to 71) vs. 46 (0 to 100), p<0.001 PCO severity 0.045 (0 to 0.83) vs. 0.74 (0 to 2.2), p<0.001 Nd:YAG rate total, n (%) 6 (10) vs. 24 (42), p<0.001) BCVA (high contrast) -0.02±0.09 vs. 0.05±0.14, p<0.01 Low contrast VA (2.5%) 0.50 ±0.15 vs. 0.61± 0.22, p<0.01 Glare 0.004± 0.11 vs. 0.12±0.18, p<0.001	Masking of patients/examiners unknown No sample size calculation 5 patients LTF (details provided) ITT not discussed POCOman software –calculates %PCO by area within whole capsulorhexis and a score for PCO severity. Low contrast VA (unknown if corrected or uncorrected). Glare measured with Brightness Acuity Test Not know how VA measured (assuming near VA). Partially supported by grant from manufacturer.
Hayashi and Hayashi (33) 2007	Compare PCO and visual functions between eyes with an **acrylic vs. silicone IOL of the same optic design and haptics** up to 36 months after implantation.	N=100 patients Acrylic implanted in one eye and silicone implanted in fellow eye in each patient. Prospective Randomized. Patients and examiners masked. 3 year follow-up	1° outcome: PCO 2° outcome: Nd:YAG logMAR BCVA Contrast VA Glare VA (contrast VA in presence of a glare source)	9 patients lost to follow-up (89 remained). No significant difference found in: PCO density value (p=0.96) Nd:YAG capsulotomy (p=0.19) BCVA (no p value reported) Photopic (daylight vision) or mesopic (intermediate light vision) contrast sensitivity with or without glare.	PCO density value measured using Scheimpflug videophotography. Post hoc power calculation showed 99% power to detect clinically meaningful PCO difference between acrylic and silicone. Actual data for PCO/VA not reported (comparisons presented in figures only). Not know how VA measured (what charts and if distance corrected). Patients and examiners masked. Nd:YAG performed when an eye lost 2 ore more decimal lines of VA or if patient complained of blurred vision. 9 patients LTF (details provided). No funding from manufacturer.

Author & Pub. Year	Objective	Method	Outcomes	Results	Comment
Leydolt et al. (34) 2007	Compare PCO between **1-piece and 3-piece haptic designs of foldable hydrophobic acrylic** IOL Follow-up of study included in PCO Cochrane review (Sacu et al. (53))	N=52 patients IOL bilaterally inserted. Prospective Randomized Double blind-stated in abstract only 5 year follow-up	1° outcome: PCO score 2° outcome: Nd:YAG BCDVA	24 patients not available for 5 year follow-up exam (25 remained). No significant difference in mean (standard deviation) PCO score at 5 years using image analysis software: 1 piece 1.7±1.7; 3 piece 1.3±1.4; p=0.30 No significant difference in PCO score at 5 years using slit lamp: 1 piece 1.6±1.9; 3 piece 1.1±1.5; p=0.24 No significant difference in BCDVA: 0.8±0.2 in both groups, p=0.40 No significant difference in Nd:YAG: 1 piece (4 patients); 3 piece (3 patients), p=0.40	No sample size calculation. VA measured with Snellen chart. Approximately 50% drop out PCO calculated subjectively using slit lamp and objectively using automated image analysis software developed by authors. Post hoc power calculation for the observed standard deviation of the 25 patients (50 eyes) showed that a clinically relevant difference of PCO score of 1 (i.e., 10%) could be calculated with a 90% power at an alpha level of 5%. Results by Sacu et al. showed a slight but significant difference with more PCO in 1 piece compared with 3 piece IOL eyes 1 year after surgery. **This was not seen 2 and 5 years after surgery.** Funding from manufacturer not specified.
Zemaitiene et al. (35) 2007	Compare PCO between **1-piece and 3-piece haptic designs of hydrophobic acrylic** IOL. Not explicitly stated by authors, but possible follow-up of study included in Cochrane review (Zemaitiene et al. (54)	N=74 patients IOL bilaterally inserted. Prospective Randomized Not blinded 2 year follow-up	1° outcome: PCO score 2° outcome: Nd:YAG BCVA	16 patients did not participate in 2 year follow-up (58 remained). **Mean (standard deviation) PCO values (measured with image analysis system)** Significant difference at 6 months 3 piece 0.002±0.009; 1 piece 0.007±0.017; p=0.04 Significant difference at 1 year 3 piece 0.004±0.016; 1 piece 0.026±0.041; p=0.001 No significant difference in PCO score at 2 years 3 piece 0.136±0.223; 1 piece 0.154±0.190; p=0.18 No significant difference in BCVA at 2 years (no data provided). Not stated whether distance or near BCVA was examined. No significant difference in Nd:YAG at 2 years: No case of PCO with a decrease of ≥2 lines of VA that required Nd:YAG laser capsulotomy in either group.	No sample size calculation. 16 LTF (details provided) PCO calculated using photographic image analysis system (EPCO2000) developed by one of the authors. No a priori or post hoc power calculation reported. Blinding of patient/examiner not reported. Results by Zemaitiene et al. in 2004 showed a slight but significant difference with more PCO in 1 piece compared with 3 piece IOL eyes 1 year after surgery. **This was not seen at 2 years after surgery.** Funding from manufacturer not specified.

BCDVA refers to best corrected distance visual acuity; BCVA, best corrected visual acuity; IOL, intraocular lens; ITT, intent to treat analysis; logMAR, logarithm of the minimum angle of resolution (score of 0 equals 6/6 or 20/20 vision); Nd:YAG, neodymium:yttrium-aluminum-garnet laser treatment; PCO, posterior capsule opacification; VA, visual acuity.

A3(2): Results of Studies on Modified Prolate Anterior Surface IOLs

<table>
<tr><th>Author & Pub. Year</th><th>Objective</th><th>Method</th><th>Outcomes</th><th>Results</th><th>Comment</th></tr>
<tr><td>Kennis et al. (36) 2004</td><td>Compare contrast sensitivity of an aspherical modified prolate anterior surface 3-piece IOL with 2 standard spherical IOLs (1 of which was single-piece blue light filtering and the other was a three-piece non-blue light filtering IOL).</td><td>98 eyes of 71 patients

Prospective
Randomized
Not blinded

6 months follow-up</td><td>No explicit primary objective.
BCVA
(Snellen chart)
Contrast sensitivity</td><td>There was no significant difference in BCVA between the groups (not reported if near or distant VA).

The BCVA results are assumed to be expressed as mean (standard deviation) decimal visual acuity since this was not explicitly reported in the study.

<table><tr><th></th><th>Aspherical modified prolate anterior surface IOL (3 piece)</th><th>Spherical IOL (3 piece)</th><th>Spherical Blue Light Filtering IOL (single piece)</th></tr><tr><td>BSCVA</td><td>1.00 ± 0.13</td><td>0.97 ± 0.12</td><td>0.99 ± 0.13</td></tr></table>
<u>Contrast Sensitivity</u>
Compared with the spherical IOL, the modified prolate IOL showed significantly better results at 1 and 12 cycles per degree in photopic conditions; at 3, 12, and 18 cycles per degree, in photopic with glare; at 3, 12, and 18 cycles per degree in mesopic and at 12 and 18 cycles per degree in mesopic with glare.

Compared with the spherical blue light filtering IOL, the modified prolate IOL provided significantly better contrast sensitivity at almost all spatial frequencies in any lighting condition.

Clinical significance of the contrast sensitivity results was not discussed by the authors.</td><td>No sample size calculation.

No information about dropouts or if consecutive patients were randomized.

3 different lenses compared (in terms of pieces and filtering).

Contrast sensitivity measured using Functional Acuity Contrast Test chart in the Stereo Optical Digital Contrast Sensitivity Tester.

VA measured with a Snellen chart.

Funding from manufacturer not specified.</td></tr>
</table>

BSCVA refers to best spectacle corrected visual acuity; IOL, intraocular lens; VA, visual acuity.

A3(3): Results of Studies on Blue Light Filtering IOLs

Publication Date	Objective	Method	Outcomes	Results	Comment
Marshall et al. (39) 2005	Evaluate safety and effectiveness of a blue light filtering IOL.	N=297 patients IOL bilaterally inserted. Prospective Randomized Patient masked 6 months to 1 year follow-up.	No 1° outcome reported Contrast sensitivity (at 6 months) BCDVA (at 1 year) using Snellen chart. PCO (6 months)	Blue filter IOL n=150 patients Regular single piece IOL (Acrysof SA30AL) n=147 patients **PCO** Blue filter: no cases of clinically significant PCO or PCO requiring Nd:YAG Regular IOL: 1 clinically significant PCO, none requiring Nd:YAG **BCDVA** No significant difference noted between the IOLs. **Contrast Sensitivity** No clinically significant differences under photopic or mesopic conditions (p=0.6220) **Colour Perception** No statistically significant differences noted between the IOLs (p=0.2669)	Concentration of chromophore in blue filtering IOL results in a transmission curve that best resembles that of a 25 year old natural crystalline lens (ability of lens to filter blue light decreases with age). Contrast sensitivity measured with CSV1000E contrast sensitivity unit at 8 feet under photopic and mesopic conditions. No sample size calculation. Possible type 2 error. For contrast sensitivity, **clinical significance was defined as a difference of ≥0.3 log units at ≥2 spatial frequencies.** Inconclusive whether blue light is a risk factor for age related macular degeneration. No clinical trials comparing effect of blue filtering IOLs and non-blue filtering IOLs on macular toxicity performed to date. Funding from manufacturer not specified.
Barisic et al. (40) 2007	Examine clinical effects of blue filter IOL.	N=60 patients IOL bilaterally implanted Prospective Randomized 6 months follow-up	No 1° outcome reported. UCVA BCVA Nd:YAG rate Patient satisfaction Subjective colour perception	**UCVA** No significant difference (UCVA better than 0.8 [20/25] was achieved in 86.7% of patients in the blue filter group and 85.0% of those in the control group), p=0.793 **BCVA** All patients achieved BCVA better than 0.8 (20/25), no p value reported. **Nd:YAG Rate** No significant difference between the groups (p=0.50). **Patient satisfaction** 96.7% of the blue filter group would implant the same IOL again. **Subjective Colour Perception** None of the patients reported any colour perception disturbances in photopic or mesopic conditions.	No sample size calculation. Limited reporting of data. Possible type 2 error. Funding from manufacturer not specified.

Publication Date	Objective	Method	Outcomes	Results	Comment
Bhattacharjee et al. (38) 2006	Compare effects of blue filter IOL with regular IOL.	N=13 patients (26 eyes) Blue filter IOL implanted in one eye and regular IOL implanted in fellow eye of each patient. Prospective Randomized Patients masked 18 months follow-up	No 1° outcome reported. BCDVA (Snellen chart) Colour vision Contrast sensitivity (Pelli Robson chart)	**BCDVA** No significant difference between groups (blue filter group: improved to 20/20 in 12 eyes and to 20/30 in 1 eye; regular IOL: improved to 20/20 in all cases, p=0.30). **Colour Vision** Postoperative improvement between groups was comparable without any significant difference in the total score (p=0.19), blue-yellow partial error scores (p=0.07), and the red-green partial error scores (p=0.66). **Contrast Sensitivity** No significant difference between groups (p=0.26).	No sample size calculation. No reporting whether patients were consecutively randomized. Contrast sensitivity measured via Pelli Robson chart. Possible type 2 error. Funded by a Health and Educational Foundation in India.
Espindle et al. (41) 2005	Compare patient reported vision related and health related functioning following implantation of a blue filter IOL and a non-blue light filtering (Acrysof single piece) IOL.	N=257 Bilateral implantation Prospective Randomized Double masked 6 month follow-up	Health related quality of life questionnaires (National Eye Institute's visual Functioning Questionnaire [NEI VFQ-39] and Short Form Health Survey [SF-12]).	N=257 **Primary treatment comparisons performed for:** VFQ composite score, colour vision driving scales SF-12 physical and mental component No significant difference in the 5 primary comparisons.	Detailed sample size calculation reported. Last observation carried forward analysis. Patient and data collector masked. Funded by competing manufacturer.

BCDVA refers to best corrected distance visual acuity; BSCVA, best spectacle corrected visual acuity; IOL, intraocular lens; Nd:YAG, neodymium:yttrium-aluminum-garnet laser treatment; PCO, posterior capsule opacification; UCDVA, uncorrected distance visual acuity; UCNVA, uncorrected near visual acuity; UCVA, uncorrected visual acuity; VA, visual acuity.

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