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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Protocol Amendments

Section	Amendment	Page	Rationale
Objectives	"aphakia following the surgical removal of a cataract" and "aphakia" were updated to "non-congenital aphakia"	8	To appropriately reflect the scope of the review, which includes all types of non-congenital aphakia, including trauma-induced aphakia, rather than limiting to cataract surgery-related aphakia
Research Questions	A research question, as follows, was added: "What is the comparative safety of IOL implantation in infants of up to 12 months of age versus IOL implantation after 12 months of age for pediatric patients with non-congenital aphakia?" Of note, this question was added as number 4; therefore, the numbering of the research questions was updated accordingly. Where appropriate, question 4 was added throughout the protocol such as in Table 1, and the wording around the comparison between infants and children was updated throughout the protocol (e.g., Introduction, Objectives, Methods) to reflect that clinical effectiveness, safety, and cost-effectiveness will all be in the scope of this review.	8	To fully assess safety outcomes of IOL implantation in all relevant age groups for this review and to complement the existing research question on comparative effectiveness in pediatric patients who received IOL implantation 12 months of age or younger versus pediatric patients who received IOL implantation after 12 months of age and up to 12 years
Protocol Amendments	The process for updating the project protocol on PROSPERO and the CADTH website was clarified as follows: "Updates to the PROSPERO submission (CRD42021231143) and the project protocol on the CADTH website will be made, as appropriate."	19	To fully describe the process that will be used to update the project protocol, which involves not only PROSPERO as described in the original protocol, but also the CADTH website

IOL = intraocular lens implantation.

Abbreviations

HTA	health technology assessment
IOL	intraocular lens
logMAR	logarithm of the minimum angle of resolution
MA	meta-analysis
PICO	population, intervention, comparator, outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life-year
RoB 2	Cochrane risk-of-bias tool for randomized trials
RoBANS	Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS)

Introduction and Rationale

Aphakia and Cataracts in Pediatric Patients

Aphakia is a condition in which the eye does not have a lens — the flexible structure that enables the focus of light on the retina. There are 3 main causes of aphakia: loss of lens following surgical removal of a cataract, trauma causing the lens to be moved from its normal position, and a genetic defect leading to congenital aphakia.[1] Cataract surgery is the leading cause of aphakia, including aphakia in pediatric patients,[1,2] whereas congenital aphakia is a rare condition usually occurring with other complications.[3,4]

A cataract, defined as the clouding of the eye's lens, is the most common treatable cause of visual disability in pediatric patients.[5,6] Congenital cataract is present at birth, whereas infantile cataract may develop in the first 6 months of life.[5] Hereditary factors and infections, metabolic problems, trauma, inflammation, or drug reactions have been associated with congenital and infantile cataracts.[5-7] An attending health care professional at birth may refer a baby with suspected congenital cataract to an ophthalmologist for a full examination. Outward signs in pediatric patients that may suggest cataract-related visual impairment include difficulty focusing on particular objects, developing a squint (strabismus), wobbly movement in the eyes (nystagmus), and holding the head at a certain angle to see.[5,6]

Importance of Early Intervention for Congenital Cataracts and Resulting Aphakia

Severe limitations in vision that persist beyond the first 3 to 4 months of life when the brain most rapidly learns to see cannot be restored completely.[8] Thus, the early diagnosis and treatment of cataracts in pediatric patients — including congenital cataracts and other limitations in vision — are crucial, as they can prevent the development of irreversible amblyopia (whereby the brain and eye do not work well together, causing poor vision) due to stimulus deprivation and the significant associated impact on neurobiological development.[9] Visually significant cataracts should therefore be removed during infancy. The optimal age for performing cataract surgery in a child is 6 weeks for unilateral congenital cataracts and 8 weeks for bilateral congenital cataracts.[6] However, according to information available on the American Academy of Ophthalmology website, surgery should be deferred if a child has visually insignificant cataracts, normal visual behaviour, and fundi that are clearly visible through an ophthalmoscope.[6] The removal of the natural crystalline lens during cataract surgery results in aphakia and the associated loss of accommodation and refractive power of the natural lens. Accommodation refers to the adjustment of the eye for seeing objects at various distances;[10] refractive power describes the ability of the lens to bend light rays that enter the eye onto the retina, allowing the eye to focus on objects.[11] Thus, in pediatric patients, the refractive error due to aphakia must be corrected promptly to ensure normal vision development and obtain a good final visual acuity.[5,12]

Interventions Currently Used for the Management of Aphakia

Refractive options for aphakic correction after cataract removal include conventional interventions (i.e., glasses or contact lenses) and intraocular lens (IOL) implantation, each with some limitations. Glasses for aphakia require a strong prescription, making them thick and heavy, causing optical and visual field distortions. As well, a well-fitting pair that stays on a baby's face is difficult to find.[5,13] Further, for unilateral aphakia, image size disparities from glasses can disrupt the proper development of binocular vision.[6] Contact lenses provide better optical quality than glasses and they allow easier adjustments in power for the

rapidly changing eyes in pediatric patients.[6] However, they can be costly, get lost easily, cause irritation and infection in the eyes, and be inconvenient to handle and keep hygienic.[13-15] These factors may lead to poor adherence with long-term use, resulting in suboptimal visual outcomes.[6,13] An IOL is a tiny, artificial lens made of silicone, acrylic, or other plastic compositions and is used to replace the eye's natural lens that is removed during cataract surgery.[11] Unlike a contact lens, the IOL is permanently fixated inside the eye so it cannot fall out or produce sensations that the patient can feel and it does not change the appearance of the eye or require cleaning.[16] An IOL offers an alternative to avoid the potential for visual distortion associated with aphakic glasses and the inconvenience and risk of nonadherence with contact lenses.[14] The IOL may be implanted at the time of lens removal (primary implantation) or the implantation may be postponed for a period of time following lens removal (secondary implantation) during which aphakia is corrected using a conventional intervention.[17] IOL implantation is meant to occur once and provide a permanent solution to aphakia; however, it is difficult to correctly estimate the power needed for an IOL in an infant's eye. The difficulty results from significant changes in the power requirements as the infant grows, due to the rapidly changing axial length (the distance between the front of the eye and the back of the eye) and given the fixed power of the IOL at the time of implantation. Thus, the growing eye will experience a myopic shift, increasing nearsightedness and requiring glasses for correction.[5,6] Also, more surgery may be needed to remove inflammatory membranes that grow across the artificial lenses after IOL implantation in pediatric patients' eyes.[5,18]

Uncertainty and Rationale for Systematic Review

Aphakic glasses and contact lenses have been used in all populations regardless of age without a debate about suitability. However, there is some controversy about the appropriate age for IOL implantation. For example, a 2017 publication by Vasavada and Vasavada has indicated a general acceptance of IOL implantation to correct aphakia in patients aged 2 years or older.[19] In contrast, a meta-analysis (MA) by Chen et al. (2020) found that after cataract extraction, primary IOL implantation achieved better visual outcomes than wearing contact lenses in patients younger than 2 years, without a higher risk for complications.[14] Yet an ophthalmic technology assessment report published by the American Academy of Ophthalmology in 2019 on IOL implantation during early childhood stated that IOL implantation in pediatric patients 6 months of age or younger is not recommended because there is a higher risk of visual axis opacities than with aphakia treated with contact lenses.[18]

The management of childhood cataracts and associated aphakia takes many years. It requires a team effort involving parents, multiple health care professionals in various specialties, and community health workers. Further, the treatment may impose a significant cost burden. For example, Kruger et al. (2015) reported that the 5-year treatment cost of cataract surgery and optical correction in an infant with a unilateral congenital cataract was US$35,293 with IOL and US$33,452 with contact lenses.[20] The evaluation was based on inflation-adjusted US Medicaid data and supply costs, and involved the mean cost of cataract surgery and all additional surgeries, examinations, and supplies used up to 5 years of age. Also, the immature visual system puts infants at a higher risk of developing amblyopia if visual input is defocused or unequal between the 2 eyes. The risk relates to the fact that the eye is in rapid growth, with radical changes during the first year of life.[13] Therefore, the optimal timing of IOL implantation is essential to optimizing visual acuity outcomes, while minimizing complications in pediatric patients, and for balancing health care resources.

The present scientific literature landscape therefore lacks clarity on the ideal timing of IOL implantation. There is a need to determine whether IOL implantation can be safely and effectively used to correct aphakia in infants up to 12 months of age, as well as its cost-effectiveness, relative to conventional treatment for this patient population, and compare the clinical effectiveness, safety, and cost-effectiveness of IOL implantation between infants and children.

Objectives

This systematic review aims to evaluate the clinical effectiveness, safety, and cost-effectiveness of IOL implantation versus conventional treatment (i.e., glasses or contact lenses) in infants with non-congenital aphakia, and to assess the clinical effectiveness, safety, and cost-effectiveness of IOL implantation in infants of up to 12 months of age versus after 12 months of age for pediatric patients with non-congenital aphakia.

Research Questions

The proposed systematic review will identify and summarize the evidence regarding the clinical effectiveness, safety, and cost-effectiveness of using IOL implantation to correct aphakia in pediatric patients by answering the following questions:

1. What is the comparative clinical effectiveness of IOL implantation versus conventional treatment in infants with non-congenital aphakia?
2. What is the safety of IOL implantation in infants with non-congenital aphakia?
3. What is the comparative clinical effectiveness of IOL implantation in infants of up to 12 months of age versus IOL implantation after 12 months of age for pediatric patients with non-congenital aphakia?
4. What is the comparative safety of IOL implantation in infants of up to 12 months of age versus IOL implantation after 12 months of age for pediatric patients with non-congenital aphakia?
5. What is the cost-effectiveness of IOL implantation, compared with conventional treatment, in infants with non-congenital aphakia?
6. What is the cost-effectiveness of IOL implantation in infants of up to 12 months of age compared with IOL implantation after 12 months of age for pediatric patients with non-congenital aphakia?

Table 1 provides details on the specific populations, interventions, comparators, and outcomes of interest in this review.

Methods

A preliminary scoping review of the existing literature, including health technology assessments (HTAs) and systematic reviews, was conducted to inform the preparation of this protocol. The protocol was written a priori in consideration of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guideline for clarity, transparency, and completeness, and it will be followed throughout the study process. Any deviations from the protocol will be disclosed in the final report and updates will be made to the PROSPERO submission accordingly (CRD42021231143).

Study Design

Research Questions 1, 2, 3, and 4 are intended for the review of clinical evidence. The topic of this review does not have a broad scope and the preliminary scoping review did not identify any high-quality systematic reviews that comprehensively address these research questions. Thus, it does not appear that an overview of systematic reviews or an update of existing systematic reviews are appropriate review methods for this review. Therefore, a de novo systematic review of all identified relevant primary studies will be conducted. This approach permits an evaluation of the various population, intervention, comparator, outcome — PICO — elements in a manner suitable to address the research questions.

For Research Questions 5 and 6, a de novo economic evaluation will not be conducted to assess the cost-effectiveness of IOL implantation for aphakia. Instead, relevant cost-effectiveness studies of IOL implantation for aphakia identified through a systematic literature search will be summarized and critically appraised.

Literature Search Methods

The literature search for clinical studies will be performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[21] The preliminary search strategy is presented in Appendix 1.

Published literature will be identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be IOL and juvenile/congenital cataracts or aphakia. Clinical trials registries will be searched: the U.S. National Library of Medicine's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the EU Clinical Trials Register.

No filters will be applied to limit the retrieval by study type. Retrieval will be limited to English-language documents published since January 1, 2010. Conference abstracts will be excluded from the search results. Where possible, retrieval will be limited to the human population.

The initial search will be completed in January of 2021. Regular alerts will update the database literature searches until the publication of the final report. The clinical trials registries search will be updated prior to the completion of the stakeholder feedback period for the draft report. Studies meeting the selection criteria of the review and identified in the alerts prior to the completion of the stakeholder feedback period will be incorporated into the analysis of the final report. Any studies identified after the stakeholder feedback period will be described in the discussion, with a focus on comparing the results of these new studies with the results of the analysis conducted for this report.

Grey literature (i.e., literature that is not commercially published) will be identified by searching sources listed in relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters),[22] which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google will be used to search for additional internet-based materials. These searches will be supplemented by reviewing bibliographies of key papers and through

contacts with experts and industry, as appropriate. The grey literature search will be updated prior to the completion of the stakeholder feedback period for the draft report.

Selection and Eligibility Criteria

Table 1 provides the study eligibility criteria for the research questions. The eligibility criteria were informed by the preliminary scoping review of the existing literature, as well as clinical expert input.

Table 1: Selection Criteria for Research Questions

Population
Questions 1, 2, and 5: • Infants (i.e., aged ≤ 12 months) with non-congenital aphakia **Questions 3, 4, and 6:** • Infants (i.e., ≤ 12 months of age) versus children (i.e., > 12 months and up to 12 years of age) with non-congenital aphakia
Intervention(s)
Questions 1 to 6: • Foldable IOLs implanted in infants (i.e., ≤ 12 months of age)
Comparator(s)
Questions 1 and 5: • Aphakic glasses • Aphakic contact lenses • Conventional treatment for aphakia (e.g., if aphakic glasses and contact lenses are not specified or reported separately) **Question 2:** • Aphakic glasses • Aphakic contact lenses • Conventional treatment for aphakia (e.g., if aphakic glasses and contact lenses are not specified or reported separately) • No comparator group[a] **Questions 3, 4, and 6:** • Foldable IOLs implanted in children (i.e., > 12 months and up to 12 years of age)
Outcomes
Questions 1 and 3 — Clinical effectiveness outcomes limited to the following: • Visual acuity, assessed using any tool (e.g., Teller acuity cards, Snellen chart, Cardiff cards, HOTV matching, LEA Symbols, Tumbling Es) • Health-related quality of life in patients, parents, or caregivers (e.g., patients' dependence on glasses, parent or caregiver stress) **Questions 2 and 4 — Safety outcomes including but not limited to the following:** • Visual axis opacification • Glaucoma • Endophthalmitis • Inflammatory complications • IOL malposition • Retinal detachment • Strabismus • Complications requiring reoperation • Other peri- and post-operative surgical complications, such as macular edema, ocular hypertension, and pupillary capture **Questions 5 and 6 — Cost-effectiveness outcomes limited to the following:** • Cost per benefit gained (e.g., cost per QALY, cost per clinical outcome, or patient adverse event avoided)

Study Design(s)
Included **Questions 1, 3, and 4:** • Randomized controlled trials • Non-randomized controlled trials • Cohort studies[b] • Case-control studies **Question 2:**[a] • Randomized controlled trials • Non-randomized controlled trials • Cohort studies[b] • Case-control studies • Single-arm before-and-after studies • Single-arm interrupted time series **Questions 5 and 6:** • Cost-effectiveness analyses • Cost-utility analyses • Cost-benefit analyses • Cost-minimization studies that provide a literature-based rationale that the outcomes of the studied interventions are equal **Excluded** • Single-arm before-and-after studies (included for Question 2) • Single-arm interrupted time series (included for Question 2) • Cross-sectional studies • Case reports • Case series • Review articles • Qualitative studies • Animal and in vitro studies • Guidelines • Editorials, letters, and commentaries • Studies of any design published as conference abstracts, presentations, posters, or thesis documents • Budget impact analyses or other costing exercises that do not describe both costs and benefits
Time Frame
Studies from 2010 to present[c]

IOL = intraocular lens; QALY = quality-adjusted life-year.

[a] In addition to comparative evidence versus aphakic glasses, aphakic contact lenses, or conventional treatment as comparators, uncontrolled data for IOL will be considered for inclusion to answer Research Question 2.

[b] Cohort studies are defined as studies in which participants are sampled on the basis of exposure and in which outcomes are assessed in a follow-up.[23] This is distinct from case series studies, in which participants are sampled on the basis of the presence of an outcome, or of both an exposure and outcome, where absolute or relative risk cannot be calculated.[23]

[c] IOL implantation for the management of pediatric cataracts became routine practice in many countries more than 10 years ago[24] and, according to clinical expert input, improvements in surgical instruments over the last decade allow for smaller surgical incisions for foldable IOLs that reduce adverse events related to cataract surgeries. Thus, studies from 2010 are likely to capture foldable IOLs and reflect current technology and instrumentation trends for cataract surgery and aphakia correction in pediatric patients.

Screening and Selecting Studies for Inclusion

Inclusion Criteria

Studies will be included if they meet the eligibility criteria outlined in Table 1 and are published in English. Publications in other languages will not be included given the evidence suggesting that excluding non-English language publications from evidence synthesis generally does not change conclusions.[25,26] If multiple publications are identified for the same study, they will all be included and cited. However, only unique data will be extracted without duplication and discussed as a single study.

The population of interest is pediatric patients with non-congenital aphakia. Studies with mixed populations that included patients who do not meet the age eligibility criteria of a specific research question will be considered for inclusion if they reported separate results for the eligible patients or if the eligible patients constituted 95% or more of the entire study population. The 95% threshold was chosen because it is consistent with the convention of setting the alpha at 0.05 (e.g., similar to the P = 0.05 threshold and 95% confidence interval). The decision to include or exclude a study that reported age in mean ± standard deviation will be made by estimating the 95% predictive interval using the t- or z-statistic. Studies with mixed populations that do not report on the age of the included participants in a manner that allows for the assessment of the ≥ 95% rule (e.g., a range without breakdowns or a mean without a standard deviation that can be used with the t- or z-statistic to determine the 95% predictive interval) will be excluded. Based on clinical expert input, it is recognized that congenital aphakia requires different treatment but is rare. Therefore, studies or findings will be excluded if they are specifically on congenital aphakia or if they are on a mix of congenital and non-congenital aphakia. Studies or findings that do not specify the type(s) of aphakia included will be eligible for inclusion.

The intervention of interest is implanted foldable IOLs. Therefore, studies or findings that focused exclusively on non-foldable IOLs or included both foldable and non-foldable IOLs will be considered out of scope. IOL implantation for the management of pediatric cataracts became routine practice in many countries more than 10 years ago[24] and, according to clinical expert input, improvements in surgical instruments over the last decade allow for smaller surgical incisions for foldable IOLs that reduce adverse events related to cataract surgeries. Therefore, on the assumption that foldable IOLs were widely implemented in many countries by 2010, studies or findings that did not report whether foldable or non-foldable IOLs were implanted will be considered for inclusion since our search will be limited to 2010 onward.

Exclusion Criteria

Studies that do not meet the eligibility criteria outlined in Table 1, are duplicate publications, or were published before 2010 will be excluded. Studies that state that they investigated experimental IOLs not available for usual clinical practice will not be eligible for inclusion.

Study Selection

Two reviewers will independently select potentially relevant citations by screening all titles and abstracts identified through the literature searches, using the eligibility criteria presented in Table 1. The study selection will be conducted using the systematic review management software DistillerSR (Evidence Partners, Ottawa, Canada). If at least one reviewer considers any titles or abstracts potentially relevant during the first-level (Level 1) screening, the full-

text articles of the citations will be retrieved for a second-level (Level 2) screening to confirm their eligibility. The same 2 reviewers will independently conduct the Level 2 screening, examining all full-text articles for inclusion in the review. Consensus between the 2 reviewers will be required for the inclusion of each article. Disagreements between the reviewers will be resolved through discussion or by involving a third reviewer, if needed.

A list of studies selected for inclusion in the review will be posted to the CADTH website for 10 business days to allow stakeholder review and feedback. All additional potentially relevant studies identified through stakeholder feedback will be reviewed following the previously described process. In addition, publications meeting the selection criteria for the review that are identified via literature search alerts prior to the completion of the stakeholder feedback period for the draft report will be incorporated into the analysis. Relevant studies identified after the stakeholder feedback period will be described in the discussion, focusing on comparing their results with those obtained from the synthesis of earlier reports included in the review.

The study selection process will be outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[27] flow chart and a list of included and excluded studies will be provided in the final report, together with the reasons for exclusion.

Data Extraction

One reviewer will perform data extraction directly into tables created in Microsoft Word and a second reviewer will independently check the extracted data for accuracy and completeness to ensure that all relevant data from each included study are extracted. Disagreements will be resolved through discussion until consensus is reached or through adjudication by a third reviewer, if necessary. The following data will be extracted:

- study characteristics (e.g., first author's name, publication year, the country where the study was conducted, funding sources)
- study methodology (e.g., study design and objectives, inclusion and exclusion criteria, recruitment method, setting)
- population details (e.g., number of participants, age, sex, gender, unilateral or bilateral cataracts, baseline characteristics)
- intervention details (e.g., information about the IOL implanted, such as the type of IOL [e.g., foldable or non-foldable], the construction material, the year of surgery)
- comparator details (e.g., aphakic glasses, aphakic contact lenses)
- outcome details (e.g., measurement method, unit of measurement, length of follow-up), results, and conclusions for the overall findings and for subgroups of interest.

For economic evaluation studies, examples of additional data that will be extracted include the type of analysis, time horizon, perspective, modelling approach, and main assumptions, as well as the sources of clinical, cost, and utility data used in analysis. Data on relevant outcomes will be extracted for any duration of follow-up reported in the included studies. All unadjusted and adjusted measures of treatment effects — such as risk ratios, odds ratios, or risk differences for dichotomous outcomes and mean differences or standardized mean differences for continuous outcomes — and any results of statistical manipulations performed or statistical tests reported on those measures will be reported.

Attempts will be made to contact corresponding authors to obtain missing relevant data, if those data are needed for a MA, or to clarify conflicting relevant data in the included studies.

Relevant data will be deemed missing if numerical data supporting qualitative statements or findings presented in figures are absent. If the authors do not provide the requested numerical data related to findings presented in a figure, the best numerical estimates based on the figure will be used in the MA. Relevant data will be deemed conflicting if there are discrepancies within the study (e.g., between the abstract and the main text of a publication) or between different publications of the same study. If the authors do not provide clarifications for the conflicting information, all data will be reported and the most conservative data available will be incorporated into an MA, if performed.

Critical Appraisal

Two reviewers will independently conduct risk-of-bias assessments of the eligible studies and compare them, resolving any disagreements and reaching consensus through discussion or by involving a third reviewer, if needed. The risk of bias in randomized controlled trials will be evaluated using the methods described in the revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[28] The RoB 2 assessment tool is structured into 5 domains to evaluate biases arising from the randomization process, deviations from intended interventions, missing outcomes data, measurement of the outcome, and selection of the reported result. Signaling questions in each domain helps the user make domain-level judgments about the risk of bias by answering "Yes," "Probably Yes," "Probably No," "No," and "No Information." A judgment of low risk of bias, high risk of bias, or some concerns will be assigned for each domain. The overall risk of bias of each trial will be rated and designated as low risk of bias, some concerns, or high risk of bias based on the domain-level determinations.[28] A rationale will be provided for decisions about the risk of bias for both the domain-level and overall assessments.

The risk of bias in non-randomized studies will be assessed using the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS).[29,30] RoBANS contains 8 domains evaluating the risk of biases in a study due to the possibility of target group comparisons, target group selection, confounder, exposure measurement, blinding of assessors, outcomes assessment, incomplete outcomes data, and selective outcomes reporting.[29,30] The tool was selected for its reliability, validity, and user-friendly design. A judgment of low risk of bias, high risk of bias, or unclear risk of bias will be assigned for each domain using the criteria provided in the instrument.[29] The overall risk of bias for each study will be classified as low, some, or high, based on the domain-level judgments about the risk of bias, following the RoB 2 guidance,[28] as RoBANS did not provide a specific approach for making study-level judgments. A rationale will be provided for decisions about the risk of bias for both the domain-level and overall assessments.

For sources of bias that may differ across outcomes within a single primary study (i.e., bias due to deviations from missing outcomes data and measurement of the outcomes in randomized controlled trials; outcomes assessment and incomplete outcomes data in non-randomized studies), the risk of bias will be assessed for individual outcomes within individual studies.

The quality of identified cost-effectiveness studies selected for this systematic review will be assessed using the Drummond checklist for economic evaluations.[31] The Drummond checklist consists of 35 items for a reviewer to critically appraise economic evaluation studies regarding the study design, data collection, and the analysis and interpretation of results.[31] A rationale will be provided for the assessments based on this checklist.

In evaluating the risk of bias in the included studies, the critical appraisal tools will be considered as guides and additional insight beyond the instruments' signaling items will be applied when necessary. The results of the risk-of-bias assessment will be reported by describing each study's strengths and limitations narratively; summary scores will not be calculated. Studies will not be excluded from the review based on the results of the critical appraisal. However, the critical appraisal results and how they affect study findings will be used to assess confidence in the evidence from the individual studies.

Data Analysis and Synthesis

Narrative Synthesis

Narrative syntheses will be performed, summarizing relevant data in tables for each study, together with descriptions in the main text for details and clarity. The study and patient characteristics will be considered in the analysis of the effectiveness and safety measures across the studies to determine the likelihood of clinical benefits or harm. The within- and between-study relationships will be evaluated, and the findings about the direction and magnitude of any observed effects, trends, and deviations will be summarized and discussed by research question and by comparator. Where data are available, results about the clinical effectiveness and safety will be reported separately for the comparison of IOL with aphakic glasses from contact lenses. If possible, any impact of applying the ≥ 95% inclusion rule for age, or including studies or findings that did not specify non-congenital aphakia or foldable IOLs, will be examined (e.g., by summarizing the findings separately). Outcomes will be reported in the measurement units used by the study authors and results will be interpreted with due consideration for the differences in the instruments of assessment across the studies.

A narrative summary of the results of the critical appraisal for each included study will be provided. Specifically, tables will be developed to present the answers to the questions within the critical appraisal tools and a narrative description of the strengths and limitations of the included studies will be provided within the main text of the report to give the reader an overview of the methodological quality of the literature. Although studies will not be excluded from this review based on the critical appraisal results, the discussions and conclusions of the final report will emphasize the findings from higher-quality studies.

Quantitative Synthesis

In addition to the narrative synthesis, the results of the included studies will be pooled in meta-analyses if data are sufficiently homogeneous in their clinical, methodological, and statistical characteristics. Clinical, methodological, and statistical heterogeneity and whether studies are sufficiently homogeneous for pooling will be assessed in consultation with clinical and methods experts.

MAs will be considered for each outcome of interest for each research question on clinical effectiveness and safety. If the included studies are deemed too heterogeneous to combine, a quantitative pooling of results from individual studies will be deemed inappropriate. In that case, the affected studies will be summarized narratively only, and the reasons for not pooling will be provided. If deemed appropriate, MAs will be conducted for each outcome of interest (e.g., visual acuity, health-related quality of life, the risk for adverse events) reported across multiple studies showing sufficient homogeneity. Results from randomized and non-randomized studies will not be pooled in analysis. Instead, separate MAs will be conducted

for these 2 types of study designs. Random and/or fixed models will be considered, as appropriate.

As aggregate data will be used, the unit of analysis will be the primary study. Dichotomous data will be analyzed as risk ratios or odds ratios to allow for comparisons across studies. Continuous data will be analyzed using either mean differences or standardized mean differences. Mean differences will be used when pooling studies that used the same outcome measure. Standardized mean differences will be applied when pooling studies with different measures of assessment of the same outcome. If both unadjusted and adjusted effects are reported, the adjusted effects will be used in MAs. If multiple adjusted estimates of effects are reported, the one that is judged to minimize the risk of bias due to confounding will be used in MAs.

Statistical heterogeneity will be assessed using graphical presentations (e.g., forest plots) and calculations of the Chi^2 statistic and the I^2 statistic, which quantifies the variability in effect estimates due to heterogeneity rather than chance (i.e., sampling error).[32] Heterogeneity will be interpreted with guidance from Higgins and colleagues,[33] which defines low, moderate, and high I^2 values as 25%, 50%, and 75%, respectively. Heterogeneity will be interpreted with true P values.

If there are 10 or more included studies of a given study design and a particular outcome, publication bias will be assessed visually using funnel plots and objectively using Egger's regression test and Begg's rank correlation test.[34]

MAs will be carried out using the Cochrane Review Manager software (version 5.3, or the most up-to-date version available at the time of analysis).

Subgroup Analyses

In addition to analyzing the individual outcomes by research questions for the overall population, narrative and quantitative analyses in the following subgroups will be conducted as data permit:

- Age (e.g., studies or findings on mixed populations versus no mixed populations based on the age eligibility criteria for each research question; 0 to ≤ 6 months versus > 6 to ≤ 12 months for Research Questions 1, 2, and 5; 0 to ≤ 6 months, > 6 to ≤ 12 months, or > 12 to ≤ 24 months versus > 24 months up to 12 years of age for Research Questions 3, 4, and 6)
- Eye involvement (e.g., bilateral versus unilateral)
- Time of surgery (e.g., before 2010 versus 2010 and beyond to evaluate any difference in outcomes that might be attributable to advances in surgical instruments and technology, and broader uptake in foldable IOL use compared with single-unit rigid IOLs in Canada).

Reporting of Findings

The systematic review will be prepared in consideration of relevant reporting guidelines (e.g., PRISMA statement,[35] PRISMA harms,[36] Meta-analysis of Observational Studies in Epidemiology [MOOSE] reporting checklist,[37] Synthesis Without Meta-analysis [SWiM] guideline[38]) and will meet the criteria outlined in A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) checklist.[39]

Opportunities for Stakeholder Feedback

All stakeholders will be given the opportunity to provide feedback on the draft included studies list and the draft report. Unpublished data identified as part of the feedback process may only be included if the source of data is in the public domain.

Patient and Family Engagement

CADTH involves patients, families, and patient groups to improve the quality and relevance of our assessments, ensuring that the affected patients and caregivers have an opportunity to provide input into the report. CADTH has adopted a *Framework for Patient Engagement in Health Technology Assessment*. The framework includes standards for patient involvement in individual HTAs and support and guide our activities involving patients. For this systematic review, the value of relevance and the belief that patients have the knowledge, perspectives, and unique experiences that contribute to essential evidence for HTA will guide our patient engagement activities. CADTH will engage people with direct experience of treatment such as parents, caregivers of pediatric patients, or older children themselves who have received treatment for aphakia.

Invitation to Participate and Consent

A CADTH Patient Engagement Officer will reach out to relevant support and advocacy groups, clinical experts, and other CADTH networks to identify potential collaborators. The Patient Engagement Officer will contact potential participants by email to explore their interest in becoming involved. The preliminary request will include the purpose and scope of this systematic review, the purpose of engagement, and the nature of engagement activities. The Patient Engagement Officer will obtain informed consent from the participants to share their information and comments with CADTH staff.

Engagement Activities

Participants will be asked to reflect on their personal experiences at several time points during the assessment, including:

- before protocol finalization
- during the drafting of the initial reviews
- upon completion of the final report.

Perspectives gained through the engagement process will be used in several ways, including ensuring the relevance of outcomes of interest for the clinical assessment, commenting on themes emerging from the participants' experiences and perspectives, implementation reviews, and commenting on other key concepts that were identified through prior scoping activities. Parents or caregivers' involvement will enable the research team to consider the evidence alongside an understanding of the wider real-life experiences. Participants may provide valuable feedback on the clarity of writing and comment on the relevance of the findings to Canadian patients and families.

Once preliminary findings are available, the parents or caregivers will be invited to a discussion with the researchers. The conversation will explore the participant's perceptions of key findings, including if the findings are understandable and if they reflect personal experiences or understandings. This conversation will be used to consider the possible need to explore avenues of analysis that have been missed or underdeveloped, add additional

concepts or experiences that relate to identified categories, or inform the processes underlying the implantation of IOLs to correct aphakia in infants and the context of analysis.

Reporting

The reporting of this section will follow the *Guidance for Reporting Involvement of Patients and the Public* reporting checklist known as the GRIPP2 Short Form[40] and include the outcomes, discussion, and reflection items, as suggested by that guidance, to outline in a final report the process of engagement and where and how participants' contributions were used in the assessment. The Patient Engagement Officer will keep track of patient engagement activities and interactions in detailed notes and communications, which will be stored on a password-protected network drive and will be permanently deleted in accordance with CADTH's document retention policy. CADTH will provide reflections and critical perspectives on the participating parents' or caregivers' involvement with the research team in the final report.

Protocol Amendments

If amendments are required at any time during the study, reasons for changes will be recorded in a study file and subsequently reported within the final report. If necessary, a rescreening of the previous literature search or an updated literature search will be performed to capture additional data, according to the amendments. Updates to the PROSPERO submission (CRD42021231143) and the project protocol on the CADTH website will be made, as appropriate.

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Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946 to present) Embase (1974 to present) Cochrane Central Register of Controlled Trials (CCTR) **Note:** Subject headings have been customized for each database. Duplicates between databases will be removed in Ovid.
Date of Search:	January 2021
Alerts:	Monthly search updates until project completion
Study Types:	No filters applied to limit by study type
Limits:	Publication date limit: 2010 to present Language limit: English-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase); keyword (CENTRAL)
.dv	Device trade name (Embase)
.dq	Candidate term word (Embase)
.jw	Journal word title (MEDLINE)
.jx	Journal word title (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	exp aphakia/
2	aphaki*.ti,ab,kf,kw.
3	((absence or absent) adj3 lens*).ti,ab,kf,kw.
4	1 or 2 or 3
5	exp Cataract Extraction/
6	exp Cataract/
7	cataract*.ti,ab,kf,kw.
8	5 or 6 or 7
9	4 or 8
10	Lens Implantation, Intraocular/
11	exp Lenses, Intraocular/
12	((intraocular or intra ocular or artificial* or implant* or prosthe*) adj3 (lens or lenses)).ti,ab,kf,kw.
13	(pseudophaki* adj3 lens*).ti,ab,kf,kw.
14	(IOL or IOLs or acrysof* or enVista* or (Alcon* adj (MA60* or SA60*)) or (Artisan* adj Aphakia*)).ti,ab,kf,kw.
15	10 or 11 or 12 or 13 or 14
16	"Congenital, Hereditary, and Neonatal Diseases and Abnormalities"/ or Congenital abnormalities/ or exp Child/ or exp Infant/ or exp Pediatrics/ or Pediatricians/ or Hospitals, Pediatric/ or Child Health/
17	(child or children or childhood or infant* or infancy or baby or babies or newborn* or new born* or neonat* or neo nat* or preemie or preemies or months old or months of age or toddler* or paediatric* or pediatric* or girl or girls or boy or boys or kid or kids or preschool* or pre school* or schoolage* or school age* or preteen* or pre teen* or ((1 year or one year or 2 year or two year or 2 years or two years) adj2 (age or aged or old)) or congenital* or juvenile*).ti,ab,kf,kw,jw.
18	16 or 17
19	9 and 15 and 18
20	Cataract/cn
21	((genetic or developmental) adj2 cataract*).ti,ab,kf,kw.
22	20 or 21
23	15 and 22
24	19 or 23
25	limit 24 to english language
26	25 use medall
27	24 use cctr
28	26 or 27
29	aphakia/
30	aphaki*.ti,ab,kw,dq.
31	((absence or absent) adj3 lens*).ti,ab,kw,dq.
32	29 or 30 or 31
33	exp cataract extraction/
34	exp cataract/

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
35	traumatic cataract/
36	cataract*.ti,ab,kw,dq.
37	33 or 34 or 35 or 36
38	32 or 37
39	exp lens implant/
40	lens implantation/
41	((intraocular or intra ocular or artificial* or implant* or prosthe*) adj3 (lens or lenses)).ti,ab,kw,dv,dq.
42	(pseudophaki* adj3 lens*).ti,ab,kw,dv,dq.
43	(IOL or IOLs or acrysof* or enVista* or (Alcon* adj (MA60* or SA60*)) or (Artisan* adj Aphakia*)).ti,ab,kw,dv,dq.
44	39 or 40 or 41 or 42 or 43
45	newborn disease/ or congenital disorder/ or congenital malformation/ or exp Child/ or pediatric patient/ or Pediatrics/ or exp pediatric surgery/ or pediatric surgeon/ or pediatric ward/ or pediatrician/ or pediatric hospital/ or child health/ or child health care/
46	(child or children or childhood or infant* or infancy or baby or babies or newborn* or new born* or neonat* or neo nat* or preemie or preemies or months old or months of age or toddler* or paediatric* or pediatric* or girl or girls or boy or boys or kid or kids or preschool* or pre school* or schoolage* or school age* or preteen* or pre teen* or ((1 year or one year or 2 year or two years or 2 years or two years) adj2 (age or aged or old)) or congenital* or juvenile*).ti,ab,kw,jx,dq.
47	45 or 46
48	38 and 44 and 47
49	exp congenital cataract/
50	cataract/cn
51	((genetic or developmental) adj2 cataract*).ti,ab,kw.
52	49 or 50 or 51
53	44 and 52
54	48 or 53
55	54 not conference abstract.pt.
56	limit 55 to english language
57	56 use oemezd
58	28 or 57
59	exp animals/
60	exp animal experimentation/ or exp animal experiment/
61	exp models animal/
62	nonhuman/
63	exp vertebrate/ or exp vertebrates/
64	or/59-63
65	exp humans/
66	exp human experimentation/ or exp human experiment/
67	or/65-66

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
68	64 not 67
69	58 not 68
70	limit 69 to yr="2010 -Current"
71	remove duplicates from 70

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. [Search terms — intraocular lenses, juvenile cataracts/aphakia]
WHO ICTRP	International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials. [Search terms — intraocular lenses, juvenile cataracts/aphakia]
Health Canada's Clinical Trials Database	Produced by Health Canada. Targeted search used to capture registered clinical trials. [Search terms — intraocular lenses, juvenile cataracts/aphakia]
EU Clinical Trials Register	Produced by the European Union. Targeted search used to capture registered clinical trials. [Search terms — intraocular lenses, juvenile cataracts/aphakia]

Grey Literature

Dates for Search:	January 2021
Keywords:	[intraocular lenses, juvenile cataracts/aphakia]
Limits:	Publication years: 2010 to present

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters), will be searched:

- Health Technology Assessment Agencies
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals