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Benefits and Harms of Femtosecond Laser Assisted Cataract Surgery: A Systematic Review

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

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Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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BACKGROUND

The preferred method of removing cataracts in the developed world is phacoemulsification. Using this technique, ultrasonic energy softens the dense lens material of the cataract, which is then extracted from the eye with suction and irrigation. Current practice includes creating manual corneal incisions and anterior capsulotomies, followed by phacoemulsification. Recently these three manual procedures have been performed in an automated fashion with the use of the femtosecond laser (FSL). Several FSL systems have been approved by the FDA for use in the U.S. for some or all of these procedural steps in cataract surgery. FSL technology has been widely used in various refractive surgery applications in recent years. Studies have suggested decreased phacoemulsification energy use with FSL cataract surgery and have examined the potential advantages of more precise corneal incisions and capsulotomy formation.

Cataract surgery is a frequently performed operation in the VHA, with more than 49,000 performed in 2012. As a result, the VHA National Surgery Office has been tasked with making a recommendation regarding whether femtosecond lasers provide appropriate cost-benefit and risk-benefit ratios to support implementation for cataract surgery in the VA. The purpose of this systematic review is to examine the effectiveness and safety of femtosecond laser assisted cataract surgery (FLACS) relative to conventional cataract surgery. Key questions were developed in conjunction with the stakeholders which address the effectiveness, safety, adverse consequences and economic implications of adopting FLACS into the VA system.

METHODS

We conducted a primary review of the literature by systematically searching, reviewing and analyzing the scientific evidence as it pertains to the research questions. To identify relevant articles, we began by searching MEDLINE®, CINAHL and the Cochrane Database of Systematic Reviews. We further evaluated the bibliographies of included primary studies and any systematic or nonsystematic reviews that were identified. To identify in-progress or unpublished studies, we searched ClinicalTrials.gov. We also searched conference proceedings of ophthalmologic societies and topic specific journals, including the following: The American Society of Cataract and Refractive Surgery; Journal of Cataract & Refractive Surgery; American Academy of Ophthalmology; Ophthalmology; International Society of Refractive Surgery; American Academy of Ophthalmic Executives; The Foundation of the American Academy of Ophthalmology, The Royal College of Ophthalmologists; COS Conference Papers Index; and Proceedings First (OCLC).

Two reviewers trained in the critical analysis of literature assessed for relevance the abstracts of citations identified from literature searches. Two reviewers independently assessed full-text articles for inclusion; disagreements were resolved through consensus. We assessed the quality of each study using published tools. We assessed the overall quality of the body of evidence for each outcome using a method developed by the Grades of Recommendation, Assessment,

Development and Evaluation (GRADE) Working Group. We critically analyzed the evidence on effectiveness and adverse effects and compiled a narrative synthesis of findings. We conducted meta-analyses of two commonly reported outcomes in FSL and conventional cataract surgery procedures, corrected distance visual acuity (CDVA) and effective phacoemulsification time (EPT).

RESULTS

We reviewed 468 titles and abstracts from the electronic search and identified 436 additional references through manual searching of reference lists, input from technical advisors and reviewing conference proceedings of ophthamalogic societies for recent unpublished or ongoing studies.

After applying inclusion/exclusion criteria at the abstract level, seventy full-text articles were reviewed, as shown in Figure 2. Of the full-text articles, we rejected fifty-four that did not meet our inclusion criteria.

Key Question 1: What is the evidence that FLACS is associated with better outcomes than conventional cataract surgery?

We identified nine studies addressing the comparative effectiveness of FLACS versus conventional surgery, including three small to medium-sized randomized controlled trials. Six of these studies (and all three of the randomized controlled trials) were conducted at Semmelweis University, Budapest, Hungary, all surgeries having been performed by the same surgeon, using the Alcon LenSx laser. Two studies were conducted in an ophthalmology group practice, at Launceton Eye Hospital, Tasmania, Australia, using the OptiMedica Catalys laser. Sample sizes in these studies ranged from 25 to 400 patients, with follow-up periods extending from two weeks to one year.

The most commonly reported relevant outcomes in these comparative studies were: post-operative corrected distance visual acuity (CDVA) and effective phacoemulsification time (EPT). We conducted a meta-analysis of CDVA and EPT, but heterogeneity precluded calculation of a reliable summary effect estimate. The results of individual studies are presented in Figures 3 and 4. Overall, there was low evidence of benefit from three randomized controlled trials and six observational studies. There were no significant differences noted between groups for CDVA outcomes. EPT outcomes were mixed, with results either comparable between FSL and conventional cataract surgery groups or favoring FSL groups. No studies addressed quality of life measures. Methodological concerns were noted regarding the generalizability of studies conducted from limited sites and potential sample selection bias from enrollment into FSL and conventional surgery groups.

Key Question 2a: What are the adverse effects that have been reported for FLACS?

Seven studies were identified addressing adverse effects, unique to FLACS. Sample sizes in these studies ranged from 25 to 1300 patients, with follow-up periods extending from immediately following the procedure, to three months post-operative.

We grouped the adverse event outcomes in these studies by either: 1) those occurring as a result of difficulties with the laser-patient interface, or 2) the change in intraocular pressure (IOP) measured during the FLACS procedure. Five studies reported difficulties related to the laser interface with the ocular surface (including the orbital structures). Two studies measured intraocular pressure (IOP) fluctuation during FLACS procedures. A small proportion of patients experienced suction breaks, second docking attempts and aborted procedure adverse events. FSL application is also associated with an increase in IOP. Overall, we found moderate to low strength of evidence for adverse events with methodological concerns raised from enrollment criteria used for FSL surgery groups.

Key Question 2b: What is the risk of adverse effects from FLACS compared to the risk associated with conventional cataract surgery?

Nine studies addressed the adverse effects of FLACS compared to conventional cataract surgery. Sample sizes in these studies ranged from 25 to 400 patients, with follow-up periods extending from one week to one year.

We grouped the adverse event outcomes of these studies by the ocular structures which were affected. Five of these studies reported, variously: capsulotomy configuration, position and the resultant effects on IOL decentration and refractive outcomes. Two of these studies reported post-operative corneal edema by measuring either corneal thickness or corneal endothelial cell loss. An additional two studies compared post-operative macular thickness and morphology, as measured by optical coherence tomography (OCT). The FSL and control groups were similar for post-operative corneal thickness and macular edema measurements, with corneal endothelial cell loss decreased in the FSL group in one study. Overall, we found moderate to low strength of evidence for comparative adverse events with methodological concerns from enrollment criteria used for the FSL and conventional surgery groups.

Key Question 3: What is the evidence that the experience of the surgeon is associated with adverse effects of FLACS?

Three studies reported outcomes relevant to the experience of the surgeon in performing the FLACS procedure. Sample sizes in these studies ranged from 200 to 1300 patients, with follow-up periods extending from two weeks to three months. Overall, one of the studies found no significant differences between outcomes for initial and subsequent groups of patients undergoing FLACS, while on the other hand, two studies from the same team of researchers found significantly fewer complications associated with greater experience with FLACS.

There were methodological concerns from enrollment criteria used for the FSL and conventional surgery groups.

DISCUSSION

We found no evidence that FLACS differs from conventional cataract surgery on measures of safety and effectiveness. The unique risks associated with FLACs are primarily related to laser docking interface difficulties, which may be reduced with increasing surgical experience with the procedure. The comparative adverse event risks of FLACS and conventional surgery were

similar. Complications rates in FLACS cohorts were found to be reduced or unchanged by surgical experience in the included studies of this review.

We found moderate evidence of comparable CDVA outcomes between FLACS and conventional cataract surgery groups. We noted limited evidence for a reduction of EPT in the FSL compared to the conventional cataract surgery group. Furthermore, meta-analyses found no statistically significant differences between FSL and conventional groups in either CDVA or EPT. No studies reported findings related to quality of life outcomes or cost effectiveness of FLACS relative to conventional cataract surgery.

Most of the included studies reported on the comparative risks of adverse effects between FSL and conventional cataract surgery. Reports of adverse events were similar between FSL and conventional groups, including IOL positioning, corneal thickness, macular edema and residual refractive error. The association between the experience of the surgeon and FLACS adverse effects was limited to three eligible studies, two of which were conducted by the same team of researchers. These studies reported mixed results of surgical experience reducing the incidence of FLACS adverse events.

There were methodological concerns for the included studies that represent potential sources of bias that threaten the validity of study findings. Many studies had small to medium sample sizes. Study methods were often unclear, particularly with regard to the application of inclusion and exclusion criteria for FSL treatment groups and the enrollment of treatment and control cohorts. Studies often excluded patients with denser cataracts, comorbidities and those deemed uncooperative from the FSL treatment groups. In addition, many study protocols centered around patients self-selecting into FSL or conventional surgery groups.

The majority of included studies (all but two) report financial conflicts of interest, with included studies clustered around a limited number of geographic sites, conducted by the same team of coauthors. All four of the included randomized trials were conducted by the same research group and every surgery (FSL or conventional) was completed by the same surgeon, who was also a study co-author. It is also unclear whether or not there was any overlap in the study patient populations of these trials, given they are conducted at the same site and at what appeared to be a similar timeframe.

CONCLUSION

This systematic review found visual outcomes (CDVA) and EPT to be similar in FLACS and conventional surgery, while quality of life and cost-effectiveness outcomes were not reported. The evidence for the relative benefit of FLACS was limited by reliance on small to moderately-sized prospective cohort studies, nearly all of which had stated financial conflicts of interest. Adverse events unique to FLACS involved difficulties in laser docking or patient suitability for the procedure. Many patients were excluded from the FSL treatment groups for orbital, corneal, cataract density, or medical co-morbidities. Comparative adverse events in FLACS and conventional surgery were found to be similar for IOL positioning, corneal thickness, macular edema and residual refractive error. A few studies reported mixed results of the effect of surgical experience on the incidence of FLACS adverse events.

Summary of the evidence table on the effects of femtosecond laser assisted cataract surgery

Outcome	For each study design: Number of studies (combined sample size)	Findings	Strength of Evidence	Comments
Visual acuity	2 RCTs (N=189) 4 NRCS (N=306)	No significant differences	Low	No differences in visual acuity outcomes found in either of the randomized trials. Unclear risk of bias for trials, low consistency, coherence and applicability of estimated effects across studies, small to medium sample sizes and conflicts of interest lower the strength of evidence.
Effective phacoemulsi-fication time	1 RCT (N=76) 4 NRCS (N=615) 1 NCS (N=160)	Mixed findings	Low	Trial found no significant reduction in EPT for FSL group. Two of the large nonrandomized studies (N=550) reported significant reductions in favor of FLACS. Remaining three studies found no significant differences. Unclear risk of bias for trial, low consistency, coherence and applicability of estimated effects across studies and conflicts of interest lower the strength of evidence.
Quality of life	None	None	No evidence	None of the included studies reported on quality of life outcomes.
Intraoperative complications*	3 NRCS (N=1,900) 3 NCS (N=285)	Higher IOP for FLACS; Few additional complications for FLACS	Moderate to Low	Low incidence of complications with FLACS, though increases in IOP reported across studies. Low applicability of estimated effects lowers the strength of evidence.
Postoperative complications**	1 RCT (N=76) 1 NRCS (N=150) 1 NCS (N=160)	Mixed findings	Low	Trial found no significant differences and medium-sized cohort study (N=150) found significantly reduced endothelial loss for the FLACS group. Unclear risk of bias for trial, low consistency and coherence of estimated effects across studies, small to medium sample sizes and conflicts of interest lower the strength of evidence.
Costs	None	None	No evidence	None of the included studies reported on costs of FLACS compared to conventional cataract surgery.

Abbreviations: RCT = randomized controlled trial; NRCS = non-randomized comparative studies; NCS = non-comparative studies; FLACS = femtosecond laser assisted cataract surgery; EPT = effective phacoemulsification time; IOP = intraocular pressure

*Intraoperative complications include: capsular blockage, capsular tear, dislocated nucleus, docking failure

**Postoperative complications include: infection, retinal swelling/cystoid macular edema, intraocular decentration, corneal edema

EVIDENCE REPORT

BACKGROUND

The preferred method of removing cataracts in the developed world is phacoemulsification.[1] Using this technique, ultrasonic energy softens the dense lens material of the cataract, which is then extracted from the eye with suction and irrigation. Current practice includes creating manual corneal incisions and anterior capsulotomies, followed by phacoemulsification.[2] Recently these three manual procedures have been performed in an automated fashion with the use of the femtosecond laser (FSL). Several FSL systems have been approved by the FDA for use in the U.S. for some or all of these procedural steps in cataract surgery. FSL technology has been widely used in various refractive surgery applications in recent years.[3] Studies have suggested decreased phacoemulsification energy use with FSL cataract surgery[4] and have examined the potential advantages of more precise corneal incisions[5] and capsulotomy formation.[6]

Cataract surgery is a frequently performed operation in the VHA,[7] with more than 49,000 performed in 2012. As a result, the VHA National Surgery Office has been tasked with making a recommendation regarding whether femtosecond lasers provide appropriate cost-benefit and risk-benefit ratios to support implementation for cataract surgery in the VA. Thus, an unbiased evidence review examining the potential benefits and adverse effects related to femtosecond laser assisted cataract surgery (FLACS) will aid VA leadership in determining policy for use of this technology. The purpose of this report is to systematically present the evidence regarding the effectiveness and safety of FLACS relative to conventional cataract surgery. Key questions were developed in conjunction with the stakeholders which address the effectiveness, safety, adverse consequences and economic implications of adopting FLACS into the VA system.

METHODS

TOPIC DEVELOPMENT

The following key questions guiding this systematic review were developed after a topic refinement process that included a preliminary review of published peer-reviewed literature, consultation with internal partners and investigators and consultation with content experts and key stakeholders.

Key Question 1: What is the evidence that FLACS is associated with better patient outcomes than conventional cataract surgery?

Population: Adults undergoing cataract surgery.

Considerations: femtosecond laser surgery is relatively contraindicated in patients with: advanced glaucoma, high anxiety, tremors, dementia, facial or ocular anatomy that precludes adequate LASER docking (i.e. small palpebral fissures, prominent brows, irregular corneal surfaces) and previous refractive surgery or corneal opacities.

Intervention: Femtosecond laser technology is used in cataract surgery to assist or replace aspects of conventional cataract surgery, including corneal incisions, capsulotomy and lens fragmentation. Lasers at or near the point of commercial release include: Alcon LenSx (Alcon Laboratories, Fort Worth, TX, USA); OptiMedica Catalys (OptiMedica Corp, Santa Clara, CA, USA); LensAR (LensAR Inc, Winter Park, FL, USA); VICTUS (Bausch + Lomb, Aliso Viejo, CA, USA; and Technolas Perfect Vision GmbH, Munich, Germany); IntraLase FS; and iFS Laser Systems (Abbott Medical Optics, Abbott Park, IL, USA).

Only a subset of these lasers is currently FDA approved for cataract surgery.[8] Still, this review is inclusive of studies concerning any femtosecond laser used for cataract surgery applications regardless of FDA status.

Comparators: Conventional cataract surgery, defined as small-incision, phacoemulsification with posterior-chamber intraocular lenses (IOL) implantation.

Outcomes: Short-term patient outcomes: visual acuity—post -operative day 1. Long-term patient outcomes: visual acuity—after post-operative day 1 (e.g., one week, one month, ninety days); quality of life measures.

Study design: Controlled studies including randomized controlled trials and non-randomized controlled clinical trials, as well as observational studies comparing FLACS to conventional cataract surgery.

Excluded study designs: Case reports, case series and studies that do not report primary data such as editorials and non-systematic reviews.

Timing: Our operational definition to be used for timing of patient outcomes is as follows:

- Short-term—patient outcomes on post-operative day 1
- Long term—patient outcomes > after post-operative day 1 (no upper limit).

Considerations: Standards for reporting timing of post-operative outcomes often have variable time-horizons. For example, potential harms such as CME or IOL decentration, may be reported from as early as post-operative day one or after months to years in some studies.

Setting: Any.

Key Question 2a: What are the adverse effects that have been reported for FLACS?

Key Question 2b: What is the risk of adverse effects from FLACS compared to the risk associated with conventional cataract surgery?

Population: Adults undergoing cataract surgery.

Intervention: Femtosecond laser technology is used to assist or replace steps in conventional cataract surgery, including corneal incisions, capsulotomy and lens fragmentation.

Comparators: Conventional cataract surgery.

Outcomes: Surgical complications (intra-operative and post-operative).

Intra-operative:
1) capsular blockage syndrome
2) dislocated nucleus
3) capsular tear
4) docking failure

Post-operative:
1) infection
2) retinal swelling/cystoid macular edema (CME)
3) corneal edema
4) intraocular (IOL) decentration

Study design: Controlled studies and observational study designs (cohort and case-control studies), case reports and case series.

Timing: Short-term—intraoperative, post-operative day 1. Long term—patient outcomes > after post-operative day 1 (no upper limit).

Setting: Any.

Key Question 3: What is the evidence that the experience of the surgeon is associated with adverse effects of FLACS?

Population: Adults undergoing cataract surgery.

Intervention: Femtosecond laser technology is used in cataract surgery to assist or replace aspects of conventional cataract surgery, including corneal incisions, capsulotomy and lens fragmentation.

Comparators: Conventional cataract surgery.

Study designs: Controlled studies and observational study designs including economic evaluation studies (cohort and case-control studies).

Excluded study designs: Case reports, case series and studies that do not report primary data such as editorials and non-systematic reviews.

Outcomes: Surgical complications (intra-operative and post-operative).

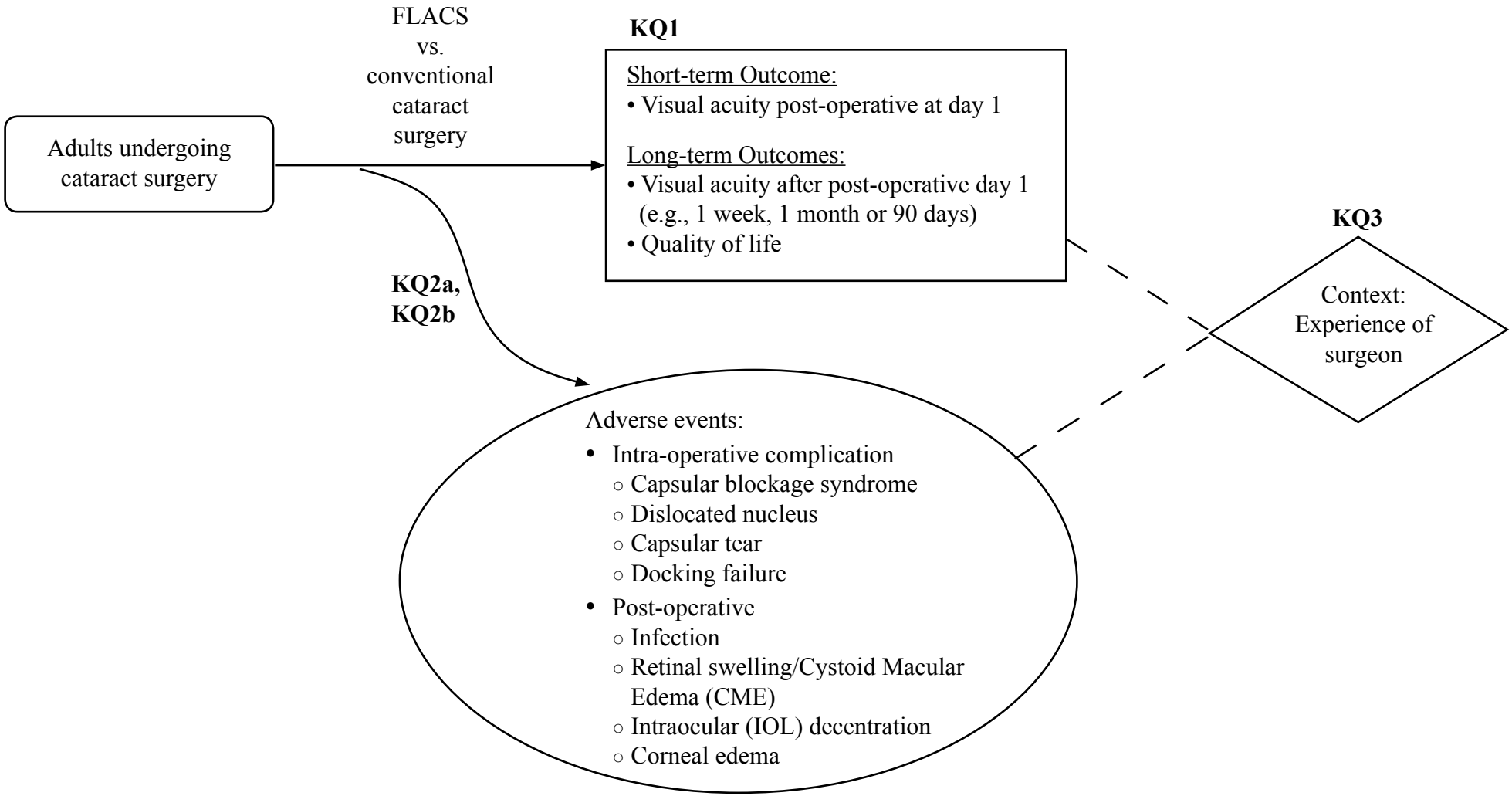
Intra-operative:	1) capsular blockage syndrome 2) dislocated nucleus 3) capsular tear 4) docking failure
Post-operative:	1) infection 2) retinal swelling/cystoid macular edema (CME) 3) corneal edema 4) intraocular (IOL) decentration

Timing: Short-term—patient outcomes on post-operative day 1. Long term—patient outcomes > after post-operative day 1 (no upper limit).

Setting: Any.

Appendix C presents these eligibility criteria for considered studies in a PICOTS (Population, Intervention, Comparators, Outcomes, Timing and Setting) table. Figure 1 illustrates the analytic framework that guided our review and synthesis.

Figure 1: Analytic Framework



SEARCH STRATEGY

Search strategies were developed in consultation with a research librarian from database inception to May 2013. We conducted a primary review of the literature by systematically searching, reviewing and analyzing the scientific evidence as it pertained to the research questions. To identify relevant articles, we began by searching MEDLINE®, the Cochrane library, ClinicalTrials.gov, premarket notification 510(k) summaries from the FDA and conference proceedings of societies for ophthalmology and refractive surgery. Searches were conducted from April 2013 to July 2013, with no limit on year of publication.

We searched ClinicalTrials.gov to identify in-progress or unpublished studies. We searched conference proceedings of ophthalmologic societies and topic specific journals, including the following: The American Society of Cataract and Refractive Surgery; Journal of Cataract & Refractive Surgery; American Academy of Ophthalmology; Ophthalmology; International Society of Refractive Surgery; American Academy of Ophthalmic Executives; The Foundation of the American Academy of Ophthalmology; The Royal College of Ophthalmologists; COS Conference Papers Index; and Proceedings First (OCLC). Appendix A provides the search strategy in detail. We obtained additional articles from reference lists of pertinent studies, reviews, editorials and by consulting experts. All citations were imported into an electronic database (EndNote X1).

STUDY SELECTION

Two reviewers assessed abstracts of citations identified from literature searches for relevance. Full-text articles of relevant abstracts were retrieved for further review. Each article retrieved was independently reviewed by two reviewers using eligibility criteria (Appendix B). Included studies were published in the English language and involved adults undergoing cataract surgery using femtosecond laser technologies.

Using pre-specified inclusion/exclusion criteria, titles and abstracts were reviewed for potential relevance to the key questions. At the full-text screening stage, two independent reviewers assessed each study. Disagreements were discussed to come to a final decision on inclusion/exclusion. If the two independent reviewers could not come to an agreement, a third reviewer assessed the study in question. For all excluded studies, full-text reviewers also came to unanimous agreement on the reason for exclusion. Articles meeting eligibility criteria were included for data abstraction.

DATA ABSTRACTION

Data from published reports were abstracted into a customized database by one investigator and reviewed for accuracy by a second investigator. From each study, we abstracted the following: study design, objectives, setting (country, institution information), population characteristics (including sex, age, medical comorbidities), subject eligibility and exclusion criteria, number of subjects, duration of follow-up, the study and comparator interventions, health outcomes, adverse events and number and experience of the surgeons.

STUDY QUALITY

We adapted the Newcastle Ottowa tool[9] to assess the quality of observational studies. For randomized studies, we used the Cochrane Collaboration tool for assessing the risk of bias. Two reviewers independently assessed the quality of each study and disagreements were resolved through discussion. We added additional criteria as necessary to account for methodological issues specific to this subject area, such as financial conflicts of interest and the number of studies produced by a small number of authors and coauthors (i.e., same team replication). We did not report an overall summary assessment for observational studies because there are no validated criteria for doing so.[10]

RATING THE BODY OF EVIDENCE

We assessed the overall quality of evidence for outcomes using a method developed by the GRADE Working Group.[11] We present the summary of evidence in Table 3. The GRADE method considers the consistency, coherence and applicability of a body of evidence, as well as the internal validity of individual studies, to classify the grade of evidence across outcomes as follows:

- High = Further research is very unlikely to change our confidence on the estimate of effect.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very Low = Any estimate of effect is very uncertain.

DATA SYNTHESIS

We summarized the primary literature by abstracting relevant data, developing data tables and qualitatively synthesizing the literature for each key question. We determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis) to estimate summary effects depending on the volume of relevant literature, conceptual homogeneity of the studies and completeness of results reporting. We conducted meta-analyses of commonly reported outcomes, following the MOOSE guidelines for conducting meta-analyses of observational studies.[12] All analyses were conducted using StataIC 11 (StataCorp, College Station, Texas). We assessed the presence of statistical heterogeneity among the studies by using standard chi-square tests and the magnitude of heterogeneity by using the I^2 statistic.[13] We explored models using both mean and ratio of means based on a random effects model. However, because of concerns of heterogeneity among studies we do not report the combined estimates and instead present forest plots as a visual aid to illustrate individual study results.

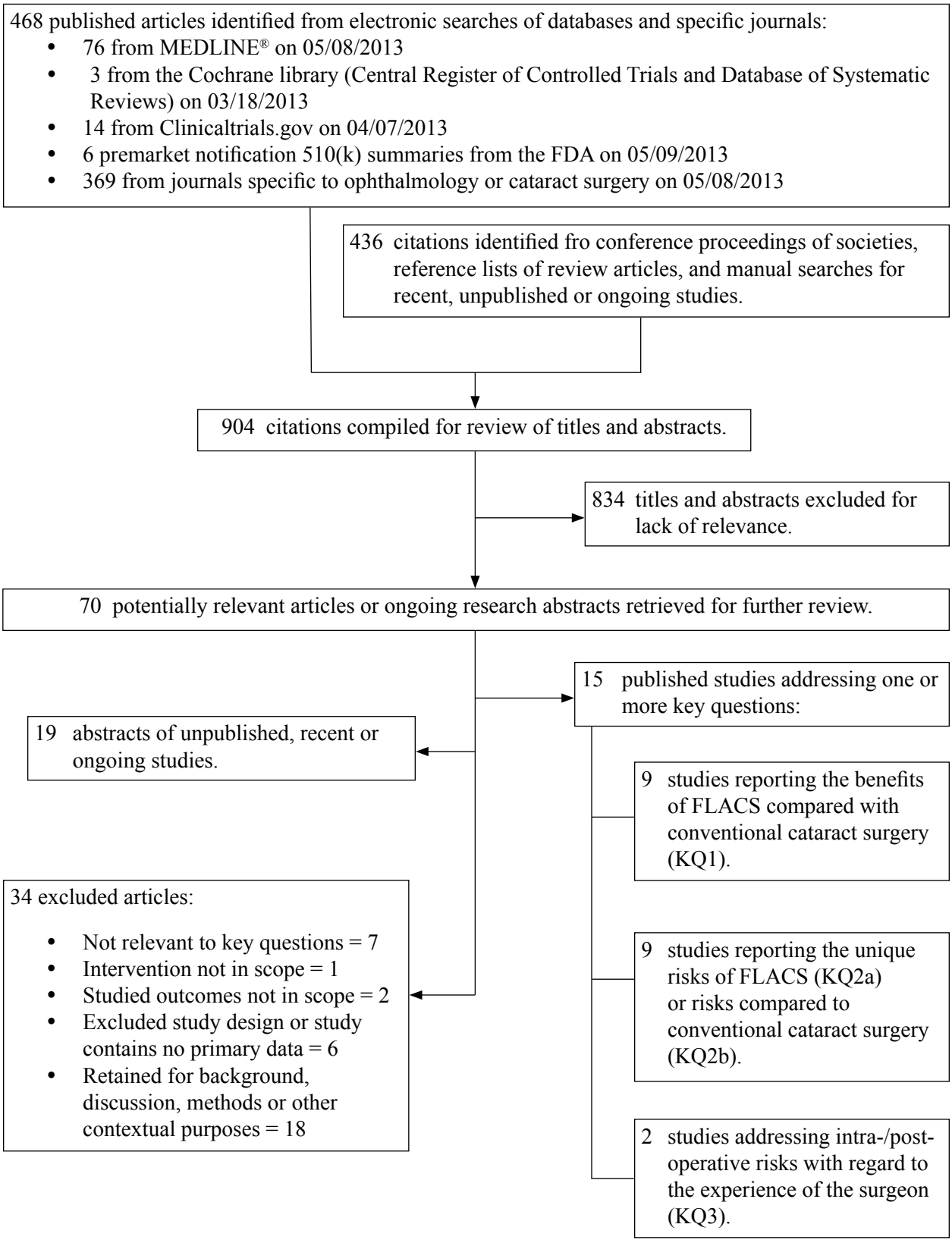
RESULTS

LITERATURE FLOW

We reviewed 468 titles and abstracts from the electronic search and identified 436 additional references through manual searching of reference lists, input from technical advisors and reviewing conference proceedings of ophthamalogic societies for recent unpublished or ongoing studies.

After applying inclusion/exclusion criteria at the abstract level, seventy full-text articles were reviewed, as shown in Figure 2. Of the full-text articles, we rejected fifty-four that did not meet our inclusion criteria.

Figure 2: Femtosecond laser assisted cataract surgery – literature flow diagram



KEY QUESTION 1: What is the evidence that FLACS is associated with better patient outcomes than conventional cataract surgery?

Summary of findings

We identified nine studies addressing the comparative effectiveness of FLACS versus conventional surgery, including three small to medium-sized randomized controlled trials. Six of these studies (and all three of the randomized controlled trials) were conducted at Semmelweis University, Budapest, Hungary, all surgeries having been performed by the same surgeon, using the Alcon LenSx laser. Two studies were conducted in an ophthalmology group practice, at Launceton Eye Hospital, Tasmania, Australia, using the OptiMedica Catalys laser. Sample sizes in these studies ranged from 25 to 400 patients, with follow-up periods extending from two weeks to one year.

The most commonly reported relevant outcomes in these comparative studies were: post-operative corrected distance visual acuity (CDVA); and, effective phacoemulsification time (EPT). We conducted a meta-analysis of CDVA and EPT, but heterogeneity precluded calculation of a reliable summary effect estimate. The results of individual studies are presented in Figures 3 and 4. Overall, there was low evidence of comparative benefit of FLACS from three randomized controlled trials and six observational studies. There were no significant differences noted between groups for CDVA outcomes. EPT outcomes were mixed, with results either comparable between FSL and conventional cataract surgery groups or favoring FSL groups. No studies addressed quality of life measures. Methodological concerns were noted regarding the generalizability of studies conducted from limited sites and potential sample selection bias from enrollment into FSL and conventional surgery groups.

Detailed findings

Table 1 shows the detailed characteristics and findings of the included comparative studies.

A randomized trial (N=134) with 77 patients in the FSL group and 57 patients in the conventional cataract surgery group utilized the Alcon LenSx laser.[14] Baseline age between groups was similar, with cataract density not reported. Reported post-operative CDVA at twelve weeks was 0.93±0.87 in the FSL group and 0.95±0.91 in the conventional group ($p>0.05$). Another randomized trial (N=45) compared a FSL group (n=25) versus a conventional group (n=20) using the Alcon LenSx laser.[15] At one year, post-operative CDVA was measured as .97±.06 for the FSL group versus .92±.09 for the conventional group ($p=.03$).

One study (n=400) enrolled consecutive patients electing for FSL (n=200). Patients who did not elect FSL underwent conventional phacoemulsification cataract surgery (n=200) and were considered the control group.[4] Five surgeons participated in this study, for which the OptiMedica Catalys laser was used in the FSL arm. Both groups were statistically similar at baseline in age and cataract density. EPT was reported as significantly decreased in the FSL group (4.3 vs 14.3 seconds; $p<0.001$).

Another study by the same author (N=201) was a case-control design, with a single surgeon using the OptiMedica Catalys laser in the FSL cases (n=150), compared to conventional cataract surgery controls (n=51).[16] Baseline demographics and cataract density were similar statistically between

groups. CDVA outcomes at three weeks post-operatively measured 0.67 in both groups ($p>0.05$). EPT was significantly decreased in the FSL group (2.33±2.28 vs 14.24±10.90 seconds; $p<0.0001$).

Another study (N=91) compared FSL groups (n=48) with conventional surgery groups (n=43), using the Alcon LenSx laser.[17] Baseline age and gender distribution was similar between groups but cataract density was not reported. At six months, post-operative CDVA was reported as as .97±.08 in the FSL group and .97±.06 in the conventional group ($p>.05$).

One study (N=76) enrolled equal groups (n=38) of FSL and conventional surgery patients, using the AlconLenSx laser.[18] Demographic characteristics and cataract density at baseline were reported as being similar between the groups. The study excluded patients with denser cataracts, low cooperation and FSL procedure contraindications such as corneal scarring. EPT was reported as 0.10±0.12 for the FSL group and 0.12±0.13 seconds for the conventional group ($p>0.05$).

Another study (N=40) enrolled patients into FSL (n=20) and conventional groups (n=20) using the Alcon LenSx laser.[19] Outcomes reported which compared FSL and conventional surgery groups were EPT (0.08 for FSL vs 0.08 for conventional; $p=0.94$) and one month post-operative CDVA (0.83±.0.65 for FSL vs 0.95±0.87 for conventional; p-value not reported).

A final study (N=25) enrolled patients in FSL (n=12) and conventional surgery (n=13) groups with similar baseline demographic characteristics, with cataract density not reported.[20] EPT was reported as not statistically different between groups. Eight week post-operative CDVA was measured as 1.0±0.0 for the FSL group and .95±.08 for the conventional group (p-value not reported).

Meta-analyses of CDVA and EPT

Figures 3 and 4 present plots of meta-analyses conducted on CDVA and EPT outcomes. Relatively few studies reported these outcomes in a consistent and combinable manner. We identified four studies for the meta-analysis of CDVA[16,17,19,20] and four studies for the meta-analysis of EPT.[4,16,18,19] Given the moderate to substantial heterogeneity among studies (for CDVA I-squared=63.9%, $p = 0.040$; for EPT I-squared=94.1%, $p = 0.000$), a summary estimate of the effect is unreliable. Instead, we present the forest plots as visual aids to illustrate individual study results.

The scales for CDVA used across studies were consistent when converted to decimal units, therefore we used mean difference to combine study results. We found moderate heterogeneity among studies. Consequently, we conducted a sensitivity analysis by excluding a presumed outlying study.[19] We found that this exclusion did not alleviate concerns with heterogeneity, nor did it change the substantive findings of the meta-analytic results. As a result, we included all four studies in the meta-analyses, represented in Figure 3 which illustrates no significant difference in CDVA for patients undergoing FSL or conventional procedures.

For EPT, we used the ratio of the mean to reduce the variation among studies and estimated the relative difference in EPT. Despite these efforts, there was still significant heterogeneity among studies. We would have included one additional study in the meta-analysis,[20] but this study did not report a point estimate for EPT and could not be included. Figure 4 shows what appears to be a reduction of mean EPT in the FLACS group, compared to the conventional group. However, since the 95% confidence interval includes one, this difference is not significant.

Figure 3: Corrected distance visual acuity (CDVA) in studies comparing femtosecond laser with conventional cataract surgery

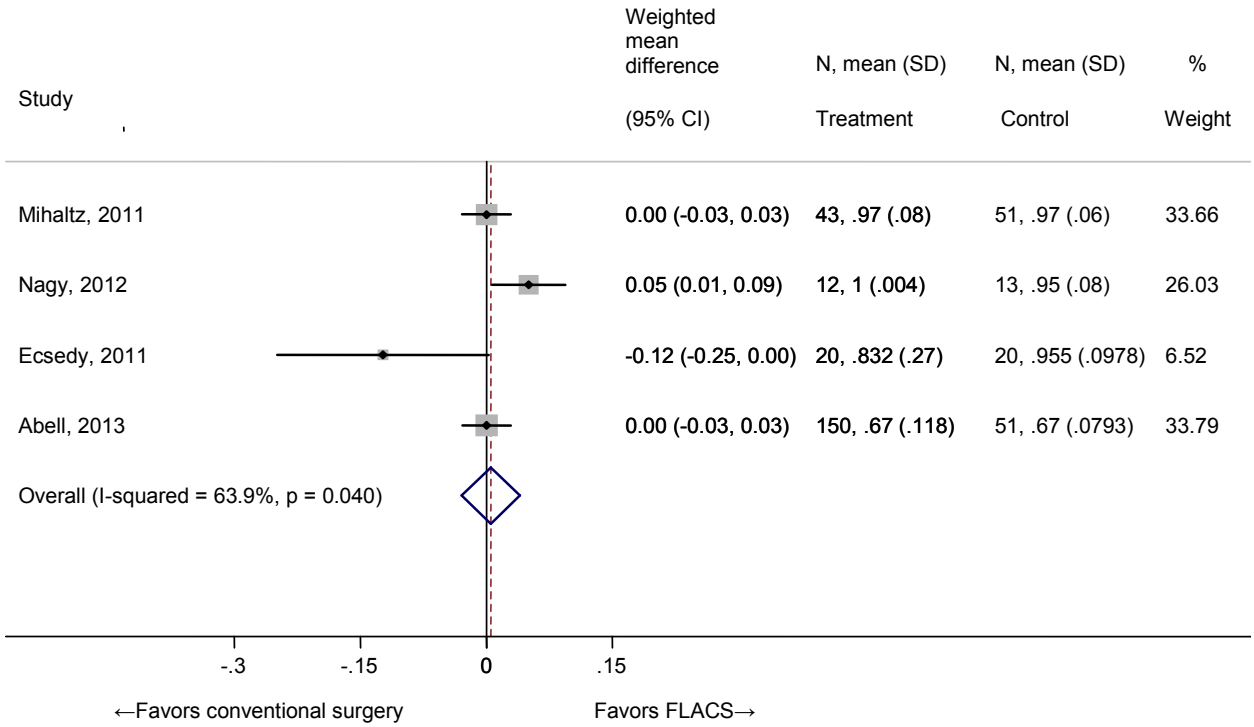
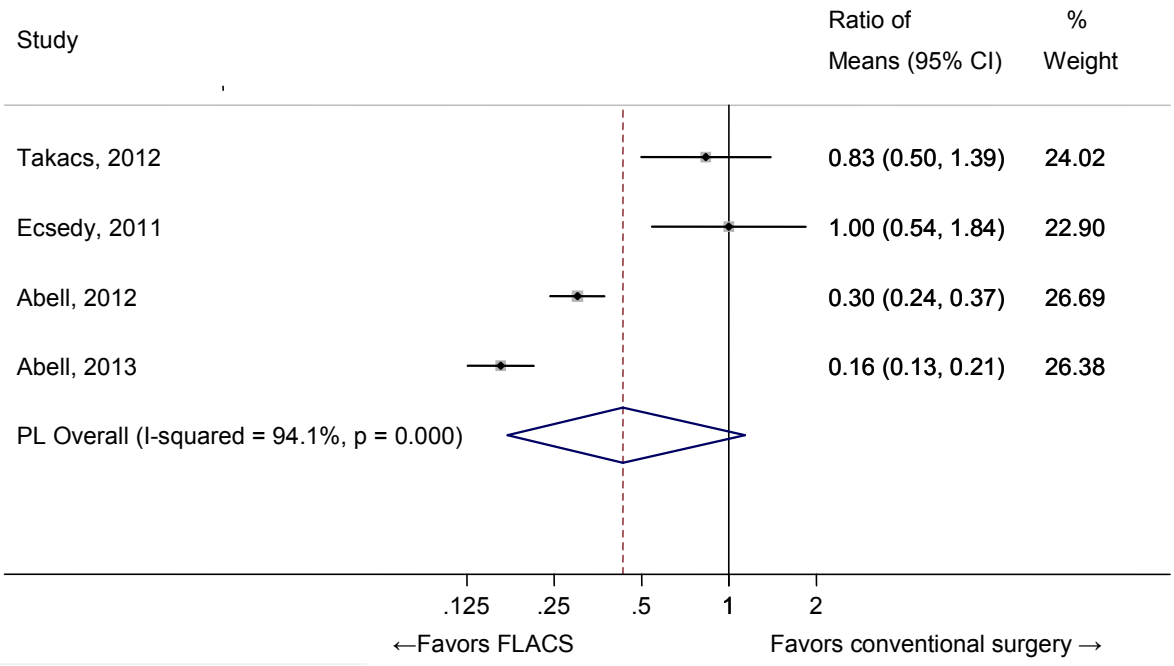


Figure 4: Effective phacoemulsification time (EPT) in studies comparing femtosecond laser with conventional cataract surgery



KEY QUESTION 2A: What are the adverse effects that have been reported for FLACS?

Summary of findings

Seven studies were identified addressing adverse effects unique to FLACS. Sample sizes in these studies ranged from 25 to 1300 patients, with follow-up periods extending from immediately following the procedure to three months post-operative.

We grouped the adverse event outcomes in these studies by either: 1) those occurring as a result of difficulties with the laser-patient interface; or, 2) the change in intraocular pressure (IOP) measured during the FLACS procedure. Five studies reported difficulties related to the laser interface with the ocular surface (including the orbital structures). Two studies measured intraocular pressure (IOP) fluctuation during FLACS procedures. A small proportion of patients experienced suction breaks, second docking attempts and aborted procedure adverse events. FSL application is also associated with an increase in IOP. Overall, we found moderate to low strength of evidence for adverse events with methodological concerns from enrollment criteria used for FSL surgery groups.

Detailed findings

Laser interface events

One study compared EPT in two groups of patients (n=80 per group) undergoing FLACS with two different laser grid-sizes.[21] In both groups, using the OptiMedica Catalys FSL, a total of twelve patients required a second docking attempt. No other intra-operative or subsequent adverse events were noted in either group after four weeks of follow-up.

A case series study (N=100) of IOP measurements during FLACS noted no patients had suction loss during FSL (Catalys) treatment.[22] No adverse events were reported at the one hour post-operative timepoint.

A comparative safety and effectiveness study of 400 patients (n=200 per group), reported four patients in the FSL (Catalys) group, for whom the laser procedure was aborted.[4] One patient was claustrophobic, one with kyphosis made postioning unsafe and two patients had excessive movement during the procedure.

A case series of the initial 200 patients undergoing FLACS (Alcon LenSx) in a single group practice reported intraoperative complications of this cohort.[23] Mean docking attempts were reported as 1.5 per eye. Five eyes had suction breaks during the FSL procedure, with no adverse events noted with the manual completion of the surgeries. A continuation study of this same group's experience, using the same FSL platform, reported intraoperative complications of FLACS for a subsequent series of 1300 patients.[24] No additional adverse effects unique to FLACS were noted, though data related to surgical experience was reported (see findings for Key Question 3).

Intraocular pressure events

The interface of any of the FSL platforms with the optical surface causes an increase in intraocular pressure (IOP).[8] This occurs due to applanation and/or suction applied during FSL

docking and laser application. This laser-patient interface must be stable throughout the phases of imaging, capsulotomy, corneal incisions and photodisruptive pre-fragmentation of the cataract. The various FSL platforms use different docking mechanisms, which can affect the degree to which the IOP increases during the FLACS procedure.[1] Both of the IOP studies included in this review utilized the OptiMedica Catalys FSL.

One case series (N=100) recorded IOP at two time-points—during and one hour following the FLACS procedure.[22] Mean IOP increased to 27.6 ±5.5 mmHg in this cohort. Patients were queried post-operatively and none reported experiencing amaurosis (blindness), during FLACS.

An additional case series study to analyze IOP during FLACS (N=25), reported measurements at baseline and at various time-points.[25] Mean baseline IOP (17.4±2.4 mmHg), increased to 36.0±4.4 mmHg during FSL application. This represented a mean increase from baseline of 18.5±4.7 mmHg.

KEY QUESTION 2B: What is the risk of adverse effects from FLACS compared to the risk associated with conventional cataract surgery?

Summary of findings

Nine studies addressed the adverse effects of FLACS compared to conventional cataract surgery. Sample sizes in these studies ranged from 25 to 400 patients, with follow-up periods extending from one week to one year.

We grouped the adverse event outcomes of these studies by the ocular structures which were affected. Five of these studies reported, variously: capsulotomy configuration, position and the resultant effects on IOL decentration and refractive outcomes. Two of these studies reported post-operative corneal edema by measuring either corneal thickness or corneal endothelial cell loss. An additional two studies compared post-operative macular thickness and morphology, as measured by optical coherence tomography (OCT). The FSL and control groups were similar for post-operative corneal thickness and macular edema measurements, with corneal endothelial cell loss decreased in the FSL group in one study. Overall, we found moderate to low strength of evidence for comparative adverse events with methodological concerns from enrollment criteria used for the FSL and conventional surgery groups.

Detailed findings

Capsulotomy sequelae

Five comparative studies of capsulotomy characteristics reported multiple aberrometry and geometric measurement outcomes.[6,14,15,17,26] However, none of the prioritized adverse events were reported in any of these studies (see Appendix C).

Corneal morphology and function

One study (n=76) compared central corneal thickness by pachymetry measurement at one month post-operatively in equal numbers of patients. At enrollment, patients with dense cataracts were excluded from participation in the study.[18] These authors reported no statistical difference

between corneal thickness between FSL vs. conventional groups (545±31µm vs. 557±42 µm; p>.05) Another study reported decreased corneal endothelial cell loss in the FSL group (n=150) vs. the control group (n=51) at three weeks post-operatively (-143.8±208.3 vs -224±188.95; p=0.02).[16]

Macular morphology

Two studies compared macular thickness between FSL and conventional surgery groups via OCT measurements. One of these studies (n=25) noted no statistically significant differences in macular thickness between groups in all but one retinal layer post-operatively at eight weeks.[20] Here, the outer nuclear layer was thicker in the control group (96.5±10.46µm vs 87.54±10.31µm; p=.04). Another study (n=40) measured macular thickness post-operatively at one month, reporting no significant differences between groups in macular total volume, foveal or outer macular ring thickness.[19]

KEY QUESTION 3: What is the evidence that the experience of the surgeon is associated with adverse effects of FLACS?

Summary of findings

Three studies reported outcomes relevant to the experience of the surgeon in performing the FLACS procedure. Sample sizes in these studies ranged from 200 to 1300 patients, with follow-up periods extending from two weeks to three months. Overall, one of the studies found no significant differences between outcomes for initial and subsequent groups of patients undergoing FLACS, while on the other hand two studies from the same team of researchers found significantly fewer complications associated with greater experience with FLACS.

There were methodological concerns from enrollment criteria used for the FSL and conventional surgery groups.

Detailed findings

One study compared the safety and effectiveness of FSL to conventional surgery in 200 consecutive patients who elected FSL or conventional surgery procedures.[4] Further sub-analysis of the FSL group into initial (n=100) and subsequent (n=100) patients reported outcomes for EPT and docking attempts. No statistically significant differences were noted between initial and subsequent groups for either of these FSL parameters (mean EPT: 3.52±4.18 for FSL vs. 4.75±5.22 for conventional group; p=0.0674; mean docking attempts: 1.49±0.64 for FSL vs. 1.36±0.79 for conventional group; p=0.2025).

Another study compared intraoperative complications in four groups of consecutive patients undergoing FLACS (n=50 in each group) who were followed for three months.[23] The number of mean docking attempts was greater in the initial 100 patients than in the subsequent 100 patients (1.85 for FSL vs 1.2 for conventional group; p<0.05). The seven surgeons participating in this study were all from a single group practice. Three of these surgeons had prior "extensive" experience with the FSL in LASIK surgery. The study noted these "refractive surgeons" had statistically fewer complications than did the "non-refractive surgeons" in their first 100 cases.

No significant difference in complications between these surgeon groups was noted after these initial 100 cases.

An extension of the above study[23] reported complication rates in a subsequent consecutive patient group (n=1300) treated with FLACS by the same surgical group practice, compared to the initial group of 200 patients.[24] Patients were followed for three months. Complications were significantly decreased in the subsequent group for docking attempts (1.5 for FSL vs 1.05 for conventional group), anterior capsular tears (4% for FSL vs 0.31% for conventional group), posterior capsular tears (3.5% for FSL vs 0.31% for conventional group) and posterior lens dislocation (2% for FSL vs 0% for conventional group). The reported p-values for all comparisons were $p<0.001$.

ONGOING STUDIES

We reviewed recent conference proceedings from ophthalmologic societies for topic relevance. We coded conference abstracts that potentially address one or more of our key questions and describe the study characteristics in Table 2.

Table 1: Characteristics and findings of studies of femtosecond laser assisted cataract surgery

Author, Year; Study Setting	Study objectives	Study Design; Number of Patients; Length of Follow-up; Laser Used	Mean age; % male; cataract density (LOC III score)	KQ 1: Benefits	KQ 2: Adverse events	KQ 3: Surgeon experience
Conrad-Hengerer, 2012[21] University of Bochum, Germany	Laser grid-size efficacy/safety study	Prospective cohort study of two FLACS techniques—no conventional surgery comparator (single surgeon) N=160 patients 4 weeks OptiMedica Catalys	Tx group 1 (350 grid): 71±12; 32%; 3.7±08 Tx group 2 (500 grid): 72±11; 60%; 3.5±08	EPT: Tx group 1=.03±.05 seconds Tx group 2=.21±.26 seconds p-value=NR	Intraoperative: -Free-floating anterior capsule noted in all eyes -12 2nd docking attempts Post operative: None noted	NA
Schultz, 2013[22] University of Bochum, Germany	Record IOP at various time-points during FLACS	Case series (2 surgeons) N=100 patients 1 hour OptiMedica Catalys	70±12; 51%; NR	NA	Intraoperative: 27.6±5.5mmHg increase in mean IOP	NA
Mihaltz, 2011[17] Semmelweis University Budapest, Hungary	Compare FSL and conventional capsulotomies	Prospective cohort study of FLACS and conventional surgery (single surgeon) N=91 patients 6 months Alcon LenSx	Tx group: 75.0; 21%; NR C group: 70.7; 18%; NR	CDVA: Tx group=.97±.08 C group= .97±.06 p>.05	NR	NA
Nagy, 2012[20] Semmelweis University Budapest, Hungary	Compare FSL and conventional OCT macular thickness changes	Prospective cohort study of FLACS and conventional surgery (single surgeon) N=25 patients 8 weeks Alcon LenSx	Tx group: 55.17±17.25; 58.3%; NR C group: 62.00±14.27; 38.5%; NR	CDVA: Tx group= 1.0±0.0 C group= .95±.08 p-value=NR EPT: Differences between Tx and C were NS	None noted	NA

Author, Year; Study Setting	Study objectives	Study Design; Number of Patients; Length of Follow-up; Laser Used	Mean age; % male; cataract density (LOC III score)	KQ 1: Benefits	KQ 2: Adverse events	KQ 3: Surgeon experience
Nagy, 2011[26] Semmelweis University Budapest, Hungary	Compare FSL and conventional capsulotomies and IOL decentration	Randomized trial of FLACS and conventional surgery (single surgeon) N=111 patients 1 week Alcon LenSx	Tx group: 65±13; 27.8%; NR C group: 68±15; 29.8%; NR	NA	NR	NA
Kranitz, 2012[15] Semmelweis University Budapest, Hungary	Compare FSL and conventional IOL decentration and tilt	Randomized trial of FLACS and conventional surgery (single surgeon) N=45 patients 1 year Alcon LenSx	Tx group: 63.55±13.65; 25%; NR C group: 68.24±10.77; 8%; NR	CDVA: Tx group=0.97±.06 C group= 0.92±.09 p=.03	NR	NA
Kranitz, 2011[6] Semmelweis University Budapest, Hungary	Compare FSL and conventional capsulotomy sizing and position	Prospective cohort study of FLACS and conventional surgery (single surgeon) N=40 patients 1 year Alcon LenSx	Tx group: 63.78±13.97; 25%; NR C group: 71.60±1.34; 30%; NR	NA	NR	NA
Takacs, 2012[18] Semmelweis University Budapest, Hungary	Compare FSL and conventional corneal edema	Prospective cohort study of FLACS and conventional surgery (single surgeon) N=76 patients 1 month Alcon LenSx	Tx group: 65.18±12.42; 26.3%; 2.32±.97 C group: 66.93±10.99; 39.5%; Schiempflug nuclear density 2.13±1.22	EPT: Tx group=0.10±0.12s C group= 0.12±0.13s p>.05	Postoperative: Central corneal thickness Tx group=545±31 µm C group= 557±42 µm p>.05	NA
Filkorn, 2012[14] Semmelweis University Budapest, Hungary	Compare FSL and conventional IOL power calculation and refractive outcome	Randomized trial of FLACS and conventional surgery (single surgeon) N=134 patients 12 weeks Alcon LenSx	Tx group: 65.18±12.6; NR; NR C group: 64.37±12.37; NR; NR	CDVA: Tx group=0.93±0.87 C group= 0.95±0.91 p>.05	NR	NA

Author, Year; Study Setting	Study objectives	Study Design; Number of Patients; Length of Follow-up; Laser Used	Mean age; % male; cataract density (LOC III score)	KQ 1: Benefits	KQ 2: Adverse events	KQ 3: Surgeon experience
Ecsedy, 2011[19] Semmelweis University Budapest, Hungary	Compare FSL and conventional macular thickness	Prospective cohort of FLACS and conventional surgery (single surgeon) N=40 patients 1 month Alcon LenSx	Tx group: 64 (median); 40%; NR C group: 66 (median); 25%; NR	CDVA (median): Tx group=0.83±0.65 C group= 0.95±0.87 EPT (median, IQR): Tx group=0.08s (0.03-0.12) C group= 0.08s (0.03-0.15) p=0.94	NA	NA
Abell, 2012[4] Launceton Eye Hospital, Tasmania, Australia	Compare FSL and conventional phacoemulsification safety and effectiveness	Parallel cohort study of FLACS and conventional surgery (5 surgeons) N=400 patients 2-3 weeks OptiMedica Catalys	Tx group: 73.3±9.9; 48%; 2.81±.82 (Pentacam Nuclear Staging) C group: 71.8±10.8; 42%; 2.71±0.72 (Pentacam Nuclear Staging)	EPT: Tx group=4.3 sec C group= 14.3 sec p<0.0001	Intraoperative: Reported for the Tx group, Imperfect capsulotomy= 0.5% Focal adhesions= 2% Reduction of pupil size= 3% Capsular rupture= 0.5% Aborted (claustrophobia), n=1 Aborted (unsafe postioning), n=1 Aborted (patient movement), n=2 Reported for C group: No adverse events noted	EPT: 1st 100 cases=3.52+-4.18 secs 2nd 100 cases=4.75+-5.22 secs; P=0.0674
Abell, 2013[16] Tasmanian Eye Institute, Launceton, Tasmania, Australia	Compare FSL and conventional phacoemulsification, visual outcomes and endothelial loss	Case control study of FLACS and conventional surgery (single surgeon) N=150 patients 3 weeks OptiMedica Catalys	Tx group: 72.8±10.5; 46%;2.59±0.71 (Pentacam Nuclear Staging) C group: 71.8±10.8; 45.1%; 2.52±0.72 (Pentacam Nuclear Staging) p>0.05	CDVA: Tx group=0.67 C group= 0.67 p>0.05 EPT: Tx group=2.33±2.28s C group=14.24±10.90 s p<0.0001	Postoperative: Endothelial loss Tx group= -143.8±208.3 C group= -224±188.95 p=0.022	NA
Kerr, 2013[25] Tasmanian Eye Institute, Launceton, Tasmania, Australia	Analyze the course of IOP during FSL cataract surgery	Prospective non-comparative cohort study N=25 patients immediate postop OptiMedica Catalys	72.5±7.7; 40%; NR	NA	Intraoperative: Mean baseline IOP=17.5±2.4mmHg Vacuum On IOP=28.9±3.2mmHg FSL application=36.0±4.4 mmHg p<0.001 (1-way ANOVA compared to baseline)	NA

Author, Year; Study Setting	Study objectives	Study Design; Number of Patients; Length of Follow-up; Laser Used	Mean age; % male; cataract density (LOC III score)	KQ 1: Benefits	KQ 2: Adverse events	KQ 3: Surgeon experience
Bali, 2012[23]; Roberts, 2013[24] Vision Eye Institute, Chatswood, Australia	Describe intraoperative complications and evaluate learning curve with FLS cataract surgery	Prospective non-comparative cohort study (7 surgeons) N=1500 patients (N=200 initial, N=1300 subsequent) 3 months Alcon LenSx	Initial Tx group: 69±9.8; NR; NR Subseqent Tx group: 70.1±10.6; NR; NR	NA	Intraoperative*: -mean docking attempts=1.5 -suction breaks=5 eyes -small anterior capsule tags=10.5% -posterior capsular rupture=3.5% (*These findings pertain to the initial study of N=200 patients)	Complications with increasing surgeon experience (docking attempts; anterior capsular tears; post capsular tears; IOL dislocation)*: 1st 200 cases= 1.5; 4%; 3.5%; 2% 2nd 1300 cases= 1.05; 0.31%; 0.31%; 0% p<0.001 for all comparisons (*These findings pertain to the initial and subsequent study of N=1500 patients)

Abbreviations: C = Conventional cataract surgery group; Tx = femtosecond laser cataract surgery treatment group; N = number of subjects; LOC III score = lens opacities classification system III grading score; EPT = effective phacoemulsification time; IOP = intraocular pressure; CDVA=corrected distance visual acuity; UDVA=uncorrected distance visual acuity; BDVA=best distance visual acuity; NOS = not otherwise specified; NR = not reported; NA = not applicable; NS = not statistically significant; FU = follow-up; FSL=femtosecond laser; FLACS=femtosecond laser-assisted cataract surgery.

Table 2: Characteristics of upcoming studies presented at recent conference proceedings or registered on ClinicalTrials.gov

Author, Year	Abstract Title	Conference, Location, Year	Population; Study Design; Setting	Study Objectives
Chee (ongoing study, registered in 2012)[27]	Prospective Evaluation of Circularity and Diameter of Femtosecond Laser Versus Manual Anterior Capsulotomy in Singapore National Eye Centre (1118)	ClinicalTrials.gov Online only	N≈22 Prospective, randomized study Singapore National Eye Centre, Singapore	Evaluate the circularity of the anterior capsulotomy performed by FLACS versus conventional cataract surgery.
Chee, 2013[28]	Early Visual Outcomes of First 100 Cases of Femtosecond Laser–Assisted Cataract Surgery in Ophthalmic Institution in Singapore	ASCRS Paper. San Francisco, CA. 2013	N=100 eyes Prospective cohort study Singapore	Examine safety and visual outcomes of FLACS versus control cases.
Culbertson, 2012[29]	Anterior Capsule Healing Patterns Following Femtosecond Laser–Assisted Cataract Surgery	ASCRS Paper,San Francisco, CA. 2013	N=24 patients Prospective randomized study NR	To evaluate size and shape of femtosecond laser anterior capsulotomy during 4 week healing.
Doane, 2011[30]	Effect on Refractive Predictability of Manual Versus Femtosecond Laser Capsulotomy in Cataract Surgery With Multifocal IOL Implantation	ASCRS Paper. San Francisco, CA. 2013	N=50 patients NR NR	To compare refractive predictability of multifocal IOL performance with manual versus laser refractive capsulotomy.
Gayton, 2013[31]	Clinical Experience With Femtosecond Laser–Assisted Cataract Surgery	ASCRS Paper. San Francisco, CA. 2013	N=5 patients NR NR	Femtosecond laser technology use in cataract surgery has several differences that can cause complications: 1) the anterior capsule is open prior to opening the eye therefore an anterior chamber collapse can result in anterior capsule tears, 2) large gas bubbles posterior to the lens can contribute to capsular block syndrome, 3) an incomplete capsulorrhexis can result in radial extension and 4) laser energy in the nucleus can be directed too anterior, too peripheral and too posterior. Adjustments to the surgical technique can help manage these complications appropriately.
Innovative Medical[32]	Clear Corneal Incisions and Arcuate Incisions Utilizing FemtoSecond Laser Technology for Cataract Surgery	ClinicalTrials.gov Online only	N=29 patients Non-Randomized trial Loden Vision Centers, Tennessee, USA	The purpose of this study is to prove the efficacy and safety of the Femtosecond laser to create a clear corneal incision during cataract surgery.
Knorz, 2011[33]	Comparison of Conventional and Femtosecond Laser-Assisted Phacoemulsification Cataract Surgery on the Macula	ASCRS Paper. San Francisco, CA. 2013	N=20 patients (N=20 eyes) NR NR	To compare the effect of conventional and femtolaser assisted (LensX) phacoemulsification cataract surgery on the macula, using optical coherence tomography (OCT).
Kurtz, 2009[34]	A Prospective Single Center Clinical Study for Capsulotomy Using the LenSx 550 Laser	ClinicalTrials.gov Online only	N=60 Prospective Single Center Trial Semmelweis University, Hungary	The objective of this study is to evaluate the ability of the LenSx 550 laser to successfully perform anterior capsulotomy during cataract surgery.

Author, Year	Abstract Title	Conference, Location, Year	Population; Study Design; Setting	Study Objectives
Loden, 2011[35]	Laser Cataract Surgery With the Femtosecond Laser Technology	ClinicalTrials.gov Online only	N=10 Non-Randomized trial Loden Vision Centers, Tennessee, USA	The purpose of this study is to prove the efficacy and safety of the Femtosecond laser to create a clear corneal incision during cataract surgery.
Mann, 2013[36]	Reduction of Cumulative Disbursement of Energy With Femtosecond Laser Cataract	ASCRS Paper. San Francisco, CA. 2013	N=151 eyes NR NR	Pretreatment with the Catalys femtosecond laser for cataract surgery allows for a greater than fifty percent reduction in ultrasound power during cataract extraction with the Infiniti phacoemulsification system with Ozil. This reduction in power may lead to quiter eyes with less edema and inflammation and a quicker visual recovery in the early postoperative period for femtosecond pretreatment group compared to a phacoemulsification group.
Nagy, 2011[37]	Comparison of Femtosecond Laser and Manual Capsulotomy on Postoperative Quality of Vision	ASCRS Poster. 2011	N=99 eyes NR NR	To compare postoperative quality of vision outcomes from capsulotomies created using a femto-second laser with those using manual continuous curvilinear capsulorrhexis (CCC).
Naranjo, 2011[38]	Laser Treatment of the Crystalline Lens	ClinicalTrials.gov Online only	N=75 A Prospective Single-Center Trial Mexico	The objective of this study is to evaluate the feasibility of the LensAR laser system to surgically intervene within the crystalline lens. The primary goal of this initial study is to establish safety parameters as compared with conventional phacoemulsification procedures and to evaluate the ability to provide an accurate and consistent anterior capsular opening (capsulotomy).
Ophthalmic Consultants of Long Island, 2012[39]	Corneal Sensation and Incidence of Dry Eye Post Refractive Cataract Extraction With FemtoSecond Laser	ClinicalTrials.gov Online only	N=40 Prospective cohort study Ophthalmic Consultants of Long Island – Rockville Centre. USA	The study objective is to assess changes in corneal sensation and dry eye signs and symptoms following cataract extraction/femtosecond arcuate relaxing incisions. Our clinical hypothesis is to determine if a combination of cataract surgery and femtosecond arcuate relaxing incisions lead to a reduction in corneal sensation and the onset or worsening of dry eye signs and symptoms.
Prickett, 2013[40]	Initial Resident Experience Performing Cataract Surgery with and without Femtosecond Laser (Conference proceeding)	ARVO Poster Session, 2013	N=44 eyes Observational study University of Illinois, USA	To document and compare the resident experience performing cataract surgery with femtosecond laser with standard cataract surgery performed without femtosecond laser.
Sándor, 2013[41]	Comparison of early corneal peripherial endothelial cell loss following femtosecond laser – assisted cataract surgery and conventional phacoemulsification (Conference proceeding)	ARVO Poster Session, 2013	N=15 patients (N=15 eyes) Observational study Semmelweis University, Hungary	To compare early corneal peripherial endothelial cell loss after femtosecond laser – assisted cataract surgery and conventional phacoemulsification, using non-contact specular microscopy.
Seibel, 2012[42]	Femtosecond Laser Pretreatment to Facilitate Cataract Surgery in Brunescent Cataracts	ASCRS Poster. 2012	Eye n=68 NR NR	To evaluate ease of removal of laser-fragmented cataracts.

Author, Year	Abstract Title	Conference, Location, Year	Population; Study Design; Setting	Study Objectives
Shah, 2013[43]	Assessment of Ease of Adoption of Femtosecond Cataract Surgery	ASCRS Poster San Francisco,CA 2013	NR NR NR	Examine the ease of use, compatibility of the system and quality of outcomes with femtosecond laser-assisted cataract surgery.
Vote, 2013[44]	Postoperative Corneal Oedema and Endothelial Cell Loss After Femtosecond Laser Pretreatment Compared With Conventional Cataract Surgery	ASCRS Paper. San Francisco, CA. 2013	Patient n=140 Prospective case-control study NR	Femtosecond laser pretreatment followed by phacoemulsification cataract surgery is associated with a significant reduction in post-operative oedema and endothelial cell loss compared to conventional phacoemulsification.
Weinstock, 2013[45]	Outcomes of Femtosecond Laser Cataract Surgery With Standardized Surgical Planning	ASCRS Poster San Francisco,CA 2013	N=180 eyes Prospective, non-randomized, multi-center study NR	The use of standardized surgical planning in femtosecond laser cataract surgery provided uncomplicated surgical planning with reproducible excellent outcomes.

Abbreviations: ASCRS = American Society of Cataract and Refractive Surgery; ASCRS♦ASO= A Symposium and Congress; ARVO= Association for Research in Vision and Ophthalmology; SPIE = the International Society for Optical Engineering; NR= not reported

DISCUSSION

We conducted a systematic review of the current FLACS literature, comparing the benefits of FLACS to conventional cataract surgery, the adverse events associated with FLACS and the influence of increasing surgical experience on these adverse events. We found moderate evidence of comparable CDVA outcomes between FLACS and conventional cataract surgery groups. We noted limited evidence for a reduction of EPT in the FSL compared to the conventional cataract surgery group. Furthermore, meta-analyses found no statistically significant differences between FSL and conventional groups in either CDVA or EPT. No studies reported findings related to quality of life outcomes or cost effectiveness of FLACS relative to conventional cataract surgery.

Several studies reporting adverse effects unique to FLACS noted docking failures to be common. These failures were successfully managed by a subsequent docking attempt. Rarely did these failures require aborting the FSL procedure, with successful completion by converting to conventional cataract surgery, resulting in no adverse outcomes. There were moderate adverse findings of orbital or ocular anatomical laser interface difficulties, causing either aborted FSL procedures or exclusion of these patients from the studies. The Catalys FSL platform, using the liquid-filled interface, was utilized in two studies of serial IOP measurements during and after the procedure. Transient elevation of IOP into the mid-20 to mid-30 mm Hg range during the FSL precedure was noted in these studies. No studies were found for IOP measurements using the Alcon LenSx FSL, which utilizes suction to effect docking. This interface mechanism has been noted to cause marked IOP elevations in other corneal refractive surgical applications.[3]

Most of the included studies reported on the comparative risks of adverse effects between FSL and conventional cataract surgery. Reports of adverse events were similar between FSL and conventional groups, including IOL positioning, corneal thickness, macular edema and residual refractive error. The rate of postoperative corneal endothelial cell was noted to be significantly decreased in the FSL group in only one included medium-sized study (N=201).[16]

The association between the experience of the surgeon and FLACS adverse effects was limited to three eligible studies, two of which were related. These studies reported mixed results of surgical experience reducing the incidence of FLACS adverse events, with very low strength of evidence.

We conducted an update search on September 18, 2013 and found two observational studies that reported decreased EPT with FSL,[46,47] consistent with the trend seen among other studies included in our review. We also identified two recent studies that found decreased initial postoperative inflammation with FSL,[47,48] although after three months no differences were observed between FSL and conventional cataract surgery.[48]

Although there were significant limitations with the body of literature, we found FLACS to be comparable to conventional cataract surgery. We found no evidence that FLACS differs from conventional cataract surgery on measures of safety and effectiveness. The unique risks associated with FLACS are primarily related to laser docking interface difficulties, which may be reduced with increasing surgical experience with the procedure. The comparative adverse event risks of FLACS and conventional surgery were similar. Complications rates in FLACS cohorts were found to be reduced or unchanged by surgical experience in the included studies of this review.

There were methodological concerns for the included studies that represent potential sources of bias that threaten the validity of study findings. Many studies had small sample sizes, with the potential for difficulty in analyzing data for low-risk events,[49] and follow-up times and outcomes reported were often variable, making study comparisons problematic. In addition, study methods were often unclear, particularly with regard to the application of inclusion and exclusion criteria for FSL treatment groups and the enrollment of treatment and control cohorts. Often studies excluded patients with denser cataracts, comorbidities and those deemed uncooperative. In addition, many study protocols called for patients self-selecting into FSL or conventional surgery groups. Further, most studies evaluated similarities between treatment and control groups only for gender and age.

All of the FSL platforms require the orbital anatomy to be accessible and the cornea to be suitable for successful laser docking. Two of the eligible studies in this review specifically excluded patients in the FSL group, who had "deep-set eyes"[4] or "narrow palpebral fissures".[24] Similarly, an adequate laser/corneal interface requires a pristine corneal surface. Most of the studies excluded patients from the laser treatment groups with corneal pathology such as scarring, previous corneal surgery and high degrees of corneal astigmatism, limiting generalizability of findings to those patients for whom FLACS is appropriate.[4,14,16,18,21-25]

Similar exclusion criteria issues were noted in studies for dense cataracts[18,22] as the FSL is unable to perform photo disruption in tissues that are not optically clear.[4,50] The Schiempflug nuclear density grading (LOC III score of increasing density from 1-5) was reported at baseline in a minority of the comparative studies.[4,16,18] Here, in the FSL groups, the LOCS III scores ranged from 2.13 to 2.59; only patients with mild to moderate density cataracts were enrolled, specifically excluding patients with dense cataracts.

The FSL procedure is unsuitable for patients who are unable to cooperate, for any reason. Thus, some studies excluded patients from the FSL groups who were "uncooperative",[18] or with hemifacial spasm.[24] Transient elevations of IOP limit FLACS suitability for patients with high-risk glaucoma, another exclusion criteria found in many studies. Patients with other medical co-morbidities, such as kyphosis and movement or behavioral disorders, were found to be unacceptable for FLACS procedures. The careful patient selection in studies of FLACS to date may significantly limit the generalizability of findings to VA cataract surgical populations.

Operating room logistics and efficiencies are made more cumbersome by the need for a two-suite surgery staging for each patient.[1] Each patient undergoes the FLACS procedure beneath the FLS platform and is moved into a second, sterile location in the operating room for the completion of the surgery. In addition, multiple laser docking attempts can extend the operating room time for each patient. This added complexity and duration of the surgical procedure may adversely impact surgical backlogs.

Device manufacturers are closely associated with most of the study authors and the majority of included studies (all but two) report financial conflicts of interest. Eligible studies were also clustered around a limited number of geographic sites and conducted by the same team of coauthors. All four of the included randomized trials were conducted by the same research group, and every surgery (FSL or conventional) was completed by the same surgeon study co-author. It is also unclear whether or not there was any overlap in the study patient populations of these

trials, given they were conducted at the same site and in what seems to be a similar timeframe.

Most of the studies in this review involved highly experienced, high-volume surgeons, supported by similarly experienced surgical teams. These findings may not apply to VA surgeons, especially with regard to ophthalmology residency training programs. The few studies which reported decreasing complication rates with increased surgical experience must be considered when evaluating the suitability of introducing FLACS into a training program environment.

The eligible studies in this review did not include any cost-effectiveness or quality of life data. The non-laser portion of the disposable costs for FLACS and conventional phacoemulsification surgery are comparable, as both involve irrigation, aspiration and phacoemulsification. The additional, incremental cost of FLACS is the $150-300 per patient charge for the sterile, single-use patient interface device.[50] The approximate initial cost of the FSL equipment is $500,000. Future studies assessing the cost-effectiveness and incremental changes to quality of life associated with FLACS and conventional cataract surgery will be needed to provide additional information to guide procedure adoption decisions.

FUTURE STUDIES

Modern, conventional cataract surgery is associated with very low risks of sight-threatening complications.[49] In this review, FLACS appears to be comparable to conventional cataract surgery, though the evidence base is limited. Greater numbers of randomized control trials (RCTs) with larger sample cohort sizes are desirable to allow detection of the relative risks of rare events. Assessment blinding is problematic, as FLACS patients are aware of their participation in the FSL treatment arm, as are the assessors due to the unique appearance of the laser versus the manual incisions. Studies that are sufficiently powered and well designed should be insulated from the device manufacturers to eliminate this potential bias. Head to head trials between FSL platforms should assist in informing potential users of their relative risks and benefits. Studies from groups other than those few included in this review should provide a more global perspective of FLACS. The applicability of the FSL technology to the overall cataract population has not been explored by the eligible studies in this review. Further studies regarding the suitability of FSL for patients with the co-morbidities found in the VA population (i.e. dense cataracts, glaucoma, corneal pathology) and studies assessing the costs relative to benefits expected from FLACS and conventional surgery will be key to determining the feasibility of widespread adoption of this procedure.

CONCLUSIONS

This systematic review found visual outcomes (CDVA) and EPT to be similar in FLACS and conventional surgery, while quality of life and cost-effectiveness outcomes were not reported. The evidence for the relative benefit of FLACS was limited by reliance on small to moderately-sized prospective cohort studies, nearly all of which had stated financial conflicts of interest. Adverse events unique to FLACS involved difficulties in laser docking or patient suitability for the procedure. Many patients were excluded from the FSL treatment groups for orbital, corneal, cataract density, or medical co-morbidities. Comparative adverse events in FLACS and conventional surgery were found to be similar for IOL positioning, corneal thickness, macular edema and residual refractive error. A few studies reported mixed results of the effect of surgical experience on the incidence of FLACS adverse events.

Table 3: Summary of the evidence on the effects of femtosecond laser assisted cataract surgery

Outcome	For each study design: Number of studies (combined sample size)	Findings	Strength of Evidence	Comments
Visual acuity	2 RCTs (N=189) 4 NRCS (N=306)	No significant differences	Low	No differences in visual acuity outcomes found in either of the randomized trials. Unclear risk of bias for trials, low consistency, coherence and applicability of estimated effects across studies, small to medium sample sizes and conflicts of interest lower the strength of evidence.
Effective phacoemulsi-fication time	1 RCT (N=76) 4 NRCS (N=615) 1 NCS (N=160)	Mixed findings	Low	Trial found no significant reduction in EPT for FSL group. Two of the large nonrandomized studies (N=550) reported significant reductions in favor of FLACS. Remaining three studies found no significant differences. Unclear risk of bias for trial, low consistency, coherence and applicability of estimated effects across studies and conflicts of interest lower the strength of evidence.
Quality of life	None	None	No evidence	None of the included studies reported on quality of life outcomes.
Intraoperative complications*	3 NRCS (N=1,900) 3 NCS (N=285)	Higher IOP for FLACS; Few additional complications for FLACS	Moderate to Low	Low incidence of complications with FLACS, though increases in IOP reported across studies. Low applicability of estimated effects lowers the strength of evidence.
Postoperative complications**	1 RCT (N=76) 1 NRCS (N=150) 1 NCS (N=160)	Mixed findings	Low	Trial found no significant differences and medium-sized cohort study (N=150) found significantly reduced endothelial loss for the FLACS group. Unclear risk of bias for trial, low consistency and coherence of estimated effects across studies, small to medium sample sizes and conflicts of interest lower the strength of evidence.
Costs	None	None	No evidence	None of the included studies reported on costs of FLACS compared to conventional cataract surgery.

Abbreviations: RCT = randomized controlled trial; NRCS = non-randomized comparative studies; NCS = non-comparative studies; FLACS = femtosecond laser assisted cataract surgery; EPT = effective phacoemulsification time; IOP = intraocular pressure.
*Intraoperative complications include: capsular blockage, capsular tear, dislocated nucleus, docking failure
**Postoperative complications include: infection, retinal swelling/cystoid macular edema, intraocular decentration, corneal edema

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APPENDIX A: SEARCH STRATEGY

MEDLINE (PubMed) searched 5/8/2013

Search	Query
#9	Search (#8) AND #7
#8	Search ((((((femtosecond) OR alcon lensx) OR optimedica catalys) OR lensar) OR victus) OR intralase) OR ifs laser systems OR "all-laser Lasik"
#7	Search (#6) OR #5
#6	Search cataract
#5	Search "Cataract"[51] OR "Cataract Extraction"[51]

76 unique cites added to EndNote Library

Cochrane Central Register of Controlled Trials and Database of Sytematic Reviews (OVID), searched 5/8/2013

#	Searches
1	exp Cataract Extraction/ or exp Cataract/ or cataract.mp.
2	femtosecond.mp.
3	alcon lensx.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4	optimedica catalys.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5	lensar.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6	victus.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7	intralase.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8	ifs laser systems.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9	All-laser lasik.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
10	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	1 and 10

3 unique cites added to EndNote Library

Additional databases, societies and journals, searched 4/17/2013 to 7/9/2013:

1. ASCRS: American Society of Cataract and Refractive Surgery http://www.ascrs.org/ [See also abstracts that were locked out at end of document]
2. Journal of Cataract & Refractive Surgery http://www.jcrsjournal.org/
3. American Academy of Ophthalmology http://www.aao.org/

4. International Society of Refractive Surgery http://www.aao.org/isrs/
5. American Academy of Opthalmic Executives http://www.aao.org/aaoe/
6. The Foundation of the American Academy of Ophthalmology http://www.faao.org/
7. The Royal College of Ophthalmologists http://www.rcophth.ac.uk/
8. The Association for Research in Vision and Ophthalmology http://www.arvo.org/
9. The Journal of Cataract and Refractive Surgery http://www.jcrsjournal.org/
10. Ophthalmology, the official journal of the American Academy of Ophthalmology – http://www.aaojournal.org/
11. COS Conference Papers Index
12. Proceedings First (OCLC)
13. http://clinicaltrials.gov/
14. http://www.fda.gov/

APPENDIX B: INCLUSION/EXCLUSION CRITERIA

Code	Definition	Exclusion criteria/notes	KQ1 – Benefits	KQ2 –Adverse effects	KQ3 – Learning curve
I-1 I-2 I-3 I-SR	Include; addresses KQ1, KQ2, or KQ3 SR = systematic review		KQ1: What are the benefits of FLACS compared with conventional cataract surgery?	KQ2a: What are the unique risks associated with FLACS? KQ2b: What are the risks of FLACS compared to conventional cataract surgery?	KQ3: What are the intra-operative and post-operative risks of FLACS with regard to the experience f the surgeon?
X1	Non-English language				
X2	Does not pertain to femtosecond laser technology				
X3	Intervention not in scope	Exclude studies of lasers used for procedures other than cataract surgery	Included interventions: femtosecond lasers used for cataract surgery applications	Same interventions as KQ1	Same interventions as KQ1
X4	Study population not in scope	Note: FLACS is contraindicated in the following populations: advanced glaucoma; high anxiety; tremors; dementia; facial or ocular anatomy that precludes docking	Included population: adults undergoing cataract surgery	Same population as KQ1.	Same population as KQ1
X5	No primary data or study design not in scope, according to each KQ.	Exclude non-systematic or narrative reviews, editorials and opinions. Add code B (e.g. X5-B) to consider using the article in Discussion, or possibly describe the study data as a lower level of evidence.	Include controlled study designs: • Randomized controlled trials (RCTs) • Non-randomized controlled clinical trials • Controlled before/after studies	Included study designs for harms: • Controlled studies • Quasi-experimental studies • Cohort studies • Case-control studies Excluded study designs: • Case reports • Case series	• Same study designs listed for KQ2 • Cost-evaluation studies
X6	Outcomes that are not in scope		Short-term patient outcomes: • Visual acuity: post-operative day 1 Long-term patient outcomes: • Visual acuity: after post-operative day 1 (typically recorded after 1 week, 1 month, or 90 days) • Quality of life (QOL) measures	Intra-operative complications: • Capsular blockage syndrome • Dislocated nucleus • Capsular tear Post-operative complications: • Infection • Retinal swelling/cystoid edema (CME) • Intraocular (IOL) decentration • Corneal edema Other reported harms	• Cost • All other specified outcomes
X7	Other reason: specify	Add comments or keywords as needed.			
X99	Full text not accessible				
B	Background	Add to any of the above X codes (e.g., X5–B) if the article contains information that may be useful for the introduction, discussion, limitations, future research, or other contextual purposes. Add comments or keywords as needed.			

APPENDIX C: ELIGIBILITY CHARACTERISTICS OF STUDIES (PICOTS TABLE)

	KQ1: Benefits What is the evidence that FLACS is associated with better outcomes than conventional cataract surgery?	KQ2: Adverse effects KQ2a: What are the adverse effects that have been reported for FLACS? KQ2b: What is the evidence that FLACS is associated with a lower risk of adverse effects than conventional cataract surgery?	KQ3: Learning curve What is the evidence that the experience of the surgeon is associated with adverse effects of FLACS?
Population	Adults undergoing cataract surgery. Considerations: femtosecond laser surgery is relatively contraindicated in patients with: advanced glaucoma, high anxiety, tremors, dementia, facial or ocular anatomy that precludes adequate LASER docking (i.e. small palpebral fissures, prominent brows) and previous refractive surgery or corneal opacities.		
Intervention	Femtosecond laser technology is used in cataract surgery to assist or replace aspects of conventional cataract surgery, including corneal incisions, capsulotomy and lens fragmentation. Lasers at or near the point of commercial release include: Alcon LenSx (Alcon Laboratories, Fort Worth, TX, USA), OptiMedica Catalys (OptiMedica Corp, Santa Clara, CA, USA), LensAR (LensAR Inc, Winter Park, FL, USA), VICTUS (Bausch + Lomb, Aliso Viejo, CA, USA; and Technolas Perfect Vision GmbH, Munich, Germany), IntraLase FS and iFS Laser Systems (Abbott Medical Optics, Abbott Park, IL, USA). This review is inclusive of studies of any femtosecond laser used for cataract surgery applications regardless of FDA status.		
Comparator	Conventional cataract surgery, defined as small-incision phacoemulsification with planned posterior-chamber intraocular lenses (IOL).		
Included study designs	Controlled studies including randomized controlled trials, non-randomized controlled clinical trials, controlled before/after studies and observational studies	Controlled studies, observational studies, case-control studies, case reports, case series.	Controlled studies; observational study designs including economic evaluation studies).
Excluded study designs	Case reports, case series and studies that do not report primary data such as editorials and non-systematic reviews.	Studies that do not report primary data such as editorials and non-systematic reviews.	Studies that do not report primary data such as editorials and non-systematic reviews.

Outcomes of interest	Short-term patient outcomes
	• Visual acuity: post-operative day 1
	Long-term patient outcomes
	• Visual acuity: after post-operative day 1 (typically recorded post-operative 1 week, 1 month, or 90 days)
	• Quality of Life (QOL) measures
		Surgical Complications
		• Intra-operative
		  • Capsular blockage syndrome
		  • Dislocated nucleus
		  • Capsular tear
		  • Docking failure or loss of docking
		• Post-operative
		  • Infection
		  • Retinal swelling/Cystoid Macular Edema (CME)
		  • Intraocular (IOL) decentration
		  • Corneal edema
			• Cost
			• All other surgical complications listed
			• Other adverse effects reported

Timing	Our operational definition to be used for timing of patient outcomes is as follows: • Short-term—patient outcomes on post-operative day 1 • Long term—patient outcomes > after post-operative day 1 (no upper limit) Considerations: Standards for reporting timing of post-operative outcomes often have variable time-horizons. For example, potential harms such as CME or IOL decentration, may be reported from as early as post-operative day one or after months to years in some studies.		
Setting	Any		

APPENDIX D: ASSESSMENT OF METHODOLOGIC QUALITY IN STUDIES OF FEMTOSECOND LASER ASSISTED CATARACT SURGERY

The Newcastle-Ottowa tool for observational studies

Author, year; study setting	Non-biased selection	High overall loss to follow-up or differential loss to follow-up	Adequate duration of follow-up	Outcomes pre-specified and defined	Ascertainment techniques adequately described	Non-biased and adequate ascertainment methods	Statistical analysis of potential confounders
Conrad-Hengerer, 2012[21] University of Bochum, Germany	Unclear "A standardized lens-softening pattern… was used in 1 study group and a 500 mm grid size in the other study group after randomization"	No	NA	Yes	Yes	Yes	No "Descriptive statistical analysis was performed using SPSS. The ttest was used to compare the sample means. Boxplots were used for analysis."
Schultz, 2013[22] University of Bochum, Germany	No "Patients scheduled for elective femtosecond laser–assisted cataract surgery"	NA. Primary outcome was intraoperative.	NA	Yes	Yes	Yes	Unclear
Mihaltz, 2011[17] Semmelweis University Budapest, Hungary	Unclear "Femtosecond capsulotomies were performed in 48 eyes of 43 patients … Continuous curvilinear capsulorrhexis by forceps was performed on 51 eyes of 38 patients, which served as a control group"	No	Yes	Yes	Yes	Yes	No "Statistical analysis was performed by comparing two samples at a time using the Student t test for analysis of mean visual and refractive values and intraocular optical quality parameters in both study groups"
Nagy, 2012[20] Semmelweis University Budapest, Hungary	No "The study group comprised 12 eyes of 12 patients. The control group comprised 13 eyes of 13 patients."	No	Yes	Yes	Yes	Yes	Yes
Nagy, 2011[26] Semmelweis University Budapest, Hungary	Yes "Using computer randomization, patients and their right/left eyes were randomly selected for femtosecond and manual surgery."	No	Yes	Yes	Yes	Yes	Unclear
Kranitz, 2012[15] Semmelweis University Budapest, Hungary	Yes "Randomization was done using computer-generated tables"	No	Yes	Yes	Yes	Yes	Unclear

Author, year; study setting	Non-biased selection	High overall loss to follow-up or differential loss to follow-up	Adequate duration of follow-up	Outcomes pre-specified and defined	Ascertainment techniques adequately described	Non-biased and adequate ascertainment methods	Statistical analysis of potential confounders
Takacs, 2012[18] Semmelweis University Budapest, Hungary	Yes "Patients were randomly assigned (using computer randomization) to either group by the surgeon"	No	Yes	Yes	Yes	Yes	Unclear
Filkorn, 2012[14] Semmelweis University Budapest, Hungary	Yes "Patients were randomly assigned to each group using a computer randomization chart."	No	Yes	Yes	Yes	Yes	Unclear
Kranitz, 2011[6] Semmelweis University Budapest, Hungary	No ""Femtosecond capsulotomies were carried out in 20 eyes of 20 patients and manual CCC was performed in 20 eyes of 20 patients undergoing cataract sugery with IOL implantation."	No	Yes	Yes	Yes	Yes	Unclear. GEE models used to correct for correlated measures for patients having both eyes operated.
Ecsedy, 2011[19] Semmelweis University Budapest, Hungary	No "…femtosecond laser-assisted phacoemulsification with the LenSx laser system was carried out in 20 eyes from 20 patients with cataract. Traditional phacoemulsification was performed on 20 eyes from 20 additional patients with cataract."	No	Yes	Yes	Yes	Yes	Unclear
Abell, 2012[4] Launceton Eye Hospital, Tasmania, Australia	No "Patients who underwent conventional cataract surgery (i.e. did not have femtosecond laser) were classified as the control group"	No	Yes	Yes	Yes	Yes	Unclear
Abell, 2013[16] Tasmanian Eye Institute, Launceton, Tasmania, Australia	No "Cases (n=150) included patients who elected to undergo femtosecond laser pretreatment "	No	Yes	Yes	Yes	Yes	Unclear
Kerr, 2013[25] Tasmanian Eye Institute, Launceton, Tasmania, Australia	No "Consecutive patients having femtosecond laser pretreatment to cataract extraction were recruited"	No	Yes	Yes	Yes	Yes	Unclear

Author, year; study setting	Non-biased selection	High overall loss to follow-up or differential loss to follow-up	Adequate duration of follow-up	Outcomes pre-specified and defined	Ascertainment techniques adequately described	Non-biased and adequate ascertainment methods	Statistical analysis of potential confounders
Bali, 2012[23] Vision Eye Institute, Chatswood, Australia	No "…study included the initial 200 consecutive femtosecond laser cataract surgeries, refractive lens exchange surgeries, or both performed at the Vision Eye Institute "	No	Yes	Yes	Yes	Yes	No
Roberts, 2013[24] Vision Eye Institute, Chatswood, Australia	No "…prospective, multicenter, nonrandomized, postmarket evaluation undertaken after local regulatory approval was obtained for clinical use of the LenSx system"	NA. Primary outcome was intraoperative.	NA	Yes	Yes	Yes	Unclear

Abbreviations: NA = not applicable.

The Cochrane Collaboration's tool for assessing risk of bias

Author, year; study setting	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Risk of bias*
Nagy, 2011[26] Semmelweis University Budapest, Hungary	Low: "Using computer randomization, patients and their right/left eyes were randomly selected for femtosecond and manual surgery."	Unclear: No information provided	Unclear: No information provided, but one of the authors completed all surgeries, suggesting a lack of personnel blinding.	Low: Report no attrition and exclusions appear to all be pre-randomization.	Unclear: Reported on key outcomes but unclear if other outcomes were assessed but not reported.	Unclear
Kranitz, 2012[15] Semmelweis University Budapest, Hungary	Low: "Randomization was done using computer-generated tables"	Unclear: No information provided	Unclear: No information provided, but one of the authors completed all surgeries, suggesting a lack of personnel blinding.	Low: Report no attrition and exclusions appear to all be pre-randomization.	Unclear: Reported on key outcomes but unclear if other outcomes were assessed but not reported.	Unclear
Takacs, 2012[18] Semmelweis University Budapest, Hungary	Low: "Patients were randomly assigned (using computer randomization) to either group by the surgeon"	Unclear: No information provided	Unclear: No information provided, but one of the authors completed all surgeries, suggesting a lack of personnel blinding.	Low: Report no attrition and exclusions appear to all be pre-randomization.	Unclear: Reported on key outcomes but unclear if other outcomes were assessed but not reported.	Unclear
Filkorn, 2012[14] Semmelweis University Budapest, Hungary	Low: "Patients were randomly assigned to each group using a computer randomization chart"	Unclear: No information provided	Unclear: No information provided, but one of the authors completed all surgeries, suggesting a lack of personnel blinding.	Low: Report no attrition and exclusions appear to all be pre-randomization.	Unclear: Reported on key outcomes but unclear if other outcomes were assessed but not reported.	Unclear

*Risk of bias: Low = Plausible bias unlikely to seriously alter the results;
Unclear = Plausible bias that raises some doubt about the results;
High = Plausible bias that seriously weakens confidence in the results.

APPENDIX E: PEER REVIEW COMMENTS AND RESPONSES

	Reviewer	Comment	Response
	Question 1: Are the objectives, scope and methods for this review clearly described?		
	1	Yes. I think the objectives were well spelled out. We did not ask specifically for any cost/benefit analysis so was done nicely.	Noted, thank you.
	3	Yes. (No comment)	Noted.
	4	Yes. (No comment)	Noted.
	5	Yes. The objectives could be more clearly stated as the purpose of this work is to systematically review and critically appraise the available evidence of FSL assisted cataract surgery vs conventional surgery.	We thank the reviewer for the comment. The reviewer is correct that one aspect of the review is to appraise available evidence of FSL compared to conventional cataract surgery. However, the harms and learning curve assessment questions were not limited to comparative studies. We have clarified the objectives of the report in the background and methods sections.
	2. Is there any indication of bias in our synthesis of the evidence?		
	1	No. I did not see any, but the papers reviewed certainly had bias as you pointed out.	Noted, thank you.
	3	No. (No comment)	Noted.
	4	No. (No comment)	Noted.
	5	No. (No comment)	Noted.
	3. Are there any published or unpublished studies that we may have overlooked?		
	1	No. None that I am aware of.	Noted.
	3	No. (No comment)	Noted.
	4	No. Given the technology is fairly new as far as FDA approval, high level evidence literature is limited.	Noted.
	5	Yes. Methods: The recommended databases to search (as a minimum) by the Cochrane Collaboration is EMBASE, MEDLINE, and CENTRAL. I suggest reviewing EMBASE and CENTRAL in addition to all the other sources searched.	We have clarified the databases searched in Figure 2 (literature flow) of the report. Our search of the Cochrane library included the CENTRAL register of controlled trials. Unfortunately, our library does not subscribe to EMBASE so we do not have access to that database. However, we are reasonably confident that we have captured the relevant literature for the topic, given that we have searched the grey literature and recent conference proceedings in this quickly evolving field.

	Reviewer	Comment	Response
	4. Please write additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.		
	1	Were any of the papers quoted funded directly by manufacturers? It seems like even in the papers quoted you had methodological questions, for instance were patients used in multiple reports and that most of the "better" papers were all done by one surgeon, so the question of learning curve remains?	We examined the acknowledgements listed for each of the papers and could only report on the consulting fees and honoraria received by study authors. In addition, there were very few papers examining the issue of learning curve. As a result, the evidence available to answer key question 3 is very sparse.
	2.	I appreciate the amount of effort the coordinators have made for this systematic review. I have the following comments. A limitation of meta-analysis restricted to methodologically sound comparison studies is failure to capture relatively infrequent but important adverse outcomes that begin to be reported as individual or small series reports several years after institution of a new technology. This pattern was seen in corneal refractive surgery after institution of LASIK (laser in situ keratomileusis). Case reports of ischemic optic neuropathy (anterior or posterior) with partial loss of vision were linked to the high intraocular pressures from the metal suction rings used for the standard microkeratome procedure (references 1-3). A similar case of optic neuropathy has been reported with a femtosecond laser using a low-pressure suction ring (reference 4). As a LASIK surgeon, I am aware of other unreported cases. As you note in your review, all docking devices currently used in femtosecond platforms lead to an increase in intraocular pressure, which puts the microcirculation of the optic nerve at risk, especially in patients with microvascular disease from diabetes or hypertension. This effect may be especially important in the VHA population. Ischemic optic neuropathy has also been reported after uncomplicated conventional phacoemulsification (References 5-7). References. 1. Lee AG, et al. Optic neuropathy associated with laser in situ keratomileusis. J Cataract Refract Surg 2000;11:1581-4. 2. Bushley DM, et al. Visual field defect associated with laser in situ keratomileusis. Am J Ophthalmol 2000;129:668-71. 3. Cameron BD, et al. Laser in situ keratomileusis-induced optic neuropathy. Ophthalmology 2001;108:660-5. 4. Maden A, et al. Nonarteritic ischemic optic neuropathy after LASIK with femtosecond laser flap creation. J Neuro-Ophthalmol 2008;28:242-3. 5. Lee H, et al. A case of decreased visual field after uneventful cataract surgery; nonarteritic anterior ischemic optic neuropathy. Korean J Ophthalmol 2010;24:57-61. 6. Luscavage LE, et al. Posterior ischemic optic neuropathy after uncomplicated cataract extraction. Am J Ophthalmol 2001;132:408-9. 7. McCulley TJ, et al. Incidence of nonarteritic anterior ischemic optic neuropathy associated with cataract extraction. Ophthalmology 2001;108:1275-8.	We thank the reviewer for the insightful comments. In an attempt to identify all of the adverse events associated with FLACS, we included various study designs, even those of case reports. As the reviewer points out, these low prevalence events are not appropriate for meta-analysis. As noted in our review, all of the FSL platforms have been associated with some elevation of IOP during the procedure. This has not been noted to be as severe as the amaurosis-inducing levels common with LASIK procedures, which generate high IOPs with the use of microkeratomes. Our report does reflect the concern with even mild elevations of IOP being potentially harmful to glaucoma patients and may therefore exclude Veterans with this common comorbidity from being candidates for FLACS.

	Reviewer	Comment	Response
	2.	You mention disposable costs for FLACS of $150-300. What are the disposable costs for conventional phaco?	Our review has been amended to reflect this cost issue. The disposable costs of FLACS and conventional phacoemulsification surgery are comparable (both involve irrigation/ aspiration and phacoemulsification procedures). The additional incremental cost of FLACS is the $150-300 per patient charge for the sterile, single-use patient interface device.
	3	The draft report addresses on point the request for information.	Noted.
	4	The review covers as one of its key questions "What is the evidence that the experience of the surgeon is associated with adverse effects of FLACS?" a couple studies showed less adverse events with more experience with FLACS. It would be nice to compare the surgical learning curve of FLACS vs Conventional cataract. There is some early literature in presentation and poster on this…not sure publications exists. This will be key for the VA given it is very involved in resident cataract surgery teaching. Prickett, 2013[40] Initial Resident Experience Performing Cataract Surgery with and without Femtosecond Laser (Conference proceeding) ARVO Poster Session, 2013	Thank you for the comment. However, the comparative learning curve of FLACS versus conventional surgery is outside of the scope of the review. This will be important in future questions of learning curve comparing surgical procedures (conventional compared to FLACS)
	5	Although meta-analyses of observational studies are not as frequent as for RCTs, there are guidelines (MOOSE) that are accepted to estimate summary effects based on observational studies. Nonetheless, if the authors consider that the quality of the observational studies (e.g., bias) preclude a meta-analysis, then is ok not to do it.	We thank the reviewer for the comment, and agree that the concerns with the included observational studies preclude meta-analyses of additional outcomes.
	Optional Dissemination and Implementation Questions		
	5. Are there any VA clinical performance measures, programs, quality improvement measures, patient care services, or conferences that will be directly affected by this report? If so, please provide detail.		
	1	None that I am aware of. I have heard of several more machines being requested and some purchased across the VA system.	Noted.
	3	The report supports the FDA approval of this technology	Noted.
	4	No. (No comment)	Noted.
	6. Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.		
	1	None. The way I interpreted your results was that there was weak to moderate support of some advantages to this technology but the same for the adverse effects. Even this information is generated from reports that have either stated or possible conflict of interest. While not in your prevue, I am hoping this report can be submitted with any application for technology across the VISN.	Noted, thank you for your comment.
	3	No recommendation	Noted.
	4	No. (No comment)	

	Reviewer	Comment	Response
	5	In methodology there are some issues that should be addresed: DATA ANALYSIS: How heterogeneity was assessed and examined (stratification, regression)?, how bias was evaluated ? , which effect measure was used for meta-analysis and which weighting method (random, fixed models)? Also, it should be stated that STATA was used for statistical analysis.	We have provided more information in the methodological details of the meta-analyses. All analyses were conducted in StataIC 11, and we assessed the presence of statistical heterogeneity among the studies by using standard chi-square tests, and the magnitude of heterogeneity by using the I^2 statistic. We explored models using both mean and ratio of means (SoM) based on a random effects model (combining means used the DL method and combining SoM used the PL method) – however, we do not report the combined estimates due to too much heterogeneity and rely on the forest plots as a visual aid for readers.