EUnetHTA Joint Action 3 WP4

**Rapid assessment of other technologies using the HTA Core Model® for Rapid Relative Effectiveness Assessment**

# FEMTOSECOND LASER-ASSISTED CATARACT SURGERY (FLACS) FOR THE TREATMENT OF AGE-RELATED CATARACT

***Project ID: OTCA07***

**Version 1.4 October 2018**

## DOCUMENT HISTORY AND CONTRIBUTORS

| Version | Date | Description |
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### Disclaimer

The assessment represents a consolidated view of the EUnetHTA assessment team members and is in no case the official opinion of the participating institutions or individuals.

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## Additional contributors

External clinical experts (listed below) contributed actively to the development of the Project Plan and were consulted during the assessment for clarification on choice of outcome measures.

Despite intense efforts on the part of the project coordinator to involve patient organizations through contacts with national and European umbrella organizations, involvement of patient representatives did not prove possible. Howerever feedback was obtained by the Spanish patients' organization representing patients undergoing refractive surgery (ASACIR) that was contacted by a dedicated reviewer and presented with a late draft of this REA.

During the Scoping phase, several attempts were made by the project coordinator to obtain contribution from manufacturers. However, all contacted manufacturers except one (listed below) expressed their lack of interest in providing a contribution.

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## Conflict of interest

All authors, dedicated reviewers, external experts and patients' representatives involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA Declaration of Interest and Confidentiality Undertaking (DOICU) statement form.

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## Tables



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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AAO | American Academy of Ophthalmology |
| ADVS | Activities of Daily Vision Scale |
| AquAS | Agency for Health Quality and Assessment of Catalonia |
| APT | Average Phacoemulsification Time |
| AUSL | Azienda Unità Sanitaria Locale |
| BCVA | Best Corrected Visual Acuity |
| CCI | Clear Corneal Incision |
| CCT | Central Corneal Thickness |
| CDSR | Cochrane Database of Systematic Reviews |
| CDVA | Corrected Distance Visual Acuity |
| CI | Confidence interval |
| CME | Cystoid macular oedema |
| CRD | Centre for Reviews and Dissemination |
| COI | Conflicts of interests |
| CTR | Clinical Trials Register |
| CUR | Health problem and current use of the technology domain |
| D | Dioptres |
| DALYs | Disability-adjusted life years |
| ECCE | Extracapsular cataract extraction |
| ECL | Endothelial Cell Loss |
| EFF | Clinical effectiveness domain |
| EPT | Effective phacoemulsification time |
| ETH | Potential ethical aspects |
| EU | European Union |
| EUREQUO | European Registry of Quality Outcomes for Cataract and Refractive Surgery |
| FLACS | Femtosecond laser-assisted cataract surgery |
| FS | Femtosecond(s) |
| FUNCANIS | Fundación Canaria de Investigación Sanitaria |
| GBD | Global Burden of Disease |
| GÖG | Gesundheit Österreich GmbH |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| ICCE | Intracapsular cataract extraction |
| ICD | International Classification of Diseases |
| ICTRP | International Clinical Trials Registry Platform |
| IOL | Intraocular lens |
| IOP | Intraocular pressure |
| IRCCS | Istituto di Ricovero e Cura a Carattere Scientifico |
| KCE | Belgian Health Care Knowledge Centre |

| | |
|---|---|
| LED | Light Emitting Diode |
| LEG | Potential legal aspects |
| LOCS | Lens opacities classification system |
| LogMAR | Logarithm of the Minimum Angle of Resolution |
| MAE | Mean Absolute Error |
| MD | Mean Difference |
| MeSH | Medical Subject Headings |
| NEI | National Eye Institute |
| NEI-VFQ | National Eye Institute - Visual Function Questionnaire |
| NIH | National Institutes of Health |
| NRS | Non-randomised studies |
| OCT | Optical Coherence Tomography |
| OR | Odds Ratio |
| ORG | Potential organisational aspects |
| OVD | Ocular Viscosurgical Device |
| PCR /PCT | Posterior capsular rupture / posterior capsular tear |
| PI | Patient interface |
| PPP | Preferred Practice Pattern |
| PPV | Pars Plana Vitrectomy |
| PROM | Patient-reported outcome measures |
| PSC | Posterior subcapsular cataract |
| RCT | Randomised Controlled Trial |
| REA | Relative Effectiveness Assessment |
| RER | Regione Emilia-Romagna |
| RFID | Radio Frequency Identification |
| RR | Relative effect |
| SAF | Safety domain |
| SD | Standard Deviation |
| SESCS | Servicio de Evaluación del Servicio Canario de la Salud (Health Service of Canary Islands) |
| SIA | Surgically Induced Astigmatism |
| SLD | Super luminescent diode |
| SMD | Standardized Mean Difference |
| SOC | Potential patient and social aspects |
| TASS | Toxic anterior segment syndrome |
| TEC | Description and technical characteristics of technology domain |
| UDVA | Uncorrected Distance Visual Acuity |
| UK | United Kingdom |
| VASPVT | State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania |
| VM | Video camera microscope |
| 3D CSI | 3-dimensional confocal structural illumination |

# SUMMARY OF RELATIVE EFFECTIVENESS OF FLACS

## *Scope*

The scope can be found here:**Scope**.

The aim of this assessment is to assess whether femtosecond laser-assisted cataract surgery (FLACS) in adult patients affected by age-related cataract is more effective and/or safer than standard cataract surgery.

The target population of this assessment is adult patients (>18 years) of either sex affected by age-related cataract and for whom the surgical treatment for cataract removal and insertion of intraocular lens could provide a gain in visual acuity and health-related quality of life.

Comparative effectiveness of FLACS has been assessed in terms of distance visual acuity (corrected and uncorrected), refractive outcomes and patient-reported outcomes. Comparative safety has been assessed in terms of intraoperative and postoperative complications.

Randomized clinical trials have been searched and included in this assessment. Non-randomized prospective comparative studies evaluating long-term safety outcomes have also been searched but not retrieved.

## *Introduction*

### Description of technology and comparators

Cataract surgery is the most commonly performed ophthalmic procedure, and phacoemulsification is the most frequently used technique for cataract removal. (1) Besides the set of skills needed to perform the steps of the intervention, cataract surgery also requires the cognitive skills, judgment, and experience necessary to recognize and respond to unexpected events, problems and complications that may arise intraoperatively. Only an ophthalmologist has the medical and microsurgical training as part of a comprehensive medical residency needed to perform cataract surgery **[B0001].**

Standard cataract surgery, current practice and comparator for the present assessment, requires manual formation of an opening in the anterior lens capsule, fragmentation and evacuation of the lens tissue with an ultrasound probe and implantation of a plastic intraocular lens into the remaining capsular bag. The size, shape and position of the anterior capsular opening (one of the most critical steps in the procedure) are controlled by freehand pulling and tearing of the capsular tissue. (2)

In developed countries, **phacoemulsification** is the preferred method to remove a cataract, with reported rates of major complications (posterior capsule rupture or vitreous loss) of 1.95% (95% confidence interval (CI) 1.89% to 2.02%) and overall intraoperative complication rates of 4.2% (95%CI 4.1 to 4.3%).(3)

Femtosecond lasers have been used to perform several stages of phacoemulsification cataract surgery since 2009. Laser-generated pulses of highly focused infrared light perform the cutting by creating localised cavitation bubbles within tissues, a process termed photo-disruption. The ultrashort duration of each pulse minimises damage to adjacent tissue. During cataract surgery, such lasers are used to create incisions, perform capsulorhexis and fragment the lens. The surgeon plans and decides the target location, then the system delivers the focus of the laser beam to

produce the desired incision. The procedure is then completed using conventional phacoemulsification equipment and techniques. (4)

*Indication for FLACS.* The femtosecond laser was initially introduced to create corneal flaps for laser *in situ* keratomileusis (LASIK). Since then, the use of femtosecond lasers has expanded to other corneal surgeries and, more recently, to cataract surgery. (5) It is indicated for use in patients undergoing cataract surgery for removal of the crystalline lens **[A0020].**

Compared to standard cataract surgery, where incisions, capsulorhexis and lens fragmentation are performed by freehand action of the surgeon, FLACS systems claim to provide several advantages to the surgeon, such as the performance of very precise circular and adjustable diameter capsulotomies, precise lens nucleus fragmentation, the creation of multi-planar self-sealing incisions with better wound architecture, exact placement of limbal relaxing incisions and the reduction of phacoemulsification time. (6) Moreover, femtosecond laser pretreatment is expected to reduce phaco energy, which may in turn reduce the heat damage to ocular tissues by ultrasound. (7) This may translate into reducing endothelial cell loss, and consequently, better outcomes in terms of visual acuity and safety **[B0002].**

## Health problem

The disease in the scope of the present assessment is acquired and age-related cataract (ICD-9 code: 366.x, ICD-10 H25). A cataract is an opacity of the lens, one of the eye structures involved in the “accommodation” function that focuses the light on the retina and allows normal vision. It can affect one or both eyes, and changes to the transparency and refractive index of the lens result in various levels of visual impairment, associated with decrease in quality of life. (4) **[A0002]** Causing lens opacity, cataract can lead to a progressive, painless loss of vision up to partial or total blindness in one or both eyes. The WHO estimates that 51% of reversible blindness worldwide was due to cataract (8), affecting more than 52 million people in 2015. (9) The pattern and rate of blinding disorders is different in developed and developing nations, depending upon different causes. While cataracts can be congenital or due to trauma or metabolic conditions, age-related cataracts are the most common and therefore have the greatest impact. (10) **[A0006]**

In Europe in 2010, the estimated prevalence of blindness (Visual Acuity Blind < 3/60) or moderate to severe vision impairment (Visual Acuity < 6/18, ≥3/60) due to cataract was 0.42% (3 million out of 725 million people) in the overall population. (11) **[A0023]**

Cataract should be investigated in any patient who complains of a painless and progressive decline in vision. The purpose of the comprehensive evaluation of the patient is to determine the presence of a cataract, to confirm that a cataract is a significant factor contributing to the visual impairment and symptoms described by the patient and to identify other ocular or systemic conditions that might contribute to visual impairment. (4) **[A0024]** Diagnostic tests recommended to evaluate cataract are reported in **Table 11.**

Cataract surgery remains one of the most cost-effective treatments and the most commonly used procedure in many countries, (12) and management of a visually significant cataract is primarily surgical. (13) Summary of recommendations from available guidelines on the management of cataract is provided in **Table A1** of **Appendix 1.**

Although numerous complications can occur intraoperatively or postoperatively with cataract surgery, those resulting in permanent loss of vision are rare. Major complications are potentially sight-threatening and include infectious endophthalmitis, cystoid macular oedema (CME), retinal

detachment, persistent corneal edema, corneal decompensation and post-operative blindness. **Table 14** describes main complications of cataract surgery and their consequences for the patients.

### *Methods*

The selection of assessment elements was based on The HTA Core Model® for Rapid Relative Effectiveness Assessment Version 4.2. (14) The selected issues (generic questions) were translated into actual research questions (answerable questions).

In order to provide transparency to the development of the Scope questions, the Assessment team agreed to form a panel and to apply during the Scoping phase the GRADE method (15) to structure the process for the selection of outcomes and the rating of their importance. A GRADE panel was therefore established, comprising authors, co-authors, dedicated reviewers and external experts (organizations and no single individuals, counted as panel members). Participation of patient representatives was actively sought in this phase, but without success.

The research question (target population, intervention and comparator) and the list of outcomes were uploaded by the authors on GRADEpro and all members were registered for participation. Each member checked and approved, through the GRADEpro platform, the research question and the list of outcomes. Subsequently, each member received an e-mail with an invitation to rate the importance of each one of the 24 listed outcomes using a pre-defined scale. The scale provided a choice between 3 categories of outcomes according to their importance for decision-making: “critical” (score between 7 and 9); “important” (score between 4 and 6); “not important” (score between 1 and 3). Based on scores applied by all panel members **(Table 2**), the median scores were calculated by the authors and final overall rating of importance assigned to each one of the 24 outcomes (**Table 3**). Results of the rating process were included in the final Scope of the Project Plan.

Details on search strategy and databases are included in **Appendix 1.**

A systematic review of the scientific literature was performed according to the Cochrane Handbook methodology (16). As four recent systematic reviews were published in 2016, (3,17–19) with searches conducted between 1946 and May 2016, our systematic search had January 2016 as a starting date and combined the search strategies of all 4 recent systematic reviews. The search for primary studies published after the included systematic reviews was thus limited from January 2016 to December 2017. The search for ongoing studies was carried out in June 2018, and literature was continuously monitored for newly published studies relevant for this assessment.

International guidelines, UpToDate (20) and relevant studies identified through the systematic search represented the main source for the “Health problem and current use” of FLACS (CUR) domain (14). Main sources used for the Description and Technical Characteristic of the technology domain (TEC) (14) were manufacturers’ brochures and information leaflets, manufacturers’ manual for use, published articles and EUnetHTA manufacturer’s submission template. Despite several attempts to obtain information from the manufacturers, only one (Alcon) of the five identified responded and provided a complete EUnetHTA submission Template.

The electronic search updated in July 2018 yielded 2473 references, of which 21 studies that met the inclusion criteria were finally included in the analyses. Inclusion criteria were: randomised clinical trials and non-randomised prospective controlled studies reporting safety outcomes assessed with a follow up of 6 months or longer; adult patients (>18 years) of either sex affected by

age-related cataract with indication for cataract surgery; interventions under assessment (FLACS vs standard cataract surgery); effectiveness and safety outcomes listed in the **Scope.**

Four review authors (FV, MV, LB and GF) independently extracted data using a data extraction form developed for this review (**Appendix 1** **Table A2-A20**). The authors resolved any discrepancies through discussion among themselves and with a fifth author (LuB).

For Description and Technical Characteristics of Technology (TEC) and Health Problem and Current Use of the Technology (CUR) domains, no quality assessment tool was used, but multiple sources were used to validate and cross-check individual sources. For Clinical Effectiveness (EFF) and Safety (SAF) domains, study quality on included randomized controlled trials was rated using the tool for assessing risk of bias described in the Cochrane Handbook for Systematic Reviews of Interventions (21)(Chapter 8 – see "assessment of risk of bias in included studies"). Overall quality of evidence for each outcome was rated using the GRADE methodology. (22)

Patient involvement was planned, and an information leaflet was prepared in order to facilitate their understanding of objectives and methods of this assessment and their participation in the early phases of this project. European umbrella organizations were contacted as well as patient representatives from Ireland; however, it was not possible to obtain early participation, which was hindered by patient representatives' logistic issues. One dedicated reviewer obtained a late feedback from a Spanish patient organization interested in refractive surgery. Comments pertinent to this REA are synthesized and reported in the main text while the complete response can be found in **Appendix 4.**

### *Results*

### Available evidence

Twenty-one randomized controlled studies (RCTs) are included in this assessment, as no prospective comparative non-randomized studies assessing long-term safety outcomes were retrieved. All included studies compared femtosecond laser-assisted cataract surgery to standard ultrasound phacoemulsification cataract surgery

Overall, the studies included in this report recruited a total of 1633 patients (range: 30-299). A total of 2118 eyes were randomized. Seventy-six percent of patients were recruited and operated in Europe, specifically in Austria, France, Germany, Hungary, Italy and the UK; the remaining 24% were recruited and operated on in Brazil, China, India, Mexico and the US.

### Clinical effectiveness

Summary of findings is reported in **Table 1**. Of the 21 studies included in this report, 7 parallel group RCTs (23–29) and 3 within person paired-eye RCTs (30–32) reported clinical effectiveness outcomes. Overall, these ten small-sized trials recruited a total of 648 patients affected by age-related cataract (range: 30-105 patients). A total of 859 eyes were randomized in these studies. Tables of included studies are reported in **Appendix 1.**

All effectiveness outcomes assessed (Corrected and Uncorrected Distance Visual Acuity at 1 and 6 months and refractive outcomes at 1 week and 1 month) were rated as "critical" by the panel.

Seven included studies assessed Corrected Distance Visual Acuity (CDVA) at 1 and/or 6 months **[D0005]**. The pooled estimates showed no evidence of a difference between study groups. Over-

all quality of evidence for Corrected Distance Visual Acuity (CDVA) at one and six months after surgery was graded “low” because of very serious risk of bias in included studies (**Figure 9**).

Four randomized controlled studies (24–26,29) were included reporting data on Uncorrected Distance Visual Acuity (UDVA) at 1 month post-surgery were included **[D0005]**. Two of these (25,26) also reported data on UDVA at 6-month follow up. The pooled estimates showed no evidence of a difference between study groups.
Overall quality of evidence for Uncorrected Distance Visual Acuity (UDVA) at one and six months after surgery was graded “very low”. In addition to risk of bias (very serious for studies assessing UDVA at one month and serious for studies assessing UDVA at 6 months), quality was downgraded for inconsistency (results from one of three trials favouring FLACS with a non-clinically relevant difference, while results from other two studies showing no difference between study arms).

Data from two studies (25,28) assessing refractive outcomes were used for the analysis and pooled estimate showed no difference between study groups. **[D0006]** At one week, one study found a marginally significant and not clinically relevant difference (less than 0.1 log MAR variation) in favour of FLACS, while the second study found no statistically significant difference between the two study arms. At one month, neither study found a statistically significant result between the two study arms and the pooled estimate provided no evidence of a difference between groups. Overall quality of evidence for Refractive outcomes was graded “low” because of imprecision and serious risk of bias.

Only one study reported data on patient-reported outcomes, showing no difference between study groups, while none of the studies retrieved reported results on health-related quality of life. (31)

### Safety

Summary of findings is reported in **Table 1**.

Fifteen small-sized RCTs assessed clinical safety outcomes selected for this REA:

- intraoperative complications: anterior and posterior capsular tear, vitreous loss;
- postoperative complications: cystoid macular oedema, infections, posterior capsule opacification, surgically induced astigmatism, endothelial cell loss at three months, elevated intraocular pressure, central corneal thickness.

Overall, the 15 trials recruited a total of 1215 patients affected by age-related cataract (range: 30-299). A total of 1641 eyes were randomized in those studies. Tables of included studies are reported in **Appendix 1**.

**Table 14** provides detailed description of safety outcomes and consequences of intraoperative and postoperative complications.

Except for surgically induced astigmatism, elevated intraocular pressure and central corneal thickness, all other safety outcomes were graded as critical by the panel members involved in rating of outcome importance.
No data were found on the following outcomes graded as critical: retinal detachment, visual acuity loss post-surgery, surgical re-intervention, secondary cataract, iridocyclitis.

Pooled analyses did not show differences between the two techniques in any of the safety outcomes.

Overall quality of evidence for critical outcomes was judged as “low” for intraoperative complications. For postoperative complications, rated as critical, overall quality of evidence was judged as “very low” for endothelial cell loss (at 3 and 6 months) and cystoid macular oedema, while it was graded as “low” for infections.

Limited evidence is available on the impact of each surgical technique on mean surgical time. Several studies assessed phaco energy time (surrogate outcome), which was not considered relevant by the panel and was excluded from the list of outcomes for this REA. As for resource use, one study showed a very limited reduction in mean surgical time that does not provide a sufficient improvement in productivity to meaningfully offset the additional costs (33).

### Patients’ feedback

ASACIR, a Spanish patients’ organization representing patients undergoing refractive surgery, was contacted by a dedicated reviewer and presented with a late draft of this REA to provide patients‘ persective on cataract surgery and on the possible added value of FLACS. According to ASACIR, allocating resources on a procedure like FLACS would not be justified since it does not provide any advantage over standard phacoemulsification and is more expensive. Moreover, complications may occur when using FLACS in patients who had previously undertaken refractive surgery. Finally, it was highlighted that the main objective within a National Health System should be investing resources to prevent cataracts, considering that preventive and non-surgical treatments such as eye drops lanosterol will be probably approved soon. (**Appendix 4)**

### Upcoming evidence

Two large publicly funded adequately powered ongoing RCTs, (34,35) much larger compared to the previous trials, are expected to add relevant evidence which may more adequately answer public health questions on cataract surgery and may help to establish whether FLACS provides any advantage over conventional phacoemulsification. This REA will be updated as soon as results of both studies are published.

### Reimbursement

Additional costs incurred by the use of FLACS do not appear to be reimbursed in the European countries for which information was made available (see **Table A28**).

**Table 1 Summary of findings table of Femtosecond Laser-Assisted Cataract Surgery (FLACS) vs standard cataract surgery**

**Question:** Femtosecond Laser-Assisted Cataract Surgery (FLACS) compared to Standard Cataract Surgery for Age-related cataract in adult patients

**Clinical Effectiveness**

| Certainty assessment | | | | | | | № of eyes | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsis-tency** | **Indi-rectness** | **Imprecision** | **Other considerations** | **Femtosecond Laser-Assisted Cata-ract Surgery (FLACS)** | **Standard Cataract Surgery** | **Relative (95% CI)** | **Absolute (95% CI)** | | |
| **CDVA 1 month (LogMAR*)** | | | | | | | | | | | | |
| 6 | randomised trials | very serious [a,b] | not serious | not serious | not serious | none | 212 | 176 | - | MD*** **-0.02** (-0.04; 0.00) | ⊕⊕◯◯ LOW | CRITICAL |
| **CDVA 6 months (LogMAR*)** | | | | | | | | | | | | |
| 4 | randomised trials | very serious [a,b] | not serious | not serious | not serious | none | 174 | 144 | - | MD***- **0.02** (-0.04; 0.00) | ⊕⊕◯◯ LOW | CRITICAL |
| **UDVA 1 month (LogMAR*)** | | | | | | | | | | | | |
| 4 | randomised trials | very serious [a,c] | serious [d] | not serious | not serious | none | 140 | 100 | - | MD*** **-0.03** (-0.12; 0.06) | ⊕◯◯◯ VERY LOW | CRITICAL |

| Certainty assessment | | | | | | | № of eyes | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsis-tency | Indi-rectness | Imprecision | Other considerations | Femtosecond Laser-Assisted Cata-ract Surgery (FLACS) | Standard Cataract Surgery | Relative (95% CI) | Absolute (95% CI) | | |
| **UDVA 6 months (LogMAR*)** | | | | | | | | | | | | |
| 2 | randomised trials | serious [c] | very serious [e] | not serious | very serious [f] | none | 90 | 60 | - | MD*** **-0.06** (-0.26; 0.14) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Refractive outcome (mean absolute error - 1 week)** | | | | | | | | | | | | |
| 2 | randomised trials | serious [a] | not serious | not serious | serious [g] | none | 85 | 59 | - | MD*** **-0.1** (-0.19; 0.01) | ⊕⊕◯◯ LOW | CRITICAL |
| **Refractive outcome (mean absolute error** - 1 month)** | | | | | | | | | | | | |
| 2 | randomised trials | serious [a] | not serious | not serious | serious [g] | none | 85 | 59 | - | MD*** **-0.11** (-0.25; 0.03) | ⊕⊕◯◯ LOW | CRITICAL |

**Abbreviations:** CI: Confidence interval; LogMAR: Logarithm of the Minimum Angle of Resolution; MD: Mean difference; OR: Odds ratio; SMD: Standardised mean difference;

**Notes**

* LogMAR stands for Logarithm of the Minimum Angle of Resolution. It is a logarithmic scale to measure visual acuity which goes from +1.5 to -0.3. A change of 0.1 on the scale shows a clinically significant change, with -0.1 meaning improvement and +0.1 meaning worsening.

**Mean absolute error is measured in dioptres as absolute deviation between the predicted and achieved spherical equivalent and a variation of +/-0.25 D is considered clinically relevant.

***Mean difference between FLACS and standard for the outcome under assessment. A negative difference is in favour of FLACS. It means that values for FLACS are lower than values for standard. Lower values in the LogMAR scale, as well as in mean absolute error, are associated with better vision.

**Explanations**

a. Lack of allocation concealment is suspected
b. Open trials, detection bias present (non-blinded assessment of outcomes)
c. Assessment of outcomes not blinded
d. Inconsistent results between trials
e. Results of the two trials are inconsistent
f. Confidence interval of pooled estimate is very large
g. Confidence interval of pooled estimate is large
h. Selective reporting
i. Allocation concealment not described

**Safety**

| Certainty assessment | | | | | | | № of eyes | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Femtosecond Laser-Assisted Cataract Surgery (FLACS)** | **Standard Cataract Surgery** | **Relative (95% CI)** | **Absolute (95% CI)** | | |
| **Posterior capsular tear** | | | | | | | | | | | | |
| 8 | randomised trials | not serious | not serious | not serious | very serious [f] | none | 0/390 (0.0%) | 1/402 (0.2%) | **OR 0.32** (0.01 to 8.23) | **1.7 fewer per 1.000** (from 2.5 fewer to 17.6 more) | ⊕⊕◯◯ LOW | CRITICAL |
| **Anterior capsular tear** | | | | | | | | | | | | |
| 9 | randomised trials | not serious | not serious | not serious | very serious [f] | none | 5/529 (0.9%) | 5/562 (0.9%) | **OR 1.10** (0.34 to 3.64) | **1.0 more per 1.000** (from 6.0 fewer to 23.0 more) | ⊕⊕◯◯ LOW | CRITICAL |
| **Vitreous loss** | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious | not serious | very serious [f] | none | 0/276 (0.0%) | 4/297 (1,3%) | **OR 0.22** (0.02 to 1.98) | **10.0 fewer per 1.000** (from 13.0 fewer to 13.0 more) | ⊕⊕◯◯ LOW | CRITICAL |

| Certainty assessment | | | | | | | № of eyes | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Femtosecond Laser-Assisted Cataract Surgery (FLACS)** | **Standard Cataract Surgery** | **Relative (95% CI)** | **Absolute (95% CI)** | | |
| **Cystoid macular oedema** | | | | | | | | | | | | |
| 4 | randomised trials | very serious [a,b] | not serious | not serious | serious [g] | none | 5/311 (1.6%) | 9/311 (2.9%) | **OR 0.58** (0.20 to 1.68) | **12.0 fewer per 1.000** (from 23.0 fewer to 18.7 more) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Infections** | | | | | | | | | | | | |
| 1 | randomised trials | very serious [h,i] | not serious | not serious | not serious | none | 0/100 (0.0%) | 0/100 (0.0%) | not estimable | | ⊕⊕◯◯ LOW | CRITICAL |

**Abbreviations:** CI: Confidence interval; SMD: Standardised mean difference; MD: Mean difference; OR: Odds ratio

**Explanations**

a. Lack of allocation concealment is suspected
b. Open trials, detection bias present (non-blinded assessment of outcomes)
c. Assessment of outcomes not blinded
d. Inconsistent results between trials
e. Results of the two trials are inconsistent
f. Confidence interval of pooled estimate is very large
g. Confidence interval of pooled estimate is large

## *Discussion*

Femtosecond laser pretreatment is expected to reduce phaco energy, which may in turn reduce the heat damage to ocular tissues by ultrasound. This may translate into reducing endothelial cell loss, and consequently, better outcomes in terms of visual acuity and safety. These systems are expensive in terms of acquisition costs and disposable and maintenance costs.

None of the trials was powered to investigate differences in effectiveness or safety; a clear definition of primary and secondary outcomes was also generally lacking, as well as rigorous sample size calculations. As for conflicts of interests, twelve RCTs reported funding by laser manufacturers and other types of conflicts of interests. Some research groups published more than one RCT, and it was not possible to assess whether patients were double-counted.

Pooled analyses did not show differences between the two techniques in any of the effectiveness or safety outcomes. Overall quality of evidence for all outcomes was judged as “low” or “very low”.
Just one study reported data on organizational and economic outcomes, suggesting a very limited reduction in mean surgical time that does not provide improvements in productivity to meaningfully offset the additional costs. Data on patient-reported outcomes is lacking

## *Conclusion*

Meta-analyses of currently available data, generally of limited quality, show either no difference or small, clinically not relevant differences between FLACS and standard cataract surgery in any of the effectiveness and safety outcomes taken into consideration. As the technology under assessment is costly and the comparator (standard cataract surgery) is considered effective and safe, equivalence or non-inferiority between the two interventions was not assessed by this REA nor by the included studies. Evidence cannot therefore be provided on FLACS being equivalent or non-inferior to standard cataract surgery.

Pending results from two large randomised studies could contribute to resolving uncertainties.

Our findings on effectiveness and safety of the assessed interventions are consistent with findings of a 2016 Cochrane systematic review on this topic, including 16 RCTs, 15 of which were included in this updated assessment on 19 trials. (3)

## SCOPE

<table>
<tr><th>Description</th><th>Project scope</th></tr>
<tr><td>Population</td><td>The target disease is age-related cataract. (ICD-9 366.1; ICD-10 H25; MeSH terms “cataract”)<br><br>The target population is adult patients (>18 years) of either sex affected by cataract and for whom surgical treatment for cataract removal and insertion of intraocular lens could provide a gain in visual acuity and health-related quality of life. (MeSH terms “Young Adult”, “Adult”, “Middle Aged”, “Aged”, “Aged 80 and over”)<br><br>The intended use of the technology is surgical treatment of age-related cataract.<br><br><u>Subpopulations:</u><br><br>Subgroup analyses planned for Lens-Opacities Classification System (LOCS) type and pseudo-exfoliation<br><br>Rationale: According to current American and European guidelines, (13,36) cataract surgery should be considered for all adult patients affected by age-related cataract who could benefit in terms of health-related quality of life. Specifically, the 2017 updated NICE guidelines state that restricting referral to cataract surgery on the basis of visual acuity thresholds is inappropriate (4).</td></tr>
<tr><td>Intervention</td><td>Cataract surgery assisted by femtosecond laser (FLACS)<br><br>The intervention under assessment is Femtosecond laser-assisted cataract surgery (FLACS) to be used during the first phases of intervention to create incisions, perform capsulorhexis and fragment the lens. To complete the surgical procedure, conventional ultrasound phacoemulsification technique is used.<br><br>The name of the products included in the assessment (and corresponding manufacturers) are: LenSx Laser System (Alcon), Catalys Precision laser system, Victus femtosecond laser platform (Bausch & Lomb), Lensar laser system (Lensar) and Femto LDV Z8 (Ziemer).</td></tr>
<tr><td>Comparison</td><td>Standard cataract surgery (manual incision and capsulorhexis followed by phacoemulsification)<br><br>Rationale: comparator has been identified in European and American guidelines. (4,13,36)</td></tr>
<tr><td>Outcomes</td><td>The claimed benefits of FLACS are related to the ultrashort duration of laser pulses that should minimise the damage to adjacent tissues. In particular, the reduction in phacoemulsification times and energy could decrease the corneal endothelial cell loss. Moreover, reproducible incisions and accurately centred and circular capsulotomies may reduce postoperative refraction issues and allow better intraocular lens centration. Use of resources and logistic issues need are relevant to determine the organizational impact of FLACS (4).<br><br>Clinical effectiveness:<br><br>
<table>
<tr><th></th><th>Rate of Importance (range of ratings)</th></tr>
<tr><td>Corrected Distance Visual Acuity (1 month; 6 months)</td><td>8.0 (7-9) “critical”</td></tr>
<tr><td>Uncorrected Distance Visual Acuity (1 month; 6 months)</td><td>7.0 (6-9) “critical”</td></tr>
<tr><td>Refractive outcomes</td><td>7.0 (4-8) “critical”</td></tr>
<tr><td>Vision-related quality of life as measured by any validated questionnaire</td><td>8.0 (6-9) “critical”</td></tr>
<tr><td>Patient-reported Outcomes</td><td>7.5 (5-8) “critical”</td></tr>
</table>
</td></tr>
</table>

| Description | Project scope |
|---|---|
| | **Safety:**<br><br>Outcome — Rate of importance* (range of ratings)<br>**Intraoperative complications**<br>Anterior capsular tear: 8.5 (6-9) "critical"<br>Posterior capsular tear/rupture: 8.5 (7-9) "critical"<br>Vitreous loss: 7.5 (3-9) "critical"<br>**Postoperative complications**<br>Retinal detachment: 8.0 (7-9) "critical"<br>Iridocyclitis: 7.0 (3-8) "critical"<br>Endothelial cells loss**: 6.5 (4-9) "critical"<br>Elevated Intraocular Pressure (1 day - 1 week): 6.0 (3-9) "important"<br>Corneal endothelial decompensation (within 90 days): 8.0 (5-9) "critical"<br>Cystoid macular oedema (within 90 days): 8.0 (3-9) "critical"<br>Infections (within 90 days): 8.0 (3-9) "critical"<br>Posterior capsule opacification: 8.0 (7-8) "critical"<br>Secondary cataract (24 months): 8.0 (3-9) "critical"<br>Surgical re-intervention (within 6 months): 8.0 (3-9) "critical"<br>Visual acuity loss post cataract surgery (1 month;6 months): 8.0 (6-9) "critical"<br>Surgically induced astigmatism: 6.0 (6-8) "important"<br>Central corneal thickness: 5.0 (3-8) "important"<br><br>**Other outcomes:**<br><br>Rate of Importance (range of ratings)<br>Resource use: 6.0 (2-9) "important"<br>Patient satisfaction: 5.5 (4-8) "important"<br>Procedural time: 5.0 (2-8) "important"<br><br>***** rate of importance results obtained through panel members' voting for each outcome using GRADEpro (37).<br>** rated as "critical" after rounding mean rate upwards |
| **Study design** | • **Safety of FLACS:** randomised controlled clinical trials; non-randomised controlled studies (for safety outcomes at > 6-month follow up)<br>• **Clinical effectiveness of FLACS:** randomised controlled clinical trials.<br>• **Other outcomes:** randomised controlled clinical trials and non-randomised controlled studies included in effectiveness (EFF) and safety (SAF) domains. |

# METHODS AND EVIDENCE INCLUDED

## *Assessment Team*

As authors, Regione Emilia-Romagna – RER:

- Coordinated the Scoping phase and conducted the GRADE process for the selection of outcomes and for rating the importance of outcomes.
- Developed the first draft of the EUnetHTA project plan.
- Performed the literature search and study selection.
- Conducted the assessment (extraction, analysis, summary and interpretation of findings).
- Sent the first draft to dedicated reviewers, compiled feedback, answered comments and made changes according to reviewers' comments.
- Performed the update of the literature search and review.
- Sent the second draft to external experts, compiled feedback, provided answers to reviewers and were responsible for making corresponding changes.
- Sent the second draft to manufacturers for fact checking, compiled feedback and made changes.
- Prepared the final assessment and wrote a final summary of the assessment.

As co-authors, Gesundheit Österreich GmbH - GÖG:

- Participated in the GRADE process for the selection of outcomes and for grading the importance of outcomes.
- Collaborated in the development of the EUnetHTA project plan.
- Checked and approved all steps (e.g., literature selection, data extraction, assessment of risk of bias) and provided methodological support.
- Reviewed the first and second drafts of the assessment, proposed amendments where necessary (performed additional manual search when needed) and provided written feedback.
- Collaborated in the development of conclusions, which were discussed and agreed on.

As dedicated reviewers, KCE, Osteba, SESCS-FUNCANIS and AquAS:

- Participated in the GRADE process for the selection of outcomes and for rating the importance of outcomes.
- Guaranteed quality assurance by thoroughly reviewing the project plan and the assessment drafts.
- Reviewed methods, results, and conclusions based on the original studies included.
- Provided constructive comments in all project phases.

The Assessment team in addition received the contribution from external experts, which:

- Reviewed and discussed the EUnetHTA project plan.
- Participated in the GRADE process for the selection of outcomes and for rating the importance of outcomes.
- Reviewed and provided comments on the second draft of the assessment.

In order to provide transparency to the development of the Scope questions, the Assessment team agreed to form a panel and to apply during the Scoping phase the GRADE method (15) to structure the process for the selection of outcomes and the rating of their importance. This process developed as follows:

- An initial draft of the Project Plan, developed and agreed upon by the authors and co-authors, was circulated to dedicated reviewers and external experts.

- A scoping e-meeting was arranged with the assessment team and external experts to discuss Project Plan and to agree on a preliminary list of outcomes of interest. During the scoping meeting it was also agreed to use GRADE and GRADEpro (37) (an electronic tool that allows and facilitates participation of panel mem-

bers in the process) in order to conduct and finalize the Scoping phase. For this purpose, a GRADE panel was established, comprising authors, co-authors, dedicated reviewers and external experts (organizations and no single individuals, counted as panel members). Participation of patient representatives was actively sought, but without success.

- The research question (target population, intervention and comparator) and the list of outcomes were uploaded by the authors on GRADEpro and all members were registered for participation.
- Each member received an e-mail for accessing the GRADEpro system to check and approve the research question and the list of outcomes.
- Following approval by the panel, each member received an e-mail with an invitation to rate the importance of each one of the 24 listed outcomes using a pre-defined scale. The scale provided a choice between 3 categories of outcomes according to their importance for decision-making: “critical” (score between 7 and 9); “important” (score between 4 and 6); “not important” (score between 1 and 3).
- Based on scores applied by all panel members (**Table 2**), the median scores were calculated by the authors and final overall rating of importance assigned to each one of the 24 outcomes (**Table 3**). Results of the rating process were included in the final Scope of the Project Plan.

## Table 2 individual panel members' ratings of outcomes

| Outcomes / Panel members | TM*9 | TM*2 | TM*6 | TM*5 | TM*3 | TM*7 | TM*4 | TM*1 | Mean | Median | Min | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Corrected Distance Visual Acuity (1 month; 6 months) | 7 | 8 | 9 | 7 | 8 | 7 | 9 | 9 | **8.00** | **8.00** | **7** | **9** |
| Uncorrected Distance Visual Acuity (1 month, 6 months) | 7 | 6 | 9 | 7 | 7 | 7 | 8 | 6 | **7.13** | **7.00** | **6** | **9** |
| Refractive outcomes | 7 | 8 | n/a** | 6 | 4 | 7 | 8 | 9 | **6.86** | **7.0** | **4** | **8** |
| Vision-related Quality of Life | 8 | 8 | 9 | 6 | 8 | 7 | 6 | 9 | **7.63** | **8.00** | **6** | **9** |
| Patient-reported Outcomes | 5 | 8 | 8 | 6 | 8 | 7 | 5 | 8 | **6.88** | **7.50** | **5** | **8** |
| Anterior capsular tear | 7 | 8 | 8 | 9 | 6 | 9 | 9 | 9 | **8.13** | **8.50** | **6** | **9** |
| Posterior capsular tear | 7 | 8 | 8 | 9 | 8 | 9 | 9 | 9 | **8.38** | **8.50** | **7** | **9** |
| Vitreous loss | 6 | 8 | 7 | 9 | 3 | 5 | 9 | 9 | **7.00** | **7.50** | **3** | **9** |
| Retinal detachment | 8 | 8 | 9 | 8 | 7 | 7 | 9 | 9 | **8.13** | **8.00** | **7** | **9** |
| Iridocyclitis | 3 | 8 | n/a** | 6 | 3 | 7 | 8 | 7 | **6.00** | **7.00** | **3** | **8** |
| Endothelial cell loss | 4 | n/a** | n/a** | 6 | 7 | 9 | 9 | 5 | **6.67** | **6.50** | **4** | **9** |
| Elevated Intraocular Pressure (1 day – 1 week) | 6 | n/a** | 7 | 9 | 3 | 5 | 6 | 8 | **6.29** | **6.00** | **3** | **9** |
| Corneal endothelial decompensation (within 90 days) | 5 | n/a** | n/a** | 9 | 7 | 9 | 7 | 9 | **7.67** | **8.00** | **5** | **9** |
| Cystoid macular oedema (within 90 days) | 5 | n/a** | 8 | 9 | 3 | 8 | 8 | 7 | **6.86** | **8.00** | **3** | **9** |
| Infections (within 90 days) | 7 | 8 | 8 | 9 | 3 | 9 | 8 | 9 | **7.63** | **8.00** | **3** | **9** |
| Posterior capsule opacification | 7 | 8 | n/a** | 8 | 7 | 7 | 8 | 8 | **7.57** | **8.00** | **7** | **8** |
| Secondary cataract (24 months) | 7 | 8 | n/a** | 6 | 3 | 8 | 8 | 9 | **7.00** | **8.00** | **3** | **9** |
| Surgical re-intervention (within 6 months) | 8 | 8 | 9 | 6 | 3 | 9 | 8 | 9 | **7.50** | **8.00** | **3** | **9** |
| Visual acuity loss post-cataract surgery (1 month; 6 months) | 6 | 8 | 9 | 6 | 7 | 8 | 8 | 9 | **7.63** | **8.00** | **6** | **9** |
| Surgically induced astigmatism | 7 | 8 | 6 | 6 | 6 | 6 | 6 | 8 | **6.63** | **6.00** | **6** | **8** |
| Central corneal thickness | 6 | 8 | 6 | 5 | 3 | 5 | 4 | 5 | **5.25** | **5.00** | **3** | **8** |
| Resource use | 2 | 5 | 7 | 4 | 6 | 9 | n/a** | 8 | **5.86** | **6.00** | **2** | **9** |
| Patient satisfaction | 5 | 8 | 6 | 4 | 5 | 7 | 5 | 6 | **5.75** | **5.50** | **4** | **8** |
| Procedural times | 2 | 5 | 7 | 4 | 4 | 8 | 8 | 5 | **5.38** | **5.00** | **2** | **8** |

**TM: Team Member*

***n/a: outcome not rated by the team member*

**Table 3 Final rating of outcomes related to research question "What is the relative effectiveness and safety of Femtosecond Laser-Assisted Cataract Surgery (FLACS) compared to standard cataract surgery for the treatment of age-related cataract in adult patients?"**

| Effectiveness outcomes | Median rating | Included | | Excluded |
|---|---|---|---|---|
| | | Critical | Important | Not important |
| Corrected Distance Visual Acuity (1 month; 6 months) | 8 | ● | ○ | ○ |
| Vision-related Quality Of Life | 8 | ● | ○ | ○ |
| Patient-reported Outcomes | 7.5 | ● | ○ | ○ |
| Refractive outcomes | 7 | ● | ○ | ○ |
| Uncorrected Distance Visual Acuity (1 month; 6 months) | 7 | ● | ○ | ○ |
| **Safety outcomes** | | | | |
| Anterior Capsular Tear | 8.5 | ● | ○ | ○ |
| Posterior Capsular Tear | 8.5 | ● | ○ | ○ |
| Vitreous loss | 7.5 | ● | ○ | ○ |
| Retinal detachment | 8 | ● | ○ | ○ |
| Iridocyclitis | 7 | ● | ○ | ○ |
| Endothelial cells loss | 6.5 | ● | ○ | ○ |
| Elevated Intraocular Pressure (1 day - 1 week) | 6 | ○ | ● | ○ |
| Corneal endothelial decompensation (within 90 days) | 8 | ● | ○ | ○ |
| Cystoid macular oedema (within 90 days) | 8 | ● | ○ | ○ |
| Infections (wthin 90 days) | 8 | ● | ○ | ○ |
| Posterior capsule opacification | 8 | ● | ○ | ○ |
| Secondary cataract (24 months) | 8 | ● | ○ | ○ |
| Surgical re-intervention (within 6 months) | 8 | ● | ○ | ○ |
| Visual acuity loss post cataract surgery (1 month; 6 months) | 8 | ● | ○ | ○ |
| Surgically induced astigmatism | 6 | ○ | ● | ○ |
| Central corneal thickness | 5 | ○ | ● | ○ |
| **Other outcomes** | | | | |
| Resource use | 6 | ○ | ● | ○ |
| Patient satisfaction | 5.5 | ○ | ● | ○ |
| Procedural times | 5 | ○ | ● | ○ |

### *Patients' involvement*

Patient involvement was planned and an information leaflet was prepared in order to facilitate their understanding of objectives and methods of this assessment and their participation in the early phases of this project. European umbrella organizations were contacted as well as patient representatives from Ireland; however, it was not possible to obtain early participation, which was hindered by patient representatives' logistic issues. One dedicated reviewer obtained a late feedback from a Spanish patient organization interested in refractive surgery. Comments pertinent to this REA are shyntetized and reported in the main text while the complete response can be found in **Appendix 4**.

### *Source of assessment elements*

The selection of assessment elements was based on The HTA Core Model® for Rapid Relative Effectiveness Assessment Version 4.2 (14). The selected issues (generic questions) were translated into actual research questions (answerable questions). Some research questions were grouped and answered together.

### *Search*

Details on search strategy and databases are included in **Appendix 1.**

A systematic review of the scientific literature was performed according to the Cochrane Handbook methodology. (16) As four high-quality systematic reviews were published in 2016, (3,17–19) with searches conducted between 1946 and May 2016, our systematic search had January 2016 as a starting date and combined the search strategies of all 4 recent systematic reviews. The most recent high-quality systematic review of effectiveness of FLACS vs standard care, (3) which included only Randomized Clinical Trials (RCTs), was the basis for setting and updating the search for RCTs to answer questions on effectiveness and safety (EFF and SAF). (14) The other three systematic reviews, (17–19) which also included observational studies, constituted the basis for setting the search for non-randomised controlled studies to answer questions on SAF related to long-term outcomes (e.g., secondary cataract at 24 months).

The search for primary studies published after the included systematic reviews was limited from January 2016 to December 2017 and updated in July 2018. The search for ongoing studies was carried out in June 2018 and literature was continuously monitored for newly published studies relevant for this assessment.

International guidelines, UpToDate (20) and relevant studies identified through the systematic search represented the main source for the "Health problem and current use" of FLACS (CUR) domain. (14)

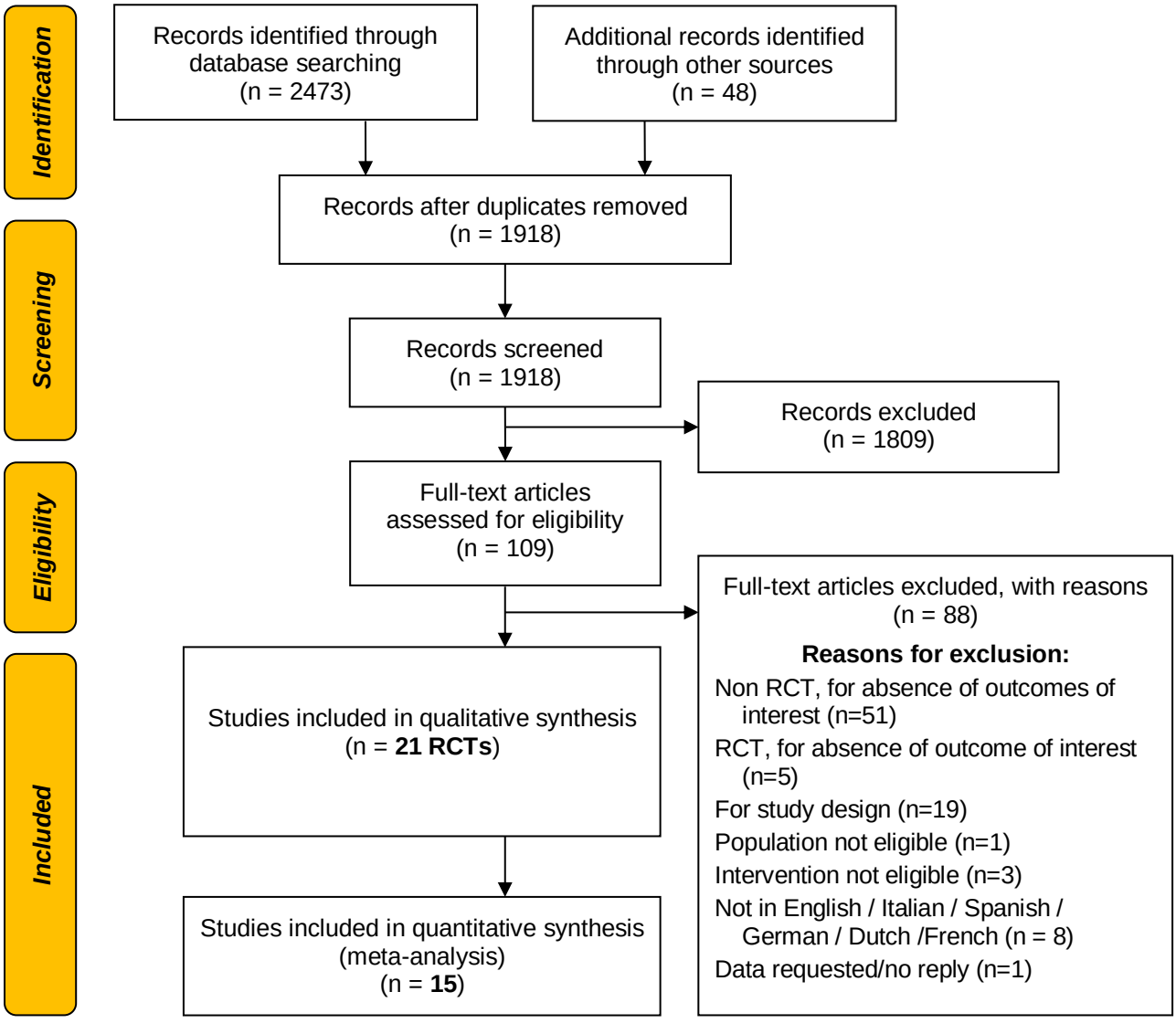
Main sources used for the Description and Technical Characteristic of the technology domain (TEC) (14) were manufacturers' brochures and information leaflets, manufacturers' user manuals, published articles and EUnetHTA manufacturer's submission template. Despite several attempts to obtain information from the manufacturers, only one (Alcon) of the five identified responded and provided a complete EUnetHTA submission Template.

### *Study selection*

All primary studies included in the 4 systematic reviews published in 2016 were retrieved and assessed for inclusion.

The electronic search yielded 2473 references. To these we added all primary studies included in the 4 systematic reviews published in 2016. After removing 603 duplicate records, we screened the remaining 1918 records. We excluded 1809 records after reading the abstracts and obtained the full-text reports of 109 references for further assessment. Eighty-eight studies were excluded, with reason (**Figure 1**); the 21 studies that met the inclusion criteria were finally included for the analyses.

**Figure 1 - PRISMA diagram for systematic literature search**




*RCTs=Randomised Controlled Trials*

## Criteria for considering studies for this review:

### Types of studies

All randomised controlled trials (RCTs) that met inclusion criteria were included for the Clinical Effectiveness (EFF) and Safety (SAF) domains. Non-randomised prospective controlled studies were also searched for inclusion if reporting safety outcomes assessed with a follow up of 6 months or longer.

Studies written in languages accessible by the assessment team, i.e., English / Italian / Spanish / German / Dutch/ French.

### Types of participants

The target disease was age-related cataract. (ICD-9 366.1; ICD-10 H25).

The target population was adult patients (≥18 years) of either sex, affected by age-related cataract and for whom the surgical treatment for cataract removal and insertion of intraocular lens could provide a gain in visual acuity and health-related quality of life.

### Types of interventions

The intervention under assessment was Femtosecond laser-assisted cataract surgery (FLACS) to be used during the first phases of intervention to create incisions, perform capsulorhexis and fragment the lens. To complete the surgical procedure, conventional ultrasound phacoemulsification technique was used.

The comparator was standard cataract surgery (i.e., with manual incision and capsulorhexis followed by conventional ultrasound phacoemulsification).

### Types of outcome measures

*Clinical Effectiveness*

Corrected Distance Visual Acuity (1 month; 6 months) and Uncorrected Distance Visual Acuity (1 month; 6 months), both measured through the logarithmic scale LogMAR, with lower values corresponding to better vision; Vision-related quality of life as measured by any validated questionnaire; Patient-reported Outcomes; Refractive outcomes, measured in dioptres as absolute deviation between the predicted and achieved spherical equivalent, the latter being the algebraic sum of the value of the sphere and half the cylindrical value.

*Safety*

Intraoperative complications: Anterior capsular tear ; Posterior capsular tear; Vitreous loss.

Postoperative complications: Corneal endothelial decompensation (within 90 days); Cystoid macular oedema (within 90 days); Infections (within 90 days); Posterior capsule opacification; Retinal detachment; (1 month;6 months); Secondary cataract (24 months); Surgical re-intervention (within 6 months); Visual acuity loss post-cataract surgery; Iridocyclitis; Endothelial cells loss; Elevated Intraocular Pressure (1 day - 1 week); Surgically induced astigmatism; Central corneal thickness.

*Other outcomes*

Resource use; Patient satisfaction; Procedural time.

## Criteria for excluding studies from this review

We excluded retrospective and case-control studies, uncontrolled prospective studies and case series, and prospective non-randomized studies that did not report long-term outcomes. Randomized controlled studies not reporting on outcomes of interest were also excluded.

Studies including patients with non-age-related cataract (e.g., congenital cataract, traumatic cataract etc.) and studies not assessing intervention and comparator defined in the Scope were excluded.

Articles in languages not accessible by assessment team were excluded.

### *Data extraction and analyses*

Four review authors (FV, MV, LB, and GF) independently extracted data using a data extraction form developed for this review (**Appendix 1** **Table A2-A20**). The authors resolved any discrepancies through discussion among themselves and with a fifth author (LuB).

For each included study, we recorded the following information: study design (within person or paired-eye RCT, parallel group RCT), unit of analysis (eye, person), length of follow up, number of participants in the intervention and control groups, average age, sex and country, patients' inclusion and exclusion criteria, data collection period, number of participants in study and within specific subpopulations (according to LOCS grade and pseudo-exfoliation), description of intervention and control, outcomes and results, funding source, conflicts of Interest, trial registration number (if available) and risk of bias (according to the Cochrane Risk of Bias Tool)(21).

## Measures of treatment effect

For the purpose of meta-analysis, we used odds ratios for binary outcomes and the mean difference for continuous outcomes. Corrected and Uncorrected Distance Acuity measures expressed in decimal were transformed in LogMAR, according to the decimal to LogMAR transformation formula (38).

## Unit of analysis issues

We used eyes as unit of analysis. Each participant could contribute with either one or both eyes. In the latter case, we considered the possibility that patient's eyes could either both be randomised to the same intervention or to have a within-person study (one eye allocated to intervention and the other eye to comparator).

## Dealing with missing data

We considered contacting principal investigators to retrieve possible unreported data and did so for the trial by Filkorn 2012; (39) the principal investigator was contacted by mail and asked for clarifications regarding 1-month post-intervention visual acuity data. The author could not be traced, and we did not receive any answer. That trial was subsequently excluded for very serious risk of selection bias (possibility of having excluded patients after surgery due to negative outcomes).

## Assessment of heterogeneity

We evaluated methodological and statistical heterogeneity of included studies by considering their risk of bias, by examining forest plots of their results and the $I^2$ statistic to assess inconsistency between studies.

## Subgroup analysis and investigation of heterogeneity

We had planned to assess specific subpopulations, according to LOCS grade and pseudo-exfoliation, but lack of data on specific subpopulations did not allow any subgroup analysis

## Data synthesis

Whenever possible, quantitative analysis methods with meta-analysis were carried out for SAF and EFF domains (14,16), using RevMan 5.3. We pooled data using a random-effects model, which is more conservative than fixed-effect model, but controls better for heterogeneity.

As included studies reported widely varying outcome measures and timings of measurement, we asked and followed advice from clinical experts on the choice of the most appropriate outcome measures and the clinically meaningful time of follow up. We sought advice from experts in relation to the measurements of refractive outcomes, surgically induced astigmatism and to the possibility of combining outcome measures. The outcome of this consultation was as follows: Best Corrected and Corrected Visual Acuity (meaning visual acuity assessed when wearing corrective devices) are to be considered analogue measures; Posterior Capsular Opacification and Secondary Cataract are to be considered analogue outcomes; Corneal Endothelial Decompensation and Corneal Oedema are to be considered analogue outcomes. Regarding measures of refractive outcomes, mean absolute error and absolute deviation of spherical equivalence could be considered analogue outcomes and combined. Concerning measures for surgically induced astigmatism (SIA), the indication was to use magnitude of SIA (in dioptres) at three months.

Descriptive analysis of information has been provided for other domains and whenever meta-analysis proved not possible or inappropriate. In some instances, forest plots have been inserted even though pooled estimates could not be calculated, in order to provide a visual representation of each study's results.

A "Summary of findings" table was created using the GRADE Pro tool (37).

### *Quality rating*

For Description and Technical Characteristics of Technology (TEC) and Health Problem and Current Use of the Technology (CUR) domains, no quality assessment tool was used, but multiple sources were used to validate and cross-check individual sources.

For Clinical Effectiveness (EFF) and Safety (SAF) domains, study quality on included randomized controlled trials was rated using the tool for assessing risk of bias described in the Cochrane Handbook for Systematic Reviews of Interventions (21)(Chapter 8 – see "assessment of risk of bias in included studies"). Overall quality of evidence for each outcome was rated using the GRADE methodology (22).

## Assessment of risk of bias in included studies

Four review authors (FV, MV, LB, GF) independently assessed risk of bias in the included studies using the aforementioned methodology, according to six criteria:

- random sequence generation, which influences the likelihood that allocation to treatments is randomized;
- allocation concealment, which influences the unpredictability of treatment allocation and the possibility that selection bias occurs. When allocation concealment was unclear or not reported, available tables reporting patients' baseline characteristics were checked and assessed for any imbalance between study groups;
- blinding of participants and personnel. To be noted that all the selected trials were open label since blinding is not possible, given the interventions being assessed;
- blinding of outcome assessors, assessing whether it had been declared and whether it was likely to be maintained. To be noted that allowances were made for the few outcomes for which the assessor could not be blinded (e.g., intraoperative complications);
- incomplete outcome data, leading to attrition bias. Besides situations where no attrition was declared and apparent, we considered studies to be at low risk of attrition bias when loss to follow up was less than 5% (40) and when reasons for missing outcome data were unlikely to be related to the outcomes;

- selective outcome reporting: study protocols were searched to assess whether all of the studies' pre-specified primary outcomes were reported, and whether they were reported in the pre-specified way. However, no study protocol was retrieved

The authors resolved any discrepancies on quality judgements through discussion among themselves and with a fifth author (LuB).

The quality of evidence for each outcome was rated across studies and assessed using the GRADE approach (22).

Based on judgements on study design, study limitations (risk of bias), inconsistency of results, indirectness of evidence, imprecision and publication bias, the quality of evidence was assessed according to one of four grades (high, moderate, low and very low) as described in **Table 4**. (15)

**Table 4 Definition of quality of evidence**

| Quality | Definition |
|---|---|
| High | "We are very confident that the true effect lies close to that of the estimate of the effect" |
| Moderate | "We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different" |
| Low | "Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect" |
| Very Low | "We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect" |

### *Patient involvement*

Patient involvement was planned, and an information leaflet was prepared in order to facilitate the understanding of objectives and methods of this assessment and participation in the early phases of this project. European umbrella organizations were contacted, as well as patient representatives from Ireland, but, it was not possible to obtain early participation, which was hindered by patient representatives' logistic issues. One dedicated reviewer obtained a late feedback from a Spanish patient organization interested in refractive surgery.

### *Description of the evidence used*

#### Design of included studies

Only randomized controlled studies (RCTs) are included in this assessment, as no prospective comparative non-randomized studies assessing long-term safety outcomes were retrieved.

Among the 21 studies included in this report, 14 were parallel group RCTs (Donnenfeld 2018, Givaudan Pedroza 2016, Hida 2014, Kovacs 2014, Kranitz 2012, Mastropasqua 2014a, Mastropasqua 2014b, Nagy 2011, Nagy 2014, Reddy 2013, Roberts 2018, Takacs 2012, Yu 2015, Yu 2016) (23–29,33,41–46) mostly including one eye

per person, except for Nagy 2011, Yu 2015 and Yu 2016 (27,28,44) (see Table 1). Seven studies (Conrad-Hengerer 2013, Conrad-Hengerer 2014, Conrad-Hengerer 2015, Dick 2014, Mursch Edlmayr 2017, Panthier 2017, Schargus 2015) (30–32,47–50) were within person, paired-eye RCTs (one eye randomized to femtosecond laser-assisted cataract surgery, the other eye to manual phacoemulsification). No non-randomized studies was included.

### Participants

Overall, the studies included in this report recruited a total of 1633 patients (range: 30-299). A total of 2118 eyes were randomized. Seventy-six percent of patients were recruited and operated on in Europe, more specifically in Austria, France, Germany, Hungary, Italy and the UK; the remaining 27% were recruited and operated in Brazil, China, India, Mexico and the US.

### Interventions

All included studies compared femtosecond laser-assisted cataract surgery to standard ultrasound phacoemulsification cataract surgery. German and US studies (Conrad-Hengerer 2013, Conrad-Hengerer 2014, Conrad-Hengerer 2015, Dick 2014, Schargus 2015 and Donnenfeld 2018) (29,30,32,47–49) used the OptiMedica Catalys laser platform (Abbott Medical Optics, Inc.). Brazilian, Hungarian, Italian, Mexican and UK studies (Hida 2014, Kovacs 2014, Kranitz 2012, Nagy 2011, Nagy 2014, Takacs 2012, Mastropasqua 2014a, Mastropasqua 2014b, Givaudan Pedroza 2016 and Roberts 2018) (23–27,33,41,43,45,46) used the LenSx platform (Alcon Laboratories, Inc., Fort Worth, TX). Mursch Edlmayr 2017 (31) (in Austria), Panthier 2017 (50) (in France) and Reddy 2013 (42) (in India) used the Victus ™laser platform (Bausch&LombTechnolas); Yu 2015, Yu 2016 (in China) and Mastropasqua 2014b (25,28,44) used the Lensar System (LENSAR).

### Risk of bias in included studies

All included studies were randomized controlled trials, but overall there was very poor reporting on the randomization process, with 6 studies describing an appropriate method for random sequence generation and only 2 studies reporting a method of allocation concealment. Blinding of surgeons to intervention not being possible, all included studies were open trials and did not allow blinding of participants and personnel. For similar reasons, blinding of outcome assessment for intraoperative outcomes was not possible. However, only 10 studies reported blinding of assessment for postoperative outcomes. Only 9 studies reported data on attrition and only one study protocol was available to ascertain selective reporting bias, which was strongly suspected in three trials (**Table A23**).
The majority of studies (n.15) were industry sponsored or had authors being paid as a consultant, employee or member of the medical advisory board of the firm producing the laser system under study.

**Figure 2** reports judgements on each risk of bias item as percentages across all included studies, while **Figure 3** reports the summary of judgements on each risk of bias for each included study.

**Figure 2 -** Assessment of risk of bias in included studies

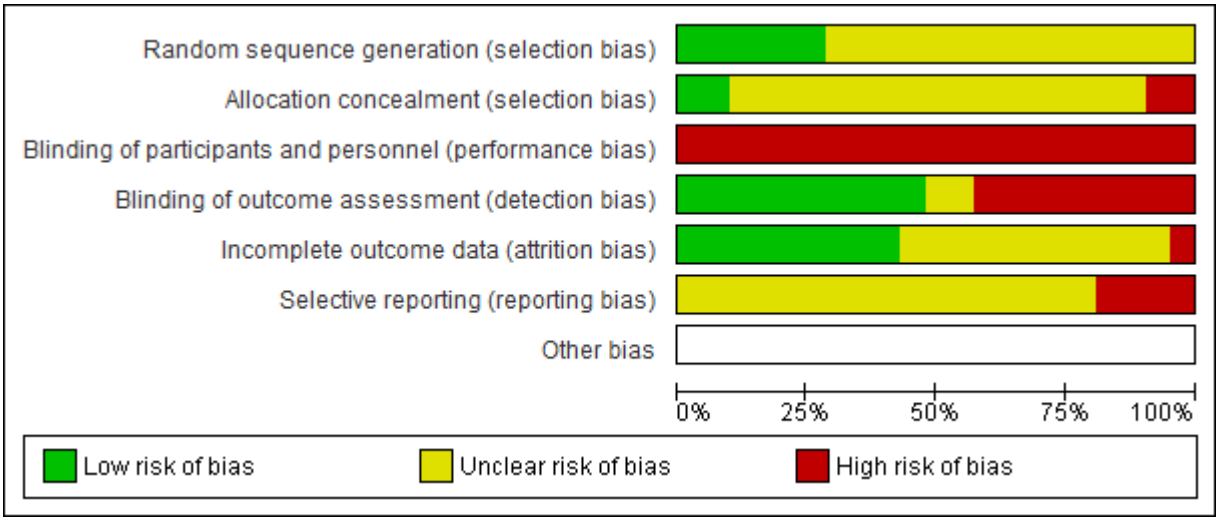


**Figure 3 -** Assessment of risk of bias of each study included

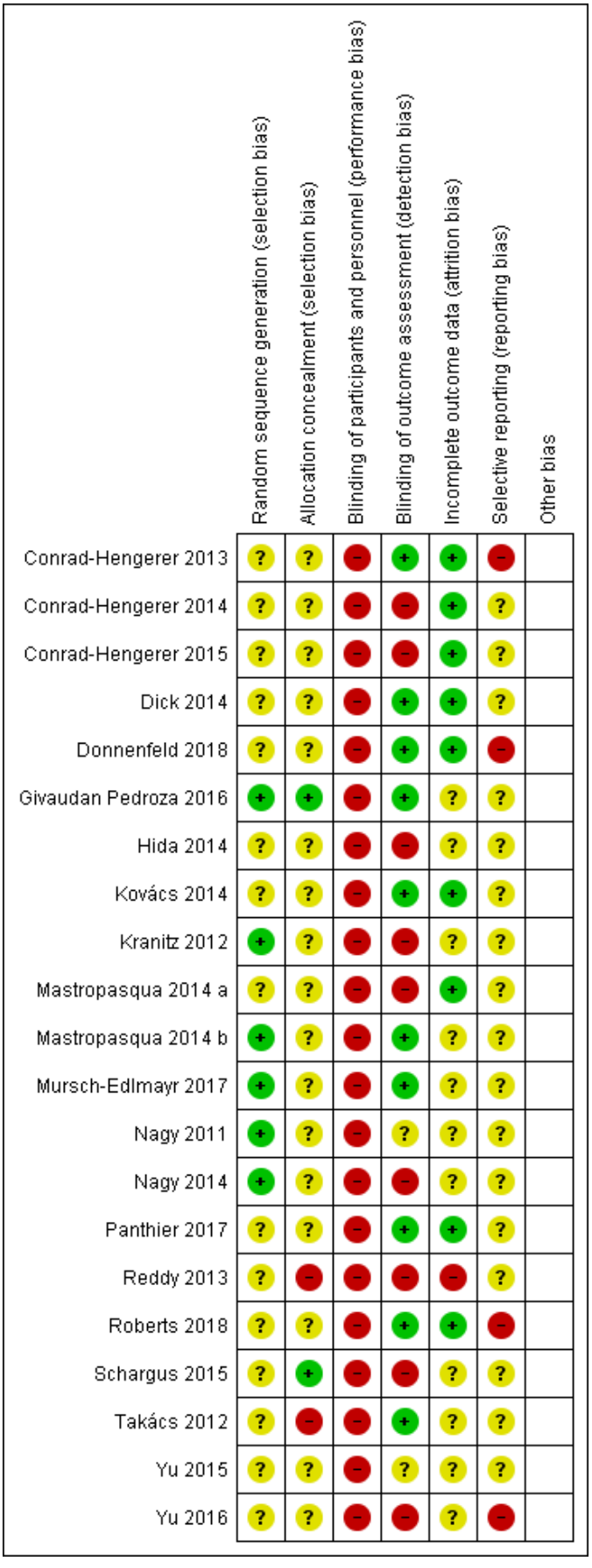


**Table 5 Main characteristics of studies included**

| Author and year or study name | Study type | Number of patients | Intervention (s) | Main endpoints | Included in clinical effectiveness and/ or safety domain |
|---|---|---|---|---|---|
| Conrad-Hengerer 2013 (47) | Within person, paired-eye, open label RCT | 75 (150 eyes) | Femtosecond Laser-Assisted phacoemulsification (OptiMedica Catalys laser platform - Abbott Medical Otics, Inc.) vs standard phacoemulsification | Anterior capsule tear; macular edema; elevated intraocular pressure (1 day and 1 week postoperatively); corneal thickness and endothelial cell loss (1, 3 and 4 days; 1 and 6 weeks; 3 months after surgery); Effective Phacoemulsification Time (EPT); total surgery time | Safety |
| Conrad-Hengerer 2014 (48) | Within person, paired-eye, open label RCT | 104 (208 eyes) | Femtosecond Laser-Assisted phacoemulsification (OptiMedica Catalys laser platform - Abbott Medical Otics, Inc.) vs standard phacoemulsification | Intraoperative and postoperative complications, absolute and effective phacoemulsification time, surgery time | Safety |
| Conrad-Hengerer 2015 (30) | Within person, paired-eye, open label RCT | 100 (200 eyes) | Femtosecond Laser-Assisted phacoemulsification (OptiMedica Catalys laser platform - Abbott Medical Otics, Inc.) vs standard phacoemulsification | Early and late CDVA, deviation from the target refraction (spherical equivalent), anterior capsular tear, vitreous loss, postoperative intraocular pressure, macular oedema, endophtalmitis | Safety Effectiveness |
| Dick 2014 (49) | Within person, paired-eye, open label RCT | 53 (106 eyes) | Femtosecond Laser-Assisted cataract surgery (OptiMedica Catalys laser platform - Abbott Medical Otics, Inc.) vs standard phacoemulsification | Effective phacoemulsification time | Other outcomes |
| Donnenfeld 2018 (29) | Parallel group 3 arm RCT (FLACS in 2 arms) | 45 (45 eyes) | Femtosecond laser–assisted 110-degree reverse side-cut incisions (group A) or 70-degree forward side-cut incisions (group B) performed with a Catalys femtosecond laser (Abbott Medical Optics, Inc.) vs standard phacoemulsification | IOP at which the primary incision began to leak, severity of wound leakage 1 day, 2 weeks and 1 month postoperatively, pupil size, sphere, cylinder, manifest refraction spherical equivalent, uncorrected distance visual acuity, corrected distance visual acuity | Effectiveness |
| Givaudan Pedroza 2016 (45) | Parallel group, open label RCT | 65 (65 eyes) | Femtosecond Laser-Assisted cataract surgery Lensx, platform – Alcon Laboraties, Inc., Fort Worth, TX) vs manual phacoemulsification surgery | Endothelial cell count, effective phacoemulsification time | Safety |
| Hida 2014 (23) | Parallel group, open label RCT | 80 (80 eyes) | Femtosecond Laser-Assisted capsulotomy (Lensx, platform – Alcon Laboraties, Inc., Fort Worth, TX) vs manually continuous curvilinear digital guided capsulorhexis | Mean postoperative spherical equivalent, difference between predicted and actual postoperative spherical equivalent, circularity of capsulorhexis, overlap area | Effectiveness |
| Kovacs 2014 (46) | Parallel group, open label RCT | 79 (79 eyes) | Femtosecond Laser-Assisted capsulotomy (Lensx, platform – Alcon Laboraties, Inc., Fort Worth, TX) vs manual anterior capsulorhexis. | Posterior capsule opacification at 18-26 months postoperatively | Safety |

| Author and year or study name | Study type | Number of patients | Intervention (s) | Main endpoints | Included in clinical effectiveness and/ or safety domain |
|---|---|---|---|---|---|
| Kranitz 2012 (24) | Parallel group, open label RCT | 45 (45 eyes) | Femtosecond Laser-Assisted circular capsulotomy (Lensx, platform – Alcon Laboraties, Inc., Fort Worth, TX) vs manually performed continuous curvilinear capsulorrhexis | UDVA and CDVA 1 month after surgery<br>Manifest refraction | Effectiveness |
| Mastropasqua 2014a (26) | Parallel group, open label RCT | 60 (60 eyes) | Femtosecond Laser CCI (Clear Corneal Incision) (Lensx, platform – Alcon Laboraties, Inc., Fort Worth, TX) vs manual CCI | UDVA, CDVA, keratometric astigmatism, endothelial cell count, corneal thickness at the incision site, astigmatic change, mean phacoemulsification time, total time | Safety<br>Effectiveness |
| Mastropasqua 2014b (25) | Parallel group, open label 3 arm RCT | 90 (90 eyes) | Femtosecond Laser-Assisted cataract surgery capsulotomy (Lensx, platform – Alcon Laboraties, Inc., Fort Worth, TX) vs Lensar System-LENSAR) vs manual continuous curvilinear capsulorhexis | UDVA (LogMAR), CDVA (LogMAR), spherical error | Effectiveness |
| Mursch Edlmayr 2017 (31) | Within person, paired-eye, open label RCT | 50 (100 eyes) | Femtosecond Laser cataract surgery (Victus ™laser platform – Bausch&LombTechnolas) vs conventional cataract surgery | CDVA, intraoperative and postoperative complications, endothelial cell loss, central corneal thickness, effective phacoemulsification time | Safety<br>Effectiveness |
| Nagy 2011 (27) | Parallel group, open label RCT | 105 (111 eyes) | Femtosecond Laser cataract surgery with capsulorrhexis (Lensx, platform – Alcon Laboraties, Inc., Fort Worth, TX) vs manual continuous curvilinear capsulorrhexis | Refractive state | Effectiveness |
| Nagy 2014 (41) | Parallel group, open label RCT | 40 (40 eyes) | Femtosecond Laser-Assisted cataract surgery (Lensx, platform – Alcon Laboraties, Inc., Fort Worth, TX) vs standard phacoemulsification | Surgically induced astigmatism, complications | Safety |
| Panthier 2017 (50) | Within person, paired-eye, open label RCT | 33 (66 eyes) | Femtosecond Laser-Assisted cataract surgery (Victus ™laser platform – Bausch&LombTechnolas) vs standard phacoemulsification | Uncorrected and corrected distance visual acuity, postoperative refractive error, posterior capsular tears | Safety |
| Reddy 2013 (42) | Parallel group, open label RCT | 131 (131 eyes) | Femtosecond Laser–Assisted lens fragmentation and anterior capsulotomy before phacoemulsification (Victus ™laser platform – Bausch&LombTechnolas) vs manual capsulorhexis with standard phacoemulsification | Posterior capsular bag tear, anterior tear, glaucoma, effective phacoemulsification time (EPT) during phacoemulsification, mean phaco time and mean phaco energy | Safety |

| Author and year or study name | Study type | Number of patients | Intervention (s) | Main endpoints | Included in clinical effectiveness and/ or safety domain |
|---|---|---|---|---|---|
| Roberts 2018 (33) | Parallel group RCT | 299 (299 eyes) | Femtosecond Laser-Assisted cataract surgery in a hub-and-spoke model, performed with LenSx (Alcon, Fort Worth, Texas, USA) vs standard phacoemulsification | Relative costs of FLACS and CPS, time in operating room, anterior capsular tear, posterior capsular tear with vitreous loss | Safety, other outcomes |
| Schargus 2015 (32) | Within person paired-eye open label RCT | 37 (74 eyes) | Laser-Assisted cataract surgery without ophthalmic viscosurgical devices (OptiMedica Catalys laser platform - Abbott Medical Otics, Inc.) vs standard phacoemulsification cataract surgery with ophthalmic viscosurgical devices | Endothelial cell loss, corneal thickness, IOP, CDVA, overall surgery time, absolute and effective phacoemulsification time, other complications | Safety Effectiveness |
| Takacs 2012 (43) | Parallel group, open label RCT | 76 (76 eyes) | Femtosecond Laser-Assisted cataract surgery (Lensx, platform – Alcon Laboraties, Inc., Fort Worth, TX) vs conventional phacoemulsification | Postoperative central corneal edema, endothelial cell count, central corneal thickness, phaco time, effective phaco time | Safety |
| Yu 2015 (28) | Parallel group, open label RCT | 36 (54 eyes) | Femtosecond Laser-Assisted cataract surgery (Lensar System – LENSAR) vs conventional phacoemulsification | Anterior and posterior capsular tear, intraoperative complications, IOL, posterior capsular opacification, reintervention, postoperative refraction, best corrected visual acuity, average phacoemulsification time (APT), effective phacoemulsification time | Safety Effectiveness |
| Yu 2016 (44) | Parallel group, open label RCT | 30 (39 eyes) | Femtosecond Laser-Assisted capsulotomy (Lensar System – LENSAR) vs conventional phacoemulsification | Complications, capsule rupture | Safety |

**Abbreviations:** RCT: Randomized Controlled Trial; EPT: Effective Phacoemulsification Time; CDVA: Corrected Distance Visual Acuity; UDVA: Uncorrected Distance Visual Acuity; IOP: Intra Ocular Pressure; APT: Average Phacoemulsification Ti

**Table 6 list of outcomes included in Scope for each included study**

| Outcomes | Givaudan Pedroza 2016 (45) | Kovacs 2014 (46) | Mastropasqua 2014a (26) | Mastropasqua 2014b (25) | Mursch-Edlmayr 2017 (31) | Kranitz 2012 (24) | Nagy 2011 (27) | Nagy 2014 (41) | Reddy 2013 (42) | Roberts 2018 (33) | Schargus 2015 (32) | Takács 2012 (43) | Panthier 2017 (50) | Yu 2015 (28) | Yu 2016 (44) | Conrad-Hengerer 2013 (47) | Conrad-Hengerer 2014 (48) | Conrad-Hengerer 2015 (30) | Dick 2014 (49) | Donnenfeld 2018 (29) | Hida 2014 (23) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SAFETY** | | | | | | | | | | | | | | | | | | | | | |
| Posterior capsular tear | | | | | X | | | | X | | X | | X | X | X | X | | X | | | |
| Anterior capsular tear | | | | | X | | | | X | X | X | | X | X | X | X | | X | | | |
| Vitreous loss | | | | | | | | | | X | X | | | | | | | X | | | |
| Cystoid macula edema (within 90 days) | | | | | | | | | | | X | | | | | X | X | X | | | |
| Elevated Intraocular Pressure (IOP) (1 day) | | | | | | | | | | | X | | | | | X | X | X | | | |
| Elevated Intraocular Pressure (IOP) (1 week) | | | | | | | | | | | | | | X | | X | X | X | | | |
| Endothelial Cell Loss (ECL) | | | | | X | | | | | | X | | | X | | X | | | | | |
| Central Corneal Thickness (CCT) | | | | | X | | | | | | X | X | | | | X | | | | | |
| Idrocyclitis | | | | | | | | | | | | | | | | | | | | | |
| Infections (within 90 days) | | | | | | | | | | | | | | | | | | X | | | |
| Corneal Endothelial Decompensation (within 90 days) | | | | | | | | | | | | | | | | | | | | | |
| Surgical induced astigmatism | | | | | | | | X | | | | | | | | | | | | | |
| Retinal detachment | | | | | | | | | | | | | | | | | | | | | |
| Posterior capsule opacification/ secondary cataract within 24 months | | X | | | | | | | | | | | | X | | | | | | | |
| Visual acuity loss post cataract surgery (1 month) | | | | | | | | | | | | | | | | | | | | | |
| Visual acuity loss post cataract surgery (6 months) | | | | | | | | | | | | | | | | | | | | | |
| Surgical re-intervention (within 6 months) | | | | | | | | | | | | | | | | | | | | | |

| Outcomes | Givaudan Pedroza 2016 (45) | Kovacs 2014 (46) | Mastropasqua 2014a (26) | Mastropasqua 2014b (25) | Mursch-Edlmayr 2017 (31) | Kranitz 2012 (24) | Nagy 2011 (27) | Nagy 2014 (41) | Reddy 2013 (42) | Roberts 2018 (33) | Schargus 2015 (32) | Takács 2012 (43) | Panthier 2017 (50) | Yu 2015 (28) | Yu 2016 (44) | Conrad-Hengerer 2013 (47) | Conrad-Hengerer 2014 (48) | Conrad-Hengerer 2015 (30) | Dick 2014 (49) | Donnenfeld 2018 (29) | Hida 2014 (23) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **EFFECTIVENESS** | | | | | | | | | | | | | | | | | | | | | |
| Corrected Distance Visual Acuity (CDVA) 1 month after surgery | | | X | X | X | X | | | | | | | | X | | | | | | X | |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | | | X | X | X | | | | | | X | | | | | | | | | | |
| Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery | | | X | X | | X | | | | | | | | | | | | | | X | |
| Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery | | | X | X | | | | | | | | | | | | | | | | | |
| Refractive outcomes | | | | X | | | X | | | | | | | X | | | | X | | | X |
| Vision-related Quality of Life (by validated questionnaire) | | | | | | | | | | | | | | | | | | | | | |
| Patient-reported outcome measures (PROMs) | | | | | X | | | | | | | | | | | | | | | | |
| **OTHER OUTCOMES** | | | | | | | | | | | | | | | | | | | | | |
| Patient satisfaction | | | | | X | | | | | | | | | | | | | | | | |
| Mean surgical time | | | | | | | | | | X | X | | | | | X | | | | | |
| Resource use | | | | | | | | | | X | | | | | | | | | | | |
| **Additional outcome** | | | | | | | | | X | | | | | | | | | | | | |

### *Deviations from project plan*

One manufacturer was cancelled from the list of contributors, as it turned out not to be available.

The term for the subpopulation was changed from “sub-exfoliation” to “pseudo-exfoliation”, as more clinically appropriate

It has been specified that data for other outcomes (patient satisfaction, resource use and procedural time) were extracted, when available, from studies included for EFF and SAF domain.

# DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

## *Research questions*

| Element ID | Research question |
|---|---|
| B0001 | What is FLACS and standard cataract surgery? |
| A0020 | For which indications have different types of FLACS received marketing authorisation or CE marking? |
| B0002 | What is the claimed benefit of FLACS over standard cataract surgery? |
| B0003 | What is the phase of development and implementation of FLACS and standard cataract surgery? |
| B0004 | Who performs FLACS and standard cataract surgery and in what context and level of care are they provided? |
| B0008 | What kind of special premises are needed to perform FLACS and standard cataract surgery? |
| B0009 | What equipment and supplies are needed to perform FLACS and standard cataract surgery? |
| E0001 | What types of resources are used when performing the different types of FLACS and standard cataract surgery? |
| A0021 | What is the reimbursement status of FLACS in the different EU countries? |

## Features of the technology and comparators

### [B0001] What is FLACS and standard cataract surgery?

#### Standard cataract surgery

Cataract surgery is the most commonly performed ophthalmic procedure, and phacoemulsification is the most frequently used technique for cataract removal. The continued development of technology related to phacoemulsification machines and handpiece tips has provided a wide choice of tools available for ophthalmologists performing cataract surgery. (1)

Beside the set of skills needed to perform the steps of the intervention, cataract surgery also requires the cognitive skills, judgment and experience necessary to recognize and respond to unexpected events, problems and complications that may arise intraoperatively. Only an ophthalmologist has the medical and microsurgical training as part of a comprehensive medical residency needed to perform cataract surgery.

Current practice, and comparator for the present assessment, is standard cataract surgery, which requires manual formation of an opening in the anterior lens capsule, fragmentation and evacuation of the lens tissue with an ultrasound probe and implantation of a plastic intraocular lens into the remaining capsular bag. The size, shape and position of the anterior capsular opening (one of the most critical steps in the procedure) are controlled by freehand pulling and tearing of the capsular tissue. (2)

In developed countries, **phacoemulsification** is the preferred method to remove a cataract, with reported rates of major complications (posterior capsule rupture or vitreous loss) of 1.95% (95% confidence interval (CI) 1.89% to 2.02%) and overall intraoperative complication rates of 4.2%(95%CI 4.1 to 4.3%).(3)

The ideal technical elements of a successful cataract procedure currently include the following:

- A secure, watertight seal that minimizes surgically induced astigmatism or reduces pre-existing corneal astigmatism;
- Thorough removal of all nuclear, epinuclear and cortical material;
- Negligible or no trauma to the corneal endothelium, iris or other ocular tissues;

- Preservation of the integrity of the anterior and posterior capsule;
- Capsular bag fixation of an appropriate posterior chamber intraocular lens (IOL).

Intraocular steps that are commonly used during phacoemulsification include the following:

- Construction of an appropriately sized incision that is tight enough to achieve a stable anterior chamber;
- Use of an opthalmic viscosurgical device (OVD) to protect the corneal endothelium, manipulate tissues, and maintain adequate working space during surgery;
- Creation of a capsulorrhexis, which is a continuous curvilinear or femtosecond laser-generated capsulotomy and aids in hydrodissection; preventing posterior capsule tears that originate from radial anterior capsule tears and facilitating the implantation, fixation and centration of the IOL within the capsular bag. A capsulorrhexis that completely overlaps the IOL edge impedes the development of posterior capsular opacification (PCO) for some IOL designs;
- Hydrodissection, which reduces zonular stress during phacoemulsification by mobilizing the nucleus and epinucleus and facilitating thorough cortical aspiration. Hydrodissection also helps to retard PCO;
- Nuclear disassembly and emulsification using techniques such as divide and conquer or chopping to allow nuclear removal through a capsulorrhexis and small incision;
- Thorough removal of remaining epinucleus and cortex (polishing the anterior and posterior capsule when appropriate);
- Implantation and centration of a small-incision IOL within the capsular bag, or as dictated by capsular anatomy, secure fixation of the IOL in the ciliary sulcus (with or without sutures or capsulorrhexis capture) or anterior chamber;
- Removal of OVD to minimize postoperative IOP elevation;
- Assurance of a watertight seal using sutures or a sealant if the incision size and architecture with adequate stromal hydration alone do not produce a secure, self-sealing wound.

Incision location, size and design may depend on several factors, including the patient's orbital anatomy, the type of IOL to be implanted, the role of the incision in astigmatism management and surgeon preference and experience. (4,13)

**Femtosecond laser-assisted cataract surgery (FLACS)**

Femtosecond lasers have been used to perform several stages of phacoemulsification cataract surgery since 2009. Laser-generated pulses of highly focused infrared light perform the cutting by creating localised cavitation bubbles within tissues, a process termed photo-disruption. The ultrashort duration of each pulse minimises damage to adjacent tissue. During cataract surgery, such lasers are used to create incisions, perform capsulorhexis and fragment the lens. The surgeon plans and decides the target location, then the system delivers the focus of the laser beam to produce the desired incision.

The procedure is then completed using conventional phacoemulsification equipment and techniques. (4)

The main steps in the FLACS procedure are:

- Docking: ensuring a stable alignment of the structure with the eye.

- Imaging: in this stage, surgeons perform an accurate analysis of the anterior segment of the eye and plan the position and depth of the incision in order to place accurately the IOL.

- Laser treatment: the system delivers the laser beam to obtain the desired incision, performs capsulorhexis and fragments the lens.

Every FLACS system uses a different type of disposable patient interface to ensure a stable docking of the eye to the optical delivery system in order to prevent eye movement and to facilitate the transmission of the laser energy. The system applies suction to fix the patient interface to the eye. (51)

The available laser platforms have varying patient interface systems (**Table 7**), which can be divided into contact (applanating) and noncontact (non-applanating). (52)

**Table 7 Available laser platforms**

| | Technology | | | | |
|---|---|---|---|---|---|
| Model | Catalys® Precision Laser System | LenSx® Laser System | Victus | Ziemer Z8 | Lensar Laser System |
| Manufacturer | Abbott | Alcon | Bausch & Lomb | Ziemer Group | Lensar |
| Type of patient interface | Noncontact, liquid optics | Contact, Softfit curved lens | Noncontact, liquid optics | Noncontact, liquid optics | Noncontact, liquid optics |
| Type of Imaging system | OCT | OCT | OCT | OCT | 3D CSI |
| Integrated bed | Yes | No | Yes | No | No |

*OCT: Optical Coherence Tomography*

*3D CSI: 3-dimensional confocal structural illumination*

Contact patient interface includes lens, suction ring and tubing; noncontact systems are composed of a liquid interface, as an alternative to the lens, which can contribute to reduce the intraocular pressure.

Concerning imaging phase, most of the FLACS systems use an Optical Coherence Tomography (OCT) as imaging system; the Lensar system uses a ray-tracing reconstruction (3-dimensional confocal structural illumination, [3D CSI]).

Certain FLACS systems can perform an in-line imaging of the anterior segment of the eye during the treatment.

As a final step, femtosecond laser produces continuous anterior capsular incisions, which are twice as strong as, and over five times more precise in size and shape than, manual capsulorhexis.

Lens segmentation and softening simplifies its emulsification and removal, decreasing the perceived cataract hardness by two grades. Depending on the system, surgeons can perform different fragmentation patterns in order to reduce the phaco energy in the next step of the procedure.

Three-dimensional cutting of the cornea guided by diagnostic imaging creates multiplanar self-sealing incisions and allows exact placement of the limbal relaxing incisions, potentially increasing the safety and performance of cataract surgery. (2)

We present a rapid overview of the laser systems available for cataract treatment.

**ABBOTT, CATALYS PRECISIONE LASER SYSTEM**.

The OPTIMEDICA Catalys Precision Laser System (**Figure 4**) is an integrated scanning laser system that is used by cataract surgeons to create a precise anterior capsulotomy and/or subsequent fragmentation (phacofragmentation) of the crystalline lens, with or without single plane and multi-plane arc cuts/incisions in the cornea. Treatment is accomplished with ultrafast ($\tau$ ~10-13s, or hundreds of femtoseconds [FS]) infrared laser pulses.
The onboard Optical Coherence Tomography (OCT) subsystem provides a three-dimensional image of the anterior segment of the eye and guides laser treatment. A common optical scanning system is used for both the OCT

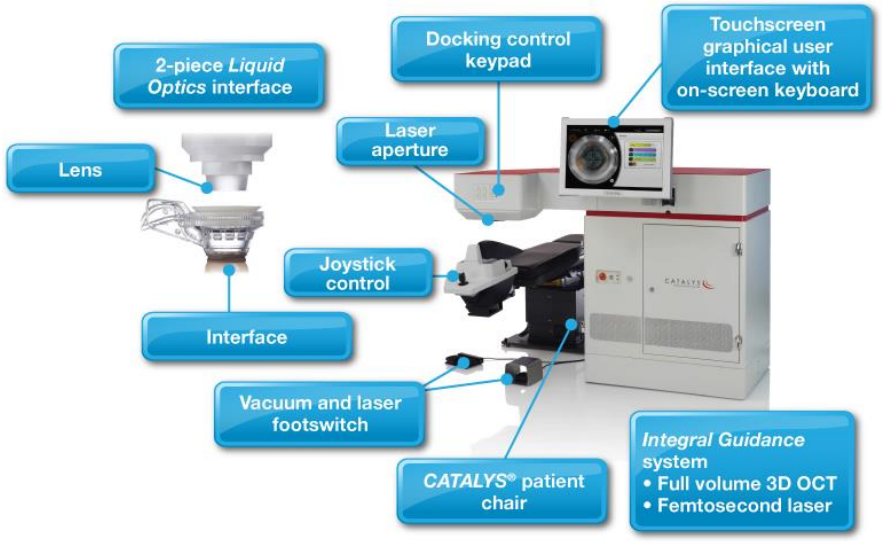
and the FS laser to provide inherent co-registration of the two optical subsystems.
The video imaging subsystem utilizes a monochrome megapixel video camera and collinear 735 nm light emitting diode (LED) illumination to provide constant live imaging of the patient's eye through the objective lens.

The Catalys System uses a laser beam, with pulse duration of 600 fs and energy of 1-10 $\mu$J, at a frequency of 120 kHz.

The Catalys System includes a custom patient chair that can be adjusted and orientated in three axes (x, y and z) by using a precision movement joystick control. The patient chair incorporates a headrest and restraint system that stabilizes the patient's head for the duration of the treatment.

After the laser treatment, the patient must be transferred to another bed for the phacoemulsification step.

**Figure 4 -** OPTIMEDICA Catalys Precision Laser System (adapted from **https://www.beye.com/category/femtosecond-lasers** )




The patient-contact component of the Catalys System, named the LIQUID OPTICS Interface, is a sterile, single patient use disposable element that functions to center and fixate the patient's eye relative to the system.

The LIQUID OPTICS Interface is an aqueous contact patient interface that applies suction via an annular ring affixed to the patient's sclera and a replaceable proximal lens that mounts to the system. The volume enclosed by the annular suction ring and its housing and the proximal lens is designed to be filled with an immersion fluid of sterile buffered saline solution. (53)

**ALCON, LENSX LASER SYSTEM**.
The LenSx® Laser (**Figure 5**) is a CDRH CFR 1040 class 4 laser system for ocular surgery consisting of the following components:

- a laser source to produce femtosecond laser pulses;
- an aiming device to localize specific targets in the eye;
- orientation of the selected surgical patterns;
- an optical delivery system to precisely deliver laser pulses to desired targets in the eye;
- computer controllers to perform clinical procedures;
- a disposable patient interface optically coupling the eye to the optical delivery system in order to prevent eye movement. (51)

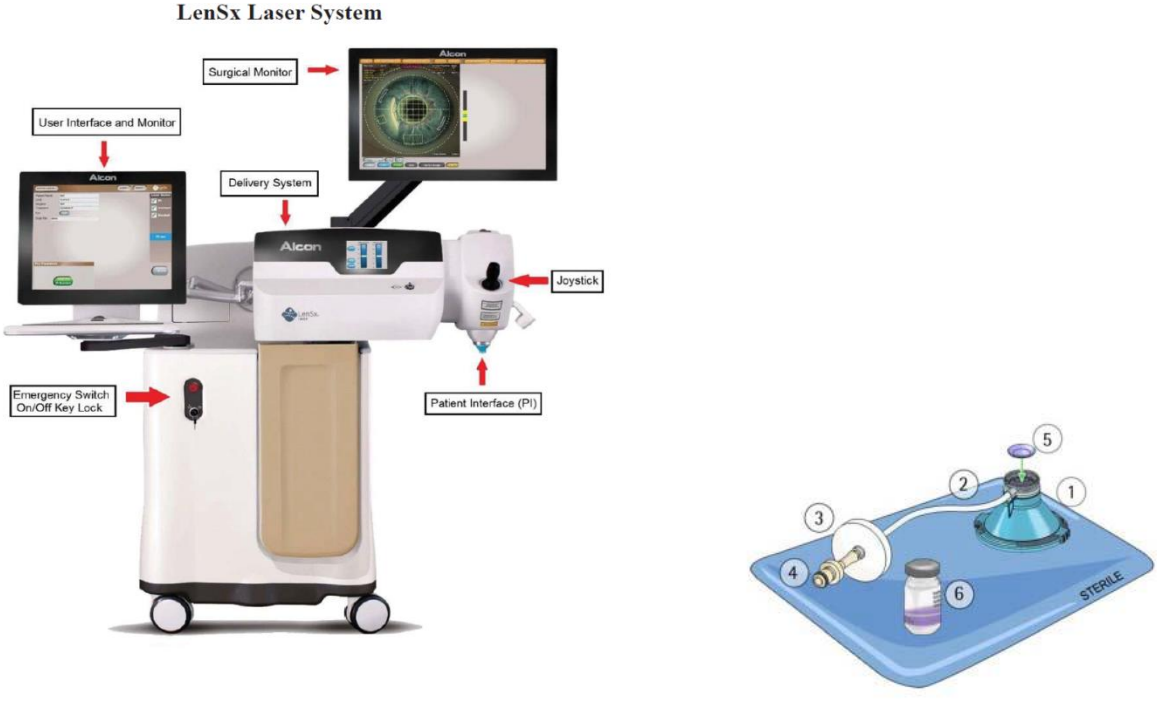
An all-solid-state laser source produces a kHz pulse train of femtosecond pulses. The amplified pulse train is routed through a beam monitoring assembly comprised of energy monitors, an energy attenuator and the primary safety shutter. An optical articulated arm directs laser light to the delivery system, where a second shutter controls the beam. Computer-controlled scanning mirrors direct the light through a beam expander and through a focusing objective onto a spot at pre-determined depth within the eye.

An optical coherence tomography (OCT) imaging device and a video camera microscope (VM) are used to localize specific targets and to view the patient's eye.

Each scanned position of the beam corresponds to an X, Y location in the focal plane of the focusing objective. The Z position of the focused laser spot is computer-controlled by optical zoom lenses located in the beam expander. The entire delivery system is mounted on a motorized gantry attached to the system console to allow the user to position the delivery system.

The LenSx System uses a laser beam, with pulses duration of 600-800 fs and energy up to 15 $\mu$J.

**Figure 5 - LenSx Laser System**




The LenSxR Laser uses a sterile, disposable Patient Interface. The Patient Interface is comprised of an applanation lens, suction ring and tubing. The suction ring and curved applanation lens are integrated into a single piece and mounted on the laser delivery system.

The disposable Patient Interface is mounted onto the distal end of the laser focusing objective and serves as a sterile barrier between the patient and the laser. Tubing is connected to a filter and to a vacuum port on the laser system. The Patient Interface also contains an integrated passive Radio Frequency Identification (RFID) device. The RFID is sensed by a reader located inside the LenSx® Laser System console. The lens is lowered onto the patient's eye until the cornea is applanated; suction is then activated. (54)

**BAUSH & LOMB, VICTUS**

The Victus system (**Figure 6**) features live-action, real-time Optical Coherence Tomography (OCT), for high quality visualization during image-guided pre-procedure planning and intraoperative monitoring. For a clear, detailed

view of the surgical field, *REALEYEZ* OCT Software delivers real-time imaging throughout the entire procedure. Live-action, high-contrast OCT facilitates planning and control of procedures.

The Victus uses a laser beam with wavelength of 1040 +/- 25 nm, pulses duration up to 550 fs and energy of 7 $\mu$J, at a frequency of 80 kHz for cataract treatment.

After the laser treatment, the patient must be transferred to another operating table for the phacoemulsification and IOL introducing steps.

**Figure 6 - Victus System**

The Victus VERAFIT Patient Interface provides a measured balance of both precision and ergonomics. And it's paired with advanced docking technology that lets you switch on the fly between cataract and corneal procedures, while maintaining the correct position of the eye. (55)

**ZIEMER, Z8**

The Ziemer Z8 (**Figure 7**) laser is a mobile system, with a small footprint and a particular arm, so that it can be used with the regular microscope and regular operating table without moving the patient.

The Femto LDV Z8 (Ziemer Ophthalmic Systems AG, Port, Switzerland) is a high-frequency femtosecond laser system for corneal surgery, corneal-refractive surgery and cataract surgery. The Z8 applies the concept of over-lapping low-energy near infrared (1030 nm) femtosecond laser pulses in the nano-Joule range (25 nJ to over 2.5 µJ), applied at high frequency, from 0.1 to 10 MHz.

The handpiece is the size of a compact camera and integrates all required electronics, optics and actuators to perform visualization and resection in the anterior chamber of the eye. The surgeon performs a manual docking of the laser handpiece through a sterile casing for handpiece.

Visual resolution is possible down to 5 microns and is performed with a combination of a colour camera and spec-tral-domain optical coherence tomography (OCT) operated at 840 nm.

The Femto LDV Z8 uses a high focusing power microscope lens integrated in the handpiece to achieve focusing on a small spot size, which enables cuts to be made with nJ pulse energy.

**Figure 7 - Ziemer Z8**


The suction ring of a disposable liquid–patient interface is applied to the eye with centration over the limbus. The system contains a liquid interface (no applanation), which prevents posterior corneal descemet folds, ensuring an unhindered laser beam transmission. (56)

**LENSAR, LENSAR LASER SYSTEM**

The Lensar system (**Figure 8**) has a small footprint and is fully mobile. The laser can be moved away from the patient's bed to allow for positioning of a surgical microscope and ultrasound phacoemulsification system, so the patient does not have to be transferred to another operating bed or moved to a separate room.

Software automatically selects a pre-programmed surgeon-customized fragmentation pattern and energy setting based upon results of automatic cataract density imaging (categories 1-5), which adds to procedural efficiency and saves time between imaging and treatment.

The LLS-fs 3D incorporates proprietary Augmented Reality imaging and anterior segment biometry built around the innovative technology of scanning structured illumination. Augmented Reality utilises super luminescent diode (SLD) technology, which scans at a variable rate depending on the target structure.

The rotating Augmented Reality camera scans and displays the structures of the anterior segment from up to five angles, unlike optical coherence tomography (OCT)-based systems, which display only two angles: one sagittal and one transverse. The Lensar system thus provides high definition imaging of the anterior chamber and lens during the treatment planning process.

Augmented Reality performs two scans from each of the five viewing angles to produce up to 10 images for 3D reconstruction. The 3D-Augmented Reality imaging software identifies major interfaces including anterior and posterior corneal surfaces and anterior and posterior lens capsules.

At the initiation of Augmented Reality imaging, the Lensar system measures and stores the pupil position. Then, prior to the initiation of laser firing, the pupil position is again measured. Any relative shift in eye position is instantaneously corrected.

The LLS-fs 3D Augmented Reality system's laser engine and delivery optics have been designed to fragment nuclei across a wide range of LOCS III grades, including deeply brunescent and white cataracts. Femtosecond cataract surgery utilises low levels of laser energy to fragment the lens nucleus.

In the most recent version, Lensar system allows data transfer from third party OCT systems: wireless transfer of pre-op diagnostic data from Pentacam® or the Cassini® Corneal Shape Analyzer and USB integration available with Nidek® OPD-Scan III and Topcon Aladdin.

This technology claims to be able to fragment even grade 4 and grade 5 cataracts, using the nuclear fragmentation in small cubes to facilitate the elimination of hard nuclei.

**Figure 8 - Lensar system**


The LLS-fs 3D patient interface incorporates a low-pressure suction ring that comfortably immobilises the eye. Once the suction ring is applied and filled with saline, the laser is docked to the interface using a servo controlled docking head and patient interface arm that limits the amount of pressure applied to the eye. (57)

**[A0020] – For which indications have different types of FLACS received marketing authorisation or CE marking?**

The femtosecond laser was initially introduced to create corneal flaps for laser *in situ* keratomileusis (LASIK). Since then, the use of femtosecond lasers has expanded to other corneal surgeries and, more recently, to cataract surgery. (5)

**Table 8** reports the intended use for the five systems designed specifically for cataract surgery.

**Table 8 Intended use for the five systems**

| | Technology | | |
|---|---|---|---|
| Model | LenSx® Laser System | Catalys® Precision Laser System | Ziemer Z8 |
| Manufacturer | Alcon | Abbott | Ziemer Group |
| CE mark | Yes | Yes | Yes |
| FDA approval | Yes | Yes | Yes |
| Indicated use | The LenSx® Laser is indicated for use in patients undergoing cataract surgery for removal of the crystalline lens. Intended uses in cataract surgery include anterior capsulotomy, phacofragmentation, and the creation of single plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure.<br>-The LenSx® Laser is indicated for use in the creation of a corneal flap in patients undergoing LASIK surgery or other treatment requiring initial lamellar resection of the cornea. | The OptiMedica Catalys Precision Laser System is indicated for use in patients undergoing cataract surgery for removal of the crystalline lens. Intended uses in cataract surgery include anterior capsulotomy, phacofragmentation and the creation of single plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure. | The FEMTO LDV™ Z8 Femtosecond Surgical Laser is an ophthalmic surgical laser intended for use in the creation of corneal incisions indicated for use in patients undergoing LASIK surgery, tunnel creation for implantation of rings, pocket creation for implantation of corneal implants, lamellar keratoplasty, penetrating keratoplasty or other treatment requiring lamellar resection of the cornea at a varying depth with respect to the corneal surface. In addition, the FEMTO LDV™ Z8 Surgical Laser is intended for use in the creation of capsulotomy, phacofragmentation and the creation of single plane, multi-plane, arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure indicated for use in patients undergoing cataract surgery for removal of the crystalline lens. |

| | Technology | |
|---|---|---|
| Model | Lensar Laser System | Victus |
| Manufacturer | Lensar | Bausch & Lomb |
| CE mark | Yes | Yes |
| FDA approval | Yes | Yes |
| Indicated use | The Lensar Laser System - fs 3D (LLS-fs 3D) is intended for use in patients undergoing cataract surgery for removal of the crystalline lens. Intended uses in cataract surgery include anterior capsulotomy, laser phacofragmentation and the creation of full and partial thickness single-plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure. | Creation of corneal flaps in patients undergoing LASIK surgery or other treatment requiring initial lamellar resection of cornea – for anterior capsulotomy during cataract surgery – creation of cuts/incisions in the cornea in patients undergoing cataract surgery or other ophthalmic treatment requiring cuts/incisions in the cornea – laser-assisted len fragmentation during cataract surgery for nuclear cataracts, not for fragmentation of posterior subcapsular (PSC) and cortical cataracts. |

Reported main contraindications include, as indicated in manual of the LenSx system (54):

- Corneal disease that precludes applanation of the cornea or transmission of laser light at 1030 nm wavelength
- Descemetocele with impending corneal rupture
- Corneal opacity that would interfere with the laser beam
- Presence of blood or other material in the anterior chamber
- Hypotony, glaucoma* or the presence of a corneal implant
- Poorly dilating pupil, such that the iris is not peripheral to the intended diameter for the capsulotomy
- Conditions which would cause inadequate clearance between the intended capsulotomy depth and the endothelium (applicable to capsulotomy only)
- Residual, recurrent, active ocular or eyelid disease, including any corneal abnormality (for example, recurrent corneal erosion, severe basement membrane disease)
- A history of lens or zonular instability
- Any contraindications to cataract or keratoplasty surgery

The technology is not intended for use in pediatric surgery. (54)

Some manufacturers (i.e., Bausch & Lomb for the Victus) warn against use in the following subjects. (55)

- Subjects with corneal disease or pathology that precludes applanation of the cornea or transmission of laser wavelength or distortion of laser light, such as:
    - subjects with residual, recurrent, active ocular or uncontrolled eyelid disease or any corneal abnormalities (including endothelial dystrophy, guttata, recurrent corneal erosion, etc.) in the eye to be treated
    - subjects with ophthalmoloscopic signs of keratoconus (or keratoconus suspect) in the eye to be treated
    - Subjects with a history of herpes zoster or herpes simplex keratitis
    - Subjects who are using ophthalmic medication(s) other than artificial tears for treatment of ocular pathology including ocular allergy
- Difference of more than 5 D between minimum and maximum K-values of the central 3 mm zone on a keratometric map of the cornea
- Maximum K-value of more than 60 D, or minimum K-value of less than 37 D.

**[B0002] – What is the claimed benefit of FLACS over standard cataract surgery?**

Compared to standard cataract surgery, where incisions, capsulorhexis and lens fragmentation are performed by freehand action of the surgeon, FLACS systems claim to provide several advantages to the surgeon, such as the performance of very precise circular and adjustable diameter capsulotomies, precise lens nucleus fragmentation, the creation of multi-planar self-sealing incisions with better wound architecture, exact placement of limbal relaxing incisions and the reduction of phacoemulsification time. (6)

Given that for toric and multifocal intraocular lenses, centration of the capsulorhexis is especially important, the precision of FLACS could have relevant impact in case of implantation of intraocular lens premium.

Moreover, femtosecond laser pretreatment is expected to reduce phaco energy, which may in turn reduce the heat damage to ocular tissues by ultrasound. (7) This may translate into reducing endothelial cell loss, and consequently, better outcomes in terms of visual acuity and safety.

**[B0003] – What is the phase of development and implementation of FLACS and standard cataract surgery?**

Standard cataract surgery is one of the most performed surgical procedures in the world, and its technique has virtually remained the same since the introduction of phacoemulsification towards the end of the 1960s.

FLACS systems for cataract surgery were developed over the last decade, with development usually oriented toward improving surgical planning (i.e., new Streamline application upgrades) and the quality of the patient interface, with new designs in the pipeline to provide better, safer and more reproducible results. (4) More details on level of diffusion and implementation of FLACS systems are provided in **Appendix 2**.

**[B0004] – Who performs FLACS and standard cataract surgery and in what context and level of care are they performed?**

A trained ophthalmologist always performs FLACS and standard cataract surgery and the outcomes of surgery are operator dependent.

The surgical intervention is performed in community hospitals as well as in teaching hospitals and is usually offered in a day-hospital regime, with patients discharged on same day. (4,36)

**[B0008] – What kind of special premises are needed to perform FLACS and standard cataract surgery?**

Cataract surgery is always performed in an operating room.

Depending on the type of FLACS system, the procedure could be performed in the same operating room where the second phase (phacoemulsification and lens implantation) is performed. Otherwise, as in case of systems with integrated bed, the use of FLACS should/could be performed in a separate clean but not necessarily sterile room. In this case, patients need to be transferred to the operating room for subsequent steps of the intervention.
The location of the femtosecond laser for cataract surgery directly affects patient flow and volumes, which have to be considered when choosing the right solution.

**[B0009] – What equipment and supplies are needed to perform FLACS and standard cataract surgery?**

**[E0001] – What types of resources are used when performing the different types of FLACS and standard cataract surgery?**

Both questions are answered in this section.

In this assessment, we consider what is necessary for the first phase of the cataract surgery procedure: the equipment and supplies for the phacoemulsification and lens insertion steps are the same for FLACS and standard surgery.

For the procedure performed with FLACS, the main supply is the patient interface.
Technologies and procedures associated with cataract surgery are reported in **Table 9**. (51)

**Table 9 Technologies and procedures associated with cataract surgery (ref Alcon)**

| **Technology is associated with:** | **Yes/No** |
|---|---|
| **Pharmaceutical** | Both FLACS and standard cataract<br>Anaesthetic drops, midriatic drops, intracameral infusions, antibiotic |
| **Medical device** | Both FLACS and standard cataract<br>Phacoemulsification pack<br>Custom pack<br>Intraocular lens<br>Associated only with FLACS: Patient Interface |
| **Procedure** | Preoperative assessment (both FLACS and standard cataract)<br>Refraction, visual acuity, keratometryendothelial cell counts, intraocular pressure and type of implanted.<br>Associated only with FLACS: tomography, pachymetry.<br><br>Perioperative assessment (both FLACS and standard cataract)<br>Perioperative acuity, refraction, keratometry, intraocular pressure, endothelial cell counts<br>Preoperative biometry<br>Preparation of patient<br>Put patient on bed, give drops (the use of sedation + peribulbar-anesthesia is sometimes necessary). Apply monitoring, checks by anesthesiologist.<br>Anesthesia steps (especially peribulbaranesthesia) and sedation may increase effort (+ need for post-op care).<br><br>Pre-op area (both FLACS and standard cataract):<br>Preparation time: Sum of all prep steps (measure, prep patient on bed, anes-thesia)<br>Surgery<br>Surgery time: highly depends on the surgeon's experience.<br><br>Associated only with FLACS:<br>Laser preparation: steps until docking is started<br>Laser core time: from docking start to removing speculum<br>Associated with both FLACS and standard cataract<br>Surgery Room:<br>Surgery preparation steps until first cut is done<br>Phacoemulsification<br>Remove lens first cut until new lens is moved towards the eye<br>Insert new lens steps until speculum is removed<br>Operating Room Cleanup.<br>Remove speculum until patient ready to leave operating room<br>Post-op-area (both FLACS and standard cataract<br>Discharge Check recovery and help patient to leave the area |

Any changes to current services that are needed to introduce FLACS include:

- any tests or investigations needed for selecting or monitoring patients above and beyond usual clinical practice
  - tests identifying presence of contraindications (see contraindications list).
- any equipment or organisational and technical conditions that will require investment before the technology can be introduced
  - extra speculum, corneal spatula for incision opening and specific dilation drops might be required; Patient Interface (PI).
- any additional human resources required to implement the technology (for example, new employees).
  - Depending on the workflow and intended use of the device, an extra operator might need to be involved. This would be required if the device is used in high volumes in most patients, for instance, preparing the patients and feeding multiple ORs. It is recommended to have a staff member trained and specialized on the device for such a scenario.
  - Surgical staff training in the use of the technology.
- any investment in infrastructure
  - Air conditioning, humidity control and/ or floor vibration insulation might be necessary, if not present.

**[A0021] – What is the reimbursement status of FLACS in the different EU countries?**

From a short survey carried out among EUnetHTA partners it appears that for most of those who replied, the additional costs incurred with femtosecond laser-assisted cataract surgery are not covered by public resources and the procedure is not reimbursed by the national health system.

Detailed information on the reimbursement status/recommendations is reported in **TableA30** in **Appendix 2.**

1

# HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

## *Research questions*

| Element ID | Research question |
|---|---|
| A0002 | What is the type of cataract in the scope of this assessment? |
| A0003 | What are the known risk factors for cataract? |
| A0004 | What is the natural course of cataract? |
| A0005 | What are the symptoms and the burden of cataract for the patient? |
| A0006 | What are the consequences of cataract for society? |
| A0024 | How is cataract currently diagnosed according to published guidelines and in practice? |
| A0025 | How is cataract currently managed according to published guidelines and in practice? |
| A0007 | What is the target population of this assessment? |
| A0023 | How many people belong to the target population? |
| A0011 | How much are standard surgery and femtosecond lasers (FLACS) utilised? |

## *Results*

### Overview of the disease or health condition

#### [A0002] – What is the type of cataract in the scope of this assessment?

The disease in the scope of the present assessment is acquired and age-related cataract (ICD-9 code: 366.x, ICD-10 H25). A cataract is an opacity of the lens, one of the eye structures involved in the “accommodation” function that focuses the light on the retina and allows normal vision. It can affect one or both eyes and changes to the transparency and refractive index of the lens result in various levels of visual impairment, associated with a decrease in quality of life. (4) The lens is located in the posterior chamber of the eye and is normally transparent. The lifelong development of the lens produces a highly ordered structure composed of stratified epithelia of specialized cells with a very high content of cytoplasmic protein. These proteins called crystalline, along with the complex structure, impart transparency to the lens. A capsule, an epithelium and a nucleus compose the lens structure. The lens capsule is a transparent elastic membrane that surrounds the lens and is composed of collagen, synthesized by the lens epithelium. The lens epithelium is located in the anterior portion of the lens between the lens capsule and the nucleus. It is a simple cuboidal epithelium and has homeostatic functions both for the capsule and for the lens fibres that form the nucleus. Unlike other epithelia, the lens epithelium does not shed its nonviable cells and is therefore particularly susceptible to the degenerative effects of aging on the cell structure. The degenerative process causes anatomic and ultrastructural correlates leading to lens opacity, although the exact pathogenetic mechanisms are not known. Epidemiologic and experimental evidence suggest a role of photo-oxidative insult, perhaps potentiated by toxic or sensitizing substances. Causing lens opacity, cataract can lead to a progressive, painless loss of vision up to partial or total blindness in one or both eyes.

The ICD-9 classifies acquired cataract by aetiology in:

- 366.0 Infantile, juvenile and pre-senile cataract
- 366.1 Senile cataract
- 366.2 Traumatic cataract
- 366.3 Cataract secondary to ocular disorders
- 366.4 Cataract associated with other disorders
- 366.8 Other cataract (Calcification of lens)

The ICD-10 classifies acquired cataract as follows:

- H25 Age-related cataract
- H25.0 Age-related incipient cataract
- H25.01 Cortical age-related cataract
- H25.03 Anterior subcapsular polar age-related cataract
- H25.04 Posterior subcapsular polar age-related cataract
- H25.09 Other age-related incipient cataract
- H25.1 Age-related nuclear cataract
- H25.2 Age-related cataract, morgagnian type
- H25.8 Other age-related cataract
- H25.81 Combined forms of age-related cataract
- H25.9 Unspecified age-related cataract

The vast majority of cataract extractions are for acquired cataract, with senile or age-related cataract predominating.

Cataract is also classified by the affected anatomical part of the lens in:

- Nuclear cataract: yellowing and hardening of the central portion of the crystalline lens which occurs slowly over years. As the core of the lens hardens, it often causes the lens to increase the refractive power and causes nearsightedness.
- Cortical cataract: opacification of lens fibers surrounding the nucleus, which impact on vision depending on how close these opacities are to the center of visual axis. Progression also varies from months to years, and patients are commonly affected by glare, which can interfere with night driving.
- Posterior subcapsular cataract: opacities located in the posterior cortical layer under the lens capsule. Progression varies, and symptoms include glare and reduction in near vision. (58)

Although these kinds of cataract have different symptoms and progression, the indication for surgery is the same. (20)

**[A0003] – What are the known risk factors for cataract?**

Many risk factors have been associated with acquired cataract in developed nations, (59,60) most of which are environmental stressors that lead to the formation of toxins or the impairment of antioxidants. These risk factors include sociodemographic characteristics (i.e., age >65 years, low education), unhealthy behaviours (i.e., alcohol consumption, malnutrition and physical inactivity), (61) and a dose-response relationship with smoking habit (62); chronic conditions (i.e., metabolic syndrome, diabetes mellitus, (59) myotonic dystrophy) and drug treatments (i.e., systemic corticosteroid, prolonged administration of high doses of inhaled corticosteroids, topical corticosteroids, certain phenothiazines, topical anticholinesterases).

Moreover, a dose-response relationship has been demonstrated with ultraviolet-B exposure in sunlight, (63) and low-level accumulated lead exposure appears to be associated with an increased risk of cataract. (64) Other generally accepted causes of acquired cataract include ocular trauma, uveitis, necrotizing scleritis and radiation of an intraocular tumour. In addition, patients with HIV/AIDS may develop cataracts at an earlier age compared with the general population. (65,66)

**Table 10** shows the risk factors for cataract reported by the American guidelines. (13)

The same guidelines state that preventive intervention should include smoking cessation (Grade II+, good quality, strong recommendation), sunglass wearing and healthy lifestyle promotion. Moreover, it is important to prevent blunt and eye trauma by wearing safety eyeglasses when recommended. The prevention and treatment of diabetes mellitus, obesity, hypertension and metabolic syndrome could also reduce the risk of cataract. Finally, patients who are treated with long-term therapy with oral or inhaled corticosteroids should be informed of the higher risk for cataract formation.

**[A0004] – What is the natural course of cataract?**

Because all light entering the eye passes through the lens, the cataract can block and scatter light and cause a progressive loss of vision in one or both eyes, leading to partial or total blindness. The development of age-related cataract is a painless, progressive process that is highly variable among individuals. Cataract formation is typically bilateral, although it is often asymmetrical. The secondary cataract could also be unilateral.

Usually, treatment delay does not result in an adverse outcome, except for cases in which an advanced cataract interferes with the diagnosis and therapy of diseases involving the retina and optic nerve.

Once visual acuity and function decline, the natural history progresses with no chance of recovery. In three studies, each using different scales for progression of cataracts, there is convincing evidence that cataracts progress over time. In the Barbados Eye Studies, investigating the prevalence, incidence, progression and risk factors for major eye diseases in the population of Barbados, individuals with pre-existing lens opacities had cumulative 9-year progression rates of 22% for cortical, 18% for nuclear and 26% for posterior subcapsular cataract (PSC) opacities. (67) The Melbourne Visual Impairment Project reported cumulative 5-year progression rates of 14% for cortical, 19% for nuclear and 20% for PSC opacities. (68) In the Longitudinal Study of Cataract, individuals with pre-existing lens opacities had cumulative 5-year progression rates of 16% for cortical, 46% for nuclear and 55% for PSC opacities. (69,70)

A small fraction of advanced cataracts can give rise to secondary intractable glaucoma, which causes a red, painful eye (71).

**Table 10 Risk factors for age-related cataract (13)**

| Cataract type | Associated Risk Factor | Type of Study | Risk |
|---|---|---|---|
| Cortical | Diabetes | Observational | Increased risk |
| | Family history | Observational | Increased risk |
| | Hypertension | Observational | Increased risk |
| | Ionizing radiation (low and high dose) | Observational | Increased risk |
| | Myopia (>1 D) | Observational | Increased risk |
| | Obesity | Observational | Increased risk |
| | Systemic corticosteroid use | Observational | Increased risk |
| | Ultraviolet-B light exposure | Observational | Increased risk |
| Nuclear | Diabetes | Observational | Increased risk |
| | Obesity | Observational | Increased risk |
| | Myopia | Observational | Increased risk |
| | Family history | Observational | Increased risk |
| | Hypertension | Observational | Increased risk if taking topical or systemic beta blockers |
| | Prior Pars Plana Vitrectomy | Observational | Increased risk |
| | Smoking | Observational | Increased risk |
| | Tobacco (smokeless) | Observational | Increased risk |
| | Ultraviolet-B light exposure | Case-control | Increased risk |
| Posterior subcapsular | Inhaled corticosteroid use | Population-based cross-sectional | Increased risk in patients aged >49 |
| | Ionizing radiation (low and high dose) | Observational | Increased risk |
| | Obesity | Observational | Increased risk |
| | Ocular trauma | Corss-sectional | Increased risk |
| | Prior Pars Plana Vitrectomy | Observational | Increased risk |
| | Retinitis pigmentosa | Case series | Increased risk |
| | Topical corticosteroid use | Case series | Increased risk |
| | Systemic corticosteroid use | Observational | Increased risk |
| | Myopia | Observational | Increased risk |
| | Hypertension | Observational | Increased risk |
| | Diabetes | Observational | Increased risk |
| | Smoking | Observational | Increased risk |
| | Trauma | Observational | Increased risk |
| Mixed | Prior Pars Plana Vitrectomy | Observational | Increased risk |
| | Tobacco use (smoking and smokel-ess) | Observational | Increased risk |
| | Ultraviolet-B light exposure | Observational | Increased risk |
| | Hypertension | Observational | Increased risk |
| | Diabetes | Observational | Increased risk |

| Cataract type | Associated Risk Factor | Type of Study | Risk |
|---|---|---|---|
| Subtypes not identified in study | Aspirin use | Randomised trials | No evidence of benefit |
| | | Observational | Increased risk |
| | | Observational | Decreased risk |
| | Diabetes | Observational | Increased risk |
| | Inhaled corticosteroid use | Case-control | Increased risk in patients aged ≥40 |
| | | Case-control | Increased risk in patients aged ≥65 |
| | | Case-control | Increased risk in patients aged ≥70 |
| | Nasal corticosteroid use | Case-control | No increased risk |
| | Intravitreal corticosteroid | Case-control | Increased risk |
| | Ionizing radiation (low and high dose) | Observational | Increased risk |
| | Smoking | Observational | Increased risk |
| | Inactivity | Observational | Increased risk |
| | Lower education | Observational | Increased risk |
| | Ocular inflammatory disease | Observational | Increased risk |

*Adapted from American Academy of Ophthalmology (AAO) Preferred Practice Pattern (PPP) Cataract/Anterior Segment Panel HC for QEC. Cataract in the Adult Eye PPP - 2016 - American Academy of Ophthalmology. 2016 PPP USA 2016*.
Note: PPV: pars plana vitrectomy (13)

## Effects of the disease or health condition

**[A0005] – What are the symptoms and the burden of cataract for the patient?**

The classic presentation of a cataract is a gradual decrease in vision over many years, typically bilateral and asymmetrical, but for some secondary cataracts (i.e., related to diabetes mellitus), a relatively sudden reduction in vision may be reported. Patients usually complain of a problem with night driving, reading road signs, difficulty with fine print or decreased richness in colours. In many cases, there is an increase in nearsightedness before the opacity of the lens, called a "myopic shift". This is caused by an increase in the refractive power of a lens that is gradually becoming cataractous and may be correctable with a change in spectacle correction.

Patients with a significant cataract exhibit a reduced best-corrected visual acuity and may also complain of inadequate corrective lenses prescription. Surgery should be deferred as long as diminished acuity can be corrected with spectacles to meet a patient's needs for activities of daily living, such as reading, driving or walking safely.

The different kind of age-related cataract have different symptoms and progression, although the indication for intervention with all types is the same:

- **Nuclear cataract** progresses very slowly. It typically affects distance vision more than near vision. Nuclear cataract also significantly dulls colours and white, but this is a patient complaint arising only after the first cataract is removed, at which time the effect on colour is noted by comparison with the brightness of colours in the operated eye.

- **Cortical cataract** tends not to degrade vision very much.

• **Posterior subcapsular cataract** tends to cause disabling glare in bright sunlight and from headlights, even if visual acuity is degraded only slightly. It tends to progress more quickly than nuclear cataract, over a period of months rather than years.

A small fraction of cataracts could also be diagnosed in patients with intractable secondary glaucoma, which causes redness of eye and pain. (11)

Therefore, the burden for patients is mainly due to the impact of visual impairment on activity of daily living. (20)

Numerous studies show that physical function, mental health, emotional well-being, safety and overall quality of life can be enhanced when visual function is restored by cataract extraction. (72,73)

**[A0006] – What are the consequences of cataract for society?**

The WHO estimates that 51% of reversible blindness worldwide was due to cataract (8), affecting more than 52 million people in 2015. (9) The pattern and rate of blinding disorders is different in developed and developing nations, depending on different causes. While cataracts can be congenital or due to trauma or metabolic conditions, age-related cataracts are the most common, and therefore have the greatest impact. (10)

*Socioeconomic impact of cataract and cataract surgery*

The Global Burden of Disease (GBD) study quantified the health loss due to cataracts using disability-adjusted life years (DALYs) at 2.9 million DALYs in 2013 among the 188 countries included. (11) Among eye diseases, cataracts caused the second largest burden, after uncorrected refractive error. In Europe in 2010, cataracts affected more than 2,700,000 people, causing more than 15% of cases of blindness and moderate-to-severe vision impairment. (11)

If left untreated, it can result in an individual leaving his/her job. (74,75) By 2020, the WHO target is to offer cataract surgery to more than 30 million people annually worldwide. (76)

## Current clinical management of the disease or health condition

**[A0024] – How is cataract currently diagnosed, according to published guidelines and in practice?**

Cataracts should be investigated in any patient who complains of a painless and progressive decline in vision. The purpose of the comprehensive evaluation of the patient is to determine the presence of a cataract, to confirm that a cataract is a significant factor contributing to visual impairment and symptoms described by the patient and to identify other ocular or systemic conditions that might contribute to visual impairment.

The current American guidelines, (13) published in 2016, and the European Guidelines, (2) published in 2012, recommend three main steps to conducting a comprehensive evaluation of a patient suspected of having a cataract:

1. Evaluation of visual impairment (subjectively and objectively);
2. Ophthalmic evaluation;
3. Supplemental ophthalmic testing (not specific for cataract).

*Evaluation of Visual Impairment*

Visual function may be assessed using tests that measure contrast sensitivity, glare disability or visual acuity, near and distance. There is no single test or measure that adequately describes the effect of a cataract on a patient's visual status or functional ability. Similarly, no single test can properly define the threshold for performing cataract surgery. **Table 11** reports the diagnostic tests recommended in Europe and the US. (13,77)

Visual acuity is measured in decimal, fraction and log MAR. Visual acuity can be assessed with or without corrective lenses (corrected or uncorrected visual acuity). The log MAR scale ranges from -0.3 (best vision) to +1.3 (worst vision) and 0.0 log MAR corresponds to 1.0 decimal (10/10). One line in the Snellen chart corresponds to a 0.1 log MAR and variation of one line or 0.1 log MAR is considered clinically relevant.

Refraction, i.e., the way light converges on the retina, influences visual acuity. Refraction error, i.e., myopia, astigmatism hypermetropia, etc., is measured in spherical equivalent (dioptres) and a 0.0 diopter indicates best refraction. A diopter can be a negative number (which indicates myopia) or a positive number (which indicates hypermetropia).

In cataract surgery refractive outcomes are assessed by measuring the mean absolute error (MAE), which represents the absolute difference between the postoperative predicted (target) refraction and the postoperative actual refraction at follow up. A variation of +/- 0.25 D is considered clinically relevant, as it represents the threshold for correction with lens.

*Ophthalmic evaluation*

The comprehensive evaluation (history and physical examination) includes components of the comprehensive adult medical eye evaluation: (78)

- Patient history, including an assessment of functional status, pertinent medical conditions, medications currently used and other risk factors that can affect the surgical plan or outcome of surgery.
- Visual acuity with current correction (the power of the present correction recorded) at distance and, when appropriate, near.
- Measurement of best-corrected distance visual acuity.
- Assessment of the degree of anisometropia after refraction.
- Glare testing when indicated.
- Assessment of pupillary function.
- Examination of ocular alignment and motility.
- External examination (eyelids, lashes, lacrimal apparatus, orbit).
- Measurement of intraocular pressure (IOP).
- Slit-lamp biomicroscopy of the anterior segment, examination of the lens, vitreous, macula, peripheral retina and optic nerve through a dilated pupil.
- Assessment of relevant aspects of the patient's mental and physical status (i.e., cooperation and ability to lie flat).
- Assessment of any barriers to communication (language or hearing impairment).

**Table 11 Diagnostic tests recommended in Europe and the US (13,77)**

| Test | Outcome | Notes: |
|---|---|---|
| Snellen visual acuity chart | Distance refractive error | Poor preoperative visual acuity correlates with significant postoperative functional improvement in many patients with cataract.<br>Underestimates the functional problems in common real-life situations.<br>The decision to recommend cataract surgery should not be made solely on the basis of Snellen visual acuity. |
| Short Form-36, Quality of Well-Being Scale, EuROQOL Q-5D | General health status | Validated questionnaires for measuring function that measure general health status.<br><br>Questionnaires that measure general health status are less strongly correlated with improvement following cataract surgery than are vision-specific measures.<br><br>EuROQOL Q-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. |
| Activities of Daily Vision Scale (ADVS), the VF-14 VF-8R,<br><br>National Eye Institute Visual Function Questionnaire (NEI-VFQ), and the Catquest-9SF. | Vision-specific instruments | Validated questionnaires, vision-specific instruments developed or used for cataract evaluation.<br><br>Responses to these questionnaires are not intended to be the sole basis for determining the need for surgery.<br>At this time, there is no single universally accepted questionnaire in clinical use for assessing functional-vision impairment. |

*Supplementary ophthalmic tests*

Supplementary preoperative ophthalmic tess (i.e., glare testing, tear function evaluation, tomography, etc.) are not specific for cataract but may help to identify both the cause and level of severity of an individual's visual symptoms as well as the extent to which comorbidities may be contributing to these symptoms. They are useful especially when patient reports visual symptoms disproportionate to the degree of cataract formation. (13)

**[A0025]– How is cataract currently managed according to published guidelines and in practice?**

Summary of the available guidelines is provided in **Table A1** of **Appendix 1.**

Cataract surgery remains one of the most cost-effective treatments and the most commonly used procedure in many countries, (12) and management of a visually significant cataract is primarily surgical. (13)

*Indications for surgery (13)*

The primary indication for surgery is visual function that no longer meets the patient's needs and for which cataract surgery provides a reasonable likelihood of improved vision.

Other indications for cataract removal include the following:

- there is clinically significant anisometropia in the presence of a cataract;

- the lens opacity interferes with optimal diagnosis or management of posterior segment conditions;
- the lens causes inflammation or secondary glaucoma (phacolytic, lens particle, phacoanaphylactic);
- the lens induces or risks angle closure.

*Contraindications to surgery (13)*

Surgery for a visually impairing cataract should not be performed under the following circumstances:

- tolerable refractive correction provides vision that meets the patient's needs and desires;
- surgery is not expected to improve visual function, and no other indication for lens removal exists;
- the patient cannot safely undergo surgery because of coexisting medical or ocular conditions;
- appropriate postoperative care cannot be arranged;
- the patient or patient's surrogate decision maker is unable to give informed consent for elective surgery.

*Nonsurgical management (13)*

Nonsurgical management includes counselling patients about cataract-related visual symptoms, providing reassurance about the cause of the visual disability and prescribing new eyeglasses to correct a lens-induced change in refractive error. Surgery can be deferred in some cases by prescribing mydriatic agents to reduce symptoms associated with small centrally located cataracts or by prescribing contact lenses when uniocular cataract development causes symptomatic anisometropia but before there is a significant degradation in visual acuity.

Currently, there are no pharmacological treatments known to eliminate existing cataracts or retard their progression in humans.

*Cataract surgical rate*

The cataract surgical rate is the most reliable and useful indicator for the assessment of the impact of cataract either on population health or organizational/costs issues. (79)
This indicator is routinely collected in most developed countries, usually in administrative databases; thus, it is more comparable and permits creating time trends. In **Table 12** are reported cataract surgery incidence rates of many European and non-European studies. Indeed, this type of surgery has shown an increasing trend over the last decade. (80) Moreover, data from the European Registry of Quality Outcomes for Cataract and Refractive Surgery database (EUREQUO) suggest that between 2009 and 2011, 40.6% of operated patients also underwent second-eye surgery. (36)

**Table 12 Annual cataract surgical rates (per 1,000,000 people) in different years and countries.**

| Cataract surgical rate (per 1,000,000 people) | Country | Study period | References |
|---|---|---|---|
| 9000 | Sweden | 2009 | (81) |
| 6170 | United King-dom | 2010 | (82) |
| 10010 | Austria | 2011 | (83) |
| 11080 | France | 2012 | (84) |

A publication with detailed data on cataract surgeries in public health hospitals in Austria shows that 61.4% of surgeries were performed on patients ages 60-79 years. Considering the data for the 40-59 years category (7.5%) and the current age of retirement in Europe, the disease also affects people in working age (83) (**Table 13**).

**Table 13 Age distribution of cataract surgeries in public hospitals in Austria, 2001, 2007, 2011 (81)**

| % of total cataract surgeries | | | |
|---|---|---|---|
| **Age groups** | **2001** | **2007** | **2011** |
| 0 - 19 years | 0.2 % | 0.2 % | 0.1 % |
| 20 - 39 years | 0.9 % | 0.6 % | 0.5 % |
| 40 - 59 years | 7.9 % | 7.8 % | 7.5 % |
| 60 - 79 years | 61.1 % | 58.6 % | 61.4 % |
| 80 + | 29.8 % | 32.8 % | 30.5 % |
| **Total** | **100.0 %** | **100.0 %** | **100.0 %** |

*Complications of cataract surgery*

Although numerous complications can occur intraoperatively or postoperatively with cataract surgery, those resulting in permanent loss of vision are rare. Major complications are potentially sight-threatening and include infectious endophthalmitis, cystoid macular oedema (CME), retinal detachment, persistent corneal edema, corneal decompensation and post operative blindness. **Table 14** describes main complications of cataract surgery.

### Table 14 Complications of cataract surgery (13)

| Safety outcomes | Description | Severity* (85) | Rates |
|---|---|---|---|
| **Intraoperative complications** | | | |
| Anterior Capsular Tear | It is the consequence of a compromised anterior capsulorrhexis which could impact on the optical result of surgery and could lead to a subsequent posterior capsular tear and nuclear drop, requiring a secondary repair procedure at a later date. The patient may not have any symptoms when it occurs. (86) | Grade I-IIIa | - |
| Posterior Capsular Tear | This is a complication of cataract surgery preserving posterior capsular to provide support for intraocular lens. When the capsule is intact at the end of cataract removal, the possibility of a stable lens support is much higher, and a barrier is maintained between the anterior segment and the vitreous cavity. In case of tear, the surgeon needs to stabilize the chamber and should carefully examine it for vitreous, as PCT could lead to vitreous loss. This complication might require conversion to an Intracapsular Cataract Extraction. The patient may not experience any symptoms. (87) | Grade IIIa | PCT rate from literature ranging from 1.5% to 3.5% (13) |
| Vitreous loss | Vitreous loss can occur when the posterior capsule is ruptured and vitreous comes forward into the anterior chamber. The surgeon will remove every trace of vitreous from the wound and anterior chamber. Failure to achieve this increases the risks of leakage, of infection due to a vitreous wick or of vitreous traction that may lead to cystoid macular oedema or retinal detachment. (88) | Grade IIIa | Vitreous loss rate from literature ranging from 0.8% to 1.1% (13) |
| **Postoperative complications** | | | |
| Retinal detachment | Retinal detachment occurs when the multilayer neurosensory retina separates from the underlying retinal pigment epithelium and choroid. This separation can occur passively due to accumulation of fluid between these two layers or it may occur actively due to vitreous traction on the retina. Retinal detachment is a sight-threatening condition which typically requires intervention in the form of laser, cryotherapy or surgery. It can result in marked loss of vision and moderate impairment although sometimes can be treated with no loss of vision. (20) | Grade IIIa | Retinal detachmnet rate from literature 0.14% – 0.9% (13) |
| Iridocyclitis | Iridocyclitis are an inflammation of both iris and ciliary body. The clinical picture of Iridocyclitis is practically the same as that of iritis, a sub-type of uveitis. Intraocular lens (IOL)-associated uveitis may range from mild inflammation to the uveitis-glaucoma-hyphema (UGH) syndrome. Surgical manipulation could result in breakdown of the blood–aqueous barrier, leading to vulnerability in the early postoperative period. Retained lens material from extracapsular cataract | Grade II-IIIa | Iridocyclitis rate from literature 1.54% (4) |

| Safety out-comes | Description | Severity* (85) | Rates |
|---|---|---|---|
| | extraction may exacerbate the usual transient postoperative inflammation. Iridocyclitis requires medical control of the intraocular inflammation in both the preoperative and post-operative periods. In many cases lenses should be removed and exchanged. (89) | | |
| Endothelial cells loss | The endothelial cell loss is calculated by the difference of endothelial cell count or density (cell/mm2) postoperatively and at baseline.<br><br>For a clear vision in a healthy cornea, the number of endo-thelial cells covering the back surface of the cornea should be sufficient.<br><br>The mean number of endothelial cells in a young adult is approximately 3000 cells/mm2, which decreases by 0.3% to 0.6% annually to approximately 2000 cells/mm2 in the age group 80-90 years. (90,91)<br><br>Cataract surgery diminishes the number of cells (92), but there is no a consensus on an acceptable threshold for en-dothelial cell loss.<br><br>The risk of corneal decompensation and corneal oedema increases when the ECD level drops below 600 to 800 cells/mm2 (93) . | Grade I | . |
| Elevated Intraoc-ular Pressure (1 day - 1 week) | The intraocular pressure of the eye is determined by the balance between the amount of aqueous humor that the eye makes and the ease with which it leaves the eye.<br><br>Normal eye pressure is usually considered to be between 10 and 20 millimeters of mercury (mmHg). Having eye pressure that is too low or too high can damage vision. Higher-than-normal eye pressure can cause glaucoma. Prolonged ele-vated intraocular pression can lead to endothelial decom-pensation and corneal oedema.<br><br>It is important to lower high eye pressure before it causes vision loss or damage to the optic nerve. Depending on eye pressure, ophthalmologist may decide for active follow up or to start medical treatment. (94,95) | Grade I-II | The rate of elevated intraocular pressure available from litera-ture only for persist-ing for 1 year post cataract surgery was 0.01% (4) |
| Corneal endothe-lial decompensa-tion (within 90 days) | The corneal endothelium governs fluid and solute transport across the posterior surface of the cornea and maintains the cornea in the slightly dehydrated state that is required for optical transparency.<br><br>Endothelial decompensation and corneal oedema resulting from failure of the corneal endothelium to maintain detu-mescence are manifested by opacity of the cornea.<br><br>The condition often occurs as a nonspecific response to | Grade I - IIIa | Corneal endothelial decompensation rate from literature ranging from 0.03% to 5.18% (13) |

| Safety outcomes | Description | Severity* (85) | Rates |
|---|---|---|---|
| | mechanical injury from incidental corneal contact by intraocular instruments during surgery as well as chronic postoperative trauma, such as from a malpositioned intraocular lens or retained nuclear fragment in the anterior chamber.<br><br>It can be mild and self-limited, but when persistent and severe, corneal endothelial decompensation requires corneal transplantation. (96,97) | | |
| Cystoid macular oedema (within 90 days) | Retinal thickening of the macula due to a disruption of the normal blood-retinal barrier. Eye surgery can induce inflammation and alter the retinal blood flow and in clinically apparent cystoid macular oedema, retinal thickening and fluid collection can distort the architecture of the photoreceptors and cause visual loss. Most cases resolve but if persistent, may require medical or surgical treatment. (98) | Grade I - IIIa | Cystoid macular oedema rate from literature ranging from 0.03% to 1.17% (4) |
| Infections (within 90 days) | Endophthalmitis is a purulent inflammation of the intraocular fluids (vitreous and aqueous) usually due to infection. Eye surgery could lead to acute (within 1-2 weeks) or chronic (within several weeks or months after surgery) postoperative endophthalmitis. Endophthalmitis is a complication that can result in markedly reduced vision and typically leaves some impairment. In all the cases medical and/or surgical therapy is warranted. (99) | Grade II –IIIa | Endophthalmitis rate from literature ranging from 0.03% to 0.1% (4) |
| Posterior capsule opacification; Secondary cataract (24 months) | Posterior capsular opacification, referred to as 'secondary cataract' or 'after cataract', can develop over the clear posterior capsule a few months to a few years after an uneventful cataract surgery. It results from the growth and abnormal proliferation of lens epithelial cells on the capsule at the time of cataract surgery. These cells migrate to the posterior capsule and cause visual axis obscuration, resulting in dimness of vision. Central posterior capsular opacification obscuring the visual axis can be successfully treated with YAG (yttrium-aluminium-garnet) laser capsulotomy but this procedure does increase the risk of retinal detachment. (20,100) | Grade I | The rate of posterior capsule opacification requiring laser capsulotomy from literature ranging from 3.1% to 19.85% (101,102) |
| Surgical re-intervention (within 6 months) | Every cataract surgery complication that leads to additional surgical interventions. | Grade IIIa | The surgical reintervention rate from literature ranging from 0.5% to 0.7%.(4) |
| Visual acuity loss post-cataract surgery (1 month; 6 months) | Defined as a postoperative decrease in visual acuity from the preoperative measurement. The management depends on the aetiology of visual impairment. | Grade I-IIIa | - |
| Surgically in- | The location, size and shape of corneal incisions and corne- | Grade I-IIIa | - |

| Safety outcomes | Description | Severity* (85) | Rates |
|---|---|---|---|
| duced astigmatism | al wound size in cataract surgery influence postoperative surgically induced astigmatism.<br><br>The amount of surgically induced astigmatism created during the cataract surgical procedure is measured through keratometry, while magnitude (in diopters) and direction (in degrees) are calculated using vector analysis.<br><br>Surgically induced astigmatism can reduce the visual acuity achieved after cataract surgery. (103)<br><br>Severity of astigmatism is directly related to the absolute value of dioptres. Thus, lower dioptres (i.e., closer to 0) correspond to a lower severity of astigmatism. As in refractive outcomes, a 0.25 D variation is considered clinically relevant. | | |
| Central corneal thickness | Normal central corneal thickness, measured using slit-lamp-based pachometry or ultrasound, is estimated to be around 536 µm (SD of 31 µm). Increases in central corneal thickness beyond the expected variance occur after a range of intraocular surgeries (cataract operations, penetrating keratoplasty). A meta-analysis revealed a statistically significant correlation between central corneal thickness and intraocular pressure. (104) A persistent postoperative increase in this parameter could be associated with elevated intraocular pressure and corneal oedema. | Grade I | .- |

*Severity of complications according to the Classification of Surgical Complications (85): Grade I Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic or radiological interventions (only some symptomatic therapeutic regimens); Grade II Requiring pharmacological treatment with drugs other than such allowed for grade I complications; Grade III Requiring surgical, endoscopic or radiological intervention, Grade IIIa Intervention not under general anesthesia.

*Cataract surgery setting*

A Cochrane review has concluded there is no difference in outcome or increased risk of postoperative complications between outpatient and inpatient cataract surgery. (105,106)

## Target population

### [A0007] – What is the target population of this assessment?

The target population of this assessment is adult patients (>18 years) of either sex affected by age-related cataract and for whom the surgical treatment for cataract removal and insertion of intraocular lens could provide a gain in visual acuity and health-related quality of life.

### [A0023] – How many people belong to the target population?

A wide range of definitions and study designs are used to describe the prevalence of cataract: population-based studies on the presence of lens opacities with or without visual impairment or studies on previous or current cataract extraction rates. (107) Highly heterogenic methods are

used to assess the presence of lens opacities, from self-administered questionnaires to ophthalmic examination with slip-lamp or with different types of classification (i.e., The Lens Opacities Classification System (LOCS) III or the Wisconsin Cataract Grading System). (108–110) This has led to a wide range of prevalence rates in literature that are very hard to compare, also due to the different ages of the studied populations.

In Europe in 2010, the estimated prevalence of blindness (Visual Acuity Blind < 3/60) or moderate-to-severe vision impairment (Visual Acuity < 6/18, ≥3/60) due to cataract was 0.42% (3 million out of 725 million people) in the overall population. (11)

Data from the 2017 National Health Survey of the Spanish Statistical Office shows that 5.3% of interviewed people aged over 15 years reported having had cataracts in the previous 12 months; this proportion increased to 15.6% in people aged 65 to 74 years and to 23.2% in those over 85 years (111). While British authors reported a prevalence of visual impairing cataract from 16% in Londoners aged 65-69 years to 71% in people aged 85 years or more (112), and 77% in British Indians over age 42 years . (113)

The Beaver Dam Eye Study in the US found that 23.5% of women and 14.3% of men had a visually significant cataract by the age of 65 years (114); these values were quite different from those reported by the National Eye Institute (NEI) for 2010 (**Table 15**), probably due to the inclusion by NEI of non-visual impairment cataracts.

Others studies reported a prevalence of 53-58% in India in people aged ≥ 60 years using the LOCS III, (108) and 49.7% among men and 53.3% among women aged 49-96 years in Australia (109) using the Wisconsin Cataract Grading System.

**Table 15 2010 U.S. Age-Specific Prevalence Rates for Cataract by Age and Race/Ethnicity (113)**

| Age | White | Black | Hispanic | Other | All |
|---|---|---|---|---|---|
| 40-49 | 2.59% | 2.30% | 2.37% | 2.40% | 2.51% |
| 50-54 | 5.01% | 5.99% | 5.52% | 5.59% | 5.22% |
| 55-59 | 8.84% | 10.37% | 9.63% | 9.73% | 9.14% |
| 60-64 | 15.28% | 16.19% | 15.84% | 15.88% | 15.45% |
| 65-69 | 24.95% | 23.55% | 24.27% | 24.25% | 24.73% |
| 70-74 | 37.41% | 31.68% | 34.39% | 34.17% | 36.49% |
| 75-79 | 51.09% | 40.13% | 45.16% | 45.06% | 49.49% |
| 80+ | 70.38% | 53.48% | 60.66% | 60.86% | 68.30% |
| **TOTAL** | **18.79%** | **12.99%** | **11.82%** | **13.32%** | **17.11%** |

### [A0011] – How much are standard surgery and Femtosecond Lasers (FLACS) utilised?

The predominant method of cataract surgery in the developed world is sutureless small-incision **phacoemulsification** with foldable intraocular lens (IOL) implantation. (115) (I+, good quality, strong recommendation)

In the developing world, extracapsular cataract extraction (ECCE) and intracapsular cataract extraction (ICCE) remain popular because of their cost-effectiveness, and sutureless ECCE with IOL performs very well in comparison to phacoemulsification with a foldable IOL. (116)

Extracapsular cataract extraction with IOL implantation was shown to produce a better visual outcome than ICCE with optical rehabilitation with aphakic eyeglasses. (117)

A recent adjunctive tool used in cataract extraction is a **femtosecond laser**, which can be used to construct corneal incisions, (118) create arcuate astigmatism correcting incisions, perform the anterior capsulotomy and cleave or soften the nucleus. (41,119,120) Although FLACS is currently gaining popularity, there is still controversy around the relative benefits and disadvantages of the femtosecond laser. (121) Femtosecond laser technology has the potential to improve safety, accuracy and clinical outcomes. However, FLACS adds cost and new financial and clinical challenges. (122,123)

Cataract surgery, including use of the femtosecond laser, should be performed only by an appropriately trained ophthalmologist. (13)

# CLINICAL EFFECTIVENESS (EFF)

## *Research questions*

| Element ID | Research question |
|---|---|
| D0005 | How does intervention with FLACS compare to standard cataract surgery in terms of Corrected Distance Visual Acuity (CDVA), Uncorrected Distance Visual Acuity (UDVA) and patients' body functions? |
| D0006 | How does intervention with FLACS compare to standard cataract surgery in terms of refractive outcomes? |
| D0012 | How does intervention with FLACS compare to standard cataract surgery in terms of patient-reported outcomes and general quality of life? |
| D0013 | What is the effect of FLACS compared to standard cataract surgery on disease-specific quality of life? |
| D0017 | How does intervention with FLACS compare to standard cataract surgery in terms of patient satisfaction? |

## *Results*

### Included studies

Of the 21 studies included in this report, 7 parallel group RCTs (Donnenfeld 2018, Hida 2014, Kranitz 2012, Mastropasqua 2014a, Mastropasqua 2014b, Nagy 2011, Yu 2015) (23–29) and 3 within person paired-eye RCTs (Conrad-Hengerer 2015, Mursch Edlmayr 2017, Schargus 2015) (30–32) reported clinical effectiveness outcomes. Overall, the 10 trials recruited a total of 648 patients affected by age-related cataract (range: 36-105 patients). A total of 859 eyes were randomized in these studies. Tables of included studies are reported in **Appendix 1**.

Follow-up periods varied among studies and, whenever possible, they have been reported according to length of follow up specified in the project plan.

Data for the following clinical effectiveness outcomes were analysed and reported:

- Corrected Distance Visual Acuity (CDVA) 1 month after surgery: 6 studies [Donnenfeld 2018, Kranitz 2012, Mastropasqua 2014a, Mastropasqua 2014b, Mursch-Edlmayr 2017, Yu 2015] (24–26,28,29,31)
- Corrected Distance Visual Acuity (CDVA) 6 months after surgery: 4 studies [Mastropasqua 2014a, Mastropasqua 2014b, Mursch-Edlmayr 2017, Schargus 2015] (25,26,31,32)
- Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery: 4 studies [Donnenfeld 2018, Mastropasqua 2014a, Mastropasqua 2014b, Kranitz 2012] (24–26,29)
- Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery: 2 studies [Mastropasqua 2014a, Mastropasqua 2014b] (25,26)
- Refractive outcomes at 7 days: 2 studies [Mastropasqua 2014b, Yu 2015] (26,28)
- Refractive outcomes at 30 days: 2 studies [Mastropasqua 2014b, Yu 2015] (26,28)
- Patient-reported outcome measures (PROM): 1 study [Mursch-Edlmayr 2017] (31)

- Patient-reported outcome measures (PROM): 1 study [Mursch-Edlmayr 2017] (31)

None of the included studies was powered enough to prove superiority of intervention against comparator for the effectiveness outcomes included in our Scope.

## Morbidity

### [D0005] How does intervention with FLACS compare to standard cataract surgery in terms of Corrected Distance Visual Acuity (CDVA), Uncorrected Distance Visual Acuity (UDVA) and patients' body functions?

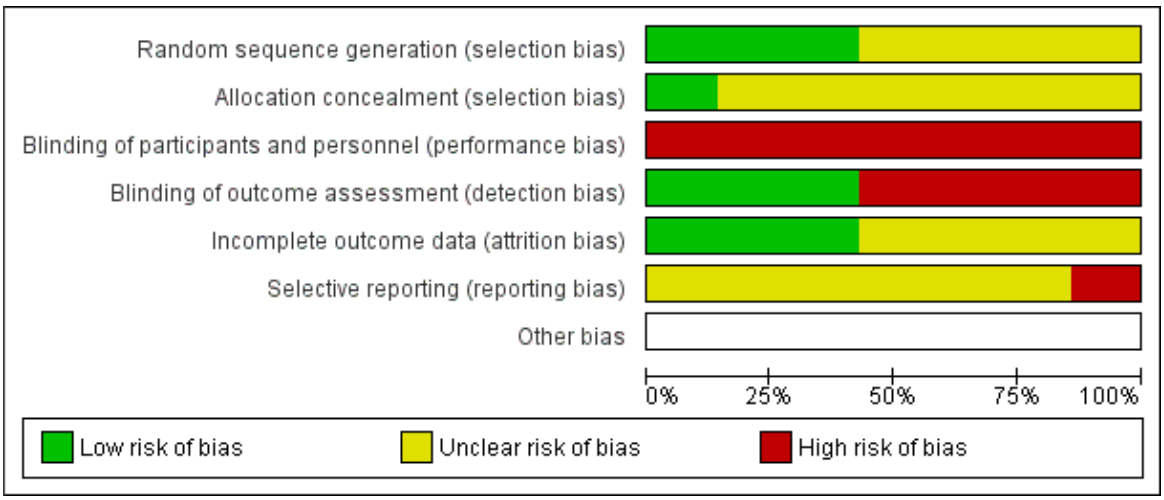
Visual acuity is measured in decimal, fraction and log MAR. Visual Acuity could be assessed with or without correction with lens (corrected or uncorrected visual acuity). The log MAR scale ranges from -0.3 (best vision) to +1.3 (worst vision) and 0.0 log MAR corresponds to 1.0 decimal (10/10). One line in the Snellen chart corresponds to a 0.1 log MAR and variation of one line or 0.1 log MAR is considered clinically relevant.

*Corrected Distance Visual Acuity (CDVA)*

A total of seven studies were included. Six randomized controlled studies (Donnenfeld 2018, Kranitz 2012, Mastropasqua 2014a, Mastropasqua 2014b, Mursch Edlmayr 2017, Yu 2015) (24–26,28,29,31) reported data on Corrected Distance Visual Acuity (CDVA) at one month after surgery and four RCTs (Mastropasqua 2014 a, Mastropasqua 2014 b, Mursch Edlmayr 2017, Schargus 2015)(25,26,31,32) reported data on CDVA at 6 months after surgery.

Risk of bias in 4 of the 7 studies reporting on CDVA at one or six months was judged as very serious (**Figure 9**). The main reasons for this judgement were limitations in blinding of outcome assessment (maintained in only three of included RCTs) and limits in allocation concealment (described in only one study). Four studies (Donnenfeld 2018, Kranitz 2012, Mursch Edlmayr 2017, Schargus 2015) (24,29,31,32) reported conflicts of interests (in terms of sponsorship or authors having been consultants for the firm producing the laser system under study).

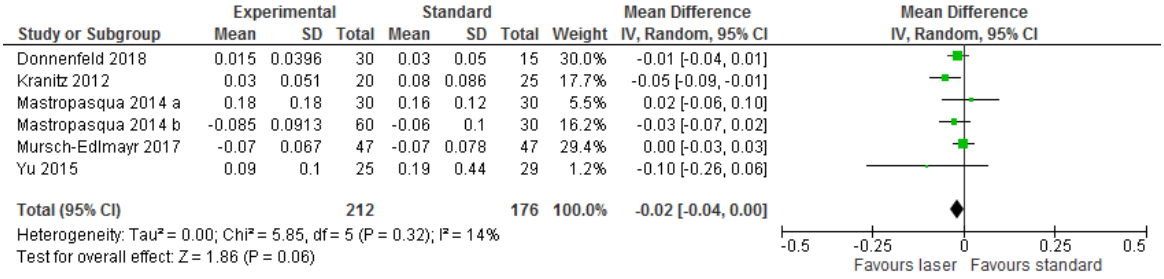
**Figure 9 - Risk of bias summary – CDVA**



*CDVA at 1 month after surgery*

The six studies assessing CDVA at 1 month included a total of 388 patients affected by age-related cataract. Except for one study (Kranitz 2012)(24), whose results favour FLACS, all other studies found no statistically significant difference between the two study arms. The pooled estimate provided no evidence of a difference between groups (MD -0.02; 95% CI -0.04; 0.00) considering the test for overall effect (p=0.06). Results and pooled estimates are represented in **Figure 10**.

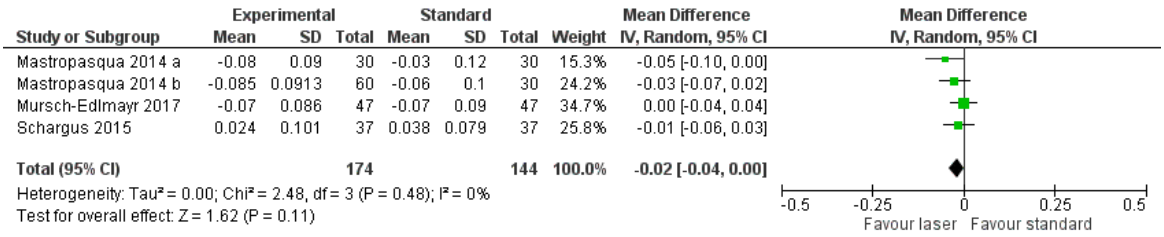
**Figure 10 - Forest Plot CDVA at 1 month**




*CDVA at 6 months after surgery*

The four studies providing data on CDVA at 6 months included a total of 318 patients affected by age-related cataract. In three out of four studies, no statistically significant difference was found between the two study arms. Just one study (Mastropasqua 2014a)(26) showed a marginally significant difference, not clinically relevant, favouring FLACS. The pooled estimate provided no evidence of a difference between groups (MD -0.02; 95% CI -0.04; 0.00) considering the test for overall effect (p=0.11). Results are represented in **Figure 11**.

**Figure 11 - Forest Plot CDVA at 6 months**



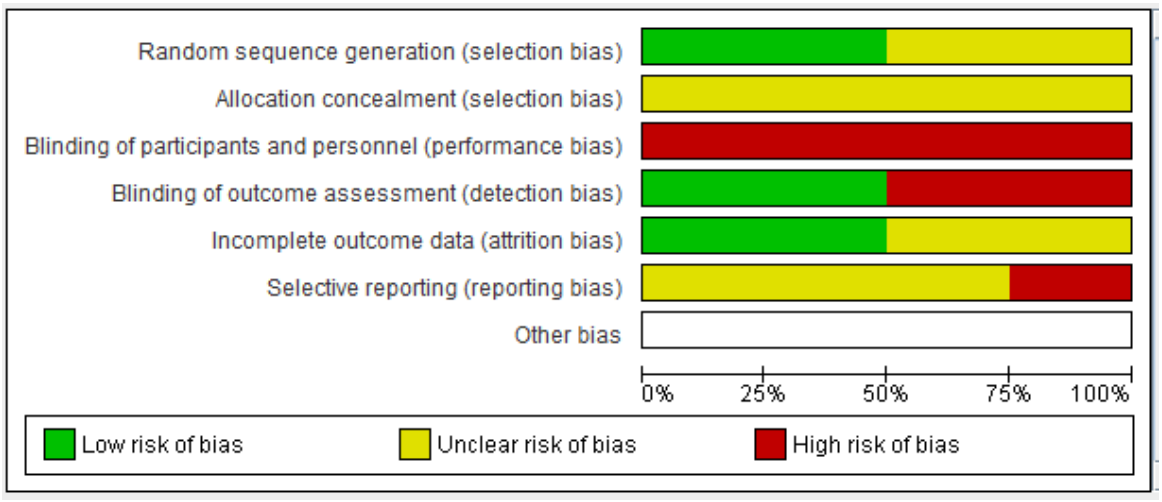

Overall quality of evidence for Corrected Distance Visual Acuity (CDVA) at one and six months after surgery was graded “low” because of very serious risk of bias in included studies. No inconsistency or imprecision were highlighted. A low quality of evidence means that further research is likely to change the size and direction of effect and confidence in the estimate is limited.

*Uncorrected Distance Visual Acuity (UDVA)*

Four randomized controlled studies (Donnenfeld 2018, Kranitz 2012, Mastropasqua 2014a, Mastropasqua2014b) (24–26,29) reporting data on Uncorrected Distance Visual Acuity (UDVA) at 1 month post-surgery were included. Two of these (Mastropasqua 2014a and Mastropasqua 2014b)(25,26) reported also data on UDVA at 6 months follow up. Similarly to CDVA, the mean difference was used to combine data

Risk of bias in the studies reporting on UDVA was judged as very serious for UDVA at 1 months and serious for UDVA at 6 months (see **Figure 12**). Reasons for this judgement were limitations in blinding of participants in all studies and blinding of outcome assessment in two studies. Two studies (Donnenfeld 2018, Kranitz 2012) (24,29) reported conflicts of interests (in terms of sponsorship, or authors having been consultants for the firm producing the laser system under study).

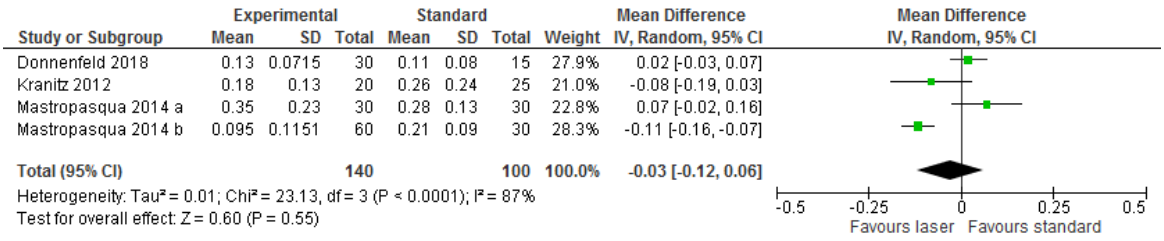
**Figure 12 - Risk of bias summary – UDVA**




*UDVA at 1 month after surgery*

The four studies assessing UDVA at 1 month included a total of 240 patients. One study found a statistically significant result in favour of FLACS, while the other three studies found no statistically significant differences between the two study arms. The pooled estimate provided no evidence of a difference between groups (MD -0.03; 95% CI -0.12; 0.06). Results are represented in **Figure 13**.

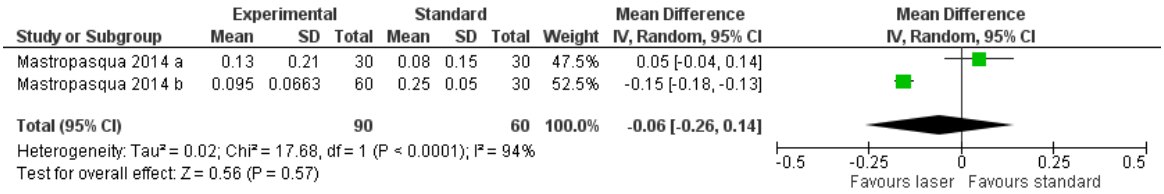
**Figure 13 - Forest Plot UDVA at 1 month**




*UDVA at 6 months after surgery*

The two studies assessing UDVA at 6 months included a total of 150 patients. One study found a statistically significant result in favour of FLACS, while the second study found no statistically significant difference between the two study arms. A significant heterogeneity among the studies was shown ($I^2$=94%). The pooled estimate provided no evidence of a difference between groups (MD –0.06; 95%CI:-0.26; 0.14). Results are represented in **Figure 14**.

**Figure 14 - Forest Plot UDVA at 6 months**




Overall quality of evidence for Uncorrected Distance Visual Acuity (UDVA) at one and six months after surgery was graded “very low”. In addition to risk of bias (very serious for studies assessing UDVA at one month and serious for studies assessing UDVA at 6 months), quality was downgraded for inconsistency (results from one of four trials favouring FLACS, while results from other three studies showing no difference between study arms). A very low quality of evidence means that any estimate of effect is very uncertain and confidence in the estimate is small.

**[D0006] – How does intervention with FLACS compare to standard cataract surgery in terms of refractive outcomes?**

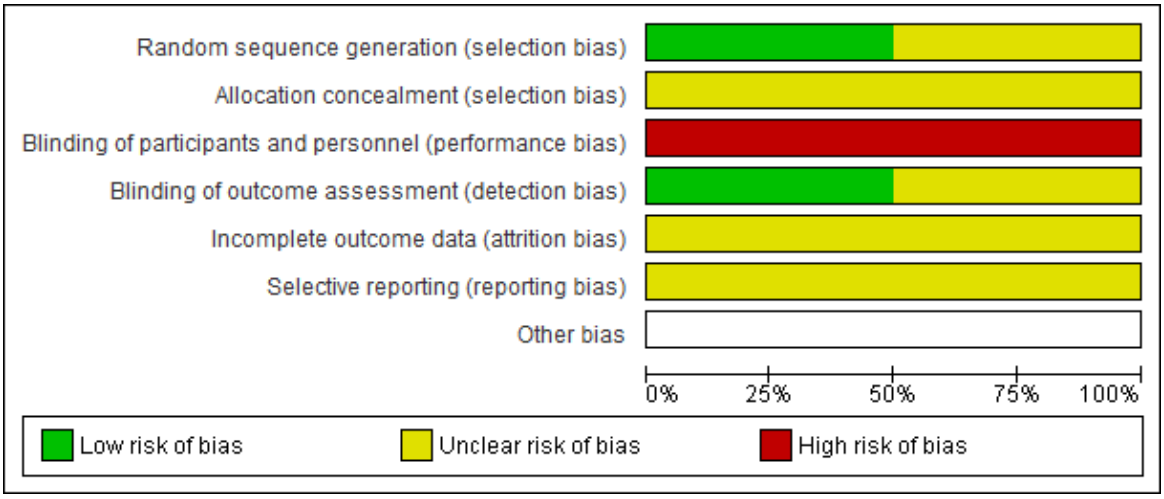
Refraction, i.e., the way light converges on the retina, influences visual acuity. Refraction error, i.e., myopia, astigmatism hypermetropia, etc., is measured in spherical equivalent (dioptres) and a 0.0 diopter indicates best refraction. A diopter can be a negative number (which indicates myopia) or a positive number (which indicates hypermetropia).

In cataract surgery refractive outcomes are assessed by measuring the mean absolute error (MAE), which represents the absolute difference between the postoperative predicted (target) refraction and the postoperative actual refraction at follow up. A variation of +/- 0.25 D is considered clinically relevant, as it represents the threshold for correction with lens.

Of the six studies (Conrad-Hengerer 2015, Donnenfeld 2018, Hida 2014, Mastropasqua 2014b, Nagy 2011, Yu 2015) (23,25,27–30) reporting on refractive outcomes, only two (Mastropasqua 2014b, Yu 2015) (25,28) measured the mean absolute error at one week and one month and were included in the analysis.

Risk of bias in the two studies was judged as serious (**Figure 15**) due to concerns on lack of allocation concealment in one of the two studies included in the quantitative analysis. No conflicts of interests were reported in these trials.

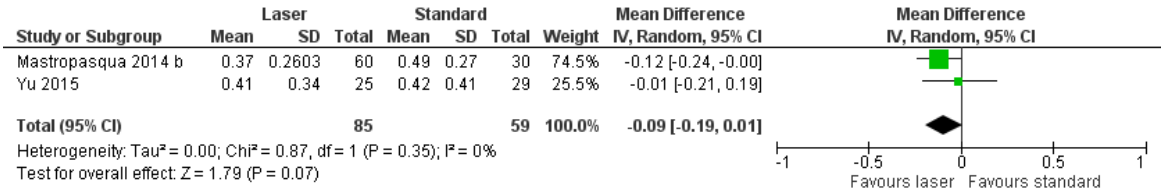
**Figure 15 - Risk of bias summary – Refractive Outcomes**




*Refractive outcomes (Mean Absolute Error at 1 week after surgery)*

The two studies assessing mean absolute error at 1 week included a total of 144 patients. One study found a marginally significant, and not clinically relevant, difference in favour of FLACS, while the second study found no statistically significant difference between the two study arms. The pooled estimate, although close to statistical significance, provided no evidence of a difference between groups (MD -0.09; 95%CI:-0.19; 0.01; p=0.07). Results are represented in **Figure 16**.

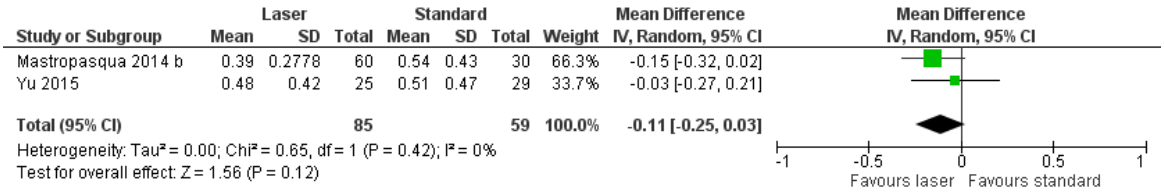
**Figure 16 - Forest Plot Refractive Outcomes (Mean Absolute Error) at 1 week**




*Refractive outcomes (Mean Absolute Error at 1 month after surgery)*

The two studies assessing mean absolute error at 1 month included a total of 144 patients. Neither study found a statistically significant difference between the two study arms. The pooled estimate provided no evidence of a difference between groups (SMD -0.11; 95%CI: -0.25; 0.03). Results are represented in **Figure 17**.

**Figure 17 - Forest Plot Refractive Outcomes (Mean Absolute Error) at 1 month**




Overall quality of evidence for refractive outcomes was graded “low” because of imprecision and serious risk of bias due to allocation concealment not adequately described in both included trials. No serious inconsistency was highlighted, but data came from only two RCTs enrolling a limited number of patients. A low quality of evidence means that further research is likely to change the size and direction of effect and confidence in the estimate is limited.

## Health-related quality of life

### [D0012] How does intervention with FLACS compare to standard cataract surgery in terms of patient-reported outcomes and general quality of life)?

Only one study conducted in Austria was included, (Mursch Edlmayr 2017)(31) which reported data from a non-validated questionnaire on mean pain during surgery (patient-reported outcome) using a scale from 1 (no pain) to 5 (intense pain). This study, judged to have serious risk of bias due to unclear allocation concealment, attrition and reporting bias, enrolled 50 patients; both patients' eyes were randomised to either FLACS or conventional surgery and the secondary endpoint of clinical efficacy was individual patient's perception, assessed through a questionnaire, of both types of surgery. Specifically, all patients were asked about their pain level in general during the cataract surgery. After surgery in the second eye, patients were asked to compare the pain level between the 2 types of surgery and which procedure they would recommend. The difference between mean pain during cataract extraction after laser treatment and mean pain during standard cataract surgery was not statistically significant, although thirty patients (63.8%) reported having experienced more pain during femtosecond laser-assisted cataract surgery than during conventional cataract surgery.(31) Data from only one RCT could not be used to grade overall quality of evidence

No study was retrieved assessing general quality of life.

### [D0013] What is the effect of FLACS compared to standard cataract surgery on disease-specific quality of life?

No study assessing disease-specific quality of life was retrieved.

### [D0017] How does intervention with FLACS compare to standard cataract surgery in terms of patient satisfaction?

The same Austrian study (Mursch Edlmayr 2017)(31) with serious risk of bias that randomized patients' eyes to either FLACS or conventional surgery also reported data on patient preferences. Twenty-seven out of the 50 patients enrolled (57.4%) said they would recommend conventional cataract surgery over femtosecond-assisted surgery.

# SAFETY (SAF)

## *Research questions*

| Element ID | Research question |
|---|---|
| C0008 | How safe is FLACS compared to standard cataract surgery in terms of intraoperative and postoperative complications? |
| C0004 | How safe is FLACS compared to the standard cataract surgery over time or in different settings of use? |
| C0005 | What are the susceptible patient groups that are more likely to be harmed through the use of FLACS? |
| C0007 | How does intervention with FLACS compare to standard cataract surgery in terms of user-dependent harms (i.e., time of surgical procedure, complications etc.)? |
| B0010 | What kind of data/records and/or registry are needed to monitor the use of FLACS and standard cataract surgery? |

For a detailed description of safety outcomes and consequences of intraoperative and postoperative complications, see **Table 14**.

## *Results*

### Included studies

Among the 21 studies included in this report, 9 parallel group RCTs (Givaudan Pedroza 2016, Kovacs 2014, Mastropasqua 2014a, Nagy 2014, Reddy 2013, Roberts 2018, Takacs 2012, Yu 2015, Yu 2016)(26,28,41–46) and 6 within person, paired-eye RCTs (Conrad-Hengerer 2013, Conrad-Hengerer 2014, Conrad-Hengerer 2015, Mursch Edlmayr 2017, Panthier 2017, Schargus 2015)(30–33,47,48,50) reported clinical safety outcomes.

Overall, the 15 trials recruited a total of 1215 patients affected by age-related cataract (range: 30-299). A total of 1641 eyes were randomized in those studies. Tables of included studies are reported in **Appendix 1**.

In our meta-analyses we did not consider studies generically stating that no complications were observed, without specifying or reporting data on specific complications.

Follow-up periods varied among studies and, whenever possible, they have been reported according to length of follow up specified in the project plan.

Data for the following safety outcomes were analysed and reported:

- anterior and posterior capsular tear: 9 studies (Conrad-Hengerer 2013, Conrad-Hengerer 2015, Mursch-Edlmayr 2017, Panthier 2017. Reddy 2013, Roberts 2018, Schargus 2015,Yu 2015, Yu 2016) (28,30–33,42,44,47,50)
- vitreous loss: 3 studies (Conrad-Hengerer 2015, Roberts 2018, Schargus 2015) (30,32,33)
- elevated intraocular pressure after one day: 4 studies (Conrad-Hengerer 2013, Conrad-Hengerer 2014, Conrad-Hengerer 2015, Schargus 2015) (30,32,47,48)
- elevated intraocular pressure after one week: 4 studies (Conrad-Hengerer 2013, Conrad-Hengerer 2014, Conrad-Hengerer 2015, Yu 2015) (28,30,47,48)
- endothelial cell loss: 4 studies (Conrad-Hengerer 2013, Mursch-Edlmayr 2017; Schargus 2015, Yu 2015)(28,31,32,47);
- Iridocyclitis: no study was retrieved

- corneal endothelial decompensation/ corneal oedema (within 90 days): 1 study (Yu 2015)(28)
- cystoid macular oedema within 90 days: 4 studies (Conrad-Hengerer 2013, Conrad-Hengerer 2014, Conrad-Hengerer 2015, Schargus 2015)(30,32,47,48)
- infections: 1 study (Conrad-Hengerer 2015)(30)
- posterior capsule opacification/ secondary cataract within 24 months: 2 studies (Kovacs 2014, Yu 2015)(28,46)
- retinal detachment: no study was retrieved
- visual acuity loss post cataract surgery: no study was retrieved
- surgically induced astigmatism: one study (Nagy 2014)(41)
- central corneal thickness: 3 studies (Conrad-Hengerer 2013, Schargus 2015, Takacs 2012)(32,43,47);
- total duration of procedure – mean surgical time: 3 studies (Conrad-Hengerer 2013, Roberts 2018, Schargus 2015) (32,33,47)

None of the above included studies was powered enough to prove superiority of intervention against comparator for any of the safety outcomes considered.

Most important safety outcomes and their frequency are reported in **Table 16**.

**Table 16 Frequency and severity of adverse events in included comparative studies (estimates derived from data of the systematic review of included trials)**

| System organ/ class/adverse events | Frequency (very common, common, uncommon, rare, very rare, not known | All grades | | | |
|---|---|---|---|---|---|
| | | Intervention n (%) | Comparator n (%) | Odds Ratio (95% CI) | Absolute Difference |
| Class 1 | | | | | |
| Posterior capsular tear | Very rare | 0/390 (0.0%) | 1/402 (0.2%) | OR 0.32 (0.01, 8.23) | 1.7 fewer per 1000 (from 2.5 fewer to 17.6 more) |
| Anterior capsular tear | Very rare | 2/390 (0.5%) | 2/402 (0.5%) | OR 1.05 (0.18, 6.12) | 0.2 more per 1000 (from 4.1 fewer to 24.7 more) |
| Vitreous loss | Very rare | 0/137 (0.0%) | 1/137 (0.7%) | OR 0.32 (0.01, 8.23) | 5.0 fewer per 1000 (from 7.2 fewer to 49.7 more) |
| Retinal detachment | Very rare | No studies | No studies | No studies | - |
| Cystoid macular oedema | Rare | 5/311 (1.6%) | 9/311 (2.9%) | OR 0.58 (0.20, 1.68) | 12.0 fewer per 1000 (from 23.0 fewer to 18.7 more) |
| Visual acuity loss | Not known | No study | No study | No study | |

**Abbreviations:** CI, confidence interval

## Patient safety

### [C0008] – How safe is FLACS compared to standard cataract surgery in terms of intraoperative and postoperative complications?

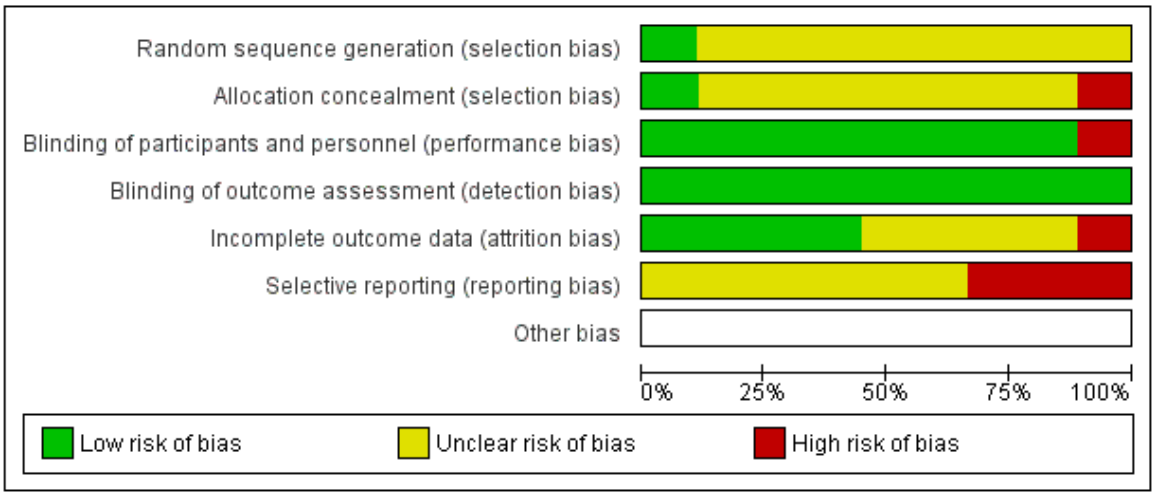
### Intraoperative Complications

*Anterior and Posterior Capsular Tear*

Nine studies (Conrad-Hengerer 2013, Conrad-Hengerer 2015, Mursch-Edlmayr 2017, Panthier 2017, Reddy 2013, Roberts 2018, Schargus 2015, Yu 2015, Yu 2016) (28,30–33,42,44,47,50) reported data on anterior and posterior capsular tear. Roberts 2018 reported only posterior capsular tears associated with vitreous loss.

The risk of bias was judged as not serious (**Figure 18**), as concerns over allocation concealment and attrition were not considered too relevant for intraoperative outcomes. Six studies (Conrad-Hengerer 2013, Conrad-Hengerer 2015, Mursch-Edlmayr 2017, Reddy 2013, Roberts 2018, Schargus 2015) (30–33,42,47) reported conflicts of interests (in terms of sponsorship, grants, lecture fees or authors being an employee or having been a consultant or member of the medical advisory board of the firm producing the laser system under study).

**Figure 18 - Risk of bias summary – Anterior and Posterior Capsular Tear**




The selected studies included a total of 1091 patients. Ten anterior tears occurred in four studies (five in each arm). No difference was found between the study arms: OR 1.10. 95% CI:0.34;3.64 (**Figure 19**). Excluding Roberts 2018 which reported only posterior tears associated with vitreous loss (included in **Figure 22**), one posterior tear occurred in one study (Schargus 2015)(32). No statistically significant difference was found between the study arms: OR 0.32. 95% CI 0.01; 8.23 (**Figure 20**).

**Figure 19 - Forest Plot – Anterior Capsular Tear**

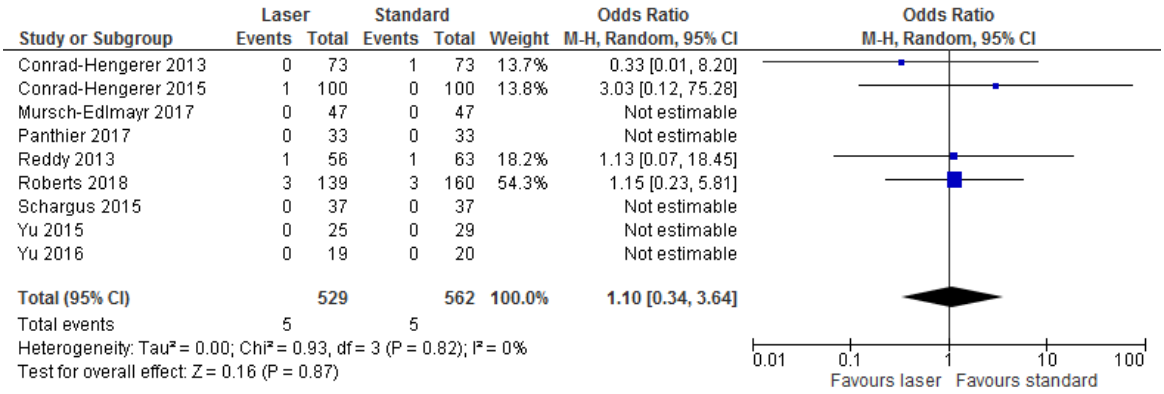
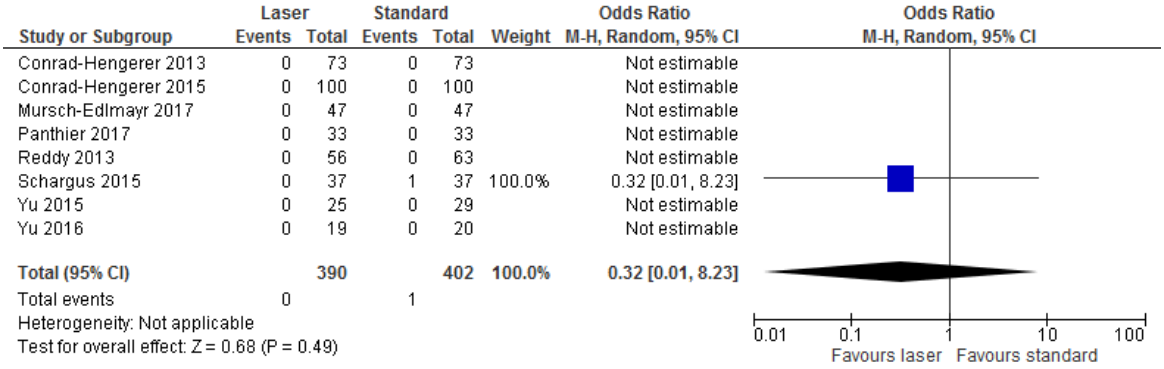


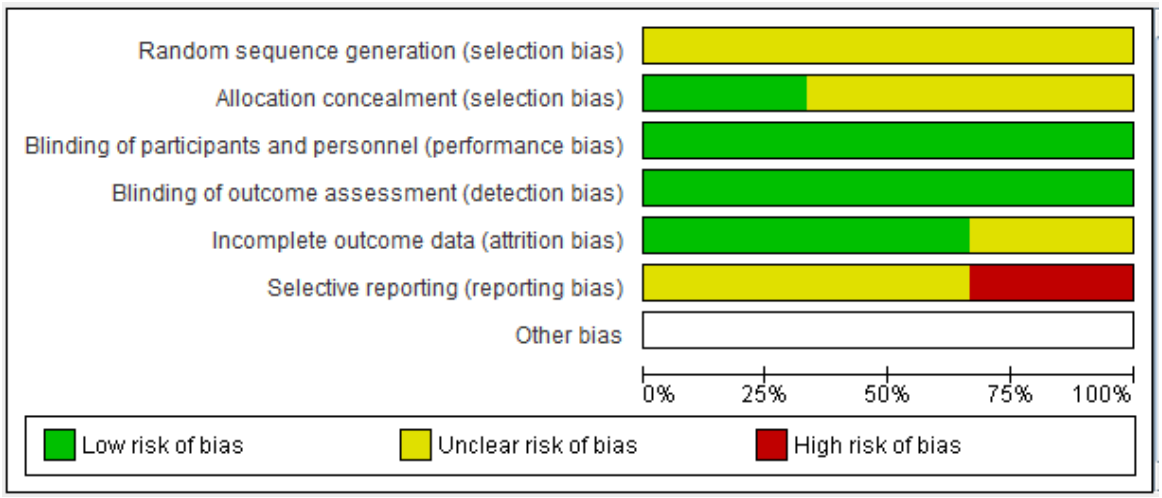

**Figure 20 - Forest Plot – Posterior Capsular Tear**




*Vitreous loss*

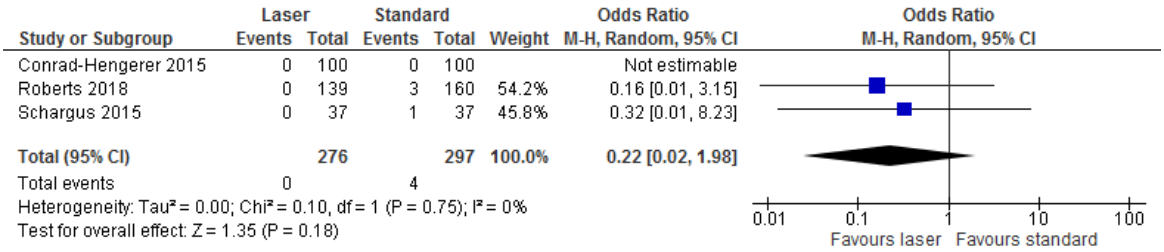
Three studies (Conrad-Hengerer 2015, Roberts 2018, Schargus 2015) (30,32,33) reported data on vitreous loss. Their risk of bias was judged as not serious (**Figure 21**). All studies reported conflicts of interests (in terms of sponsorship or an author being consultant or member of the medical advisory board of the firm producing the laser system under study).

**Figure 21 - Risk of bias summary – Vitreous loss**




The selected studies included a total of 573 patients. Four events occurred in two studies (all in the standard phacoemulsification arms). No statistically significant difference was found between the study arms (OR 0.22. 95% CI 0.02;1,98) (**Figure 22**).

**Figure 22 - Forest Plot – Vitreous loss**




Overall quality of evidence for intraoperative complications (anterior and posterior capsular tear and vitreous loss) was graded “low”: no serious risk of bias was detected but quality was downgraded for very serious imprecision (very large confidence intervals), considering that only four anterior tears, one posterior tear and four vitreous loss occurred in the selected trials. A low quality of evidence means that further research is likely to change size and direction of effect and confidence in the estimate is limited.

**Postoperative complications**

*Retinal detachment*

No study was retrieved that assessed retinal detachment.

*Iridocyclitis*

No study was retrieved assessing Iridocyclitis.

*Endothelial Cell Loss*

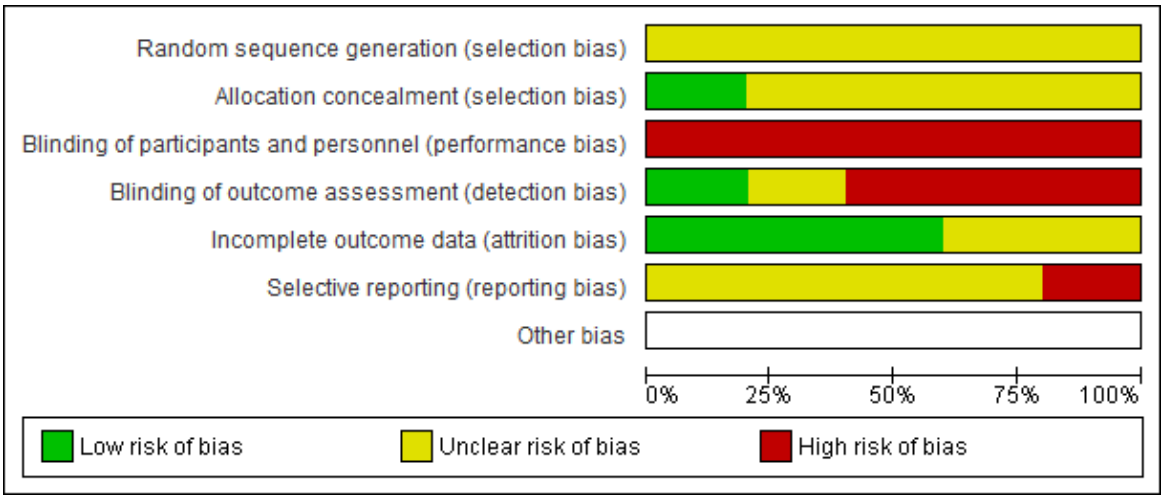
The 4 studies that reported data on endothelial cell loss (ECL) (Conrad-Hengerer 2013, Mursch-Edlmayr 2017, Schargus 2015 and Yu 2015)(28,31,32,47) used different types of measurement (cell density and percentage loss) at different times of follow up.
Only one study (Conrad-Hengerer 2013)(47) reported a statistically significant difference in percentage of cell loss between the two surgical techniques over the whole postoperative period (point estimates at three months were 8.1% loss for FLACS vs 13.7% loss for control).
The other two studies evaluating percentage of cell loss at 3 or 6 months after surgery (Schargus 2015 and Yu 2015)(28,32) reported no statistically significant difference in percentage loss between study arms.
One study (Mursch-Edlmayr, 2017) (31) assessed difference in cell density at 1, 3 and 6 months after surgery, reporting that study groups were comparable throughout follow up.
The risk of bias for this outcome was judged as very serious due to limitations for lack of blinding of outcome assessment and of allocation concealment.
In order to attempt a metanalysis of the above studies we considered applying the methods suggested in the Cochrane Handbook [Chapter 16.1.3.2] to estimate the standard deviation of endothelial cell loss derived from data of before-and-after cell count. To calculate the correlation coefficient needed to obtain the standard deviation of the change, use of several studies is recommended. As only one study provided the necessary information (47) the method could not be applied and pooled estimate could not be calculated.

*Elevated intraocular pressure (IOP) at 1 day and at 1 week*

This outcome was not rated as “critical“ and has not been included in Summary of Findings table. Overall, five studies (Conrad-Hengerer 2013, Conrad-Hengerer 2014, Conrad-Hengerer 2015,

Schargus 2015, Yu 2015)(28,30,32,47,48) reported data on elevated intraocular pressure at one day or at one week after surgery (the first three studies evaluated IOP at both periods). Their risk of bias was judged as very serious. Reasons for this judgement were limits in blinding of outcome assessment (maintained in only one of these RCTs) and limits in allocation concealment (described in none of the aforementioned RCTs). All but one of these studies reported conflicts of interests (an author being consultant or member of the medical advisory board of the firm producing the laser system under study). Risk of bias summary is reported in **Figure 23.**

**Figure 23 - Risk of bias summary – Elevated Intraocular Pressure (IOP)**




A total of sixteen events occurred one day after surgery (seven in the FLACS arm and nine in the conventional technique arm). None of the studies nor the pooled estimate (OR 0.80. 95 CI 0.28; 2.26) showed statistically significant differences between the study arms. Just three events occurred after one week (two in the FLACS arm and one in the conventional technique arm). No statistically significant difference was found between study arms (pooled estimate: OR 1.53. 95% CI 0.24; 9.82) (**Figure 24** and **Figure 25**).

**Figure 24 - Forest Plot – Elevated Intraocular Pressure (IOP) at 1 day**

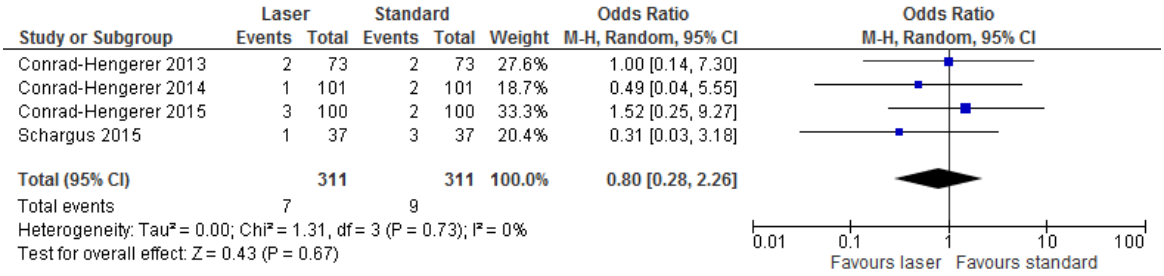
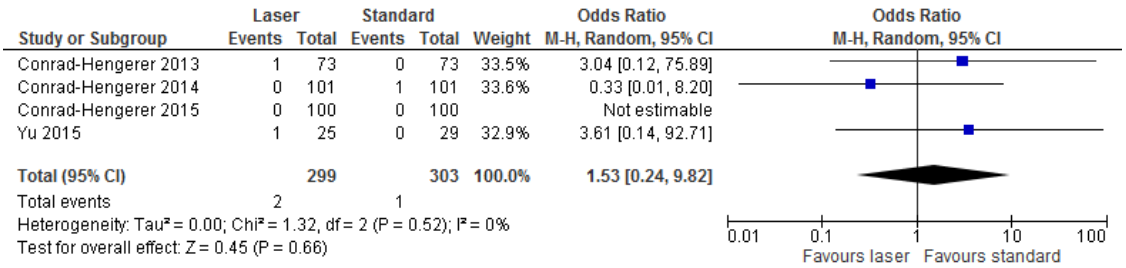



**Figure 25 - Forest Plot – Elevated Intraocular Pressure (IOP) at 1 week**




Overall quality of evidence for postoperative complication (ECL at 3 and 6 months and elevated IOP at 1 day and 1 week) was graded “very low” due to very serious risk of bias and inconsistency

(ECL) or imprecision (IOP). A very low quality of evidence means that any estimate of effect is very uncertain and confidence in the estimate is small.

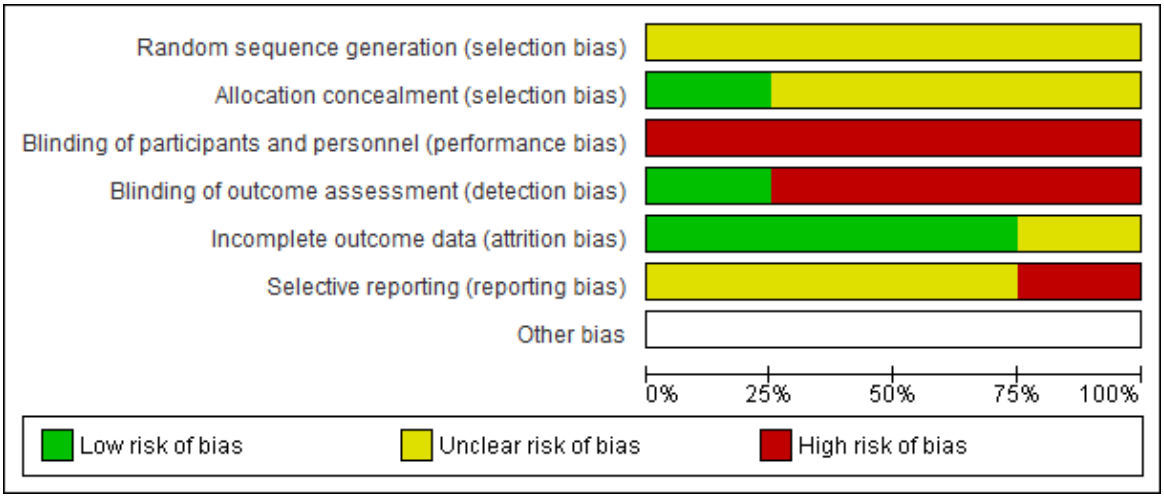
*Corneal Endothelial Decompensation/ Corneal Oedema (within 90 days)*

Only one study (Yu 2015)(28) assessed this outcome on the 19 patients included and reported no event in either study arm.

*Cystoid Macular Oedema (within 90 days)*

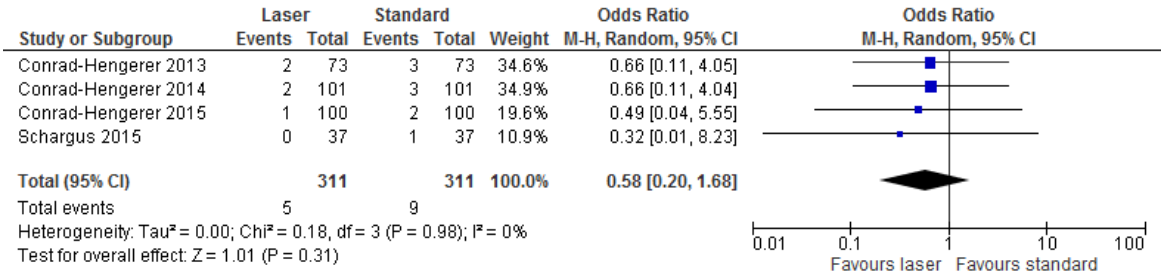
Four studies (Conrad-Hengerer 2013, Conrad-Hengerer 2014, Conrad-Hengerer 2015, Schargus 2015) (30,32,47,48) reported data on cystoid macular oedema. Their risk of bias was judged as very serious (**Figure 26**). Reasons for this judgement were limits in blinding of outcome assessment (maintained in only one of these RCTs) and limits in allocation concealment (described in none of the aforementioned RCTs). All four studies reported conflicts of interests (an author being consultant or member of the medical advisory board of the firm producing the laser system under study).

**Figure 26 - Risk of bias summary – Cystoid Macular Oedema**




A total of fourteen events occurred (five in the FLACS arm and nine in the conventional technique arm). None of the studies nor the pooled estimate (OR 0.58. 95 CI 0.20; 1.68) showed statistically significant differences between the study arms (**Figure 27**).

**Figure 27 - Forest Plot – Cystoid Macular Oedema**




*Infections (within 90 days)*

Only one study on 100 patients included infections among its outcomes (Conrad-Hengerer 2015)(30), reporting no event in either study arm. Quality of the single study was judged to be low due to very serious risk of bias.

*Posterior Capsule Opacification / Secondary cataract (within 24 months)*

Two studies assessed this outcome and their risk of bias was judged to be serious. Reasons for this judgement were limits in blinding of outcome assessment in one of the RCTs and limits in allocation concealment (described in neither of the two RCTs). Conflicts of interests were reported in one RCT (two authors being consultants of the firm producing the laser system under study). One study (Kovacs 2014)(46) reported a Open-Access Systematic Capsule Assessment score for Posterior Capsule Opacification, which was found to be higher (i.e., worse) in the standard surgery group (0.58 ± 0.30 in the FLACS group versus 0.84 ± 0.52 in the control group; P = .01). According to the study authors, the clinical relevance of this difference cannot be established. Another study (Yu 2015)(28) reported that in two patients in the control group, posterior capsular opacification occurred at 1 and at 3 months after surgery, respectively, requiring treatment with YAG laser capsulotomy. Data could not be pooled and do not allow drawing any conclusion.

*Visual Acuity Loss Post-Cataract Surgery (1 month; 6 months)*

No study was retrieved that assessed visual acuity loss post-cataract surgery at 1 and 6 months and surgical re-intervention within 6 months.

*Surgically Induced Astigmatism*

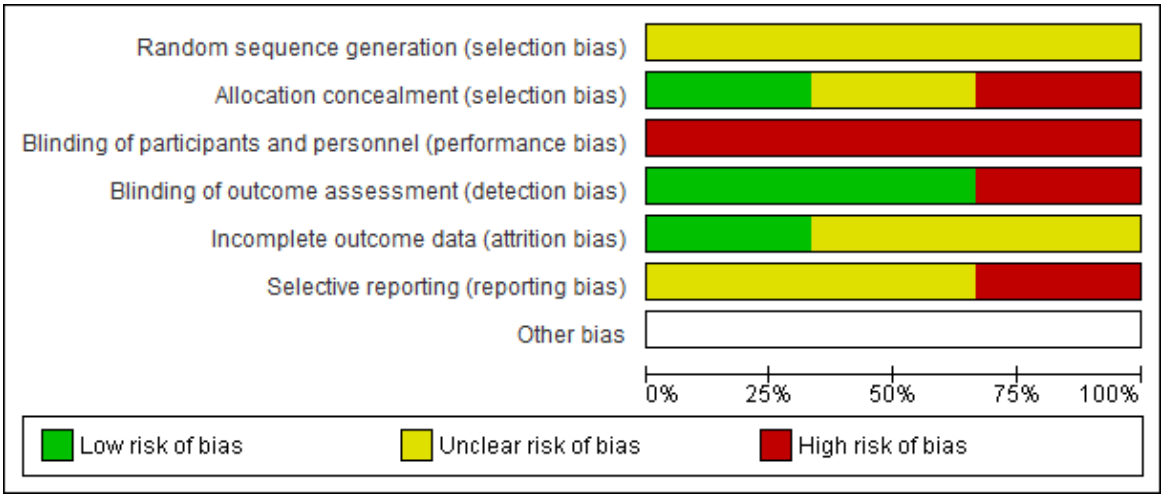
This outcome was not rated as “critical “and has not been included in Summary of Findings table. One study (Nagy 2014)(41) reported data on surgically induced astigmatism three months after surgery. Its risk of bias was judged as very serious. Reasons for this judgement were limits in blinding of outcome assessment and lack of information about allocation concealment. The study did not show statistically significant differences between the study arms (MD 0.06 (95% CI -0.02;0.14).

*Central Corneal Thickness up to 1 week and up to 6 months*

Four studies (Conrad-Hengerer 2013, Mursch-Edlmayr 2017, Schargus 2015, Takacs 2012) (31,32,43,47) reported data on central corneal thickness. It was not possible to include Mursch-Edlmayr 2017 (31) in the pooled analysis since standard deviations of mean absolute CCT values were not provided. Data were pooled from the other three RCTs that reported results at one week and at 1 to 6 months after surgery. Their risk of bias was judged as very serious (**Figure 28**). Reasons for this judgement were limits in blinding of outcome assessment in one study, limits in allocation concealment in another study and selective reporting in the third study. All the three

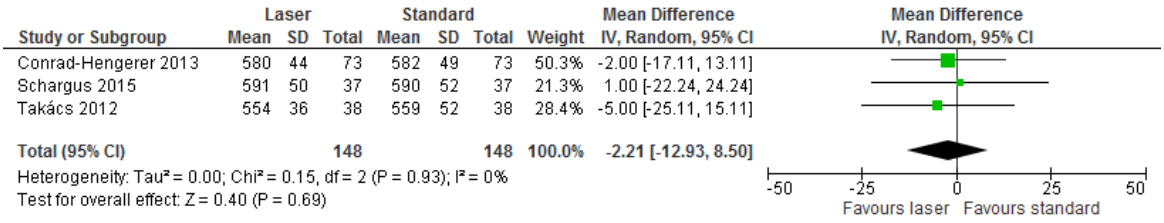
studies reported conflicts of interests (some authors being consultant or member of the medical advisory board of the firm producing the laser system under study, or trial sponsored by the producer).

**Figure 28 - Risk of bias summary – Central Corneal Thickness**



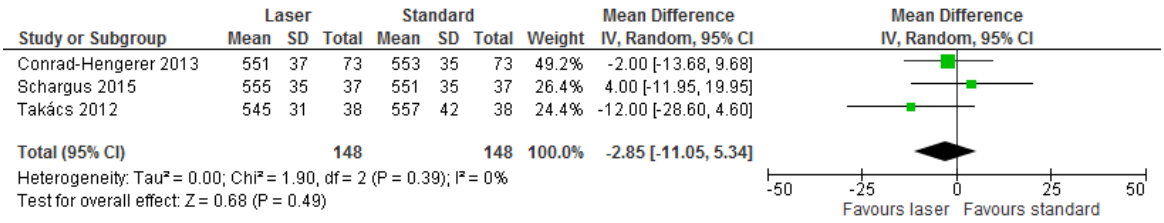

None of the studies nor the pooled estimates showed statistically significant differences between the study arms (up to one week: MD -2.21. 95% CI -12.93; 8.50. One to six months: MD -2.85. 95% CI -11.05; 5.34)(**Figure 29** and **Figure 30**).

**Figure 29 - Forest Plot - Central Corneal Thickness up to 1 week**




*Central Corneal Thickness from 1 to 6 months*

**Figure 30 - Forest Plot - Central Corneal Thickness from 1 to 6 months**




Overall quality of evidence was judged to be “low” for infections due to very serious risk of bias in the only RCT assessing this outcome and reporting no events in either arm. Availability of only one small trial strongly limits our level of certainty about the effect of intervention. Therefore, such quality of evidence means that further research is likely to change the size and direction of effect and confidence in the estimate is limited.

For the remaining over-time postoperative complications, overall quality of evidence was judged to be “very low” due to very serious risk of bias and imprecision (large confidence intervals). A very low quality of evidence means that any estimate of effect is very uncertain and confidence in the estimate is small.

**[C0004] – How safe is FLACS compared to the standard cataract surgery over time or in different settings of use?**

No data allowing analysis for different settings of use were retrieved.

**[C0005] – What are the susceptible patient groups that are more likely to be harmed through the use of FLACS?**

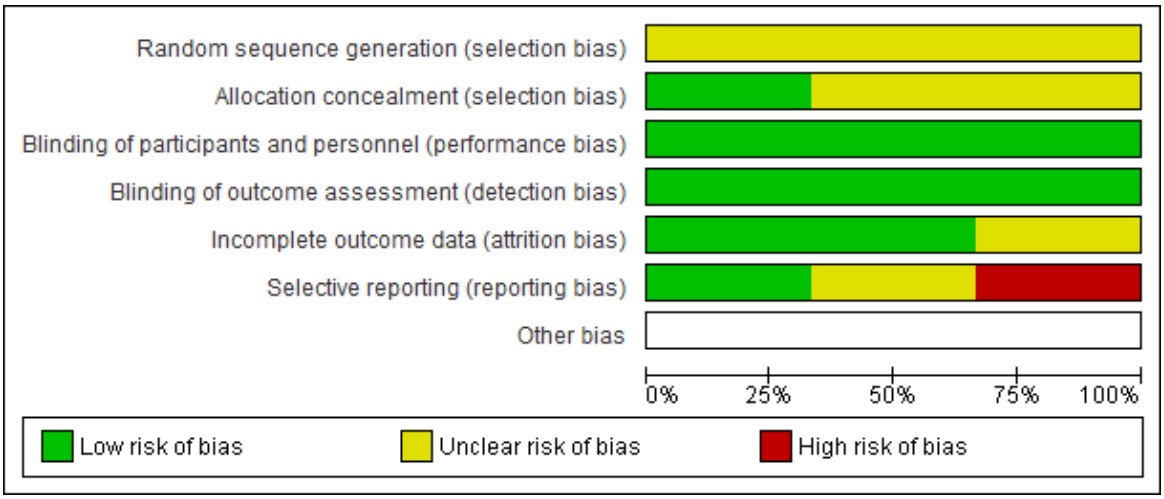
No evidence was retrieved suggesting that some patient groups are more likely to be harmed through the use of FLACS in comparison to the use of standard cataract surgery. Patient exclusion criteria were homogeneous across studies and reflected clinical practice for standard cataract surgery.

**[C0007] – How does intervention with FLACS compare to standard cataract surgery in terms of surgeon-dependent harms (i.e., time of surgical procedure, complications, etc.)?**

*Total duration of procedure – mean surgical time (minute)*

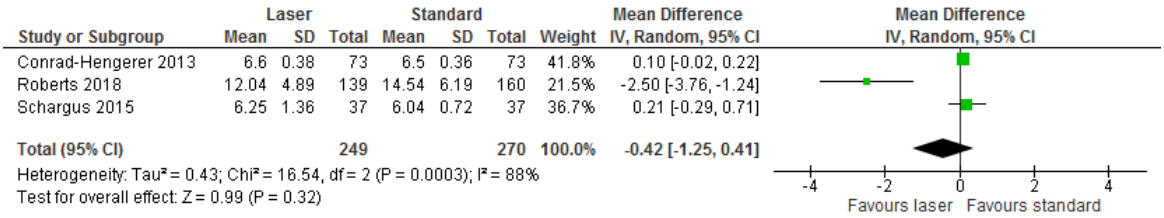
This outcome was not rated as "critical" and has not been included in Summary of Findings table. Three studies (Roberts 2018, Schargus 2015, Conrad-Hengerer 2013) (32,33,47) reported data on mean surgical time. Their risk of bias was judged as not serious (**Figure 31**), although there were concerns over selective reporting in one study (Conrad-Hengerer 2013)(47). The three studies reported conflicts of interests (in terms of sponsorship or one author being consultant or member of the medical advisory board of the firm producing the laser system under study).

**Figure 31 - Risk of bias summary – Mean surgical time**




Results on mean surgical time showed no statistically significant difference between the study arms (**Figure 32**). Overall quality of evidence was judged to be "moderate" due to inconsistency.

**Figure 32 - Forest Plot - Mean surgical time (minutes)**




*Resource use*

One study (Roberts 2018) showed that, within a hub and spoke model (with a single femtosecond laser treating and then feeding patients into several operating rooms), each case treated with FLACS cost £144.60 more than treating it with standard phacoemulsification (£500.02 vs £355.42); an average reduction of 3.05 minutes per case did not provide a sufficient improvement in productivity to meaningfully offset those additional costs (33).

**[B0010] – What kind of data/records and/or registry are needed to monitor the use of FLACS and standard cataract surgery?**

The European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO) is a web-based registry established in 2008 (124) with the aim of improving quality of care and providing a reference database for benchmarking. Participation of centres from all over Europe and input from national registries (81) are very high, with over two and half million cataract surgeries recorded in the past 10 years and around 4.000 cases added annually.

Data from the registry have been used for a preliminary report on performance of FLACS compared to standard cataract surgery (125) with important limitations, as the data are self-reported by self-selected physicians. Despite these limitations, the registry represents a valuable opportunity to collect real world data and could contribute to standardizing outcome measurements to be used in clinical audit programmes.

## DISCUSSION

Cataract is opacity in the crystalline lens of the eye, resulting in various levels of visual impairment.
Cataract tends to be progressive and the speed and extent of decline in visual function depends on several risk factors and presence of ocular comorbidities. Reduction in vision caused by cataract can be reversible if treated with cataract surgery, which is highly successful in restoring visual function with a very favorable risk/benefit ratio.
Age-related cataract is the leading cause of visual impairment worldwide. According to the World Health Organization, 51% of reversible blindness worldwide is due to cataract and more than 30 million people annually worldwide are predicted to undergo cataract surgery by 2020. (126)

Cataract surgery is the most commonly performed ophthalmic procedure, and phacoemulsification is a highly successful technique introduced over 40 years ago. In higher income countries, phacoemulsification is the standard method of cataract surgery and the most frequently used technique for cataract removal.

Standard cataract surgery, and comparator for the present assessment, requires manual formation of an opening in the anterior lens capsule, fragmentation and evacuation of the lens tissue with an ultrasound probe and implantation of a plastic intraocular lens into the remaining capsular bag. The size, shape and position of the anterior capsular opening (one of the most critical steps in the procedure) are controlled by freehand pulling and tearing of the capsular tissue.

Femtosecond lasers were introduced and have been used to perform several stages of phacoemulsification cataract surgery since 2009. Laser-generated pulses of highly focused infrared light perform the cutting by creating localised cavitation bubbles within tissues, a process termed photo-disruption. The ultrashort duration of each pulse is expected to minimise damage to adjacent tissue. During cataract surgery, such lasers are used to create incisions, perform capsulorhexis and fragment the lens. The surgeon plans and decides the target location, then the system delivers the focus of the laser beam to produce the desired incision. The procedure is then completed using conventional phacoemulsification equipment and techniques.

Beside the set of skills needed to perform the steps of the intervention, cataract surgery also requires the cognitive skills, judgment, and experience necessary to recognize and respond to unexpected events, problems, and complications that may arise intraoperatively.

Compared to standard cataract surgery, FLACS systems claim to provide several advantages to the surgeon, such as the performance of very precise circular and adjustable diameter capsulotomies, precise lens nucleus fragmentation, the creation of multi-planar self-sealing incisions with better wound architecture, exact placement of limbal relaxing incisions and the reduction of phacoemulsification time. Femtosecond laser pretreatment is expected to reduce phaco energy, which may in turn reduce the heat damage to ocular tissues by ultrasound. This may translate into reducing endothelial cell loss, and consequently, better outcomes in terms of visual acuity and safety. These systems are expensive both in terms of acquisition costs and disposable and maintenance costs.

There are currently five commercially available systems in Europe and these systems are expensive to acquire. However, the costs may be mitigated if a reduction in complication rates, less repeat surgery and better patient outcomes were to be demonstrated.

## *CLINICAL EFFECTIVENESS OF FLACS COMPARED TO CONVENTIONAL PHACOEMULSIFICATION*

### Selected studies

Ten small-sized RCTs assessed clinical effectiveness outcomes selected for this REA:

- corrected distance visual acuity (CDVA) and uncorrected distance visual acuity (UDVA), measured at one and/or six months post-surgery;
- refractive outcomes (measured as mean absolute error or as absolute deviation spherical equivalent at one week or one month post-surgery);
- patient-reported outcomes.

All the above outcomes were graded as critical by the panel members involved in rating outcome importance (authors, co-authors, dedicated reviewers and external clinical experts).

Of the selected studies, seven provided data that could be used for meta-analysis: five were parallel RCTs and two were paired-eye RCTs, which presented only group data without providing paired data analyses. Three RCTs (Conrad Hengerer 2015, Hida 2014, Nagy 2011)(23,27,30) provided measures and/or follow-up times on refractive outcomes that could not be included in quantitative synthesis. None of the three trials excluded from the meta-analysis reported statistically significant differences between study groups.

### Results and their internal validity

Pooled analyses did not show differences between the two techniques in any of the effectiveness outcomes. Only the pooled estimate for CDVA at 1 and 6 months after surgery were close to statistical significance; however, the effect size, if subsequently proven, would have dubious clinical relevance (a mean difference of 0.06 corresponds to a difference of less than one line in the LogMAR chart).
Not enough data were available for subgroup analyses (according to LOCS type and pseudoexfoliation).

Only one paired-eye trial assessed patient-reported outcomes and reported a slightly higher preference for conventional surgery, although differences were not statistically significant.

Confidence in these results, based on the quality of evidence, is variable according to specific outcomes, ranging from moderate to very low. Overall, studies were judged to carry a serious or very serious risk of bias, due to lack of blinded outcome assessment in most of the studies and allocation concealment was not adequately described in most studies. All RCTs were open label as blinding of surgical procedure is not possible; this could influence the evaluation of effectiveness outcomes if blinded assessment is not ensured. In addition, study protocols could not be retrieved, and we were not able to assess whether selective reporting and post-hoc statistical analyses might have occurred. Finally, poor reporting in most of the studies precluded assessment of any important attrition bias (i.e., more than 5% of randomised patients lost to follow up). Moreover, inconsistency was observed for UDVA at 1 and 6 months.

None of the trials was powered to investigate differences in effectiveness; a clear definition of primary and secondary outcomes was also generally lacking, as well as rigorous sample size calculations. As for conflicts of interests (COI), four RCTs reported funding by laser producers and

other types of COI. Some research groups published more than one RCT, and it was not possible to assess whether patients were double-counted.

Overall quality of evidence was judged as “low” for CDVA at one and six months, as “very low” for UDVA at one and six months and “low” for refractive outcomes. Quality of evidence for patient-reported outcomes could not be assessed due to the very limited data available.

### External validity

Except for Yu 2015 (28) and Donnenfeld 2018 (29), all included RCTs were carried out in Europe. Patient characteristics seem to adequately reflect the target population for cataract surgery: despite some heterogeneity among trials, most recruited patients aged over 65 and excluded patients with glaucoma, astigmatism > 1.5 or >2 dioptres, endothelial cell count less than 1,200 cells/mm, CDVA decreased by less than 0.1 LogMAR, poorly dilated pupils, corneal scars, corneal diseases, previous ocular surgery or trauma. As for surgery techniques assessed, they adequately reflect the general modus operandi in cataract surgery, with few and not relevant differences in terms of surgery protocols. In most studies FLACS procedure was performed by a single, very experienced surgeon.

It should be noted that effectiveness outcomes described in the selected studies are quite heterogeneous in terms of measurements (e.g., for refractive outcomes we found data on spherical error, spherical equivalent, absolute deviation spherical equivalent, manifest refraction spherical equivalent, mean absolute error), reporting (e.g., visual acuity expressed in decimal or log scale) and length of follow up (from 1 day to six months). Future research and assessment would certainly benefit from a definition, shared and agreed upon by researchers and clinicians, of outcome measurements and follow-up timings best representing clinically relevant benefits.

## *SAFETY OF FLACS COMPARED TO CONVENTIONAL PHACOEMULSIFICATION*

### Selected studies

No non-randomized study meeting our inclusion criteria was retrieved.

Fifteen small-sized RCTs assessed clinical safety outcomes selected for this REA:

- intraoperative complications: anterior and posterior capsular tear, vitreous loss;
- postoperative complications: cystoid macular oedema, infections, posterior capsule opacification, surgically induced astigmatism, endothelial cell loss at three months, elevated intraocular pressure, central corneal thickness.

Except for surgically induced astigmatism, elevated intraocular pressure and central corneal thickness, all other safety outcomes were graded as critical by the panel members involved in rating of outcome importance (authors, co-authors, dedicated reviewers and external experts).

No data were found on the following outcomes graded as critical: retinal detachment, visual acuity loss post-surgery, surgical re-intervention, secondary cataract, iridocyclitis.

Twelve trials provided data that could be used for meta-analysis: six were parallel RCTs and six were paired-eye RCTs, which presented only group data without providing paired data analyses. The remaining three RCTs (Givaudan Pedroza 2016, Kovacs 2014, Nagy 2014)(41,45,46) provided measures and/or follow-up times on safety outcomes that could not be included in quantitative synthesis. None of the trials excluded from the meta-analysis reported statistically significant differences between study groups.

### Results and their internal validity

Pooled analyses did not show differences between the two techniques in any of the safety outcomes. Not enough data were available for subgroup analyses (according to LOCS type and pseudo-exfoliation).

Confidence in these results, based on the quality of evidence, varies according to specific outcomes, ranging from “low” to “very low”. Specifically risk of bias was evaluated differently for intraoperative and for postoperative complications, as relevance of blinding of outcome assessment differed: judged as "not serious" for intraoperative hard outcomes and as "very serious" for postoperative softer outcomes.

Study protocols could not be retrieved, and we were not able to assess whether selective reporting and post-hoc statistical analyses might have occurred. Finally, poor reporting in most of the studies precluded assessment of any important attrition bias (i.e., more than 5% of randomised patients lost to follow up).

None of the trials was powered to investigate differences in complications; a clear definition of primary and secondary outcomes was also generally lacking, as well as rigorous sample size calculations. As for conflicts of interests, eleven RCTs reported funding by laser producers and other types of conflicts of interests. Some research groups published more than one RCT, and it was not possible to assess whether patients were double-counted.

Overall quality of evidence for critical outcomes was judged as “low” for intraoperative complications. For postoperative complications, rated as critical, overall quality of evidence was judged as “very low” for endothelial cell loss (at 3 and 6 months and cystoid macular oedema), while it was graded as “low” for infections.

### External validity

Except for Yu 2015 and Reddy 2013 (28,42), all included RCTs were carried out in Europe. Patient characteristics in all the selected studies seem to adequately reflect the target population for cataract surgery: despite some heterogeneity among trials, most recruited patients aged over 65 and excluded patients with glaucoma, astigmatism > 1.5 or >2 diopters, endothelial cell count less than 1,200 cells/mm, CDVA decreased by less than 0.1 LogMAR, poorly dilated pupils, corneal scars, corneal diseases, previous ocular surgery or trauma. As for surgery techniques assessed, they adequately reflect the general modus operandi in cataract surgery, with few and not relevant differences in terms of technology producers and surgery protocols. In most studies FLACS procedure was performed by a single, very experienced surgeon.

It should be noted that safety outcomes described in the selected studies are quite heterogeneous in terms of measurements and/or reporting (e.g., endothelial cell loss vs density) and length of follow up (from 1 day to six months). It would be desirable that researchers of future RCTs agreed on common and clinically relevant measures and follow-up times for primary endpoints.

## *PROCEDURAL TIME AND RESOURCE USE*

Limited evidence is available on the impact of each surgical technique on mean surgical time. Four studies reported data on mean surgical time, three of which reporting conflicts of interests. Two studies reported a statistically significant difference in favour of FLACS, whereas the pooled estimate showed no difference between the study arms. A significant heterogeneity among the studies was shown. As for resource use, one UK study showed that, within a hub and spoke model (with a single femtosecond laser treating and then feeding patients into several operating

rooms), the FLACS service cost £144.60 more than standard phacoemulsification per case and that an average reduction of about 3 minutes per case did not provide a sufficient improvement in productivity to meaningfully offset those additional costs. Several studies assessed phaco energy time (surrogate outcome), which was not considered relevant by the panel and was excluded from the list of outcomes for this REA.
Additional data from high quality RCTs may help better define whether FLACS provides any advantage in terms of organization of care and resource use.

### *Evidence gaps and ongoing studies*

Eight ongoing studies have been identified relevant to our Scope. Four small studies, conducted in Spain, India, Mexico and Brasil, appear to be completed but with no results. Two small studies ongoing in the United States and Singapore are expected to be completed in 2019. Two large publicly funded adequately powered ongoing RCTs (34,35) of much larger size compared to the previous trials are expected to add relevant evidence which may more adequately answer public health questions on cataract surgery and may help to establish whether FLACS provides any advantage over conventional phacoemulsification. Principal investigators of both trials have been contacted during this assessment and assurance of publication has been provided. This REA will be updated as soon as results are published.

### *Patients' opinions about the added value of FLACS*

**Feedback from ASACIR** (Asociación Española de Afectados por la Cirugía Refractiva)**: patients' perspective regarding FLACS**

ASACIR, a Spanish patients' organization interested in refractive surgery, was contacted by a dedicated reviewer and was presented with a late draft of this REA. Its representatives were specifically asked to provide their opinion on cataract surgery and, in this regard, on the possible added value of FLACS. Following is an agreed summary of their opinions and statements.

According to their knowledge and to the opinion of their trusted ophthalmologist, ASACIR representatives stated that "standard phacoemulsification works just as well or better" than FLACS and that "spending money in such an expensive procedure (FLACS) does not make sense". Moreover, they suggest that the use of a suction ring during the FLACS procedure can cause post-operative problems such as posterior vitreous detachment, the appearance of floaters, rhegmatogenous retina detachment and other possible pathologies of the posterior segment of the eye, and that people who undertook refractive surgery could be particularly at risk of suffering such sequelae. They raise an ethical issue related to FLACS use, considering that it "is yet to be perfected … requires a period of learning by surgeons, and all that at the expense of patients … the problem is not only scientific and economic-political, but also ethical".

They highlighted that, within their National Health System, the main objective should be investing resources to prevent cataracts. This goal seems achievable in the near future considering that "preventive and non-surgical treatments for cataracts, such as eye drops lanosterol, will be probably approved in 2021 for humans" (they are already approved and marketed for animal use), so that any "possible long-term benefit of the new surgical technology may perhaps become obsolete in a few years". To support this view they provided links to several articles, which refer to in vitro or animal studies.

Finally, they emphasized the need to allocate public budgets efficiently, and specifically on technologies "that are much more necessary" than FLACS, "such as endothelial cell counting machines or intraocular lenses with customized asphericity for cataract surgery", or other technologies related to refractive surgery, which is their main area of interest. . The original ASACIR's statements, which includes also comments on issues relevant for refractive surgery and not recounted here, is reported in **Appendix 4.**

### *Limitations of the present assessment*

Great attention was dedicated to systematically searching the literature and references were cross-checked, but it is still possible that relevant studies were missed. Despite the availability of several RCTs, heterogeneity in outcome measurement hindered the use of all available data in pooled analyses. As the technology under assessment is costly and the comparator (standard cataract surgery) is considered effective and safe, we did not assess equivalence or non-inferiority between the two interventions. None of the trials included in this assessment was sufficiently powered to prove superiority, equivalence or non-inferiority.

The lack of submission templates from most of the manufacturers did not allow retrieval of potentially relevant grey literature.

Obtaining patients' participation from the start of the project did not prove feasible, despite several attempts. Comments on a late draft from a patient organization representing patients undergoing refractive surgery have been collected and reported.

## CONCLUSION

Regarding the claimed benefits in terms of reduced phacoemulsification time and energy leading to potential clinical advantages for safety and better visual outcomes, there is insufficient evidence to determine whether FLACS leads to any improvement compared to standard cataract surgery in terms of effectiveness, safety or organization of care.

Meta-analysis of currently available data, generally of limited quality, shows either no difference or small, clinically not relevant differences between FLACS and standard cataract surgery in any of the effectiveness and safety outcomes taken into consideration. As the technology under assessment is costly and the comparator (standard cataract surgery) is considered effective and safe, equivalence or non-inferiority between the two interventions was not assessed by this REA nor by the included studies. Evidence cannot therefore be provided on FLACS being equivalent or non-inferior to standard cataract surgery.

Pending results from two large randomised studies could contribute to solving uncertainties. This report will be updated once the results from both studies will be available.

Included studies did not report sufficient data on patient-reported outcomes. As for organizational impact and resource use, available data from one relatively large trial suggest a very limited impact of FLACS on surgery time, which, even within a hub and spoke model, does not provide an improvement in productivity to meaningfully offset the additional costs.

Our findings on effectiveness and safety of the assessed interventions are consistent with findings of a 2016 Cochrane systematic review on this topic, including 16 RCTs, 15 of which were included in this updated assessment on 21 trials. (3)

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# APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

## *Documentation of the Search Strategies*

As the literature search of the included systematic reviews had been run between 1946 and May 2016, our systematic search of the scientific literature had January 2016 as a start date and December 2017 as end date and was re-launched in June 2018. The search was performed using the following databases:

- Cochrane Database of Systematic Reviews (CDSR),
- Centre for Reviews and Dissemination (CRD) Databases,
- CENTRAL.
- Medline (PubMed),
- Embase (Embase.com),
- Web of Science (Web of Knowledge),
- Scopus,
- References of included studies.

In addition, the following clinical trial databases were searched to identify ongoing studies
- Clinicaltrials.gov,
- International ClinicalTrials Registry Platform (ICTRP),
- UK Clinical Trials gateway,
- EU Clinical Trials Register (EU CTR).

The search strategy developed for all databases was the following:

(exp Lasers/ OR exp Laser Therapy/) AND (exp Cataract Extraction/ OR exp Cataract/ OR exp Capsulorhexis/ OR exp Phacoemulsification/) OR ((femtosecond or laser* or bladeless or alcon LenSx or Optimedica Catalys or Lensar or Victus or intralase or IFS laser systems) AND (capsulor?hexis or phacoemulsification or phaco or phako OR cataract* OR capsulotom*))

## SEARCH STRATEGY FOR ONGOING STUDIES

The search was performed using the following databases:

Clinicaltrials.gov
International Clinical Trials Registry Platform
UK Clinical Trials Gateway
ISRCTN Registry
EU Clinical Trials Register

The search strategy developed for all databases was the following:

(phacoemulsification OR capsulorhexis OR capsulotom*) AND (femtosecond OR lenxs OR lensar OR victus)

## *DESCRIPTION OF THE EVIDENCE USED*

## Guidelines for diagnosis and management

**Table A 1 - Overview of guidelines**

| Name of society/organisation issuing guidance | Date of issue | Country/ies to which applicable | Summary of recommendation | Level of evidence |
|---|---|---|---|---|
| American Academy of Ophthalmology<br>"Cataract in the Adult Eye PPP – 2016" (13) | 09 Sep 2016 | USA | The standard of care in cataract surgery in the United States is a small-incision phacoemulsification with foldable intraocular lens (IOL) implantation. It is a standard of care that has withstood the test of time. | Not reported |
| The Royal College of Ophthalmiologists<br>"Cataract surgery Guidelines" (127) | Sep 2010 | UK | 4.10 Surgery<br>Phacoemulsification is the preferred method of cataract surgery in the developed world, but extracapsular surgery is still occasionally necessary. | Not reported |
| NICE<br>Cataracts in adults: management (4) | 26 Oct 2017 | UK | 1.2 Referral for cataract surgery<br>1.2.1 Base the decision to refer a person with a cataract for surgery on a discussion with them (and their family members or carers, as ppropriate) that includes: how the cataract affects the person's vision and quality of life whether 1 or both eyes are affected what cataract surgery involves, including possible risks and benefits how the person's quality of life may be affected if they choose not to have cataract surgery whether the person wants to have cataract surgery.<br>1.2.2 Do not restrict access to cataract surgery on the basis of visual acuity.<br>1.6.1 Only use femtosecond laser-assisted cataract surgery as part of a randomised controlled trial that includes collection of resource-use data, comparing femtosecond laser-assisted cataract surgery with ultrasound phacoemulsification. | Not reported |
| Canadian Ophthalmolgical Society<br>Canadian Ophthalmological | Oct 2008 | CANADA | 1. Cataract surgery is indicated primarily for the correction of visual impairment that cannot be | 1 [Level 3] * |

| Name of society/organisation issuing guidance | Date of issue | Country/ies to which applicable | Summary of recommendation | Level of evidence |
|---|---|---|---|---|
| Society evidence-based clinical practice guidelines for cataract surgery in the adult eye (128) | | | adequately improved nonsurgically and that is directly attributable to the presence of a lens opacity<br>2. Even in the absence of functional symptoms, cataract surgery is indicated to meet visual acuity standards when a patient's visual acuity falls below legal standards for activities (such as driving, military service, or flying) and the patient wishes to continue to perform these activities<br>3. Small-incision phacoemulsification is recommended, as it provides faster, improved, and more stable visual acuity with reduced surgical complications compared with ECCE<br>Planned ECCE may be performed in select cases, such as in the presence of extremely advanced cataracts or hard lenses [Consensus].<br>4. Incision type selection and placement should be performed based on ideal construction, providing optimal access to the anterior chamber, watertight closure, and minimal undesired impact on surgically induced astigmatism<br>5. Smaller incisions are less prone to inducing corneal cylinder<br>6. A continuous curvilinear capsulorhexis with overlap over the periphery of the IOL optic is recommended to aid in retarding PCO<br>7. Hydrodissection should be routinely performed (except in the presence of posterior polar cataract) to reduce zonular stress and facilitate cortical removal with reduction of PCO | 2 [Consensus]*<br>3 [Level 1A] *<br>4 [Consensus]*<br>5 [Level 3] *<br>6 [Level 1A] *<br>7 [Level 3] * |
| European Registry of Quality Outcomes for Cataract and Refractive Surgery<br>(EUREQUO)(36) | 2012 | EU | Phacoemulsification is the preferred surgical technique. However, extracapsular cataract extraction<br>(ECCE) may be the preferred technique in specific cases. | Not reported |

| Name of society/organisation issuing guidance | Date of issue | Country/ies to which applicable | Summary of recommendation | Level of evidence |
|---|---|---|---|---|
| Evidence-based guidelines for cataract surgery: Guidelines based on data in the European Registry of Quality Outcomes for Cataract and Refractive Surgery database | | | | |

* Level of evidence of “Canadian Ophthalmological Society evidence-based clinical practice guidelines for cataract surgery in the adult eye“: Level 1A Systematic review or meta-analysis of high-quality randomized, controlled trials; Level 3 Non-randomized clinical trial or cohort study; Consensus: In the absence of direct evidence, recommendations were written to reflect unanimous consensus of the Expert Committee. (128)

## Evidence tables of individual studies included for clinical effectiveness and safety

**Table A 2 - Characteristics of randomised controlled studies, Conrad-Hengerer 2013** (47)

| RANDOMIZED CONTROLLED TRIALS | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Conrad-Hengerer 2013 (47) |
| Authors: | Ina Conrad-Hengerer, Mayss Al Juburi, Tim Schultz, Fritz H. Hengerer, H. Burkhard Dick |
| English Title: | Corneal endothelial cell loss and corneal thickness in conventional compared with femtosecond laser–assisted cataract surgery: Three-month follow up |
| Original Title: | See English Title |
| Journal/Book/Source: | J Cataract Refract Surg |
| Date of Publication: | September 2013 |
| Volume: | 39 |
| Issue: | |
| Pages: | 1307–1313 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up)) | Intraindividual prospective randomly distributed trial with 3 months follow up<br><br>Within person, paired-eye RCT |
| **Participants** | |
| Total Number of Participants randomized | 75 |
| Total Number of eyes randomized | 150 (75 patients)<br>The study evaluated 146 eyes (73 patients) |
| Country of participants | Germany |
| Data collection period | From February to July 2012, and 3 months of f.u. |
| Inclusion criteria | Visually significant cataract, dilated pupil width of 6.0 mm or larger |
| Exclusion criteria | • a history of serious coexisting ocular disease,<br>• uncontrolled glaucoma,<br>• optic atrophy or ocular tumors,<br>• use of topical or systemic steroids or nonsteroidal anti-inflammatory drugs (NSAIDs) during the previous 3 months,<br>• relevant corneal opacities,<br>• poorly dilating pupils (pupil % 6.0 mm),<br>• known zonular weakness,<br>• age less than 22 years,<br>• participation in another clinical study. |
| Average age (intervention and control) | 70.9 years (range 46 to 86) |
| Sex % (intervention and control) | 46 women of 73 patients (63%) |
| Number of patients in Intervention group | 75 (2 lost at follow up) |
| Number of patients in control group | 75 (2 lost at follow up) |
| Sub population 1 – LOCS GRADE | LOCSIII (for EPT analysis) |
| Sub population 2 - SUBEX-FOLIATION | |
| Professional participant | All femtosecond laser–assisted and phacoemulsification |

<table>
<tr><td></td><td colspan="2">procedures and IOL implantations were performed by the same experienced surgeon (H.B.D.).</td></tr>
<tr><td>Intervention</td><td colspan="2">Femtosecond Laser-Assisted PhacCDoemulsification</td></tr>
<tr><td>Comparator</td><td colspan="2">Standard Phacoemulsification</td></tr>
<tr><td>Outcomes (list all outcomes)</td><td colspan="2">• Endothelial cell count (ECC) 1 day, 3 to 4 days, 1 week, 6 weeks, 3 months after surgery<br>• Corneal thickness 1 day, 3 to 4 days, 1 week, 6 weeks, 3 months after surgery<br>• Endothelial cell loss % 1 day, 3 to 4 days, 1 week, 6 weeks, 3 months day after surgery<br>• CDVA 1 day, 3 to 4 days, 1 week after surgery<br>• Effective Phacoemulsification Time (EPT)<br>• Used balanced salt irrigation solution (ml)<br>• Total surgery time (second)<br>• Anterior capsule tear<br>• Macular edema<br>• Subclinical macular edema<br>• Elevated Intraocular pressure after surgery 1 day and 1 week postoperatively</td></tr>
<tr><td>Notes (Funding source; Conflicts of Interest; trial registration number; any other note)</td><td colspan="2">Dr. Dick is a member of the medical advisory board of Optimedica Corp. No<br>other author has a financial or proprietary interest in any material or method mentioned.</td></tr>
<tr><td>Risk of bias RCTs</td><td>Authors' judgment</td><td>Support for judgement</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Unclear risk</td><td>Insufficient information about the sequence generation process</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear risk</td><td>Assignment envelopes are used but it remains unclear whether envelopes are numbered, opaque and sealed</td></tr>
<tr><td>Blinding of participants and personnel (performance bias)</td><td>High risk</td><td>No blinding, open trial</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>All patients had a full clinical examination by the same masked trained technician.</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>No missing outcome data (only 2 lost to follow up)</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>High risk</td><td>No protocol available, no results for CDVA</td></tr>
<tr><td>Outcomes</td><td colspan="2"></td></tr>
<tr><td>SAFETY</td><td colspan="2"></td></tr>
<tr><td>Posterior capsular tear</td><td></td><td></td></tr>
<tr><td>Anterior capsular tear</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0</td><td>73</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>1</td><td>73</td></tr></table></td></tr>
<tr><td>Vitreous loss</td><td></td><td></td></tr>
<tr><td>Cystoid macula edema (within 90 days)</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>2</td><td>73</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>3</td><td>73</td></tr></table></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 day)</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>2</td><td>73</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>2</td><td>73</td></tr></table></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 week)</td><td></td><td></td></tr>
</table>

| | | |
|---|---|---|
| | Experimental<br>Events: 1 / Total: 73 | Control<br>Events: 0 / Total: 73 |
| Endothelial Cell Loss (ECL) | 1 week<br>Experimental<br>Events Mean ± sd: 7.9% ±7.8% / Total: 73<br><br>3 months<br>Experimental<br>Events Mean ± sd: 8.1% ±8.1% / Total: 73 | 1 week<br>Control<br>Events Mean ± sd: 12.1%±7.3% / Total: 73<br><br>3 months<br>Control<br>Events Mean ± sd: 13.7%±8.4% / Total: 73 |
| Central Corneal Thickness (CCT) | 1 day<br>Experimental<br>Events Mean relative change ± sd: -0.0%±1.9% / Total: 73<br><br>1 week<br>Experimental<br>Events Mean relative change ± sd: 2.8%±1.8% / Total: 73<br><br>3 months<br>Experimental<br>Events Mean relative change ± sd: 3.3%±1.7% / Total: 73 | 1 day<br>Experimental<br>Events Mean relative change ± sd: -0.9%±2.3% / Total: 73<br><br>1 week<br>Experimental<br>Events Mean relative change ± sd: 2.4%±1.5% / Total: 73<br><br>3 months<br>Experimental<br>Events Mean relative change ± sd: 3.2%±1.4% / Total: 73 |
| Idrocyclitis | | |
| Infections (within 90 days) | | |
| Corneal Endothelial Decompensation (within 90 days) | | |
| Surgical induced astigmatism | | |
| Retinal detachment | | |
| Posterior capsule opacification | | |
| Visual acuity loss post cataract surgery (1 month) | | |
| Visual acuity loss post cataract surgery (6 months) | | |
| Surgical re-intervention (within 6 months) | | |
| Secondary cataract (24 months) | | |
| **EFFECTIVENESS** | | |
| Corrected Distance Visual Acuity (CDVA) 1 month after surgery | | |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | | |

<table>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery</td><td></td><td></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery</td><td></td><td></td></tr>
<tr><td>Refractive outcomes</td><td></td><td></td></tr>
<tr><td>Vision-related Quality of Life (by validated questionnaire)</td><td></td><td></td></tr>
<tr><td>Patient-reported outcome measures (PROMs)</td><td></td><td></td></tr>
<tr><td>OTHER OUTCOMES</td><td></td><td></td></tr>
<tr><td>Patient satisfaction</td><td></td><td></td></tr>
<tr><td>Procedural time</td><td>Mean Surgical Time (second)<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>396±23</td><td>73</td></tr></table>Effective Phacoemusification Time (EPT)<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events mean±sd</td><td>Total</td></tr><tr><td>0.0±0.1</td><td>73</td></tr></table></td><td>Mean Surgical Time (second)<table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>390±22</td><td>73</td></tr></table>Effective Phacoemusification Time (EPT)<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events mean±sd</td><td>Total</td></tr><tr><td>1.4±0.1</td><td>73</td></tr></table></td></tr>
<tr><td>Resource use</td><td></td><td></td></tr>
<tr><td>Additional outcomes</td><td></td><td></td></tr>
<tr><td>Notes</td><td></td><td></td></tr>
</table>

**Table A 3 - Characteristics of randomised controlled studies, Conrad-Hengerer 2014** (48)

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Conrad-Hengerer 2014 (48) |
| Authors: | Conrad-Hengerer I, Hengerer FH, Al Juburi M, Schultz T, Dick HB |
| English Title: | Femtosecond Laser-Induced Macular Changes and Anterior Segment Inflammation in Cataract Surgery |
| Original Title: | |
| Journal/Book/Source: | J Refract Surg |
| Date of Publication: | 2014 |
| Volume: | 30 |
| Issue: | 4 |
| Pages: | 222-226 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Within person – paired-eye RCT. Follow up: 6 months |
| **Participants** | |
| Total Number of Participants randomized | 104 |

| | | |
|---|---|---|
| Total Number of eyes randomized | 208 | |
| Country of participants | Germany | |
| Data collection period | Patient enrolment from March to October 2012, plus follow up (6 months) | |
| Inclusion criteria | Visually significant cataracts | |
| Exclusion criteria | History of coexistent ocular disease (eg, glaucoma, high myopia, retinal diseases affecting the macula, optic atrophy, or ocular tumors), use of topical or systemic steroids or nonsteroidal anti-inflammatory drugs during the prior 3 months, relevant corneal opacities, age younger than 22 years, or participation in another clinical study | |
| Average age | 71.3 | |
| Sex % | 55.8% females | |
| Number of patients in Intervention group | 104 patients (104 eyes) | |
| Number of patients in control group | 104 patients (104 eyes) | |
| Sub population 1 – LOCS GRADE | Mean LOCS grade: 3.2 (interv)<br>Mean LOCS grade: 3.1 (control) | |
| Sub population 2 - SUBEX-FOLIATION | | |
| I**nterventions** (experimental and control) | Femtosecond laser-assisted cataract surgery (Catalys Precision Laser System; OptiMedica, CA) | |
| **Comparator** | Standard phacoemulsification | |
| **Outcomes** (list all outcomes) | Central macular thickness, central foveal thickness, total macular volume, total foveal volume, absolute and effective phacoemulsification time, surgery time, volume of irrigation fluid instilled, laser flare counts from the anterior chamber, changes in macular thickness and volume, intraoperative and postoperative complications | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | One of the authors (Dr. Dick) was a member of the medical advisory board of Optimedica Corp., the firm producing the laser system used in this study | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | No information available |
| Allocation concealment (selection bias) | Unclear risk | Envelopes used (although it is not clear whether they were opaque and sealed) |
| Blinding of participants and personnel (performance bias) | High risk | Open trial |
| Blinding of outcome assessment (detection bias) | High risk | No blinding of assessment is described |
| Incomplete outcome data (attrition bias) | Low risk | Two hundred and two eyes (97%) were included and analyzed at 6 months postoperatively. Information has not been provided on reasons for |

| | | |
|---|---|---|
| | | not including the remaining 6 eyes |
| Selective reporting (reporting bias) | Unclear risk | A study protocol is not available |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | | |
| Anterior capsular tear | | |
| Vitreous loss | | |
| Cystoid macula oedema (within 90 days) | Experimental: Events 2, Total 101 | Control: Events 3, Total 101 |
| Elevated Intraocular Pressure (IOP) (postoperatively) | Experimental: Events 1, Total 101 | Control: Events 2, Total 101 |
| Elevated Intraocular Pressure (IOP) (1 week) | Experimental: Events 0, Total 101 | Control: Events 1, Total 101 |
| Endothelial Cell Loss (ECL) 1 week | | |
| Endothelial Cell Loss (ECL) 3 months | | |
| Central Corneal Thickness (CCT) 1 day | | |
| Central Corneal Thickness (CCT) 1 week | | |
| Central Corneal Thickness (CCT) 3 months | | |
| Idrocyclitis | | |
| Infections (within 90 days) | | |
| Corneal Endothelial Decompensation (within 90 days) | | |
| Surgical induced astigmatism | | |
| Retinal detachment | | |
| Posterior capsule opacification | | |
| Visual acuity loss post cataract surgery (1 month) | | |
| Visual acuity loss post cataract surgery (6 months) | | |
| Surgical re-intervention (within 6 months) | | |

| | | |
|---|---|---|
| Secondary cataract (24 months) | | |
| **EFFECTIVENESS** | | |
| Corrected Distance Visual Acuity (CDVA) 1 month after surgery | | |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery | | |
| Refractive outcomes | | |
| Vision-related Quality of Life (by validated questionnaire) | | |
| Patient-reported outcome measures (PROMs) | | |
| **OTHER OUTCOMES** | | |
| Patient satisfaction | | |
| Effective phacoemulsification time | Experimental<br>Mean ± SD (sec): 0.035±0.11<br>Total: 101 | Control<br>Mean ± SD (sec): 1.39±0.13<br>Total: 101 |
| Procedural time | | |
| Resource use | | |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 4 - Characteristics of randomised controlled studies, Conrad-Hengerer 2015** (30)

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Conrad-Hengerer 2015 (30) |
| Authors: | Conrad-Hengerer I, Al Sheikh M, Hengerer FH, Schultz T, Dick HB |
| English Title: | Comparison of visual recovery and refractive stability between femtosecond laser–assisted cataract surgery and standard phacoemulsification: Six months follow up |
| Original Title: | See English Title |
| Journal/Book/Source: | J Cataract Refract Surg |
| Date of Publication: | 2015 |
| Volume: | 41 |
| Issue: | |

| | | |
|---|---|---|
| Pages: | 1356–1364 | |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up)) | Intraindividual prospective randomly distributed trial with 6 months follow up<br><br>Within person, paired-eye RCT | |
| **Participants** | | |
| Total Number of Participants randomized | 100 | |
| Total Number of eyes randomized | 200 (100 patients) | |
| Country of participants | Germany | |
| Data collection period | | |
| Inclusion criteria | Visually significant cataract, a potential corrected visual acuity of 0.8 (20/25) in both eyes, dilated pupil of at least 6.0 mm preoperatively | |
| Exclusion criteria | Amblyopia, a history of serious coexistent ocular disease (eg, pseudoexfoliation, uncontrolled glaucoma, macular pathologies, high myopia, or hyperopia, defined as an axial length [AL]<21.5mm or > 27.5 mm), corneal astigmatism of more than 1.5 diopters (D), optic atrophy, ocular tumors, use of topical or systemic steroids or nonsteroidal anti-inflammatory drugs during the previous 3 months, relevant corneal opacities, Fuchs dystrophy, cornea guttata, an age younger than 22 years, and participation in another clinical study. | |
| Average age (intervention and control) | 71.6 years (range 49 to 86) | |
| Sex % (intervention and control) | 56% women | |
| Number of patients in Intervention group | 100 (100 eyes) | |
| Number of patients in control group | 100 (100 eyes) | |
| Subpopulation 1 – LOCS GRADE | | |
| Subpopulation 2 - SUBEXFOLIATION | Excluded | |
| Professional participant | All femtosecond laser–assisted and phacoemulsification procedures and IOL implantations were performed by the same experienced surgeon (H.B.D.). | |
| I**ntervention** | Femtosecond Laser-Assisted surgery (Catalys Precision Laser System, Abbott Medical Optics, Inc.) | |
| **Comparator** | Standard Phacoemulsification | |
| **Outcomes** (list all outcomes) | Early and late corrected distance visual acuity (CDVA), deviation from the target refraction using the spherical equivalent (SE) refraction, anterior chamber depth (ACD) and keratometry values, anterior capsular tear, vitreous loss, postoperative intraocular pressure, macular oedema, endophtalmitis | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | Dr. Dick is a member of the medical advisory board of Optimedica Corp. No other author has a financial or proprietary interest in any material or method mentioned. | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | No information available |
| Allocation concealment (selection bias) | Unclear risk | Envelopes used (although it is not clear whether they were opaque and sealed) |
| Blinding of participants and personnel (performance bias) | High risk | Open trial |
| Blinding of outcome assessment (detection bias) | High risk | No blinding of assessment is described |
| Incomplete outcome data (attrition | Low risk | No eyes were lost to follow-up |

| | | |
|---|---|---|
| bias) | | |
| Selective reporting (reporting bias) | Unclear risk | A study protocol is not available |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | | |
| Anterior capsular tear | Experimental: Events 1, Total 100 | Control: Events 0, Total 100 |
| Vitreous loss | Experimental: Events 0, Total 100 | Control: Events 0, Total 100 |
| Cystoid macula edema (postoperatively) | Experimental: Events 1, Total 100 | Control: Events 2, Total 100 |
| Cystoid macula edema (30 days) | Experimental: Events 0, Total 100 | Control: Events 1, Total 100 |
| Elevated Intraocular Pressure (IOP) (2 hours) | Experimental: Events 3, Total 100 | Control: Events 2, Total 100 |
| Elevated Intraocular Pressure (IOP) (1 week) | Experimental: Events 0, Total 100 | Control: Events 0, Total 100 |
| Endothelial Cell Loss (ECL) | | |
| Central Corneal Thickness (CCT) | | |
| Idrocyclitis | | |
| Infections (endophtalmitis - within 90 days) | Experimental: Events 0, Total 100 | Control: Events 0, Total 100 |
| Corneal Endothelial Decompensation (within 90 days) | | |
| Surgically induced astigmatism | | |
| Retinal detachment | | |
| Posterior capsule opacification | | |
| Visual acuity loss post cataract surgery (1 month) | | |
| Visual acuity loss post cataract surgery (6 months) | | |
| Surgical re-intervention (within 6 months) | | |
| Secondary cataract (24 months) | | |
| **EFFECTIVENESS** | | |
| Corrected Distance Visual Acuity (CDVA) 1 month after surgery | | |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery | | |

| | | |
|---|---|---|
| Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery | | |
| Refractive outcomes (spherical equivalent) – 1 month | Experimental<br>Mean ± SD: -0.05±0.28<br>Total: 100 | Control<br>Mean ± SD: -0.18±0.54<br>Total: 100 |
| Refractive outcomes (spherical equivalent) – 6 months | Experimental<br>Mean ± SD: -0.05±0.28<br>Total: 98 | Control<br>Mean ± SD: -0.11±0.55<br>Total: 98 |
| Vision-related Quality of Life (by validated questionnaire) | | |
| Patient-reported outcome measures (PROMs) | | |
| **OTHER OUTCOMES** | | |
| Patient satisfaction | | |
| Procedural time | Effective Phacoemusification Time (EPT)<br>Experimental<br>Events mean±sd: 0.0±0.1<br>Total: 100 | Effective Phacoemusification Time (EPT)<br>Control<br>Events mean±sd: 1.3±1.1<br>Total: 100 |
| Resource use | | |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 5 - Characteristics of randomised controlled studies, Dick 2014** (49)

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Dick 2014 (49) |
| Authors: | H. Burkhard Dick, Ina Conrad-Hengerer, Tim Schultz |
| English Title: | Intraindividual Capsular Bag Shrinkage Comparing Standard and Laser-Assisted Cataract Surgery |
| Original Title: | See English Title |
| Journal/Book/Source: | J Refract Surg. |
| Date of Publication: | April 2014 |
| Volume: | 30 |
| Issue: | 4 |
| Pages: | 228-233 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Intraindividual trial, 3 months follow up<br><br>paired-eye RCT-within period |
| **Participants** | |
| Total Number of Participants randomized | 53 |
| Total Number of eyes randomized | 106 (53 patients) |
| Country of participants | Germany |
| Data collection period | - |
| Inclusion criteria | All patients enrolled had a visually significant cataract (corrected distance visual acuity < 20/25) in both eyes, dilated pupil width of 6.0 mm or greater and were willing to volun- |

| | | |
|---|---|---|
| | teer for the trial after giving an informed consent. | |
| Exclusion criteria | • corneal scars<br>• corneal diseases<br>• corneal astigmatism of 1.5 diopters or greater<br>• reduced endothelial cells<br>• glaucoma<br>• pseudoexfoliation syndrome<br>• zonular weakness<br>• single eye<br>• malformations<br>• history of ocular surgery<br>• intraocular tumors<br>• active or past inflammations<br>• age-related macular degeneration<br>• diabetic retinopathy<br>• axial length difference (greater than 0.5 mm and less than 21.5 mm or greater than 26 mm),<br>• pregnancy<br>• Reduced compliance<br>• age younger than 22 years<br>• participation in another clinical study | |
| Average age (intervention and control) | 70.8±7.9 (range: 54 to 86 year) | |
| Sex % (intervention and control) | 32 women of 53 patients (60%) | |
| Number of patients in Intervention group | 53 | |
| Number of patients in control group | 53 | |
| Subpopulation 1 – LOCS GRADE | | |
| Subpopulation 2 - SUBEXFOLIATION | Exclued | |
| Professional participant | All laser-assisted cataract surgery and standard phacoemulsification procedures were followed by IOL implantation and performed by the same experienced surgeon (H.B.D) | |
| I**ntervention** | Laser-assisted cataract surgery (Catalys Percision Laser System; Abbott Medicak Optics) | |
| **Comparator** | Standard cataract surgery | |
| **Outcomes** (list all outcomes) | • Capsular bag diameters postoperatively, at 3 days, at 7 days, at 1 month, at 2 months, at 3 months<br>• Intraindividual difference in capsular bag diameters (ml) postoperatively, at 3 days, at 7 days, at 1 month, at 2 months, at 3 months<br>Effective Phscoemulsification Time (EPT) | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | The authors have no financial or proprietary interest in the materials presented herein. | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Insufficient information about the sequence generation process |
| Allocation concealment (selection bias) | Unclear risk | Assignment envelopes are used but it remains unclear whether envelopes are numbered, opaque and sealed |
| Blinding of participants and personnel (performance bias) | High risk | No blinding, open trial |
| Blinding of outcome assessment (detection bias) | Low risk | Masked technician |
| Incomplete outcome data (attrition | Low risk | No patient lost to follow up |

<table>
<tr><td>bias)</td><td></td><td></td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Unclear risk</td><td>Protocol not available</td></tr>
<tr><td>Outcomes</td><td></td><td></td></tr>
<tr><td>SAFETY</td><td></td><td></td></tr>
<tr><td>Posterior capsular tear</td><td></td><td></td></tr>
<tr><td>Anterior capsular tear</td><td></td><td></td></tr>
<tr><td>Vitreous loss</td><td></td><td></td></tr>
<tr><td>Cystoid macula oedema (within 90 days)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 day)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 week)</td><td></td><td></td></tr>
<tr><td>Endothelial Cell Loss (ECL)</td><td></td><td></td></tr>
<tr><td>Central Corneal Thickness (CCT)</td><td></td><td></td></tr>
<tr><td>Idrocyclitis</td><td></td><td></td></tr>
<tr><td>Infections (within 90 days)</td><td></td><td></td></tr>
<tr><td>Corneal Endothelial Decompensation (within 90 days)</td><td></td><td></td></tr>
<tr><td>Surgical induced astigmatism</td><td></td><td></td></tr>
<tr><td>Retinal detachment</td><td></td><td></td></tr>
<tr><td>Posterior capsule opacification</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (1 month)</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (6 months)</td><td></td><td></td></tr>
<tr><td>Surgical re-intervention (within 6 months)</td><td></td><td></td></tr>
<tr><td>Secondary cataract (24 months)</td><td></td><td></td></tr>
<tr><td>EFFECTIVENESS</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 1 month after surgery</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 6 months after surgery</td><td></td><td></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery</td><td></td><td></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery</td><td></td><td></td></tr>
<tr><td>Refractive outcomes</td><td></td><td></td></tr>
<tr><td>Vision-related Quality of Life (by validated questionnaire)</td><td></td><td></td></tr>
<tr><td>Patient-reported outcome measures (PROMs)</td><td></td><td></td></tr>
<tr><td>OTHER OUTCOMES</td><td></td><td></td></tr>
<tr><td>Patient satisfaction</td><td></td><td></td></tr>
<tr><td>Procedural time</td><td>Effective Phacoemusification Time (EPT)<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events mean±sd</td><td>Total</td></tr><tr><td>0.03±0.01</td><td>53</td></tr></table></td><td>Effective Phacoemusification Time (EPT)<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events mean±sd</td><td>Total</td></tr><tr><td>1.25±1.06</td><td>53</td></tr></table></td></tr>
<tr><td>Resource use</td><td></td><td></td></tr>
<tr><td>Additional outcomes</td><td></td><td></td></tr>
<tr><td>Notes</td><td></td><td></td></tr>
</table>

**Table A 6 - Characteristics of randomised controlled studies, Donnefeld 2018** (29)

| RANDOMIZED CONTROLLED TRIALS | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Donnenfeld 2018 (29) |
| Authors: | Eric Donnenfeld, MD, Eric Rosenberg, DO, Henry Boozan, BA, Zac Davis, BA, Alanna Nattis, DO |
| English Title: | Randomized prospective evaluation of the wound integrity of primary clear corneal incisions made with a femtosecond laser versus a manual keratome |
| Original Title: | |
| Journal/Book/Source: | J Cataract Refract Surg |
| Date of Publication: | 2018 |
| Volume: | 44 |
| Issue: | 3 |
| Pages: | 329–335 |
| Methods (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up)) | Prospective case series, parallel group 3-arm RCT (FLACS in 2 arms) with 1 month follow up |
| Participants | |
| Total Number of Participants randomized | 45 |
| Total Number of eyes randomized | 45 |
| Country of participants | USA |
| Data collection period | July 2015 |
| Inclusion criteria | • Grade 1 to Grade 3 nuclear cataracts<br>• normal wound healing<br>• no systemic corticosteroids |
| Exclusion criteria | • Grade 4 nuclear cataracts<br>• Collagen vascular disease<br>• systemic corticosteroids<br>• patients who could not cooperate with the docking mechanism at the time of surgery<br>• eyes that did not dilate to at least 6.0 mm<br>• keratoconus |
| Average age (intervention and control) | Group A (intervention): 66.9±6.1<br>Group B (intervention) : 67.2±13.5<br>Group C (control) : 67.8±10.1 |
| Sex % (intervention and control) | Group A (intervention): female 53%<br>Group B (intervention) : female 53%<br>Group C (control) : female 67% |
| Number of patients in Intervention group | 30 (15+15) |
| Number of patients in control group | 15 |
| Sub population 1 – LOCS GRADE | Inclusion/Exclusion criteria |
| Sub population 2 - SUBEXFOLIATION | - |
| Professional participant | A separate surgeon performed the femtosecond laser primary incision and was masked from the surgeon performing the cataract surgery, so the forward side cut and the reverse side cut was masked intraoperatively. All the femtosecond laser incisions were performed by 1 experienced femtosecond laser surgeon and all the phacoemulsifications |

| | | |
|---|---|---|
| | were performed by 1 surgeon (E.D.), who is experienced in both femtosecond laser and phacoemulsification surgery. The manual incision was performed by the cataract surgeon (E.D.) and this incision was not masked | |
| Intervention | Group A: femtosecond laser–assisted 110-degree reverse side-cut incisions (the primary CCI was performed with a Catalys femtosecond laser (Abbott Medical Optics, Inc.). Instead of the routine forward anterior side-cut incision (%90 degrees), a 110-degree reverse anterior side-cut incision was performed.)<br><br>Group B: femtosecond laser–assisted 70-degree forward side-cut incisions (Catalys laser treatment was performed with settings similar to those in Group A except the anterior and posterior side-cut angles. A forward anterior side-cut angle of 70 degrees and posterior side-cut angle of 70 degrees were performed.) | |
| Comparator | primary corneal incisions created manually with a metal blade (Group C) | |
| Outcomes (list all outcomes) | - IOP at which the primary incision began to leak<br>- Seidel's test (to assess wound leakage as a measure of wound integrity) with pressure and without pressure, 1 day, 2 weeks and 1 month postoperatively<br>- Severity of wound leakage 1 day, 2 weeks and 1 month postoperatively<br>- IOP measured by Godmann applanation tonometry preoperatively, 1 day, 2 weeks and 1 month postoperatively<br>- pupil size, sphere, cylinder<br>- manifest refraction spherical equivalent<br>- uncorrected distance visual acuity<br>- corrected distance visual acuity<br>- topography<br>- slitlamp examination<br>- adverse events | |
| Notes (Funding source; Conflicts of Interest; trial registration number; any other note) | Supported by an unrestricted grant from Abbott Medical Optics.<br>Dr. Donnenfeld is a consultant to Abbott Medical Optics, Inc. None of the other authors has a financial or proprietary interest in any material or method mentioned. | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | The authors refer to a random number generation list but there is no information about the sequence generation process |
| Allocation concealment (selection bias) | Unclear risk | The method concealment is not described |
| Blinding of participants and personnel (performance bias) | High risk | No blinding of participants and personnel |
| Blinding of outcome assessment (detection bias) | Low risk | The ophthalmologist performing the postoperative evaluations (A.N.) was not the operating surgeon and was masked to all incision types |
| Incomplete outcome data (attrition bias) | Low risk | No missing outcome data |
| Selective reporting (reporting bias) | High risk | One or more outcomes of |

| | | |
|---|---|---|
| | | interest in the review are reported incompletely so that cannot be entered in a meta-analysis (e.g., IOP) |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | Experimental: Events / Total | Control: Events / Total |
| Anterior capsular tear | Experimental: Events / Total | Control: Events / Total |
| Vitreous loss | Experimental: Events / Total | Control: Events / Total |
| Cystoid macular edema (postoperatively) | Experimental: Events / Total | Control: Events / Total |
| Cystoid macular edema (30 days) | Experimental: Events / Total | Control: Events / Total |
| Elevated Intraocular Pressure (IOP) (1 day) | Experimental: Events / Total | Control: Events / Total |
| Elevated Intraocular Pressure (IOP) (1 week) | Experimental: Events / Total | Control: Events / Total |
| Endothelial Cell Loss (ECL) | Experimental: Events / Total | Control: Events / Total |
| Central Corneal Thickness (CCT) | Experimental: Events / Total | Experimental: Events / Total |
| Idrocyclitis | | |

| | | |
|---|---|---|
| | Experimental<br>Events \| Total | Control<br>Events \| Total |
| Infections (within 90 days) | Experimental<br>Events \| Total | Control<br>Events \| Total |
| Corneal Endothelial Decompensation (within 90 days) | Experimental<br>Events \| Total | Control<br>Events \| Total |
| Surgical induced astigmatism | Experimental<br>Events \| Total | Control<br>Events \| Total |
| Retinal detachment | Experimental<br>Events \| Total | Control<br>Events \| Total |
| Posterior capsule opacification | Experimental<br>Events \| Total | Control<br>Events \| Total |
| Visual acuity loss post cataract surgery (1 month) | Experimental<br>Events \| Total | Control<br>Events \| Total |
| Visual acuity loss post cataract surgery (6 months) | Experimental<br>Events \| Total | Control<br>Events \| Total |
| Surgical re-intervention (within 6 months) | Experimental<br>Events \| Total | Control<br>Events \| Total |
| Secondary cataract (24 months) | Experimental<br>Events \| Total | Control<br>Events \| Total |

| | | |
|---|---|---|
| | <table><tr><td></td><td></td></tr></table> | <table><tr><td></td><td></td></tr></table> |
| **EFFECTIVENESS** | | |
| Corrected Distance Visual Acuity (CDVA) 1 month after surgery | <table><tr><td colspan="2">Experimental (GROUP A)<br>logMAR</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>0.01±0.04</td><td>15</td></tr></table><br><table><tr><td colspan="2">Experimental (GROUP B)<br>logMAR</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>0.02±0.04</td><td>15</td></tr></table> | <table><tr><td colspan="2">Control<br>logMAR</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>0.03±0.05</td><td>15</td></tr></table> |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | <table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td></td><td></td></tr></table> | <table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td></td><td></td></tr></table> |
| Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery | <table><tr><td colspan="2">Experimental (GROUP A)<br>logMAR</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>0.13±0.09</td><td>15</td></tr></table><br><table><tr><td colspan="2">Experimental (GROUP B)<br>logMAR</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>0.13±0.05</td><td>15</td></tr></table> | <table><tr><td colspan="2">Control<br>logMAR</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>0.11±0.08</td><td>15</td></tr></table> |
| Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery | <table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td></td><td></td></tr></table> | <table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td></td><td></td></tr></table> |
| Refractive outcomes (MRSE Manifest Refraction Spherical Equivalent, D) | <table><tr><td colspan="2">Experimental (GROUP A)<br>D</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>-0.27±0.32</td><td>15</td></tr></table><br><table><tr><td colspan="2">Experimental (GROUP B)<br>D</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>-0.27±0.27</td><td>15</td></tr></table> | <table><tr><td colspan="2">Control<br>D</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>-0.10±0.29</td><td>15</td></tr></table> |
| Vision-related Quality of Life (by validated questionnaire) | | |

| | | |
|---|---|---|
| | Experimental<br>Events \| Total | Control<br>Events \| Total |
| Patient-reported outcome measures (PROMs) | Experimental<br>Events \| Total | Control<br>Events \| Total |
| **OTHER OUTCOMES** | | |
| Patient satisfaction | Experimental<br>Events \| Total | Control<br>Events \| Total |
| Procedural time | Mean Surgical Time<br>Experimental<br>Events \| Total | Mean Surgical Time<br>Control<br>Events \| Total |
| Resource use | Experimental<br>Events \| Total | Control<br>Events \| Total |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 7 - Characteristics of randomised controlled studies, Givaudan Pedroza 2016** (45)

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Givaudan Pedroza 2016 (45) |
| Authors: | Georgina Givaudan Pedroza, Karime Pérez Bailóna, Susana Peniche Morenob y Lourdes Fernández de Ortegac |
| English Title: | Endothelial cell count and central corneal volume in conventional phacoemulsification compared with femtosecond laser-assisted surgery |
| Original Title: | Grosor corneal central y conteo de células endoteliales en pacientes sometidos a cirugía de catarata asistida con láser de femtosegundos comparada con cirugía facoemulsificación tradicional |
| Journal/Book/Source: | Revista Mexicana de Oftalmología |
| Date of Publication: | February 12, 2016 |
| Volume: | 90 |

| | |
|---|---|
| Issue: | 5 |
| Pages: | 223-228 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Parallel group RCT<br><br>Unit of analysis: eye<br><br>Follow up: 1 day, 1 week and 1 month |
| **Participants** | |
| Total Number of Participants randomized | 65 |
| Total Number of eyes randomized | 65 |
| Country of participants | Mexico |
| Data collection period | May and August of 2013 |
| Inclusion criteria | Male and female patients older than 45 years without corneal diseases and with good pupillary dilation were included. |
| Exclusion criteria | Patients with prior ophthalmologic surgery were excluded. |
| Average age (intervention and control) | (mean ± SD)<br>Int: 66.68 ± 11.74<br>Cont: 72.2 ± 8.82 |
| Sex % (intervention and control) | Female n (%):<br>Int: 21/35 (60.0%)<br>Cont: 21/30 (70.0%) |
| Number of patients in<br>Intervention group | 35 |
| Number of patients in control group | 30 |
| Sub population 1 – LOCS GRADE | N.A. |
| Sub population 2 - SUBEXFOLIATION | N.A. |

| | | |
|---|---|---|
| Professional participant | The surgeries were performed by 2 surgeons with the same level of training. | |
| I**ntervention** | Cataract surgery with Femtosecond laser | |
| **Comparator** | Manual phacoemulsification cataract surgery. | |
| **Outcomes** (list all outcomes) | endothelial cell count, central corneal volume, phaco time, effective phaco time, phaco energy | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | Funding: The authors did not receive funding for this study.<br><br>COI: The authors declare that they have no conflicts of interest. | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | **Low risk** | *"On the surgical day, a randomization of balanced blocks was performed to determine the type of procedure that would be carried out. The patient was assigned the phacoemulsification group (phaco) or the phacoemulsification group with femtosecond laser (femto)."* |
| Allocation concealment (selection bias) | **Low risk** | *"On the surgical day, a randomization of balanced blocks was performed to determine the type of procedure that would be carried out."* |
| Blinding of participants and personnel (performance bias) | **High risk** | Open trial |
| Blinding of outcome assessment (detection bias) | **Low risk** | *"All the studies were performed by the same trained technician, without association to the research protocol."* |
| Incomplete outcome data (attrition bias) | **Unclear risk** | No data on lost to follow up was reported. |
| Selective reporting (reporting bias) | **Unclear risk** | Study protocol was not available. |
| **Outcomes** | | |

| | | |
|---|---|---|
| **SAFETY** | | |
| Posterior capsular tear | | |
| Anterior capsular tear | | |
| Vitreous loss | | |
| Cystoid macula oedema (within 90 days) | | |
| Elevated Intraocular Pressure (IOP) (1 day) | | |
| Elevated Intraocular Pressure (IOP) (1 week) | | |
| Endothelial Cell Loss (ECL) | Figure 1<br><br>En este análisis se determinó que tanto para el conteode células endoteliales como paquimetría sí existen cambiosen cada una de ellas a lo largo del tiempo, dependientes dela maniobra quirúrgica, pero no existen diferencias en estecomportamiento entre ambos grupos ([fig. 1] t = p = 0.002 y tiempo/grupos 0.528 [fig. 2] t = p < 0.0001 y tiempo/grupos0.640). | |
| Central Corneal Thickness (CCT) | Figure 2<br><br>See above | |
| Idrocyclitis | | |
| Infections (within 90 days) | | |
| Corneal Endothelial Decompensa-tion (within 90 days) | | |
| Surgical induced astigmatism | | |
| Retinal detachment | | |

<table>
<tr><td>Posterior capsule opacification</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (1 month)</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (6 months)</td><td></td><td></td></tr>
<tr><td>Surgical re-intervention (within 6 months)</td><td></td><td></td></tr>
<tr><td>Secondary cataract (24 months)</td><td></td><td></td></tr>
<tr><td>EFFECTIVENESS</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 1 month after surgery</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 6 months after surgery</td><td></td><td></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery</td><td></td><td></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery</td><td></td><td></td></tr>
<tr><td>Refractive outcomes</td><td></td><td></td></tr>
<tr><td>Vision-related Quality of Life (by validated questionnaire)</td><td></td><td></td></tr>
<tr><td>Patient-reported outcome measures (PROMs)</td><td></td><td></td></tr>
<tr><td>OTHER OUTCOMES</td><td></td><td></td></tr>
<tr><td>Patient satisfaction</td><td></td><td></td></tr>
<tr><td>Procedural time</td><td>Phaco time (mean ± SD) (seconds)<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>24.87 ± 11.07</td><td>35</td></tr></table></td><td>Phaco time (mean ± SD) (seconds)<table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>32.24 ± 18.93</td><td>30</td></tr></table></td></tr>
</table>

| | | |
|---|---|---|
| | Effective phaco time (mean ± SD) (seconds)<br>Experimental: Events 4.17 ± 3.26; Total 35 | Effective phaco time (mean ± SD) (seconds)<br>Control: Events 8.21 ± 7.00; Total 30 |
| Resource use | | |
| Additional outcomes | | |
| Notes | | |

**Table A 8 - Characteristics of randomised controlled studies, Hida 2014 (23)**

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Hida 2014 (23) |
| Authors: | Hida WT, Pereira Dias Chaves MA, Rodrigues Gonçalves M, Frenzel Tzeliks P, Nakano CT, Pimenta Motta AF, Hirai FE, Silva Guimaraes A, Malta de Alencar L, Yamane I, Ruiz Alves M |
| English Title: | Comparison between femtosecond laser capsulotomy and manual continuous curvilinear digital image guided capsulorrhexis |
| Original Title: | Comparação entre capsulotomia assistida por laser de femtossegundo e capsulorrexe curvilínea contínua guiada por imagem digital |
| Journal/Book/Source: | Rev Bras Oftalmol |
| Date of Publication: | 2014 |
| Volume: | 73 |
| Issue: | 6 |
| Pages: | 329-334 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up)) | parallel group RCT |
| **Participants** | |
| Total Number of Participants randomized | 80 |
| Total Number of eyes randomized | 80 |
| Country of participants | Brazil |
| Data collection period | October 2013 - January 2014 |
| Inclusion criteria | patients submitted to phakectomy with implantation of an IOL to treat cataract |
| Exclusion criteria | |
| Average age (intervention and control) | 66.8 years ±8.7 intervention<br>65.2 years ±8.8 control |
| Sex % (intervention and control) | |
| Number of patients in Intervention group | 40 (40 eyes) |

| | | |
|---|---|---|
| Number of patients in control group | 40 (40 eyes) | |
| Sub population 1 – LOCS GRADE | | |
| Sub population 2 - SUBEXFOLIATION | | |
| Professional participant | All procedures were carried out by the same experienced surgeon (W.T.H) | |
| I**ntervention** | Femtosecond Laser-Assisted capsulotomy (LenSx, Alcon) | |
| **Comparator** | Digital guided capsulorhexis | |
| **Outcomes** (list all outcomes) | Mean postoperative spherical equivalent, difference between predicted and actual postoperative spherical equivalent, circularity of capsulorhexis, overlap area | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | No information provided |
| Allocation concealment (selection bias) | Unclear risk | No information provided |
| Blinding of participants and personnel (performance bias) | High risk | Open trial |
| Blinding of outcome assessment (detection bias) | High risk | No blinding of assessment is described |
| Incomplete outcome data (attrition bias) | Unclear risk | No reporting on the lost to follow up |
| Selective reporting (reporting bias) | Unclear risk | A study protocol is not available |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | | |
| Anterior capsular tear | | |
| Vitreous loss | | |
| Cystoid macula edema (postoperatively) | | |
| Cystoid macula edema (30 days) | | |
| Elevated Intraocular Pressure (IOP) (2 hours) | | |
| Elevated Intraocular Pressure (IOP) (1 week) | | |
| Endothelial Cell Loss (ECL) | | |
| Central Corneal Thickness (CCT) | | |
| Idrocyclitis | Experimental: Events / Total | Control: Events / Total |
| Infections (within 90 days) | | |
| Corneal Endothelial Decompensation (within 90 days) | | |
| Surgical induced astigmatism | | |
| Retinal detachment | | |
| Posterior capsule opacification | | |
| Visual acuity loss post cataract surgery (1 month) | | |

| | | |
|---|---|---|
| Visual acuity loss post cataract surgery (6 months) | | |
| Surgical re-intervention (within 6 months) | | |
| Secondary cataract (24 months) | | |
| **EFFECTIVENESS** | | |
| Corrected Distance Visual Acuity (CDVA) 1 month after surgery | | |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery | | |
| Refractive outcomes (mean post-operative spherical equivalent) | Experimental<br>Mean ± SD: -0.16±0.38<br>Total: 40 | Control<br>Mean ± SD: -0.03±0.28<br>Total: 40 |
| Refractive outcomes (difference between predicted and actual postoperative spherical equivalent) | Experimental<br>Mean ± SD: 0.13±0.09<br>Total: 40 | Control<br>Mean ± SD: 0.30±0.29<br>Total: 40 |
| Vision-related Quality of Life (by validated questionnaire) | | |
| Patient-reported outcome measures (PROMs) | | |
| **OTHER OUTCOMES** | | |
| Patient satisfaction | | |
| Procedural time | | |
| Resource use | | |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 9 - Characteristics of randomised controlled studies, Kovács 2014** (46)

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Kovács 2014 (46) |
| Authors: | Illés Kovács; Kinga Kránitz; Gábor L. Sándor; Michael C. Knorz;<br><br>Eric D. Donnenfeld; Rudy M. Nuijts; Zoltán Z. Nagy |
| English Title: | The Effect of Femtosecond Laser Capsulotomy on the Development of Posterior Capsule Opacification |
| Original Title: | The Effect of Femtosecond Laser Capsulotomy on the Development of Posterior Capsule Opacification |
| Journal/Book/Source: | J Refract Surg. |
| Date of Publication: | February 28, 2014 |

| | |
|---|---|
| Volume: | 30 |
| Issue: | 3 |
| Pages: | 154-158 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Retrospective evaluation of all patients from a previous prospective parallel group randomized study on femtosecond laser surgery with a minimum follow-up time of 18 months.<br>Unit of analysis: Eye<br>Follow up: 18 to 26 months |
| **Participants** | |
| Total Number of Participants randomized | 79 |
| Total Number of eyes randomized | 79 |
| Country of participants | Hungary |
| Data collection period | N.A. |
| Inclusion criteria | N.A. |
| Exclusion criteria | Patients with previous ocular surgery, trauma, active ocular disease (eg, pseudoexfoliation syndrome and uveitis), poorly dilated pupils or known zonular weakness were excluded. |
| Average age (intervention and control) | Int: 65.50 ± 12.94;<br>Cont: 68.95 ± 10.84. |
| Sex % (intervention and control) | Int: female (28/40 70.0%)<br>Cont: female (29/39 74,4%) |
| Number of patients in<br>Intervention group | 40 |
| Number of patients in control group | 39 |
| Sub population 1 – LOCS GRADE | N.A. |
| Sub population 2 - SUBEXFOLIATION | Excluded (Verificare se =pseudo) |
| Professional participant | Single surgeon |
| I**ntervention** | Capsulorhexis with LenSx; Alcon Laboratories, Inc. |

| | | |
|---|---|---|
| **Comparator** | Manual anterior capsulorhexis. | |
| **Outcomes** (list all outcomes) | Posterior Capsule Opacification (Axial length, Horizontal tilt, Vertical tilt, Vertical decentration, Horizontal decentration, Total decentration) | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | COI: Drs. Nagy, Donnenfeld, and Knorz are consultants of LenSx Lasers, Inc. The remaining authors have no financial or proprietary interest in the materials presented herein.<br><br>Data on the original trial are not available. | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | The only information about randomization methods is to state that the study is randomized. |
| Allocation concealment (selection bias) | Unclear risk | The only information about randomization methods is to state that the study is randomized. |
| Blinding of participants and personnel (performance bias) | High risk | Open tiral |
| Blinding of outcome assessment (detection bias) | Low risk | The use of a software tool for masked had been reported for an objective PCO evaluation. |
| Incomplete outcome data (attrition bias) | Low risk | No attrition were reported. |
| Selective reporting (reporting bias) | Unclear risk | No available protocol |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | | |
| Anterior capsular tear | | |
| Vitreous loss | | |
| Cystoid macula oedema (within 90 days) | | |

<table>
<tr><td>Elevated Intraocular Pressure (IOP) (1 day)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 week)</td><td></td><td></td></tr>
<tr><td>Endothelial Cell Loss (ECL)</td><td></td><td></td></tr>
<tr><td>Central Corneal Thickness (CCT)</td><td></td><td></td></tr>
<tr><td>Idrocyclitis</td><td></td><td></td></tr>
<tr><td>Infections (within 90 days)</td><td></td><td></td></tr>
<tr><td>Corneal Endothelial Decompen-sation (within 90 days)</td><td></td><td></td></tr>
<tr><td>Surgical induced astigmatism</td><td></td><td></td></tr>
<tr><td>Retinal detachment</td><td></td><td></td></tr>
<tr><td>Posterior capsule opacification</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0.58±0.30 (mean and SD - OSCA score)</td><td>40</td></tr></table><br>FU: 18 to 26 months</td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0.84±0.52<br><br>(mean and SD - OSCA score)</td><td>39</td></tr></table></td></tr>
<tr><td>Visual acuity loss post cataract surgery (1 month)</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (6 months)</td><td></td><td></td></tr>
<tr><td>Surgical re-intervention (within 6 months)</td><td></td><td></td></tr>
<tr><td>Secondary cataract (24 months)</td><td></td><td></td></tr>
<tr><td>EFFECTIVENESS</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 1 month after surgery</td><td></td><td></td></tr>
</table>

| | | |
|---|---|---|
| | | |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery | | |
| Refractive outcomes | | |
| Vision-related Quality of Life (by validated questionnaire) | | |
| Patient-reported outcome measures (PROMs) | | |
| **OTHER OUTCOMES** | | |
| Patient satisfaction | | |
| Procedural time | | |
| Resource use | | |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 10 - Characteristics of randomised controlled studies, Kranitz 2012 (24)**

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Kranitz 2012 (24) |
| Authors: | Kinga Kránitz, Kata Miháltz, Gábor L. Sándor, Agnes Takacs, Michael C. Knorz, Zoltán Z. Nagy |
| English Title: | Intraocular Lens Tilt and Decentration Measured By Scheimpfl ug Camera Following Manual or Femtosecond Laser–created Continuous Circular Capsulotomy |
| Original Title: | See English Title |
| Journal/Book/Source: | Journal of Refractive Surgery |
| Date of Publication: | 2012 |
| Volume: | 28 |
| Issue: | 4 |
| Pages: | 259-263 |
| **Methods** (study design and unit of analysis (within person – paired- | Prospective randomized study with 1 year follow up |

| | | |
|---|---|---|
| eye RCT; parallel group RCT; length of follow up)) | Parallel group | |
| **Participants** | | |
| Total Number of Participants randomized | 45 | |
| Total Number of eyes randomized | 45 | |
| Country of participants | | |
| Data collection period | | |
| Inclusion criteria | patients undergoing cataract surgery with IOL implantation | |
| Exclusion criteria | Patients with:<br>• previous ocular surgery,<br>• trauma,<br>• active ocular disease,<br>• poorly dilated pupils,<br>• or known zonular weakness | |
| Average age (intervention and control) | Control: 68.24±10.77<br>Intervention: 63.55±13.65 | |
| Sex % (intervention and control) | M:F<br>Control: 2:23 (92% females)<br>Intervention: 5:15 (75% females) | |
| Number of patients in Intervention group | 20 | |
| Number of patients in control group | 25 | |
| Sub population 1 – LOCS GRADE | No | |
| Sub population 2 - SUBEXFOLIATION | No | |
| Professional participant | All surgeries were performed by the same surgeon (Z.Z.N.) | |
| I**ntervention** | Laser CCC: circular capsulotomy created with a femtosecond laser ((Alcon LenSx Inc, Aliso Viejo, California) | |
| **Comparator** | Manual CCC: manually performed continuous curvilinear capsulorrhexis | |
| **Outcomes** (list all outcomes) | • UDVA 1 week, 1 month, 1 year after surgery<br>• CDVA 1 week, 1 month, 1 year after surgery<br>• Manifest refraction<br>• Intraocular lens decentration and tilt 1 year after surgery | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | Drs Knorz and Nagy are consultants to Alcon LenSx Inc. The remaining authors have no financial interest in the materials presented herein. | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Randomization was done using computer-generated tables (Microsoft Excel; Microsoft Corp, Redmond, Washington). |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to judge |
| Blinding of participants and personnel (performance bias) | High risk | No blinding, open trial |
| Blinding of outcome assessment (detection bias) | High risk | No blinding of assessment described |
| Incomplete outcome data (attrition bias) | Unclear risk | Attrition has not been addressed |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | | |
| Anterior capsular tear | | |

| | | |
|---|---|---|
| Vitreous loss | | |
| Cystoid macula edema (within 90 days) | | |
| Elevated Intraocular Pressure (IOP) (1 day) | | |
| Elevated Intraocular Pressure (IOP) (1 week) | | |
| Endothelial Cell Loss (ECL) | | |
| Central Corneal Thickness (CCT) | | |
| Idrocyclitis | | |
| Infections (within 90 days) | | |
| Corneal Endothelial Decompensation (within 90 days) | | |
| Surgical induced astigmatism | | |
| Retinal detachment | | |
| Posterior capsule opacification | | |
| Visual acuity loss post cataract surgery (1 month) | | |
| Visual acuity loss post cataract surgery (6 months) | | |
| Surgical re-intervention (within 6 months) | | |
| Secondary cataract (24 months) | | |
| **EFFECTIVENESS** | | |
| Corrected Distance Visual Acuity (CDVA) 1 month after surgery | Experimental: 0.94±0.11; Total: 20 | Control: 0.84±0.16; Total: 25 |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery | Experimental: 0.69±0.19; Total: 20 | Control: 0.61±0.28; Total: 25 |
| Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery | | |
| Refractive outcomes | | |
| Vision-related Quality of Life (by validated questionnaire) | | |
| Patient-reported outcome measures (PROMs) | | |
| **OTHER OUTCOMES** | | |
| Patient satisfaction | | |
| Procedural time | | |
| Resource use | | |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 11 - Characteristics of randomised controlled studies, Mastropasqua 2014a (26)**

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Mastropasqua 2014a (26) |
| Authors: | Leonardo Mastropasqua, Lisa Toto, Alessandra Mastropasqua, Luca Vecchiarino, Rodolfo Mastropasqua, Emilio Pedrotti, Marta Di Nicola |

| | |
|---|---|
| English Title: | Femtosecond Laser Versus Manual Clear Corneal Incision in Cataract Surgery |
| Original Title: | See English Title |
| Journal/Book/Source: | J Refract Surg |
| Date of Publication: | 2014 |
| Volume: | 30 |
| Issue: | 1 |
| Pages: | 27-33 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up)) | Prospective randomized study<br>Parallel group, 6 months follow up |
| **Participants** | |
| Total Number of Participants randomized | 60 |
| Total Number of eyes randomized | 60 |
| Country of participants | Italy |
| Data collection period | |
| Inclusion criteria | • age between 65 and 75 years,<br>• axial length between 23.0 and 24.0 mm,<br>• Corneal astigmatism less than 2.00 diopters (D),<br>• Nuclear cataract of grade 2 to 3 (nuclear opalescence 3/4) (Lens Opacities Classification System III),<br>• corneal endothelial cell count greater than 1,200/mm.1 |
| Exclusion criteria | • pathological alterations of the anterior segment (eg, corneal opacities, keratoconus, chronic uveitis, zonular dialysis, pseudoexfoliation syndrome, glaucoma and diabetes mellitus),<br>• other ocular pathologies impairing visual function,<br>• previous anterior or posterior segment surgery,<br>• intraoperative or postoperative complications. |
| Average age (intervention and control) | Intervention group: 70.2 ± 2.9 years (range: 65 to 75 years)<br>Control group: 70.5± 3.2 years (range: 65 to 75 years) |
| Sex % (intervention and control) | |
| Number of patients in Intervention group | 30 |
| Number of patients in control group | 30 |
| Sub population 1 – LOCS GRADE | Inclusion criteria |
| Sub population 2 - SUBEXFOLIATION | Exclusion criteria |
| Professional participant | All femtosecond laser–assisted and phacoemulsification procedures and IOL implantations were performed by the same experienced surgeon (LM). |
| I**ntervention** | Femtosecond laser CCI (Clear Corneal Incision)<br>LenSx platform (Alcon Laboratories, Inc., Fort Worth, TX) |
| **Comparator** | Manual CCI (Clear Corneal Incision) |
| **Outcomes** (list all outcomes) | • UDVA<br>• CDVA<br>• Keratometric astigmatism<br>• Corneal endothelial cell count centrally<br>• Corneal endothelial cell count at the tunnel site<br>• Corneal thickness at the incision site<br>• Higher-order corneal aberrations<br>• Astigmatic change<br>• Power vector analysis of keratometric astigmatic change<br>• Mean torsional time<br>• Mean phacoemulsification time |

<table>
<tr><td></td><td colspan="2">• Total time<br>• Mean cumulative dissipated energy<br><br>Follow up at 1,7, 30 and180 days postoperatively</td></tr>
<tr><td>Notes (Funding source; Conflicts of Interest; trial registration number; any other note)</td><td colspan="2">The authors have no financial or proprietary interest in the materials presented herein.</td></tr>
<tr><td>Risk of bias RCTs</td><td>Authors' judgment</td><td>Support for judgement</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Unclear risk</td><td>No information</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear risk</td><td>No information</td></tr>
<tr><td>Blinding of participants and personnel (performance bias)</td><td>High risk</td><td>No blinding, open trial</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>High risk</td><td>No blinding</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>All eyes included in the analysis</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Unclear risk</td><td>No study protocol</td></tr>
<tr><td>Outcomes</td><td></td><td></td></tr>
<tr><td>SAFETY</td><td></td><td></td></tr>
<tr><td>Posterior capsular tear</td><td></td><td></td></tr>
<tr><td>Anterior capsular tear</td><td></td><td></td></tr>
<tr><td>Vitreous loss</td><td></td><td></td></tr>
<tr><td>Cystoid macula edema (within 90 days)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 day)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 week)</td><td></td><td></td></tr>
<tr><td>Endothelial Cell Loss (ECL)</td><td></td><td></td></tr>
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<tr><td>Infections (within 90 days)</td><td></td><td></td></tr>
<tr><td>Corneal Endothelial Decompensation (within 90 days)</td><td></td><td></td></tr>
<tr><td>Surgical induced astigmatism</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Mean ±sd</td><td>Total</td></tr><tr><td>0.64±0.32</td><td>30</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Mean ±sd</td><td>Total</td></tr><tr><td>0.69±0.50</td><td>30</td></tr></table></td></tr>
<tr><td>Retinal detachment</td><td></td><td></td></tr>
<tr><td>Posterior capsule opacification</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (1 month)</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (6 months)</td><td></td><td></td></tr>
<tr><td>Surgical re-intervention (within 6 months)</td><td></td><td></td></tr>
<tr><td>Secondary cataract (24 months)</td><td></td><td></td></tr>
<tr><td>EFFECTIVENESS</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 1 month after surgery</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>0.18±0.18</td><td>30</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>0.16±0.12</td><td>30</td></tr></table></td></tr>
</table>

<table>
<tr><td></td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 6 months after surgery</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>-0.08±0.09</td><td>30</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>-0.03±0.12</td><td>30</td></tr></table></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>0.35±0.23</td><td>30</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Mean ± sd</td><td>Total</td></tr><tr><td>0.28±0.13</td><td>30</td></tr></table></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0.13±0.21</td><td>30</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0.08±0.15</td><td>30</td></tr></table></td></tr>
<tr><td>Refractive outcomes</td><td></td><td></td></tr>
<tr><td>Vision-related Quality of Life (by validated questionnaire)</td><td></td><td></td></tr>
<tr><td>Patient-reported outcome measures (PROMs)</td><td></td><td></td></tr>
<tr><td>OTHER OUTCOMES</td><td></td><td></td></tr>
<tr><td>Patient satisfaction</td><td></td><td></td></tr>
<tr><td>Procedural time</td><td>Phacoemulsification time<table><tr><td colspan="2">Experimental</td></tr><tr><td>Mean ±sd</td><td>Total</td></tr><tr><td>9.1±4.8</td><td>30</td></tr></table></td><td>Phacoemulsification time<table><tr><td colspan="2">Control</td></tr><tr><td>Mean ±sd</td><td>Total</td></tr><tr><td>11.2±5.7</td><td>30</td></tr></table></td></tr>
<tr><td>Resource use</td><td></td><td></td></tr>
<tr><td>Additional outcomes</td><td></td><td></td></tr>
<tr><td>Notes</td><td></td><td></td></tr>
</table>

**Table A 12 - Characteristics of randomised controlled studies, Mastropasqua 2014b (25)**

| RANDOMIZED CONTROLLED TRIALS | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Mastropasqua 2014b (25) |
| Authors: | Leonardo Mastropasqua, MD, Lisa Toto, MD, PhD, Peter A. Mattei, MD, PhD, Luca Vecchiarino, MD,<br><br>Alessandra Mastropasqua, MD, Riccardo Navarra, PhD, Marta Di Nicola, PhD, Mario Nubile, MD, PhD |
| English Title: | Optical coherence tomography and 3-dimensional confocal structured imaging system–guided femtosecond laser capsulotomy versus manual continuous curvilinear capsulorhexis |
| Original Title: | Optical coherence tomography and 3-dimensional confocal structured imaging system–guided femtosecond laser capsulotomy versus manual continuous curvilinear capsulorhexis |
| Journal/Book/Source: | J Refract Surgery |
| Date of Publication: | May 23, 2014 |
| Volume: | 40 |
| Issue: | 12 |
| Pages: | 2035-2043 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Parallel group RCT: 3 arms<br><br>Unit of analysis: eye<br><br>Follow up: Postoperatively at 7, 30, and 180 days |
| **Participants** | |
| Total Number of Participants randomized | 90 |
| Total Number of eyes randomized | 90 |
| Country of participants | Italy |
| Data collection period | |
| Inclusion criteria | age between 65 years and 75 years, nuclear cataract grade 3 to 4 (nuclear opalescence [NO] 3/4 on Lens Opacities Classification System III14), and a corneal endothelial cell count greater than 1200 cells/mm2. |

| | | |
|---|---|---|
| Exclusion criteria | poor pupil dilation, pathology that could alter the anterior segment (eg, corneal opacities, keratoconus, chronic uveitis, zonular dialysis, pseudoexfoliation syndrome, glaucoma, diabetes), other ocular pathology that can impair visual function, previous anterior or posterior segment surgery and intraoperative<br>or postoperative complications. | |
| Average age (intervention and control) | LASER 1: 69.3±3.4<br>LASER 2: 69.2±2.7<br>MANUAL (CTRL): 69.1±3.9 | |
| Sex % (intervention and control) | Not reported | |
| Number of patients in<br>Intervention group | LASER 1: 30 (30 eyes)<br>LASER 2: 30 (30 eyes) | |
| Number of patients in control group | 30 (30 eyes) | |
| Sub population 1 – LOCS GRADE | N.A. | |
| Sub population 2 - SUBEXFOLIATION | Exclusion criteria | |
| Professional participant | Single surgeon | |
| I**ntervention** | In laser group 1, the capsulotomy, lens fragmentation and corneal incisions were performed using the femtosecond laser (Alcon).<br>In laser group 2, the capsulotomy and lens fragmentation were performed using the femtosecond laser (Lensar). | |
| **Comparator** | In the manual group, a temporal 2.75 mm 3- plane primary clear corneal incision and a secondary 1-plane corneal incision were made using disposable keratome knives. | |
| **Outcomes** (list all outcomes) | UDVA (LogMAR), CDVA (LogMAR), spherical error, MAE, Circularity, cap area (mm2), IOL centroid pupil, cap centroid pupil, centroid distance (mm) | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | No author has a financial or proprietary interest in any material or method mentioned. | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | A computer-generated, 6-block, 15-patient randomiza- |

| | | |
|---|---|---|
| | | tion list was generated using an in-house closed-source software<br><br>developed in Matlab 2009b. |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias) | High risk | Open trial. The surgeon and the operating room staff were aware of group assignment. |
| Blinding of outcome assessment (detection bias) | Low risk | The patients and examiners performing preoperative and postoperative assessments were masked to group assignment until the study was completed. |
| Incomplete outcome data (attrition bias) | Unclear risk | Not reported |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | | |
| Anterior capsular tear | | |
| Vitreous loss | | |
| Cystoid macula oedema (within 90 days) | | |
| Elevated Intraocular Pressure (IOP) (1 day) | | |
| Elevated Intraocular Pressure (IOP) (1 week) | | |
| Endothelial Cell Loss (ECL) | | |
| Central Corneal Thickness (CCT) | | |
| Idrocyclitis | | |
| Infections (within 90 days) | | |
| Corneal Endothelial Decompensation | | |

<table>
<tr><td>(within 90 days)</td><td></td><td></td></tr>
<tr><td>Surgical induced astigmatism</td><td></td><td></td></tr>
<tr><td>Retinal detachment</td><td></td><td></td></tr>
<tr><td>Posterior capsule opacification</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (1 month)</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (6 months)</td><td></td><td></td></tr>
<tr><td>Surgical re-intervention (within 6 months)</td><td></td><td></td></tr>
<tr><td>Secondary cataract (24 months)</td><td></td><td></td></tr>
<tr><td>EFFECTIVENESS</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 7days after surgery</td><td>
<table>
<tr><td colspan="2">Experimental 1</td></tr>
<tr><td>Events</td><td>Total</td></tr>
<tr><td>-0.03 ± 0.05</td><td>30</td></tr>
</table>
<table>
<tr><td colspan="2">Experimental 2</td></tr>
<tr><td>Events</td><td>Total</td></tr>
<tr><td>-0.03 ± 0.14</td><td>30</td></tr>
</table>
</td><td>
<table>
<tr><td colspan="2">Control</td></tr>
<tr><td>Events</td><td>Total</td></tr>
<tr><td>0.01 ± 0.07</td><td>30</td></tr>
</table>
</td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 30 days after surgery</td><td>
<table>
<tr><td colspan="2">Experimental 1</td></tr>
<tr><td>Events</td><td>Total</td></tr>
<tr><td>-0.08 ± 0.05</td><td>30</td></tr>
</table>
<table>
<tr><td>Experimental 2</td></tr>
</table>
</td><td>
<table>
<tr><td colspan="2">Control</td></tr>
<tr><td>Events</td><td>Total</td></tr>
<tr><td>-0.06 ± 0.10</td><td>30</td></tr>
</table>
</td></tr>
</table>

| | | |
|---|---|---|
| | Events: -0.09 ± 0.12; Total: 30 | |
| Corrected Distance Visual Acuity (CDVA) 180 days after surgery | Experimental 1: Events: -0.09 ± 0.12; Total: 30<br>Experimental 2: Events: -0.08 ± 0.05; Total: 30 | Control: Events: -0.06 ± 0.10; Total: 30 |
| Uncorrected Distance Visual Acuity (UDVA) 7 days after surgery | Experimental 1: Events: 0.08 ± 0.08; Total: 30<br>Experimental 2: Events: 0.07 ± 0.09; Total: 30 | Control: Events: 0.18 ± 0.05; Total: 30 |
| Uncorrected Distance Visual Acuity (UDVA) 30 days after surgery | Experimental 1: Events: 0.10 ± 0.10; Total: 30<br>Experimental 2: Events: | Control: Events: 0.21 ± 0.09; Total: 30 |

| | | |
|---|---|---|
| | 0.09 ± 0.13 \| 30 | |
| Uncorrected Distance Visual Acuity (UDVA) 180 days after surgery | Experimental 1<br>Events: 0.09 ± 0.08 \| Total: 30<br><br>Experimental 2<br>Events: 0.10 ± 0.05 \| Total: 30 | Control<br>Events: 0.25 ± 0.05 \| Total: 30 |
| Refractive outcomes 1 month<br><br>(available at 7 and 30 days) | Spherical error (SE)<br>Experimental 1<br>Events: -0.25 ± 0.38 \| Total: 30<br><br>Experimental 2<br>Events: -0.23 ± 0.64 \| Total: 30 | Control<br>Events: -0.39 ± 0.33 \| Total: 30 |
| Refractive outcomes 1 month (available at 7 and 30 days) | MAE (Mean absolute error)<br>Experimental 1<br>Events: 0.42 ± 0.16 \| Total: 30 | Control<br>Events: 0.54 ± 0.43 \| Total: 30 |

| | | |
|---|---|---|
| | Experimental 2<br>Events: 0.36 ± 0.36<br>Total: 30 | |
| Vision-related Quality of Life (by validated questionnaire) | | |
| Patient-reported outcome measures (PROMs) | | |
| **OTHER OUTCOMES** | | |
| Patient satisfaction | | |
| Procedural time | | |
| Resource use | | |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 13 - Characteristics of randomised controlled studies, Mursch-Edlmayr 2017** (31)

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Mursch-Edlmayr 2017 (31) |
| Authors: | Anna S. Mursch-Edlmayr, Matthias Bolz, Nikolaus Luft, Michael Ring, Thomas Kreutzer, Christoph Ortner, Matthias Rohleder, Siegfried G. Priglinger |
| English Title: | Intraindividual comparison between femtosecond laser–assisted and conventional cataract surgery |
| Original Title: | |
| Journal/Book/Source: | J Cataract Refract Surg |
| Date of Publication: | November 26, 2016 |
| Volume: | 43 |
| Issue: | |
| Pages: | 215-222 |

| | |
|---|---|
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Within person – paired-eye RCT<br><br>Unit of analysis: eye (patient for patients reported outcomes)<br><br>Follow up: 1 day, 1 week, 1 month, 3 months and 6 months |
| **Participants** | |
| Total Number of Participants randomized | 50 |
| Total Number of eyes randomized | 100 |
| Country of participants | Austria |
| Data collection period | N.A. |
| Inclusion criteria | Inclusion criteria were a minimum age of 18 years and “bilateral” age-related cataract. |
| Exclusion criteria | Exclusion criteria were small pupils (<6.0 mm with therapeutic mydriasis) and manifest glaucoma treated with antiglaucoma drugs. |
| Average age (intervention and control) | Overall mean age (±SD):<br>72 ± 6 years |
| Sex % (intervention and control) | Female (overall %):<br>31/50 (62.0%) |
| Number of patients in<br>Intervention group | 50 (3 lost to follow up) |
| Number of patients in control group | 50 (3 lost to follow up) |
| Sub population 1 – LOCS GRADE | N.A. |
| Sub population 2 - SUBEXFOLIATION | N.A. |
| Professional participant | Five experienced surgeons (S.P., M.B., C.O., R.S., T.K.) performed the procedures, and the same surgeon operated on both eyes of an individual patient. |
| I**ntervention** | femtosecond laser cataract surgery (Victus femtosecond platform) |

| | | |
|---|---|---|
| **Comparator** | Conventional cataract surgery group | |
| **Outcomes** (list all outcomes) | CDVA, endothelial cell density (ECD) and loss (delta), central corneal thickness (CCT), and central retinal thickness, intraoperative and postoperative complications and the effective phacoemulsification time (EPT), IOL and capsulotomy centration, Patients' Perceptions | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | Funding: Supported by a grant from Technolas Perfect Vision GmbH.<br><br>COI: The Ars Ophthalmica Study Center received research grants from Technolas Perfect Vision GmbH. No author has a financial or proprietary interest in any material or method mentioned. | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Allocation of the eyes to the respective procedure group was by balanced block randomization using Excel software (Microsoft Corp.). |
| Allocation concealment (selection bias) | Unclear risk | No information on allocation concealment was reported. |
| Blinding of participants and personnel (performance bias) | High risk | Open trial |
| Blinding of outcome assessment (detection bias) | Low risk | "All examiners at the postoperative follow-up visits were blinded to the randomization of the patient." |
| Incomplete outcome data (attrition bias) | Low risk | "Three patients (6 eyes) were lost to follow up."<br><br>Even if higher than 5%, the missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups. |
| Selective reporting (reporting bias) | Unclear risk | The study protocol is not available. |
| **Outcomes** | | |
| **SAFETY** | | |

<table>
<tr><td>Posterior capsular tear</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0</td><td>47</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0</td><td>47</td></tr></table></td></tr>
<tr><td>Anterior capsular tear</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0</td><td>47</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0</td><td>47</td></tr></table></td></tr>
<tr><td>Vitreous loss</td><td></td><td></td></tr>
<tr><td>Cystoid macula oedema (within 90 days)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 day)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 week)</td><td></td><td></td></tr>
<tr><td>Endothelial Cell Loss (ECL)</td><td>Delta Endothelial cell density (before surgery – 6 months) (cells/mm2)<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>-39.40±298.3</td><td>47</td></tr></table>Also available at 1 day, 1 month, 3 months.<br><br>(p=0.57)</td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>-76.80±338.6</td><td>47</td></tr></table></td></tr>
<tr><td>Central Corneal Thickness (CCT)</td><td>Mean (µm) at 6 months<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>551.6</td><td>47</td></tr></table>Also available at 1 day, 1 month, 3 months.</td><td>Mean (µm) at 6 months<table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>551.0</td><td>47</td></tr></table></td></tr>
</table>

<table>
<tr><td>Idrocyclitis</td><td></td><td></td></tr>
<tr><td>Infections (within 90 days)</td><td></td><td></td></tr>
<tr><td>Corneal Endothelial Decompensation (within 90 days)</td><td></td><td></td></tr>
<tr><td>Surgical induced astigmatism</td><td></td><td></td></tr>
<tr><td>Retinal detachment</td><td></td><td></td></tr>
<tr><td>Posterior capsule opacification</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (1 month)</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (6 months)</td><td></td><td></td></tr>
<tr><td>Surgical re-intervention (within 6 months)</td><td></td><td></td></tr>
<tr><td>Secondary cataract (24 months)</td><td></td><td></td></tr>
<tr><td>EFFECTIVENESS</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 1 month after surgery</td><td>(mean±SD) decimal<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>1.20±0.18</td><td>47</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>1.20±0.21</td><td>47</td></tr></table></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 6 months after surgery</td><td>(mean±SD) decimal<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>1.20±0.23</td><td>47</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>1.20±0.24</td><td>47</td></tr></table></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery</td><td></td><td></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery</td><td></td><td></td></tr>
<tr><td>Refractive outcomes</td><td></td><td></td></tr>
<tr><td>Vision-related Quality of Life (by</td><td></td><td></td></tr>
</table>

<table>
<tr><td>validated questionnaire)</td><td></td><td></td></tr>
<tr><td>Patient-reported outcome measures (PROMs)</td><td>Dedicated patient questionnaire on pain (1= no pain; 5= intense pain) in general and comparing the two techniques:<br><br>“mean pain during the laser procedure” (mean ± SD)<br><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>1.6 ± 0.82</td><td>47</td></tr></table>“mean during cataract extraction after laser treatment” (mean ± SD)<br><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>1.4 ± 0.61</td><td>47</td></tr></table></td><td>Dedicated patient questionnaire on pain (1= no pain; 5= intense pain) in general and comparing the two techniques:<br><br>“mean pain during cataract surgery in the conventional group.” (mean ± SD)<br><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>1.34 ± 0.63</td><td>47</td></tr></table></td></tr>
<tr><td>OTHER OUTCOMES</td><td></td><td></td></tr>
<tr><td>Patient satisfaction</td><td>Thirty patients (63.8%) reported that they had more pain during femtosecond laser–assisted cataract surgery than during conventional cataract surgery.<br><br>Twenty-seven patients (57.4%) said they would recommend conventional cataract surgery over femtosecond-assisted surgery.</td><td></td></tr>
<tr><td>Procedural time</td><td>Effective Phacoemulsification time (EPT) (seconds) (mean±SD)<br><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr></table></td><td>Effective Phacoemulsification time (EPT) (seconds) (mean±SD)<br><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr></table></td></tr>
</table>

| | | |
|---|---|---|
| | 2.51±1.7 \| 47<br>Intervention time (minutes) (mean±SD)<br>Experimental<br>Events \| Total<br>16.6±4.4 \| 47 | 2.82±1.6 \| 47<br>Intervention time (minutes) (mean±SD)<br>Control<br>Events \| Total<br>10.21±2.8 \| 47 |
| Resource use | Experimental<br>Events Total | Control<br>Events Total |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 14 - Characteristics of randomised controlled studies, Nagy 2011 (27)**

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Nagy 2011 (27) |
| Authors: | Zoltán Zsolt Nagy; Kinga Kránitz; Agnes I. Takacs; Kata Miháltz;<br>Illés Kovács; Michael C. Knorz |
| English Title: | Comparison of Intraocular Lens Decentration Parameters After Femtosecond and Manual Capsulotomies |
| Original Title: | Comparison of Intraocular Lens Decentration Parameters After Femtosecond and Manual Capsulotomies |
| Journal/Book/Source: | J Refract Surgery |
| Date of Publication: | June 20, 2011 |
| Volume: | 27 |
| Issue: | 8 |
| Pages: | 564-569 |

| | |
|---|---|
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Parallel group RCT<br><br>Unit of analysis: eye<br><br>Follow up: 1 week after surgery. |
| **Participants** | |
| Total Number of Participants randomized | 105 |
| Total Number of eyes randomized | 111 |
| Country of participants | Hungary |
| Data collection period | N.A. |
| Inclusion criteria | Patients with cataract in one or both eyes with or without myopia. |
| Exclusion criteria | “Patients with previous ocular surgery, trauma, active ocular disease, poorly dilated pupils, or known zonular weakness were excluded from the study.” |
| Average age (intervention and control) | Int: 65± 13<br><br>Cont: 68±15 |
| Sex % (intervention and control) | Female (eyes)<br><br>Int: 39/54 (72.2%)<br><br>Cont: 40/57 (70.2%) (p>.05) |
| Number of patients in<br><br>Intervention group | 53 patients (54 eyes) |
| Number of patients in control group | 52 patients (57 eyes) |
| Sub population 1 – LOCS GRADE | N.A. |
| Sub population 2 - SUBEXFOLIATION | N.A. |
| Professional participant | Single surgeon |
| I**ntervention** | Cataract surgery with<br><br>capsulorrhexis performed with LenSx femtosecond laser system (LenSx Lasers<br><br>Inc, Aliso Viejo, California) |

| | | |
|---|---|---|
| **Comparator** | Cataract surgery with manual continuous curvilinear capsulorrhexis was performed with the aid of a cystotome and a capsulorrhexis forceps. | |
| **Outcomes** (list all outcomes) | Axial length, Refractive state, Area of capsulotomy, Circularity of capsulotomy, Complete and incomplete overlap. | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | COI: Drs Nagy and Knorz are consultants to LenSx Lasers Inc. The remaining<br>authors have no proprietary interest in the materials presented herein. | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Using computer randomization, patients and their right/left eyes were randomly selected for femtosecond and manual surgery." |
| Allocation concealment (selection bias) | Unclear risk | The method of concealment is not described. |
| Blinding of participants and personnel (performance bias) | High risk | Open trial |
| Blinding of outcome assessment (detection bias) | Unclear risk | No blinding of outcome assessment has been described but it is not clear whether the outcomes are likely to be influenced by lack of blinding. |
| Incomplete outcome data (attrition bias) | Unclear risk | Not reported |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | | |
| Anterior capsular tear | | |
| Vitreous loss | | |
| Cystoid macula oedema (within 90 days) | | |

| | | |
|---|---|---|
| Elevated Intraocular Pressure (IOP) (1 day) | | |
| Elevated Intraocular Pressure (IOP) (1 week) | | |
| Endothelial Cell Loss (ECL) | | |
| Central Corneal Thickness (CCT) | | |
| Idrocyclitis | | |
| Infections (within 90 days) | | |
| Corneal Endothelial Decompensation (within 90 days) | | |
| Surgical induced astigmatism | | |
| Retinal detachment | | |
| Posterior capsule opacification | | |
| Visual acuity loss post cataract surgery (1 month) | | |
| Visual acuity loss post cataract surgery (6 months) | | |
| Surgical re-intervention (within 6 months) | | |
| Secondary cataract (24 months) | | |
| **EFFECTIVENESS** | | |
| Corrected Distance Visual Acuity (CDVA) 1 month after surgery | | |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery | | |

<table>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery</td><td></td><td></td></tr>
<tr><td>Refractive outcomes</td><td>Refractive state (SE= spherical equivalent refraction)<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>-0.75±7.1</td><td>54</td></tr></table>FU: 1 week after surgery.</td><td>Refractive state (SE= spherical equivalent refraction)<table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>-0.75±5.5</td><td>57</td></tr></table>FU: 1 week after surgery.</td></tr>
<tr><td>Vision-related Quality of Life (by validated questionnaire)</td><td></td><td></td></tr>
<tr><td>Patient-reported outcome measures (PROMs)</td><td></td><td></td></tr>
<tr><td>OTHER OUTCOMES</td><td></td><td></td></tr>
<tr><td>Patient satisfaction</td><td></td><td></td></tr>
<tr><td>Procedural time</td><td></td><td></td></tr>
<tr><td>Resource use</td><td></td><td></td></tr>
<tr><td>Additional outcomes</td><td></td><td></td></tr>
<tr><td>Notes</td><td></td><td></td></tr>
</table>

**Table A 15 - Characteristics of randomised controlled studies, Nagy 2014** (41)

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Nagy 2014 (41) |
| Authors: | Zoltán Z. Nagy, MD, PhD, DSC; Árpád Dunai, MD; Kinga Kránitz, MD; Ágnes Ildikó Takács, MD; Gábor László Sándor, MD; Réka Hécz; Michael C. Knorz, MD |
| English Title: | Evaluation of Femtosecond Laser-Assisted and Manual Clear Corneal Incisions and Their Effect on Surgically Induced Astigmatism and Higher-Order Aberrations |
| Original Title: | Evaluation of Femtosecond Laser-Assisted and Manual Clear Corneal Incisions and Their Effect on Surgically Induced Astigmatism and Higher-Order Aberrations |
| Journal/Book/Source: | J Refract Surgery |
| Date of Publication: | August, 2014 |
| Volume: | 30 |
| Issue: | 8 |
| Pages: | 522-525 |

| | | |
|---|---|---|
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Parallel group RCT: 2 arms<br><br>Unit of analysis: eye<br>Follow up: Preoperatively and 90 days | |
| **Participants** | | |
| Total Number of Participants randomized | 40 | |
| Total Number of eyes randomized | 40 | |
| Country of participants | Hungary | |
| Data collection period | NA | |
| Inclusion criteria | Not described | |
| Exclusion criteria | previous ocular surgery, trauma, active ocular disease, poorly dilated pupils, or known zonular weakness were excluded. | |
| Average age (intervention and control) | LASER: 70.40±11.57<br>MANUAL (CTRL): 62.27±13.41 | |
| Sex % (intervention and control) | Not reported | |
| Number of patients in Intervention group | LASER: 20 (20 eyes) | |
| Number of patients in control group | 20 (20 eyes) | |
| Sub population 1 – LOCS GRADE | N.A. | |
| Sub population 2 - SUBEXFOLIATION | N.A. | |
| Professional participant | Single surgeon | |
| I**ntervention** | cataract surgery was performed in 20 eyes of 20 patients (femtosecond laser group) using a femtosecond laser system (Alcon Laboratories, Inc., Aliso Viejo, CA) to create corneal wounds, capsulotomy, and lens fragmentation | |
| **Comparator** | Manually performed conventional phacoemulsification was also performed in 20 eyes of 20 patients (manual group) | |
| **Outcomes** (list all outcomes) | Keratometry, surgical induced astigmatism, Low order aberration, high order aberration, complication. | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | Dr. Nagy is a consultant for Alcon Laboratories, Inc. The remaining authors have no financial or proprietary interest in the materials presented herein | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Randomization was done using computer-generated tables (Microsoft Excel; Microsoft Corporation, Redmond, WA). |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias) | High risk | Open trial. |
| Blinding of outcome assessment (detection bias) | High risk | Not well described but probably not masked |
| Incomplete outcome data (attrition bias) | Unclear risk | Not reported |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | | |
| Anterior capsular tear | | |

<table>
<tr><td>Vitreous loss</td><td></td><td></td></tr>
<tr><td>Cystoid macula oedema (within 90 days)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 day)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 week)</td><td></td><td></td></tr>
<tr><td>Endothelial Cell Loss (ECL)</td><td></td><td></td></tr>
<tr><td>Central Corneal Thickness (CCT) preoperative</td><td></td><td></td></tr>
<tr><td>Idrocyclitis</td><td></td><td></td></tr>
<tr><td>Infections (within 90 days)</td><td></td><td></td></tr>
<tr><td>Corneal Endothelial Decompensation (within 90 days)</td><td></td><td></td></tr>
<tr><td>Surgical induced astigmatism</td><td><table><tr><td colspan="2">Experimental (magnitude, dioptres)</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0.47 ± 0.13</td><td>20</td></tr></table><table><tr><td colspan="2">Experimental (deviation, degrees)</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>4.47± 2.59</td><td>20</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0.41 ± 0.14</td><td>20</td></tr></table><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>7.38 ± 4.72</td><td>20</td></tr></table></td></tr>
<tr><td>Retinal detachment</td><td></td><td></td></tr>
<tr><td>Posterior capsule opacification</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (1 month)</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (6 months)</td><td></td><td></td></tr>
<tr><td>Surgical re-intervention (within 6 months)</td><td></td><td></td></tr>
<tr><td>Secondary cataract (24 months)</td><td></td><td></td></tr>
<tr><td>EFFECTIVENESS</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 7days after surgery</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 30days after surgery</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 180days after surgery</td><td></td><td></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 7days after surgery</td><td></td><td></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 30 days after surgery</td><td></td><td></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 180 days after surgery</td><td></td><td></td></tr>
<tr><td>Refractive outcomes (3 months, available preoperative)</td><td>Low order aberration</td><td></td></tr>
<tr><td>Refractive outcomes (3 months, available preoperative)</td><td>High order aberration</td><td></td></tr>
<tr><td>Vision-related Quality of Life (by validated questionnaire)</td><td></td><td></td></tr>
<tr><td>Patient-reported outcome measures (PROMs)</td><td></td><td></td></tr>
<tr><td>OTHER OUTCOMES</td><td></td><td></td></tr>
</table>

| | | |
|---|---|---|
| Patient satisfaction | | |
| Procedural time | | |
| Resource use | | |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 16 - Characteristics of randomised controlled studies, Panthier, 2017** (50)

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Panthier, 2017 (50) |
| Authors: | Christophe Panthier, MD; Florent Costantini, MD; Jean Claude Rigal-Sastourné, MD, PhD; Antoine Brézin, MD, PhD; Chadi Mehanna, MD; Mikael Guedj, MD; Dominique Monnet, MD, PhD |
| English Title: | Change of Capsulotomy Over 1 Year in Femtosecond Laser-Assisted Cataract Surgery and Its Impact on Visual Quality |
| Original Title: | Change of Capsulotomy Over 1 Year in Femtosecond Laser-Assisted Cataract Surgery and Its Impact on Visual Quality |
| Journal/Book/Source: | J Refract Surg. 2017 |
| Date of Publication: | September 21, 2016 |
| Volume: | 33 |
| Issue: | 1 |
| Pages: | 44-49 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | RCT: 2 arms (within person – paired-eye)<br><br>Unit of analysis: eye<br>Follow up: 7 days, 6 months, 1 year |
| **Participants** | |
| Total Number of Participants randomized | 33 |
| Total Number of eyes randomized | 66 |
| Country of participants | France |
| Data collection period | from May 2012 to June 2013 |
| Inclusion criteria | NA |
| Exclusion criteria | Exclusion criteria were a patient who had only one eye or poor pupillary dilation |
| Average age (intervention and control) | NA |
| Sex % (intervention and control) | NA |
| Number of patients in Intervention group | LASER: 33 (33 eyes)<br>Paired eyes |
| Number of patients in control group | 33 (33 eyes) |
| Sub population 1 – LOCS GRADE | NA |
| Sub population 2 - SUBEXFOLIATION | NA |
| Professional participant | Four experienced surgeons performed all surgeries (including AB, DM, and JCR-S). |
| **Intervention** | The Victus femtosecond laser (Bausch + Lomb Company, München, Germany) was used for FLACS. The femtosecond laser was programmed to make a 5.5-mm anterior capsulotomy and nucleus fragmentation |
| **Comparator** | manual anterior capsulotomy of 5.5 mm was made with the same capsulorhexis forceps. Surgery was completed in both groups using standard phacoemulsification procedures, including removal of the lens cortex and |

<table>
<tr><td></td><td colspan="2">IOL implantation.</td></tr>
<tr><td>Outcomes (list all outcomes)</td><td colspan="2">free-floating capsulotomy, tears, and bridging tags, uncorrected and corrected distance visual acuity and anterior and posterior segment examination, postoperative refractive error, posterior capsular tears</td></tr>
<tr><td>Notes (Funding source; Conflicts of Interest; trial registration number; any other note)</td><td colspan="2">The authors have no financial or proprietary interest in the materials presented herein.</td></tr>
<tr><td>Risk of bias RCTs</td><td>Authors' judgment</td><td>Support for judgement</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Unclear risk</td><td>For all patients, one eye was randomly included.</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear risk</td><td>Not described</td></tr>
<tr><td>Blinding of participants and personnel (performance bias)</td><td>High risk</td><td>Open trial.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>Low risk</td><td>For the review of the capsulorhexis, a single masked operator performed the anterior segment photographs. To evaluate the quality of the rhexis in terms of circularity and sizing, photographs were digitalized and analyzed by a single operator, ignoring the surgical procedure.<br>Not likely to influence outcome of interest</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td></td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>Unclear risk</td><td>No protocol available</td></tr>
<tr><td>Outcomes</td><td></td><td></td></tr>
<tr><td>SAFETY</td><td></td><td></td></tr>
<tr><td>Posterior capsular tear</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0</td><td>33</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0</td><td>33</td></tr></table></td></tr>
<tr><td>Anterior capsular tear</td><td></td><td></td></tr>
<tr><td>Vitreous loss</td><td></td><td></td></tr>
<tr><td>Cystoid macula oedema (within 90 days)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 day)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 week)</td><td></td><td></td></tr>
<tr><td>Endothelial Cell Loss (ECL)</td><td></td><td></td></tr>
<tr><td>Central Corneal Thickness (CCT) preoperative</td><td></td><td></td></tr>
<tr><td>Idrocyclitis</td><td></td><td></td></tr>
<tr><td>Infections (within 90 days)</td><td></td><td></td></tr>
<tr><td>Corneal Endothelial Decompensation (within 90 days)</td><td></td><td></td></tr>
<tr><td>Surgical induced astigmatism</td><td></td><td></td></tr>
<tr><td>Retinal detachment</td><td></td><td></td></tr>
<tr><td>Posterior capsule opacification</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (1 month)</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (6 months)</td><td></td><td></td></tr>
</table>

| | | |
|---|---|---|
| Surgical re-intervention (within 6 months) | | |
| Secondary cataract (24 months) | | |
| **EFFECTIVENESS** | | |
| Corrected Distance Visual Acuity (CDVA) **7days after** surgery | Reported in graph | |
| Corrected Distance Visual Acuity (CDVA)1 month after surgery | | |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) **7days** after surgery | Reported in graph at 12 months | |
| Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery | | |
| Refractive outcomes (3 months, available preoperative) | | |
| Refractive outcomes (3 months, available preoperative) | | |
| Vision-related Quality of Life (by validated questionnaire) | | |
| Patient-reported outcome measures (PROMs) | | |
| **OTHER OUTCOMES** | | |
| Patient satisfaction | | |
| Procedural time | | |
| Resource use | | |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 17 - Characteristics of randomised controlled studies, Reddy 2013** (42)

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Reddy 2013 (42) |
| Authors: | Kasu Prasad Reddy; Jochen Kandulla; Gerd U. Auffarth |
| English Title: | Effectiveness and safety of femtosecond laser–assisted lens fragmentation and anterior capsulotomy versus the manual technique in cataract surgery |
| Original Title: | |
| Journal/Book/Source: | J Cataract Refract Surg |
| Date of Publication: | May 23, 2013 |
| Volume: | 39 |

| | |
|---|---|
| Issue: | |
| Pages: | 1297–1306 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Parallel group RCT<br><br>Unit of analysis: eye<br><br>Follow up: 1 day after surgery |
| **Participants** | |
| Total Number of Participants randomized | 131 |
| Total Number of eyes randomized | 131 |
| Country of participants | India |
| Data collection period | N.A. |
| Inclusion criteria | Eligible patients were at least 18 years old with clear corneal media and elected to have routine cataract surgery. |
| Exclusion criteria | All patients:<br>• Poorly dilating pupil or other pupil defect that prevents iris from adequate retraction peripherally<br>• Lens/zonule instability such as, but not restricted to, Marfan syndrome, pseudoexfoliation syndrome<br>• Previous intraocular or corneal surgery of any kind, including any type of surgery for refractive or therapeutic purposes I either eye<br>• Known sensitivity to planned concomitant medications<br>• Disorders of the ocula muscle, such as nystagmus or strabismus<br>• Keratoconus<br>• Wound-healing disorders, such as connective tissue disease, autoimmune illnesses, immunodeficiency illnesses, ocular herpes zoster or simplex, endocrine diseases, lupus, rheumatoid arthritis<br>• Abnormal examination results from slitlamp, fundus, partial coherence interferometry<br>• Autoimmune disease, collagenosis, or clinically significant atopy<br>• Pregnancy or nursing<br>Patients Having Laser-Assisted Procedure:<br>• Minimal or Maximal K values in central 3.0 mm zone that do not differ by more than 5.0 dioptres (D) on a keratometric map of the cornea<br>• Maximum K-value that does not exceed 60.0 D and a minimum value that is smaller than 37.0 D<br>• Corneal diseased or pathology that precludes |

| | |
|---|---|
| | transmission of laser wavelength or distortion of laser light<br>• Abnormal examination results from scanning-slit corneal topography<br>• Anterior chamber depth <2.4 mm or >4.5 mm measured by ultrasonic examination |
| Average age (intervention and control) | (mean ± SD years)<br>Int: 58.5 ± 11.6 (56 eyes)<br>Con: 61.3 ± 9.7 (63 eyes) |
| Sex % (intervention and control) | Female:<br>Int: 26/56 (46.4%)<br>Con: 26/63 (41.3%) |
| Number of patients in<br>Intervention group | 64 (56 included in the analysis) |
| Number of patients in control group | 67 (63 included in the analysis) |
| Sub population 1 – LOCS GRADE | N.A. |
| Sub population 2 - SUBEXFOLIATION | Excluded |
| Professional participant | Multisurgeon trial (4 surgeons) |
| I**ntervention** | Femtosecond laser–assisted lens fragmentation and anterior capsulotomy before phacoemulsification (Victus femtosecond<br>laser platform; Bausch & Lomb Technolas) |
| **Comparator** | manual capsulorhexis and standard phacoemulsification |
| **Outcomes** (list all outcomes) | Effective phacoemulsification time (EPT) during phacoemulsification; mean phaco time; mean phaco energy; subjective surgeon assessment of the ease of phacoemulsification; volume of balanced salt solution used; Capsulorhexis quality measures; posterior capsular bag tear; IOL malposition; iris damage; Incomplete capsulotomy (being completed manually); Decentered capsulotomy; Corneal burn; anterior tear; glaucoma; other complications |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | Dr. Reddy has received travel and research grants from Technolas Perfect Vision GmbH, Dr. Kandulla is an employee of Technolas Perfect Vision GmbH (a Bausch & Lomb company), and Dr. Auffarth has received travel and research grants as well as lecture fees from Technolas Perfect Vision GmbH/Bausch & Lomb. |

| Risk of bias RCTs | Authors' judgment | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No information on random sequence generation was reported |
| Allocation concealment (selection bias) | High risk | The use of different exclusion criteria for intervention group and comparator group led to a strong selection bias. |
| Blinding of participants and personnel (performance bias) | High risk | Open trial |
| Blinding of outcome assessment (detection bias) | High risk | No blinding of outcome assessment was reported. |
| Incomplete outcome data (attrition bias) | High risk | The number of patients enrolled was 131 while the analysis included only 119 selected patients. |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available. |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | | |
| Anterior capsular tear | Experimental: Events 1, Total 56 | Control: Events 1, Total 63 |
| Vitreous loss | | |
| Cystoid macula oedema (within 90 days) | | |
| Elevated Intraocular Pressure (IOP) (1 day) | | |
| Elevated Intraocular Pressure (IOP) (1 week) | | |
| Endothelial Cell Loss (ECL) | | |

| | | |
|---|---|---|
| Central Corneal Thickness (CCT) | | |
| Idrocyclitis | | |
| Infections (within 90 days) | | |
| Corneal Endothelial Decompensation (within 90 days) | | |
| Surgical induced astigmatism | | |
| Retinal detachment | | |
| Posterior capsule opacification | | |
| Visual acuity loss post cataract surgery (1 month) | | |
| Visual acuity loss post cataract surgery (6 months) | | |
| Surgical re-intervention (within 6 months) | | |
| Secondary cataract (24 months) | | |
| **EFFECTIVENESS** | | |
| Corrected Distance Visual Acuity (CDVA) 1 month after surgery | | |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery | | |
| Refractive outcomes | | |
| Vision-related Quality of Life (by validated questionnaire) | | |
| Patient-reported outcome measures (PROMs) | | |

<table>
<tr><td>OTHER OUTCOMES</td><td></td><td></td></tr>
<tr><td>Patient satisfaction</td><td></td><td></td></tr>
<tr><td>Procedural time</td><td>Effective Phaco Time<br><br>(seconds mean ± SD)<br><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>5.2 ± 5.7</td><td>56</td></tr></table><br>Mean Phaco Time<br><br>(seconds mean ± SD)<br><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>30.4 ± 16.0</td><td>56</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>7.7 ± 6.0</td><td>63</td></tr></table><br><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>34.5 ± 19.6</td><td>63</td></tr></table></td></tr>
<tr><td>Resource use</td><td></td><td></td></tr>
<tr><td>Additional outcomes</td><td>Incomplete capsulotomy<br><br>(being completed manual-ly): 2 patients (3.6%) in the laser group</td><td></td></tr>
<tr><td>Notes</td><td></td><td></td></tr>
</table>

**Table A 18 - Characteristics of randomised controlled studies, Roberts 2018** (33)

| RANDOMIZED CONTROLLED TRIALS | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Roberts 2018 (33) |
| Authors: | Harry W Roberts, Vijay K Wagh, Isabella J M Mullens, Simone Borsci, Melody Z Ni, David P S O'Brart |
| English Title: | Evaluation of a hub-and-spoke model for the delivery of femtosecond laser-assisted cataract surgery within the con-text of a large randomised controlled trial |
| Original Title: | |
| Journal/Book/Source: | Br J Ophthalmol |
| Date of Publication: | 2018 |
| Volume: | 0 |
| Issue: | |
| Pages: | 1-9 |
| Methods (study design and unit of analysis (within person – paired eye RCT; parallel group RCT; length of follow up)) | Randomised-controlled trial (subgroup analysis of a larger trial)<br>Parallel group |

| Participants | - |
|---|---|
| Total Number of Participants randomized | 299 |
| Total Number of eyes randomized | 299 |
| Country of participants | UK |
| Data collection period | |
| Inclusion criteria | • Patients must have reduced visual acuity or visual symptoms attributed to the presence of cataract in one or both eyes by the examining ophthalmologist or else must require cataract surgery on clinical grounds other than visual symptoms.<br>• Patients must be willing to attend for follow-up at 3–4 weeks after cataract surgery.<br>• Patients must have sufficient English language for informed consent and completion of the patient reported outcome questionnaires. |
| Exclusion criteria | • Children below the age of 18 years<br>• Patients already enrolled in another study<br>• Clinical contraindications for femtosecond laser-assisted cataract surgery, such as<br>– Significant corneal opacities<br>– Small pupils (<4 mm) following pharmacological dilatation<br>– Patients unable to lie sufficiently flat so as to be positioned underneath the laser machine. |
| Average age (intervention and control) | Intervention: 69.07±11.55<br>Control: 69.78±10.14 |
| Sex % (intervention and control) | Intervention: female 54%<br>Control: female 53% |
| Number of patients in Intervention group | 134 (5 patients originally randomized to FLACS did not receive FL treatment but CPS) |
| Number of patients in control group | 165 |
| Sub population 1 – LOCS GRADE | - |
| Sub population 2 - SUBEXFOLIATION | - |
| Professional participant | The femtosecond laser was operated by the same two ophthalmologists (Harry W Roberts, Vijay K Wagh) |
| Intervention | Femtosecond laser assisted cataract surgery (FLACS) in a hub-and-spoke model.<br>Femtosecond laser cataract surgery is performed with LenSx (Alcon, Fort Worth, Texas, USA) |
| Comparator | Dual Conventional Phacoemulsification Surgery (CPS) theatre list |
| Outcomes (list all outcomes) | • Relative costs of FLACS and CPS<br>• Number of cases on FLACS and CPS lists<br>• Time from entering operating room to start of operation<br>• Duration of operation<br>• Time from end of operation to exiting operating room<br>• Total time in operating room<br>• Time operating room is empty<br>• Intraoperative complications: Anterior capsular tear, posterior capsular tear with vitreous loss, descemet's membrane tears, suprachoroidal haemorrhage, abandoned-extreme zonular weakness |

| | | |
|---|---|---|
| Notes (Funding source; Conflicts of Interest; trial registration number; any other note) | **Funding** This research has been supported by a non-commercial research grant from Alcon Incorporated (Grant number: IIT #17440075) and by the NIHR Diagnostic Evidence Co-operative London. The funding organisation had no role in the design or conduct of this research. **Competing interests** DPSOB has undertaken consultancy work for Sooft Italia SPA and Alcon in the past 12 months. No other conflicting relationship exists for any author. | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Insufficient information about the sequence generation process |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information |
| Blinding of participants and personnel (performance bias) | High risk | No blinding of participants and personnel |
| Blinding of outcome assessment (detection bias) | Low risk | No blinding but outcome measurement not likely to be influenced by lack of blinding |
| Incomplete outcome data (attrition bias) | Low risk | No missing outcome data |
| Selective reporting (reporting bias) | High risk | Safety outcomes not included in the protocol |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | Experimental: Events / Total | Control: Events / Total |
| Anterior capsular tear | Experimental: Events 3 / Total 139 | Control: Events 3 / Total 160 |
| Vitreous loss | Experimental: Events 0 / Total 139 | Control: Events 3 / Total 160 |
| Cystoid macula edema (postoperatively) | Experimental: Events / Total | Control: Events / Total |
| Cystoid macula edema (30 days) | Experimental: Events / Total | Control: Events / Total |
| Elevated Intraocular Pressure (IOP) (1 day) | Experimental: Events / Total | Control: Events / Total |

| | | |
|---|---|---|
| | | |
| Elevated Intraocular Pressure (IOP) (1 week) | Experimental<br>Events / Total | Control<br>Events / Total |
| Endothelial Cell Loss (ECL) | Experimental<br>Events / Total | Control<br>Events / Total |
| Central Corneal Thickness (CCT) | Experimental<br>Events / Total | Experimental<br>Events / Total |
| Idrocyclitis | Experimental<br>Events / Total | Control<br>Events / Total |
| Infections (within 90 days) | Experimental<br>Events / Total | Control<br>Events / Total |
| Corneal Endothelial Decompensation (within 90 days) | Experimental<br>Events / Total | Control<br>Events / Total |
| Surgical induced astigmatism | Experimental<br>Events / Total | Control<br>Events / Total |
| Retinal detachment | Experimental<br>Events / Total | Control<br>Events / Total |
| Posterior capsule opacification | Experimental<br>Events / Total | Control<br>Events / Total |
| Visual acuity loss post cataract surgery (1 month) | Experimental | Control |

| | | |
|---|---|---|
| | Events \| Total | Events \| Total |
| Visual acuity loss post cataract surgery (6 months) | Experimental: Events \| Total | Control: Events \| Total |
| Surgical re-intervention (within 6 months) | Experimental: Events \| Total | Control: Events \| Total |
| Secondary cataract (24 months) | Experimental: Events \| Total | Control: Events \| Total |
| **EFFECTIVENESS** | | |
| Corrected Distance Visual Acuity (CDVA) 1 month after surgery | Experimental: Mean ± sd \| Total | Control: Mean ± sd \| Total |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | Experimental: Events \| Total | Control: Events \| Total |
| Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery | Experimental: Mean ± sd \| Total | Control: Mean ± sd \| Total |
| Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery | Experimental: Events \| Total | Control: Events \| Total |
| Refractive outcomes | Experimental: Mean ± sd \| Total | Control: Mean ± sd \| Total |
| Vision related Quality of Life (by validated questionnaire) | Experimental: Events \| Total | Control: Events \| Total |
| Patient reported outcome measures (PROMs) | Experimental: Events \| Total | Control: Events \| Total |
| **OTHER OUTCOMES** | | |
| Patient satisfaction | | |

| | | |
|---|---|---|
| | Experimental<br>Events \| Total<br>\| | Control<br>Events \| Total<br>\| |
| Procedural time | Duration of operation (min)<br>Experimental<br>m±sd \| Total<br>12.04±4.89 \| 139<br><br>Total time in Operating Room (OR) (min)<br>Experimental<br>m±sd \| Total<br>20.34±5.82 \| 139 | Duration of operation (min)<br>Control<br>m±sd \| Total<br>14.54±6.19 \| 160<br><br>Total time in Operating Room (OR) (min)<br>Control<br>m±sd \| Total<br>23.39±6.89 \| 160 |
| Resource use | Experimental<br>Events \| Total<br>\|<br><br>£500.02 | Control<br>Events \| Total<br>\|<br><br>£355.42 |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 19 - Characteristics of randomised controlled studies, Schargus 2015** (32)

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Schargus 2015 (32) |
| Authors: | Marc Schargus; Nathanael Suckert; Tim Schultz; Vinodh Kakkassery;<br><br>H. Burkhard Dick |
| English Title: | Femtosecond Laser-Assisted Cataract Surgery Without OVD: A Prospective Intraindividual Comparison |
| Original Title: | Femtosecond Laser-Assisted Cataract Surgery Without OVD: A Prospective Intraindividual Comparison |
| Journal/Book/Source: | J Refract Surg. |
| Date of Publication: | January 22, 2015 |
| Volume: | 31 |
| Issue: | 3 |
| Pages: | 146-152 |

| | |
|---|---|
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Prospective, randomized<br><br>single-center trial (within person – paired-eye RCT)<br><br>Follow up: 1 day to 6 months.<br><br>Unit of analysis: eye |
| **Participants** | |
| Total Number of Participants randomized | 37 |
| Total Number of eyes randomized | 74 |
| Country of participants | Germany |
| Data collection period | October 2012 – May 2013 |
| Inclusion criteria | Both eyes with visually significant cataract (NC2 to NC5 on the Lens Opacities Classification System III [LOCS III], corrected distance visual acuity (CDVA) decreased 0.1 LogMAR in both eyes, dilated pupil width of 6.0 mm or greater, and were willing to volunteer for the trial after giving informed consent. |
| Exclusion criteria | The exclusion criteria included corneal scars, corneal diseases, corneal astigmatism of 1.5 diopters or greater, reduced endothelial cell count (ECC) (less than 1,500 cells/mm²), CCT less than 500 µm, glaucoma, pseudoexfoliation syndrome, zonular weakness, single eye, malformations, history of ocular surgery, intraocular tumors, active or past inflammations, age-related macular degeneration, diabetic retinopathy, axial length difference (greater than 0.5 mm) and axial length less than 21.5 mm or greater than 26 mm, pregnancy, reduced compliance, age younger than 22 years, or participation in another<br><br>clinical study within 30 days of the preoperative visit. |
| Average age (intervention and control) | 71.8 years (range 48-85) |
| Sex % (intervention and control) | Female 22/37 (59.5%) |
| Number of patients in<br><br>Intervention group | 37 patients (37 eyes) |
| Number of patients in control | 37 patients (37 eyes) |

| | | |
|---|---|---|
| group | | |
| Sub population 1 – LOCS GRADE | N.A. | |
| Sub population 2 - SUBEXFOLIATION | Excluded | |
| Professional participant | single experienced surgeon (HBD) | |
| I**ntervention** | laser-assisted cataract surgery without<br><br>Ophthalmic viscosurgical devices (Catalys Precision Laser System; Abbott Medical Optics, Santa Ana, CA) | |
| **Comparator** | standard phacoemulsification cataract surgery with ophthalmic viscosurgical devices | |
| **Outcomes** (list all outcomes) | Endothelial Cell Count, Endothelial cell loss, Corneal thickness, IOP, CDVA, overall surgery time, quantity of fluid passing through the eye during surgery, absolute and effective phacoemulsification time, other complications | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | COI: Dr. Dick is a paid consultant for Abbott Medical Optics. The remaining authors have no financial or proprietary interest in the materials presented herein. | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | "Both treatment group allocations were printed on a separate sheet, which were sealed in sequentially numbered identical envelopes according to the randomized allocation sequence." |
| Allocation concealment (selection bias) | Low risk | "The enclosed assignments were inserted into sequentially numbered, opaque, wellsealed envelopes for allocation concealment, which were continuously monitored. Investigators ensured that the envelopes were opened sequentially and only after the participant's name and other details were written on the appropriate envelope." |
| Blinding of participants and personnel (performance bias) | High risk | Open trial |

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) | High risk | No blinding of outcome assessment was reported. |
| Incomplete outcome data (attrition bias) | Unclear risk | Insufficient reporting on attrition |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | Experimental: Events 0, Total 37 | Control: Events 1, Total 37 |
| Anterior capsular tear | | |
| Vitreous loss | Experimental: Events 0, Total 37 | Control: Events 1, Total 37 |
| Cystoid macula oedema (within 90 days) | Experimental: Events 0, Total 37 | Control: Events 1, Total 37 |
| Elevated Intraocular Pressure (IOP) (1 day) | Experimental: Events 1, Total 37 | Control: Events 3, Total 37 |
| Elevated Intraocular Pressure (IOP) (1 week) | | |
| Endothelial Cell Loss (ECL) | 6 months; Experimental: Events, Total | 6 months; Control: Events, Total |

<table>
<tr><td></td><td><table><tr><td>2.4%</td><td>37</td></tr></table></td><td><table><tr><td>2.7%</td><td>37</td></tr></table></td></tr>
<tr><td>Central Corneal Thickness (CCT)</td><td>3 days<table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>591±50</td><td>37</td></tr></table>6 months<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>555 ± 35 µm</td><td>37?</td></tr></table></td><td>3 days<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>590±52</td><td>37</td></tr></table>6 months<table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>551 ± 35 µm</td><td>37?</td></tr></table></td></tr>
<tr><td>Idrocyclitis</td><td></td><td></td></tr>
<tr><td>Infections (within 90 days)</td><td></td><td></td></tr>
<tr><td>Corneal Endothelial Decompensation (within 90 days)</td><td></td><td></td></tr>
<tr><td>Surgical induced astigmatism</td><td></td><td></td></tr>
<tr><td>Retinal detachment</td><td></td><td></td></tr>
<tr><td>Posterior capsule opacification</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (1 month)</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (6 months)</td><td></td><td></td></tr>
<tr><td>Surgical re-intervention (within 6 months)</td><td></td><td></td></tr>
<tr><td>Secondary cataract (24 months)</td><td></td><td></td></tr>
<tr><td>EFFECTIVENESS</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 1 month after surgery</td><td></td><td></td></tr>
<tr><td>Corrected Distance Visual Acuity (CDVA) 6 months after surgery</td><td>Mean CDVA improvement</td><td>Mean CDVA improvement</td></tr>
</table>

<table>
<tr><td></td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0.024 ± 0.101 Log-MAR</td><td>37</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0.038 ± 0.079 Log-MAR</td><td>37</td></tr></table></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery</td><td></td><td></td></tr>
<tr><td>Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery</td><td></td><td></td></tr>
<tr><td>Refractive outcomes</td><td></td><td></td></tr>
<tr><td>Vision-related Quality of Life (by validated questionnaire)</td><td></td><td></td></tr>
<tr><td>Patient-reported outcome measures (PROMs)</td><td></td><td></td></tr>
<tr><td>OTHER OUTCOMES</td><td></td><td></td></tr>
<tr><td>Patient satisfaction</td><td></td><td></td></tr>
<tr><td>Procedural time</td><td>Effective phacoemulsification time<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0 seconds</td><td>37?</td></tr></table>Mean total surgery time<table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>6.25 ± 1.36 minutes</td><td>37?</td></tr></table></td><td>Effective phacoemulsification time<table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>1.59 ± 1.09 seconds</td><td>37?</td></tr></table>Mean total surgery time<table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>6.04 ± 0.72 minutes</td><td>37?</td></tr></table></td></tr>
<tr><td>Resource use</td><td></td><td></td></tr>
<tr><td>Additional outcomes</td><td></td><td></td></tr>
<tr><td>Notes</td><td></td><td></td></tr>
</table>

**Table A 20 - Characteristics of randomised controlled studies, Takács 2012** (43)

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | Takács 2012 (43) |
| Authors: | Ágnes I. Takács; Illés Kovács; Kata Miháltz; Tamás Filkorn; Michael C. Knorz; Zoltán Z. Nagy |
| English Title: | Central Corneal Volume and Endothelial Cell Count Following Femtosecond Laser–assisted Refractive Cataract Surgery Compared to Conventional Phacoemulsification |
| Original Title: | |
| Journal/Book/Source: | J Refract Surg. |
| Date of Publication: | April 24, 2012 |
| Volume: | 28 |
| Issue: | 6 |
| Pages: | 387-391 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Parallel group RCT<br><br>Unit of analysis: eye<br>Follow up: 1 day, 1 week, 1 month postoperatively |
| **Participants** | |
| Total Number of Participants randomized | 76 |
| Total Number of eyes randomized | 76 |
| Country of participants | Hungary |
| Data collection period | February 2010 – February 2011 |
| Inclusion criteria | with various grades of cataract |
| Exclusion criteria | “Patients showing low cooperation, dense (grade 4+) or white cataract,<br>corneal scars or opacities, anterior segment abnormalities, floppy iris syndrome, and poor pupillary dilation were not included in the study.” |
| Average age (intervention and control) | Int: 65.81 ± 12.42<br>Cont: 66.93 ± 10.99 |
| Sex % (intervention and control) | Female<br>Int: 73.7% (28/38)<br>Cont: 60.5% (23/38) |
| Number of patients in Intervention group | 38 patients (38 eyes) |
| Number of patients in control group | 38 patients (38 eyes) |
| Sub population 1 – LOCS GRADE | N.A. |
| Sub population 2 - SUBEXFOLIATION | N.A. |
| Professional participant | Same surgeon (Z.Z.N.) |
| I**ntervention** | FLACS LenSx (Alcon LenSx Inc, Aliso Viejo, California) laser corneal incisions, capsulotomy and lens fragmentation |
| **Comparator** | Manual corneal incisions, capsulorhexis and a divide-and- |

| | | |
|---|---|---|
| | conquer phaco technique. | |
| **Outcomes** (list all outcomes) | central corneal volume,<br>central corneal thickness, nucleus density, Central endothelial cell count, Volume stress index, Phaco time (s), Effective Phaco Time (s) | |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | COI: Drs Nagy and Knorz are consultants to Alcon LenSx Inc. The remaining authors have no financial interest in the materials presented herein. | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | "Patients were randomly assigned (using computer randomization) to either group by the surgeon (Z.Z.N.)."<br><br>Limitations:<br>"…and randomization was done by the surgeon and not by randomization tables." |
| Allocation concealment (selection bias) | High risk | Insufficient information on allocation concealment.<br>"Patients were randomly assigned (using computer randomization) to either group by the surgeon (Z.Z.N.)."<br>Limitations:<br>"…and randomization was done by the surgeon and not by randomization tables." |
| Blinding of participants and personnel (performance bias) | High risk | Open trial |
| Blinding of outcome assessment (detection bias) | Low risk | "Examiners were not aware of which surgical procedure had been used when performing the postoperative examinations." |
| Incomplete outcome data (attrition bias) | Unclear risk | No Information on the number of patients assessed in the follow up phases. |
| Selective reporting (reporting bias) | Unclear risk | No study protocol available. |
| **Outcomes** | | |
| **SAFETY** | | |
| Posterior capsular tear | | |
| Anterior capsular tear | | |
| Vitreous loss | | |
| Cystoid macula oedema (within 90 days) | | |
| Elevated Intraocular Pressure (IOP) (1 day) | | |
| Elevated Intraocular Pressure | | |

<table>
<tr><td>(IOP) (1 week)</td><td></td><td></td></tr>
<tr><td>Endothelial Cell Loss (ECL)</td><td>ECC available at baseline and at each follow-up step available.</td><td></td></tr>
<tr><td>Central Corneal Thickness (CCT)</td><td>1 day (µm) (mean ± SD)<br><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>580 ± 42</td><td>38</td></tr></table>1 week<br><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>554 ± 36</td><td>38</td></tr></table>1 month<br><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>545 ± 31</td><td>38</td></tr></table></td><td>1 day<br><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>607 ± 91</td><td>38</td></tr></table>1 week<br><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>559 ± 52</td><td>38</td></tr></table>1 month<br><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>557 ± 42</td><td>38</td></tr></table></td></tr>
<tr><td>Idrocyclitis</td><td></td><td></td></tr>
<tr><td>Infections (within 90 days)</td><td></td><td></td></tr>
<tr><td>Corneal Endothelial Decompensation (within 90 days)</td><td></td><td></td></tr>
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<tr><td>Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery</td><td></td><td></td></tr>
<tr><td>Refractive outcomes</td><td></td><td></td></tr>
<tr><td>Vision-related Quality of Life (by validated questionnaire)</td><td></td><td></td></tr>
<tr><td>Patient-reported outcome measures (PROMs)</td><td></td><td></td></tr>
<tr><td>OTHER OUTCOMES</td><td></td><td></td></tr>
<tr><td>Patient satisfaction</td><td></td><td></td></tr>
<tr><td>Procedural time</td><td>Phaco time (s) (mean ± SD)</td><td>Phaco time (s) (mean ± SD)<br><table><tr><td>Control</td></tr></table></td></tr>
</table>

| | | |
|---|---|---|
| | Experimental<br>Events \| Total<br>0.56 ± 0.6 \| 38<br>Effective Phaco Time (s) (mean ± SD)<br>Experimental<br>Events \| Total<br>0.10 ± 0.12 \| 38 | Events \| Total<br>0.67 ± 0.75 \| 38<br>Effective Phaco Time (s) (mean ± SD)<br>Control<br>Events \| Total<br>0.12 ± 0.13 \| 38 |
| Resource use | | |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 21 - Characteristics of randomised controlled studies, Yong Yu,2015 (28)**

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | A-Yong Yu,2015 (28) |
| Authors: | A-Yong Yu, MD, PhD, Li-Yang Ni, MD, Qin-Mei Wang, MD, Fang Huang, MD, Shuang-Qian Zhu, MD, Lin-Yan Zheng, MD, and Yan-Feng Su, MD |
| English Title: | Preliminary Clinical Investigation of Cataract Surgery With a Noncontact Femtosecond Laser System |
| Original Title: | Preliminary Clinical Investigation of Cataract Surgery With a Noncontact Femtosecond Laser System |
| Journal/Book/Source: | Lasers in Surgery and Medicine |
| Date of Publication: | May 23, 2014 |
| Volume: | 47 |
| Issue: | 9 |
| Pages: | 698-703 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Parallel group RCT: 2 arms<br><br>Unit of analysis: eye<br>Follow up: Postoperatively at 1 day, 1 week, 1 and 3 months |
| **Participants** | |
| Total Number of Participants randomized | 36 |
| Total Number of eyes randomized | 54 |
| Country of participants | China |
| Data collection period | |
| Inclusion criteria | Normal and transparent cornea; (ii) Pupillary diameter of at least 6mm under dilation; (iii)<br>Preoperative best corrected visual acuity worse than LogMAR 0.3, No local or systematic contraindications for cataract surgery |
| Exclusion criteria | Not described |
| Average age (intervention and control) | LASER: 62.3±11.6<br>MANUAL (CTRL): 56.5±16.6 |

| | | |
|---|---|---|
| Sex % (intervention and control) | Not reported | |
| Number of patients in Intervention group | 17 (25 eyes) | |
| Number of patients in control group | 19 (29 eyes) | |
| Sub population 1 – LOCS GRADE | N.A. | |
| Sub population 2 - SUBEXFOLIA-TION | N.A. | |
| Professional participant | Single surgeon | |
| I**ntervention** | FLACS for the trial group: after pupillary dilation and topical anesthesia, FLACS was performed using the Lensar femto-second laser platform. | |
| **Comparator** | Conventional phacoemulsification for the control group | |
| **Outcomes** (list all outcomes) | average phacoemulsification time (APT), effective phacoemulsification time (EPT, equaling to average ultra-sonic energy multiplied by APT), total time of cataract pro-cedure from the opening to closing of corneal incision, and complications during operation were recorded, IOL, corneal endothelial density, best corrected visual acuity (LogMAR), nucleus hardness, axial length (mm), posterior capsular opacification, reintervention, corneal edema, anterior and posterior capsular tear. | |
| **Notes** (Funding source; Conflicts of Interest; trial registration num-ber; any other note) | Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported. Contract grant sponsor: International Cooperation Project of the Science and Technology Bureau | |
| **Risk of bias RCTs** | **Authors' judgment** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | randomly assigned |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and per-sonnel (performance bias) | High risk | Open trial |
| Blinding of outcome assessment (detection bias) | Unclear risk | Masked examiner using a digital slit lamp image anal-ysis system (SLM-7E, Chongqing Kanghuaruim-ing, China). Corneal endo-thelial density was meas-ured by a masked examin-er.<br>Not described other out-comes |
| Incomplete outcome data (attrition bias) | Unclear risk | Not reported |
| Selective reporting (reporting bias) | Unclear risk | Study protocol not available |
| **Outcomes** | | |
| **SAFETY** | | |

| | | |
|---|---|---|
| Posterior capsular tear | Experimental: Events 0; Total 25 | Control: Events 0; Total 29 |
| Anterior capsular tear | Experimental: Events 0; Total 25 | Control: Events 0; Total 29 |
| Vitreous loss | | |
| Cystoid macula oedema (within 90 days) | | |
| Elevated Intraocular Pressure (IOP) (1day) | | |
| Elevated Intraocular Pressure (IOP) (1 week) | | |
| Endothelial Cell Loss (ECL) 1 month | Experimental: Events 15.6%; Total 25 | Control: Events 14.2%; Total 29 |
| Endothelial Cell Loss (ECL) 3 months | Experimental: Events 2.9%; Total 25 | Control: Events 4.2%; Total 29 |
| Central Corneal Thickness (CCT) | | |
| Idrocyclitis | | |
| Infections (within 90 days) | | |
| Corneal Endothelial Decompensa-tion (within 90 days) | | |
| Surgical induced astigmatism | | |
| Retinal detachment | | |
| Posterior capsule opacification | Experimental: Events 0; Total 25 | Control: Events 2; Total 29 |
| Visual acuity loss post cataract surgery (6 months) | | |
| Surgical re-intervention (within 6 months) | | |
| Secondary cataract (24 months) | | |
| **EFFECTIVENESS** | | |
| (Best) Corrected distance Visual Acuity (BCVA) **1months after** surgery | Experimental 1: Events 0.09±0.10; Total 25<br>**p=0.37** | Control: Events 0.19±0.44; Total 29 |

| | | |
|---|---|---|
| Refractive outcomes **Absolute deviation spherical equivalent 1 day** | Experimental 1<br>Events: 0.54±0.54<br>Total: 25 | Control<br>Events: 0.57±0.57<br>Total: 29 |
| Refractive outcomes **Absolute deviation spherical equivalent 1 week** | Experimental 1<br>Events: 0.41±0.34<br>Total: 25 | Control<br>Events: 0.42±0.41<br>Total: 29 |
| Refractive outcomes **Absolute deviation spherical equivalent 1 month** | Experimental 1<br>Events: 0.48±0.42<br>Total: 25 | Control<br>Events: 0.51±0.47<br>Total: 29 |
| Refractive outcomes **Absolute deviation spherical equivalent 3 months** | Experimental 1<br>Events: 0.16±0.16<br>Total: 25 | Control<br>Events: 0.74±0.65<br>Total: 29 |
| Vision-related Quality of Life (by validated questionnaire) | | |
| Patient-reported outcome measures (PROMs) | | |
| **OTHER OUTCOMES** | | |
| Patient satisfaction | | |
| Procedural time | Average phacoemulsification time (second)<br>Experimental<br>Events: 8.41 ± 5.43<br>Total: 25<br>p = 0.02 | Control<br>Events: 17.35 ± 14.11<br>Total: 29 |
| Procedural time | Effective phacoemulsification time (second)<br>Experimental<br>Events: 0.09 ± 0.13<br>Total: 25<br>p = 0.02 | Control<br>Events: 0.09 ± 0.13<br>Total: 29 |
| Procedural time | Total time of cataract procedure (minute)<br>Experimental<br>Events: 10.04 ± 1.37<br>Total: 25<br>p = 0.31 | Control<br>Events: 10.52 ± 1.92<br>Total: 29 |
| Resource use | | |
| **Additional outcomes** | | |
| **Notes** | | |

**Table A 22 - Characteristics of randomised controlled studies, A-Yong Yu, 2016** (44)

| **RANDOMIZED CONTROLLED TRIALS** | |
|---|---|
| **Study ID** (surname first author and year – add a, b, c if same author same year) | A-Yong Yu, 2016 (44) |
| Authors: | A-Yong Yu, Cai-Xia Lin, Qin-Mei Wang, Mei-Qing Zheng and Xiao-Yi Qin |
| English Title: | Safety of femtosecond laser-assisted cataract surgery: assessment of aqueous humour and lens capsule |
| Original Title: | Safety of femtosecond laser-assisted cataract surgery: assessment of aqueous humour and lens capsule |
| Journal/Book/Source: | Acta Ophthalmologica 2016 |
| Date of Publication: | Nov 2016 |
| Volume: | 94 |
| Issue: | 7 |
| Pages: | 534-540 |
| **Methods** (study design and unit of analysis (within person – paired-eye RCT; parallel group RCT; length of follow up) | Parallel group RCT: 2 arms<br><br>Unit of analysis: eye<br>Follow up: 6 months |
| **Participants** | |
| Total Number of Participants randomized | 30 |
| Total Number of eyes randomized | 39 |
| Country of participants | China |
| Data collection period | from 21 October to 20 November 2013 |
| Inclusion criteria | The inclusion criteria included normal cornea, and dilated pupillary diameter greater than 6 mm |
| Exclusion criteria | Exclusion criteria were previous ocular, trauma or surgery, and any local or systemic abnormalities other than cataract, such as extensive corneal scarring, pseudoexfoliation syndrome, glaucoma, ocular inflammation, retinal abnormalities, infections and diabetes mellitus. |
| Average age (intervention and control) | LASER: 64.2±11.2<br>MANUAL (CTRL): 71.0±11.7 |
| Sex % (intervention and control) | LASER F/M: 6/7<br>MANUAL (CTRL) F/M: 9/8 |
| Number of patients in Intervention group | LASER: 13 (19 eyes) |
| Number of patients in control group | 17 (20 eyes) |
| Sub population 1 – LOCS GRADE | N.A. |
| Sub population 2 - SUBEXFOLIATION | Exclusion criteria |
| Professional participant | Single surgeon |
| **Intervention** | the femtosecond laser platform (LLS-fs 3D; LensAR) was used to generate capsulotomy |
| **Comparator** | Manually conventional phacoemulsification |
| **Outcomes** (list all outcomes) | Morphology of lens capsule, analysis of electrolyte in aqueous humour, complications such as miosis, incomplete capsulotomy and capsule rupture |
| **Notes** (Funding source; Conflicts of Interest; trial registration number; any other note) | This work was funded by the Zhejiang Provincial Natural Science Foundation of China (Grant No. Y2110784), Zhejiang Provincial Foundation of China for Distinguished Young Talents in Medicine and Health (Grant No. 2010QNA018), and International Cooperation Project of the |

<table>
<tr><td></td><td colspan="2">Science and Technology Bureau of Zhejiang province, China (Grant No. 2013C14010).</td></tr>
<tr><td>Risk of bias RCTs</td><td>Authors' judgment</td><td>Support for judgement</td></tr>
<tr><td>Random sequence generation (selection bias)</td><td>Unclear risk</td><td>Consecutive patients, but not described randomization procedure and type</td></tr>
<tr><td>Allocation concealment (selection bias)</td><td>Unclear risk</td><td>Not described</td></tr>
<tr><td>Blinding of participants and personnel (performance bias)</td><td>High risk</td><td>Open trial.</td></tr>
<tr><td>Blinding of outcome assessment (detection bias)</td><td>High risk</td><td>The only masked outcome was morphology of lens capsule</td></tr>
<tr><td>Incomplete outcome data (attrition bias)</td><td>Low risk</td><td>All patients</td></tr>
<tr><td>Selective reporting (reporting bias)</td><td>High risk</td><td>Clinical trial registration: NCT02492659, https://register.clinicaltrials.gov<br>Reported “other outcomes” but not described</td></tr>
<tr><td>Outcomes</td><td></td><td></td></tr>
<tr><td>SAFETY</td><td></td><td></td></tr>
<tr><td>Posterior capsular tear</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0</td><td>19</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0</td><td>20</td></tr></table></td></tr>
<tr><td>Anterior capsular tear</td><td><table><tr><td colspan="2">Experimental</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0</td><td>19</td></tr></table></td><td><table><tr><td colspan="2">Control</td></tr><tr><td>Events</td><td>Total</td></tr><tr><td>0</td><td>20</td></tr></table></td></tr>
<tr><td>Vitreous loss</td><td></td><td></td></tr>
<tr><td>Cystoid macula oedema (within 90 days)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 day)</td><td></td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (IOP) (1 week)</td><td></td><td></td></tr>
<tr><td>Endothelial Cell Loss (ECL)</td><td></td><td></td></tr>
<tr><td>Central Corneal Thickness (CCT) preoperative</td><td></td><td></td></tr>
<tr><td>Idrocyclitis</td><td></td><td></td></tr>
<tr><td>Infections (within 90 days)</td><td></td><td></td></tr>
<tr><td>Corneal Endothelial Decompensation (within 90 days)</td><td></td><td></td></tr>
<tr><td>Surgical induced astigmatism</td><td></td><td></td></tr>
<tr><td>Retinal detachment</td><td></td><td></td></tr>
<tr><td>Posterior capsule opacification</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (1 month)</td><td></td><td></td></tr>
<tr><td>Visual acuity loss post cataract surgery (6 months)</td><td></td><td></td></tr>
<tr><td>Surgical re-intervention (within 6 months)</td><td></td><td></td></tr>
<tr><td>Secondary cataract (24 months)</td><td></td><td></td></tr>
<tr><td>EFFECTIVENESS</td><td></td><td></td></tr>
</table>

| | | |
|---|---|---|
| Corrected Distance Visual Acuity (CDVA) 1 month after surgery | | |
| Corrected Distance Visual Acuity (CDVA) 6 months after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 1 month after surgery | | |
| Uncorrected Distance Visual Acuity (UDVA) 6 months after surgery | | |
| Refractive outcomes | | |
| Vision-related Quality of Life (by validated questionnaire) | | |
| Patient-reported outcome measures (PROMs) | | |
| **OTHER OUTCOMES** | | |
| Patient satisfaction | | |
| Procedural time | | |
| Resource use | | |
| **Additional outcomes** | | |
| **Notes** | | |

## List of ongoing and planned studies

### Table A 23 - List of ongoing studies with FLACS

| Study Identifier<br>Country<br>Sponsor | Estimated completion date | Study type | Number of patients | Intervention | Comparator | Patient population | Endpoints |
|---|---|---|---|---|---|---|---|
| NCT03351894<br>Singapore<br>Singapore Eye Research Institute | Status recruiting<br>August 2019 | RCT open label<br>Parallel groups | 95 patients | FLACS | PHACO | Sex: both<br>Age: 55+ | Cumulative Dissipated Energy (CDE)<br>Best corrected distance visual acuity (snellen) [ Time Frame: 12 months]<br>Refraction (diopters) [ Time Frame: 12 months]<br>Corneal endothelial count [ Time Frame: 12 months]<br>Anterior chamber inflammation (by flaremeter) [ Time Frame: 12 months]<br>Effective intraocular lens position (UBM) [ Time Frame: 12 months]<br>Intraocular pressure (mmHg) [ Time Frame: 12 months]<br>Patient surgery experiences (questionnaire) [ Time Frame: 12 months]<br>Optic disc nerve (OCT) [ Time Frame: 12 months] |
| NCT03050008<br>Brasil<br>Alfredo Tranjan Centro Oftalmologico LTDA | Completed November 2016<br>No results available | RCT open label<br>Parallel groups | 71 patients | FLACS | PHACO | Sex: both<br>Age: 40-80 | Difference in Balance Saline Solution<br>Difference in Cumulativoe Dissipated Energy, Phaco time (seconds), Endothelial Cell Count, Visual Acuity, Best Corrected Visual Acuity, Corneal Topography, Intraocular Pressure, |

| Study Identifier<br>Country<br>Sponsor | Estimated completion date | Study type | Number of patients | Intervention | Comparator | Patient population | Endpoints |
|---|---|---|---|---|---|---|---|
| | | | | | | | Adverse Events. |
| NCT01014702<br>Mexico<br>LensAR Incorporated | June 2011<br>Status unknown<br>Last update April 2011 | Non-Randomized Clinical Trial Open Label | 100 patients | FLACS LensAR | PHACO | Sex: both<br>Age: 21+ | Completeness capsulotomy, reduced need for ultrasound phacoemulsification compared to control eye, rate of adverse events |
| NCT01373853<br>India<br>Technolas Perfect Vision GmbH | Completed<br>Last update May 2015<br>No result posted | Non-Randomized<br>Factorial Assignment<br>Clinical Trial Open Label | 131 patients | FLACS | PHACO | Sex: both<br>Age: 18+ | Effective Phaco Time, Adverse Events, Severe Events |
| NCT02561104<br>United States<br>University of Texas Southwestern Medical Center | Recruiting<br>July 2019 | Randomized<br>Parallel Assignment<br>Clinical Trial Open Label | 180 patients | FLACS | PHACO | Sex: both<br>Age: 18+ | Complication Rate, Visual Acuity, Patient Benefit Perception, Endothelial Cell Count, Lens Removal Time |
| NCT01982006<br>France<br>University Hospital, Bordeaux | Completed<br>Last update February 2017<br>No result posted | Randomized<br>Parallel Assignment<br>Single masking (patient) | 920 patients | FLACS | PHACO | Sex: both<br>Age: 22+ | Incremental cost effectiveness, quality of life, learning curve, overall cost of cataract surgery, Incremental cost utility ratio cost/QALY, no severe intraoperative complication, best corrected visual acuity (logMar), Refractive error, Surgically induced astigmatism |
| ISRCTN77602616<br>United Kingdom<br>National Institute for Health Research | Completed<br>Last update 2015<br>No result posted | Randomized<br>Parallel Assignment<br>Single masking (patient) | 808 patients | FLACS | PHACO | Sex: both<br>Age: 18+ | Unaided distance visual acuity (UDVA, logMAR) at 3 months, Unaided distance visual acuity (UDVA), Corrected distance visual acuity (logMAR) at 3 and 12 months, Ocular complications within 3 and 12 months, Unaided and corrected visual distance acuity and complications in the second eye (for those with bilateral cataracts), |

| Study Identifier<br>Country<br>Sponsor | Estimated completion date | Study type | Number of patients | Intervention | Comparator | Patient population | Endpoints |
|---|---|---|---|---|---|---|---|
| | | | | | | | Percentage of patients within 0.5 and within 1 dioptre of intended refractive outcome, Patient-reported outcomes measures, Cost-utility analysis, Corneal endothelial cell count change (additional safety measure) at 3 and 12 months |
| ISRCTN14007865<br>Spain<br>Mediker Spain | Completed<br>Last update 2017<br>No result posted<br>Intention to publish date 31/12/2017 | Randomized<br>Parallel Assignment<br>Single masking (patient) | 100 patients | FLACS | PHACO | Sex: both<br>Age: 50+ | 1. Uncorrected distance visual acuity is measured using the logMAR scale preoperatively, 1 day, 1 week, 1, 3 and 6 months after surgery<br>2. Best distance corrected visual acuity is measured using the logMAR scale preoperatively, 1 week, 1, 3 and 6 months after surgery.<br>3. Objective optical quality is measured using the OQAS -Optical Quality Analysis System preoperatively, 1 day, 1 week, 1, 3 and 6 months after surgery<br>4. Refraction is measured using an autorefractometer preoperatively, 1 day, 1 week, 1, 3 and 6 months after surgery<br>Endothelial cell quantitative and morphologic analysis, IOL position is assessed by measuring, Macular thickness, Optic nerve retinal nerve fiber layer (RNFL) and morphologic parameters |

**Abbreviations:** FLACS (Femtosecond laser-assisted cataract surgery), IOL (Intraocular lens), IOP (Intraocular pressure), PHACO (Phacoemulsification), CDE (Cumulative Dissipated Energy), CDVA (Corrected Distance Visual Acuity), UDVA (Uncorrected Distance Visual Acuity)

Sources: ClinicalTrial.gov, ICTRP, UK Clinical Trial Gateway

## List of excluded studies

**Table A 24 - Excluded studies and reason for exclusion**

| Author, year | Reason for exclusion |
|---|---|
| Abell, 2013a (129) | Non RCT, excluded for absence of outcomes of interest |
| Abell, 2013b (130) | Non RCT, excluded for absence of outcomes of interest |
| Abell, 2013c (131) | Non RCT, excluded for absence of outcomes of interest |
| Abell, 2014a (132) | Non RCT, excluded for absence of outcomes of interest |
| Abell, 2014b (133) | Non RCT, excluded for absence of outcomes of interest |
| Abell, 2015 (134) | Non RCT, excluded for absence of outcomes of interest |
| Ahn, 2016 (135) | Not in English / Italian / Spanish / German / Dutch /French (in Korean) |
| Al-Mohtaseb, 2017 (136) | Non RCT, excluded for absence of outcomes of interest |
| Ang, 2018 (137) | Non RCT, excluded for absence of outcomes of interest |
| Anisimova 2016 (138) | Not in English / Italian / Spanish / German / Dutch /French (in Russian) |
| Bali, 2012 (139) | Non RCT, excluded for absence of outcomes of interest |
| Brunin 2017 (140) | Non RCT, excluded for absence of outcomes of interest |
| Chang, 2014 (141) | Excluded for study design |
| Chee, 2015a (142) | Excluded for study design |
| Chen, 2015b (143) | Excluded for study design |
| Chen, 2015c (144) | Excluded for study design |
| Chen, 2016 (145) | Non RCT, excluded for absence of outcomes of interest |

| | |
|---|---|
| Chen, 2017 (146) | Non RCT, excluded for absence of outcomes of interest |
| Conrad-Hengerer, 2012 (147) | Non RCT, excluded for absence of outcomes of interest |
| Conrad-Hengerer, 2014 (148) | Non RCT, excluded for absence of outcomes of interest |
| Daya, 2014 (149) | Non RCT, excluded for absence of outcomes of interest |
| De Bernardo, 2018 (150) | Excluded for study design |
| Dick, 2016 (151) | Excluded for study design |
| Duan, 2017 (152) | Non RCT, excluded for absence of outcomes of interest |
| Ecsedy, 2011 (153) | Non RCT, excluded for absence of outcomes of interest |
| Enz, 2018 (154) | Non RCT, excluded for absence of outcomes of interest |
| Espaillat, 2016 (155) | Non RCT, excluded for absence of outcomes of interest |
| Ewe, 2016 (156) | Non RCT, excluded for absence of outcomes of interest |
| Fan, 2018 (157) | RCT, excluded for population not eligible |
| Ferreira, 2018 (158) | RCT, excluded for intervention not eligible |
| Filkorn, 2012 (39) | Data requested/no reply |
| Friedman, 2011 (159) | RCT, excluded for absence of outcomes of interest |
| Gao, 2018 (160) | Not in English / Italian / Spanish / German / Dutch /French (Chinese) |
| Grewal, 2016 (161) | Non RCT, excluded for absence of outcomes of interest |
| Gupta, 2016 (162) | Excluded for study design |
| Hida, 2017 (163) | RCT, excluded for absence of outcomes of interest |
| Ibrahim, 2018 (164) | Non RCT, excluded for absence of outcomes of interest |
| Ibrahim, 2018 (165) | Non RCT, excluded for absence of outcomes of interest |

| | |
|---|---|
| Inoue, 2018 (166) | Non RCT, excluded for absence of outcomes of interest |
| Kanellopoulos, 2016 (167) | Non RCT, excluded for absence of outcomes of interest |
| Kerr, 2012 (168) | Non RCT, excluded for absence of outcomes of interest |
| Khan, 2017 (169) | Non RCT, excluded for absence of outcomes of interest |
| Khandekar, 2015 (170) | Excluded for study design |
| Kiss, 2016 (171) | RCT, excluded for intervention not eligible |
| Kojima, 2017 (172) | Non RCT, excluded for absence of outcomes of interest |
| Kranitz, 2011 (173) | Non RCT, excluded for absence of outcomes of interest |
| Krarup, 2014 (174) | Non RCT, excluded for absence of outcomes of interest |
| Lawless, 2012 (175) | Excluded for study design |
| Li, 2017 (176) | Excluded for study design |
| Liu, 2016 (177) | Not in English / Italian / Spanish / German / Dutch /French (Chinese) |
| Lockwood, 2016 (178) | Excluded for study design |
| Lundstrom, 2018 (179) | Non RCT, excluded for absence of outcomes of interest |
| Manning, 2016 (125) | Non RCT, excluded for absence of outcomes of interest |
| Mayer, 2014 (180) | Excluded for study design |
| Mihaltz, 2011 (181) | Non RCT, excluded for absence of outcomes of interest |
| Nagy, 2012 (182) | Non RCT, excluded for absence of outcomes of interest |
| Oakley, 2016 (183) | Non RCT, excluded for absence of outcomes of interest |
| Pachtaev, 2018 (184) | Not in English / Italian / Spanish / German / Dutch /French (Russian) |
| Packer, 2014 (185) | Excluded for study design |

| | |
|---|---|
| Pahlitzsch, 2017 (186) | Non RCT, excluded for absence of outcomes of interest |
| Pahlitzsch, 2018 (187) | RCT, excluded for absence of outcomes of interest |
| Pajic, 2017 (56) | Non RCT, excluded for absence of outcomes of interest |
| Palanker, 2010 (2) | Excluded for study design |
| Parra-Rodríguez, 2017 (188) | RCT, excluded for absence of outcomes of interest |
| Pisciotta, 2018 (189) | Non RCT, excluded for absence of outcomes of interest |
| Pittner, 2017 (190) | Non RCT, excluded for absence of outcomes of interest |
| Ranjini, 2017 (191) | Non RCT, excluded for absence of outcomes of interest |
| Rostami, 2016 (192) | Excluded for study design |
| Rothschild, 2018 (193) | Excluded for study design |
| Schultz, 2013 (194) | Non RCT, excluded for absence of outcomes of interest |
| Schultz, 2014 (195) | Non RCT, excluded for absence of outcomes of interest |
| Schultz, 2015 (196) | Non RCT, excluded for absence of outcomes of interest |
| Scott, 2016 (197) | Non RCT, excluded for absence of outcomes of interest |
| Serrao, 2017 (198) | RCT, excluded for intervention not eligible |
| Sun, 2018 (199) | RCT, excluded for absence of outcomes of interest |
| Tackman, 2011 (200) | Non RCT, excluded for absence of outcomes of interest |
| Titiyal, 2016 (201) | Non RCT, excluded for absence of outcomes of interest |
| Titiyal, 2018 (202) | Non RCT, excluded for absence of outcomes of interest |
| Tran, 2016 (203) | Non RCT, excluded for absence of outcomes of interest |
| Uy, 2017 (204) | Excluded for study design |

| | |
|---|---|
| Vasquez-Perez, 2018 (205) | Non RCT, excluded for absence of outcomes of interest |
| Wang EF, 2018 (206) | Excluded for study design |
| Wang X, 2018 (207) | Non RCT, excluded for absence of outcomes of interest |
| Wu, 2017 (208) | Not in English / Italian / Spanish / German / Dutch /French (Chinese) |
| Yesilirmak, 2018 (209) | Non RCT, excluded for absence of outcomes of interest |
| Yu, 2016 (210) | Excluded for study design |
| Zhang, 2016 (211) | Not in English / Italian / Spanish / German / Dutch /French (Chinese) |
| Zhouh, 2018 (212) | Not in English / Italian / Spanish / German / Dutch /French (Chinese) |

## Risk of bias tables

**Table A 25 - Risk of bias – study level (RCTs) (see Handbook Cochrane Chapter 8 (16))**

| Trial | Random sequence generation | Allocation concealment | Blinding of | | | Incomplete outcome data (short-term, long-term) | Selective outcome reporting |
|---|---|---|---|---|---|---|---|
| | | | Participants | Medical personnel | Outcome assessment (patient-reported outcomes,) | | |
| Conrad-Hengerer 2013 (47) | Unclear* | Unclear * | High*** | High*** | Low | Low | High***** |
| Conrad-Hengerer 2014 (48) | Unclear* | Unclear * | High*** | High*** | High**** | Low | Unclear* |
| Conrad-Hengerer 2015 (30) | Unclear* | Unclear * | High*** | High*** | High**** | Low | Unclear* |
| Dick 2014 (49) | Unclear* | Unclear * | High*** | High*** | Low | Low | Unclear* |
| Donnenfeld 2018 (29) | Unclear* | Unclear * | High*** | High*** | Low | Low | High***** |
| Givaudan Pedroza 2016 (45) | Low | Low | High*** | High*** | Low | Unclear* | Unclear* |
| Hida 2014 (23) | Unclear* | Unclear * | High*** | High*** | High**** | Unclear* | Unclear* |
| Kovàcs 2014 (46) | Unclear* | Unclear * | High*** | High*** | Low | Low | Unclear* |
| Kranitz 2012 (24) | Low | Unclear * | High*** | High*** | High**** | Unclear* | Unclear* |
| Mastropasqua 2014a (26) | Unclear* | Unclear * | High*** | High*** | High**** | Low | Unclear* |
| Mastropasqua 2014b (25) | Low | Unclear * | High*** | High*** | Low | Unclear* | Unclear* |
| Mursch-Edlmayr 2017 (31) | Low | Unclear * | High*** | High*** | Low | Unclear* | Unclear* |
| Nagy 2011 (27) | Low | Unclear * | High*** | High*** | Unclear* | Unclear* | Unclear* |
| Nagy 2014 (41) | Low | Unclear * | High*** | High*** | High**** | Unclear* | Unclear* |
| Panthier 2017 (50) | Unclear* | Unclear * | High*** | High*** | Low | Low | Unclear* |
| Reddy 2013 (42) | Unclear* | High ** | High*** | High*** | High**** | High ******* | Unclear* |
| Roberts 2018 (33) | Unclear | Unclear | High*** | High*** | Low | Low | High***** |
| Schargus 2015 (32) | Unclear* | Low | High*** | High*** | High**** | Unclear* | Unclear* |
| Takàcs 2012 (43) | Unclear* | High** | High*** | High*** | Low | Unclear* | Unclear* |
| Yu 2015 (28) | Unclear* | Unclear* | High*** | High*** | Unclear* | Unclear* | Unclear* |
| Yu 2016 (44) | Unclear* | Unclear* | High*** | High*** | High**** | Unclear* | High****** |

comments: [If unclear or high, give reasons for the classification (mandatory)]

* Unclear: information not reported/not retrieved; ** High: documented selection bias ; *** High: Open trial ; **** High: no blinding of assessment is described; ***** High: documented selective reporting of outcomes

**Table A 26 - Risk of bias – outcome level (RCTs) – for "critical" outcomes only**

| **Outcome**<br>Trial | **Blinding – outcome assessors** | **ITT principle adequately realized** | **Selective outcome reporting unlikely** | **No other aspect according to risk of bias (allocation concealment)** | **Risk of bias – outcome level** |
|---|---|---|---|---|---|
| **CDVA at 1 month after surgery** | | | | | |
| Donnenfeld 2018 (29) | Low | Low | High | Unclear | High |
| Kranitz 2012 (24) | High | Unclear | Unclear | Unclear | High |
| Mastropasqua 2014a (26) | High | Low | Unclear | Unclear | High |
| Mastropasqua 2014b (25) | Low | Unclear | Unclear | Unclear | Unclear |
| Mursch Edlmayr 2017 (31) | Low | Unclear | Unclear | Unclear | Unclear |
| Yu 2015 (28) | High | Unclear | High | Unclear | High |
| **CDVA at 6 months after surgery** | | | | | |
| Mastropasqua 2014a (26) | High | Low | Unclear | Unclear | High |
| Mastropasqua 2014b (25) | Low | Unclear | Unclear | Unclear | Unclear |
| Mursch Edlmayr 2017 (31) | Low | Unclear | Unclear | Unclear | Unclear |
| Schargus 2015 (32) | High | Unclear | Unclear | Low | High |
| comments: concerns for lack of blinding of outcome assessors in open trial, on lack of prespecification of outcomes/lack of protocol and on allocation concealment | | | | | |
| **UDVA at 1 month after surgery** | | | | | |
| Donnenfeld 2018 (29) | Low | Low | High | Unclear | High |
| Kranitz 2012 (24) | High | Unclear | Unclear | Unclear | High |
| Mastropasqua 2014a (26) | High | Low | Unclear | Unclear | High |
| Mastropasqua 2014b (25) | Low | Unclear | Unclear | Unclear | Unclear |
| comments: concerns for lack of blinding of outcome assessors in open trial, on lack of prespecification of outcomes/lack of protocol and on allocation concealment | | | | | |
| **UDVA at 6 months after surgery** | | | | | |
| Mastropasqua 2014a (26) | High | Low | Unclear | Unclear | High |
| Mastropasqua 2014b (25) | Low | Unclear | Unclear | Unclear | Unclear |
| comments: concerns for lack of blinding of outcome assessors in open trial, on lack of prespecification of outcomes/lack of protocol and on allocation concealment | | | | | |
| **Refractive outcomes at 1 week and at 1 month after surgery** | | | | | |
| Mastopasqua 2014b (25) | Low | Unclear | Unclear | Unclear | Unclear |
| Yu 2015 (28) | High | Unclear | High | Unclear | High |
| comments: concerns for lack of blinding of outcome assessors in open trial, on lack of prespecification of outcomes/lack of protocol and on allocation concealment | | | | | |
| **Anterior and Posterior Capsular Tear** | | | | | |
| Conrad-Hengerer 2013 (47) | Low | Low | High | Unclear | High |
| Conrad-Hengerer 2015 (30) | Low | Low | Unclear | Unclear | Unclear |
| Mursch Edlmayr 2017 (31) | Low | Unclear | Unclear | Unclear | Unclear |

| **Outcome**<br>Trial | **Blinding – outcome assessors** | **ITT principle adequately realized** | **Selective outcome reporting unlikely** | **No other aspect according to risk of bias (allocation concealment)** | **Risk of bias – outcome level** |
|---|---|---|---|---|---|
| Panthier 2017 (50) | Low | Low | Unclear | Unclear | Unclear |
| Reddy 2013 (42) | Low | High | Unclear | High | High |
| Roberts 2018 (33) | Low | Low | High | Unclear | High |
| Schargus 2015 (32) | Low | Unclear | Unclear | Low | Unclear |
| Yu 2015 (28) | Low | Unclear | High | Unclear | High |
| Yu 2016 (44) | Low | Unclear | High | Unclear | High |
| comments: concerns for lost to follow up, on lack of prespecification of outcomes/lack of protocol and lack of allocation concealment | | | | | |
| **Vitreous loss** | | | | | |
| Conrad-Hengerer 2015 (30) | Low | Low | High | Unclear | High |
| Roberts 2018 (33) | Low | Low | High | Unclear | High |
| Schargus 2015 (32) | Low | Unclear | Unclear | Low | Unclear |
| comments: concerns on lack of prespecification of outcomes/lack of protocol and on lack of allocation concealment | | | | | |
| **Elevated Intraocular pressure (IOP) at 1 day and at 1 week** | | | | | |
| Conrad-Hengerer 2013 (47) | Low | Low | High | Unclear | High |
| Conrad-Hengerer 2014 (48) | High | Low | Unclear | Unclear | High |
| Conrad-Hengerer 2015 (30) | High | Low | Unclear | Unclear | High |
| Schargus 2015 (32) | High | Unclear | Unclear | Low | High |
| comments: concerns for lack of blinding of outcome assessors in open trial, on lack of prespecification of outcomes/lack of protocol and on lack of allocation concealment | | | | | |
| **Endothelial Cell Loss** | | | | | |
| Conrad-Hengerer 2015 (30) | High | Low | Unclear | Unclear | High |
| Mursch-Edlmayr 2017 (31) | Low | Unclear | Unclear | Unclear | Unclear |
| comments: concerns for lack of blinding of outcome assessors in open trial and lack of allocation concealment | | | | | |
| **Cystoid Macular Oedema (within 90 days)** | | | | | |
| Conrad-Hengerer 2013 (47) | Low | Low | High | Unclear | High |
| Conrad-Hengerer 2014 (48) | High | Low | Unclear | Unclear | High |
| Conrad-Hengerer 2015 (30) | High | Low | Unclear | Unclear | High |
| Schargus 2015 (32) | High | Unclear | Unclear | Low | High |
| comments: concerns for lack of blinding of outcome assessors in open trial, on lack of prespecification of outcomes/lack of protocol and lack of allocation concealment | | | | | |

**Table A 27 - Template for GRADE assessment (e.g., using GRADEproGDT)**

**Question:** Femtosecond Laser-Assisted Cataract Surgery (FLACS) compared to Standard Cataract Surgery for age-related cataract in adult patients

**CLINICAL EFFECTIVENESS**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsis-tency** | **Indi-rectness** | **Imprecision** | **Other considerations** | **Femtosecond Laser-Assisted Cata-ract Surgery (FLACS)** | **Standard Cataract Surgery** | **Relative (95% CI)** | **Absolute (95% CI)** | | |
| **CDVA 1 month (LogMAR)** | | | | | | | | | | | | |
| 6 | randomised trials | very serious [a,b] | not serious | not serious | not serious | none | 212 | 176 | - | MD*** **-0.02** (-0.04; 0.00) | ⊕⊕◯◯ LOW | CRITICAL |
| **CDVA 6 months (LogMAR*)** | | | | | | | | | | | | |
| 4 | randomised trials | very serious [a,b] | not serious | not serious | not serious | none | 174 | 144 | - | MD***- **0.02** (-0.04; 0.00) | ⊕⊕◯◯ LOW | CRITICAL |
| **UDVA 1 month (LogMAR*)** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsis-tency** | **Indi-rectness** | **Imprecision** | **Other considerations** | **Femtosecond Laser-Assisted Cata-ract Surgery (FLACS)** | **Standard Cataract Surgery** | **Relative (95% CI)** | **Absolute (95% CI)** | | |
| 4 | randomised trials | very serious [a,c] | serious [d] | not serious | not serious | none | 140 | 100 | - | MD*** **-0.03** (-0.12; 0.06) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **UDVA 6 months (LogMAR)** | | | | | | | | | | | | |
| 2 | randomised trials | serious [c] | very serious [e] | not serious | very serious [f] | none | 90 | 60 | - | MD **-0.06** (-0.26; 0.14) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Refractive outcome (mean absolute error - 1 week)** | | | | | | | | | | | | |
| 2 | randomised trials | serious [a] | not serious | not serious | not serious | none | 85 | 59 | - | MD **-0.1** (-0.19; 0.01) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Refractive outcome (mean absolute error - 1 month)** | | | | | | | | | | | | |
| 2 | randomised trials | serious [a] | not serious | not serious | not serious | none | 85 | 59 | - | MD **-0.11** (-0.25; 0.03) | ⊕⊕⊕◯ MODERATE | CRITICAL |

**Abbreviations:** CI: Confidence interval; SMD: Standardised mean difference; MD: Mean difference; OR: Odds ratio

**Explanations**

a. Lack of allocation concealment is suspected
b. Open trials, detection bias present (non-blinded assessment of outcomes)
c. Assessment of outcomes not blinded
d. Inconsistent results between trials
e. Results of the two trials are inconsistent
f. Confidence interval of pooled estimate is very large
g. Confidence interval of pooled estimate is large
h. Selective reporting
i. Allocation concealment not described

**SAFETY**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsis-tency** | **Indirectness** | **Imprecision** | **Other considera-tions** | **Femtosecond Laser-Assisted Cataract Sur-gery (FLACS)** | **Standard Cataract Surgery** | **Relative (95% CI)** | **Absolute (95% CI)** | | |
| **Posterior capsular tear** | | | | | | | | | | | | |
| 8 | randomi-sed trials | not serious | not serious | not serious | very seri-ous [f] | none | 0/390 (0.0%) | 1/402 (0.2%) | **OR 0.32** (0.01 to 8.23) | **1.7 fewer per 1.000** (from 2.5 fewer to 17.6 more) | ⊕⊕◯◯ LOW | CRITICAL |
| **Anterior capsular tear** | | | | | | | | | | | | |
| 9 | randomi-sed trials | not serious | not serious | not serious | very seri-ous [f] | none | 5/529 (0.9%) | 5/562 (0.9%) | **OR 1.10** (0.34 to 3.64) | **1.0 more per 1.000** (from 6.0 fewer to 23.0 more) | ⊕⊕◯◯ LOW | CRITICAL |
| **Vitreous loss** | | | | | | | | | | | | |
| 3 | randomi-sed trials | not serious | not serious | not serious | very seri-ous [f] | none | 0/276 (0.0%) | 4/297 (1,3%) | **OR 0.22** (0.02 to 1.98) | **10.0 fewer per 1.000** (from 13.0 fewer to 13.0 more) | ⊕⊕◯◯ LOW | CRITICAL |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsis-tency** | **Indirectness** | **Imprecision** | **Other considera-tions** | **Femtosecond Laser-Assisted Cataract Sur-gery (FLACS)** | **Standard Cataract Surgery** | **Relative (95% CI)** | **Absolute (95% CI)** | | |
| **Cystoid macular oedema** | | | | | | | | | | | | |
| 4 | randomi-sed trials | very seri-ous [a, b] | not serious | not serious | serious [g] | none | 5/311 (1.6%) | 9/311 (2.9%) | **OR 0.58** (0.20 to 1.68) | **12.0 fewer per 1.000** (from 23.0 more to 18.7 fewer) | ⊕◯◯◯ VERY LOW | CRITICAL |
| **Infections** | | | | | | | | | | | | |
| 1 | randomi-sed trials | very seri-ous [h, i] | not serious | not serious | not serious | none | 0/100 (0.0%) | 0/100 (0.0%) | not e-stimable | | ⊕⊕◯◯ LOW | CRITICAL |

**Abbreviations: CI: Confidence interval; SMD: Standardised mean difference; MD: Mean difference; OR: Odds ratio**

**Explanations**

b. Lack of allocation concealment is suspected
b. Open trials, detection bias present (non-blinded assessment of outcomes)
c. Assessment of outcomes not blinded
d. Inconsistent results between trials
e. Results of the two trials are inconsistent
f. Confidence interval of pooled estimate is very large
g. Confidence interval of pooled estimate is large
i. Allocation concealment not described

## Applicability tables

**Table A 28 - Summary table characterising the applicability of a body of studies**

| Domain | Description of applicability of evidence |
|---|---|
| Population | The target population was adult patients (>18 years) of either sex affected by cataract and for whom the surgical treatment for cataract removal and insertion of intraocular lens could provide a gain in visual acuity and health-related quality of life.<br><br>Patients' characteristics seem to adequately reflect the target population for cataract surgery: in spite of some heterogeneity among trials, in most, patients were aged over 65 and were excluded in case of glaucoma, astigmatism > 1.5 or >2 diopters, endothelial cell count less than 1,200 cells/mm, CDVA decreased by less than 0.1 LogMAR, poorly dilated pupils, corneal scars, corneal diseases, previous ocular surgery or trauma. However, in some of the studies, inclusion and exclusion criteria have been poorly described. |
| Intervention | The intervention under assessment was Femtosecond laser-assisted cataract surgery (FLACS) to be used during the first phases of intervention to create incisions, perform capsulorhexis and fragment the lens. To complete the surgical procedure conventional ultrasound phacoemulsification technique was used. German and US studies (Conrad-Hengerer 2013, Conrad-Hengerer 2014, Conrad-Hengerer 2015, Dick 2014, Schargus 2015 and Donnenfeld 2018) (29,30,32,47–49) used the Catalys laser platform (OptiMedica, AMO). Brazilian, Hugarian. Italian, Mexican and UK studies (Hida 2014, Kovacs 2014, Kranitz 2012, Nagy 2011, Nagy 2014, Takacs 2012, Mastropasqua 2014a, Mastropasqua 2014b, Givaudan Pedroza 2016 and Roberts 2018) (23–27,33,41,43,45,46) used the LenSx platform (Alcon Laboratories, Inc., Fort Worth, TX). Mursch Edlmayr 2017 (31)(in Austria), Panthier 2017 (50)(in France) and Reddy 2013 (42)(in India) used the Victus ™laser platform (Bausch&LombTechnolas); Yu 2015, Yu 2016 (in China) and Mastropasqua 2014b used the Lensar platform (25,28,44).<br><br>Surgery techniques assessed adequately reflect the general modus operandi in cataract surgery in spite of differences of limited relevance in terms of technology producers and surgery protocols. |
| Comparators | Standard cataract surgery, i.e., with manual capsulorhexis and conventional ultrasound phacoemulsification, which reflects current best clinical practice. |

| Domain | Description of applicability of evidence |
|---|---|
| Outcomes | **Clinical Effectiveness**<br><br>Corrected Distance Visual Acuity (1 month; 6 months); Uncorrected Distance Visual Acuity (1 month; 6 months); Refractive outcomes (measured as mean absolute error or as absolute deviation spherical equivalent at one week or one-month post-surgery); Vision-related quality of life as measured by any validated questionnaire; Patient-reported Outcomes.<br><br>**Safety**<br><br>Intraoperative complications; Anterior capsular tear ; Posterior capsular tear; Vitreous loss.<br><br>Postoperative complications: Elevated Intraocular Pressure (1 day - 1 week); Endothelial cells loss; Central corneal thickness; Iridocyclitis; Cystoid macular oedema (within 90 days); Infections (within 90 days; Corneal endothelial decompensation (within 90 days); Surgically induced astigmatism; Retinal detachment; Posterior capsule opacification; Visual acuity loss post-cataract surgery (1 month;6 months); Surgical re-intervention (within 6 months); Secondary cataract (24 months)<br><br>**Other outcomes**<br><br>Patient satisfaction ; Procedural time; Resource use.<br><br>It should be noted that both effectiveness and safety outcomes described in the selected studies are quite heterogeneous in terms of measurements (e.g., for refractive outcomes we found data on spherical error, spherical equivalent, absolute deviation spherical equivalent, mean absolute error; as for endothelial cell loss, sometimes data were reported as endothelial cell density), reporting (e.g., visual acuity expressed in decimal or log scale) and length of follow up (from 1 day to six months). It would be desirable that researchers agreed on specific measurements and follow-up times as primary endpoints in future RCTs, based on their clinical relevance (for example, preferring longer to shorter follow ups). |
| Setting | Seventy-six percent of patients were recruited and operated on in Europe, specifically in Austria, France, Germany, Hungary, Italy and the UK; the remaining 24% were recruited and operated in Brazil, China, India, Mexico and the US. Surgery techniques assessed adequately reflect the general modus operandi in cataract surgery in spite of differences of limited relevance in terms of technology producers and surgery protocols.<br><br>It should be noted that in most studies, procedures were performed by very experienced surgeons. |

# APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

### Table A 29 - Regulatory status

| Model | Country | Institution issuing approval | Authorisation status yes/no/ ongoing | Verbatim wording of the (anticipated) indication(s) | Specified contra-indications | Date of approval (include expiry date for country of assessment) | Launched yes/no If not, include date of launch | Approval number (if available) |
|---|---|---|---|---|---|---|---|---|
| LenSx® Laser System | European Union | CE mark delivered through BSI | yes | Design and manufacture of ophthalmic surgical lasers and patient interfaces for cataract surgery and creation of flaps, corneal pockets and corneal tunnels | Contraindications for the anterior capsulotomy, phacofragmentation of the lens using the LenSx* Laser include, but are not limited to, the following: Corneal disease precluding applanation of the cornea or transmission of laser light at 1030 nm wavelength; Descemetocele with impending corneal rupture; Corneal opacity that would interfere with the laser beam; Presence of blood or other material in the anterior chamber; Hypotony, glaucoma*, or the presence of a corneal implant; Poorly dilating pupil; Conditions causing inadequate clearance between the intended capsulotomy depth and the endothelium (applicable to capsulotomy only); Residual, recurrent, active ocular or eyelid disease, including any corneal ab- | 16 august 2011 (Italy) | yes | EC Cert CE 568180 |
| LenSx® Laser System | US | FDA | yes | The LenSx Laser is indicated for use in patients undergoing cataract surgery for removal of the crystalline lens. Intended use in cataract surgery include anterior capsulotomy, phacofragmentation, and the creation of single plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure. The LenSx Laser is indicated for use in patients undergoing penetrating keratoplasty for full thickness corneal replacement and in patients undergoing keratoplasty for partial thickness corneal replacement. The intended use in penetrating and lamellar keratopasty includes the creation single plane and multi-plane arc and circular cuts/incisions in the cornea. | | 18 October 2010 | yes | K101626 |

| Model | Country | Institution issuing approval | Authorisation status yes/no/ ongoing | Verbatim wording of the (anticipated) indication(s) | Specified contra-indications | Date of approval (include expiry date for country of assessment) | Launched yes/no If not, include date of launch | Approval number (if available) |
|---|---|---|---|---|---|---|---|---|
| | | | | | normality; A history of lens or zonular instability; Any contrain-dications to cataract or keratoplasty surgery; the device is not intended for use in pediat-ric surgery. | | | |
| Catalys® Precision Laser System | Europea n Union | CE mark delivere d through 0044 TUV Nord Cert GmbH | yes | Not available | Not available | Not available | yes | Not available |
| Catalys® Precision Laser System | US | FDA | yes | The OptiMedica Catalys Precision Laser System is indicated for use in patients undergoing cataract surgery for removal of the crystalline lens. Intended uses in cataract surgery include anterior capsulotomy, phacofragmentatio n, and the creation of single plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure. | Not available | 21 December 2011 | yes | K113479 |
| Ziemer Z8 | Europea n Union | CE mark delivere d through DQS Medizinp rodukte GmbH | yes | Not available | Not available | May 2015 | yes | Not available |
| Ziemer Z8 | US | FDA | yes | The FEMTO LDV™ Z8 Femtosecond Surgical Laser is an ophthalmic surgical laser intended for use in the creation of | Not available | October 2015 | yes | K150323 |

| Model | Country | Institution issuing approval | Authorisation status yes/no/ ongoing | Verbatim wording of the (anticipated) indication(s) | Specified contra-indications | Date of approval (include expiry date for country of assessment) | Launched yes/no If not, include date of launch | Approval number (if available) |
|---|---|---|---|---|---|---|---|---|
| | | | | corneal incisions indicated for use in patients undergoing LASIK surgery, tunnel creation for implantation of rings, pocket creation for implantation of corneal implants, lamellar keratoplasty, penetrating keratoplasty or other treatment requiring lamellar resection of the cornea at a varying depth with respect to the corneal surface.<br>In addition, the FEMTO LDV™ Z8 Surgical Laser is intended for use in the creation of capsulotomy, phacofragmentation and the creation of single plane, multi-plane, arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure indicated for use in patients undergoing cataract surgery for removal of the crystalline lens. | | | | |
| Lensar Laser System | European Union | Not available | yes | Not available | Not available | Not available | yes | Not available |
| Lensar Laser System | US | FDA | yes | The Lensar Laser System - fs 3D (LLS-fs 3D) is intended for use in patients undergoing cataract surgery for removal of the crystalline lens. Intended uses in cataract surgery include anterior capsulotomy, laser phacofragmentation, and the creation | Not available | 13 May 2010 | yes | K090633 |

| Model | Country | Institution issuing approval | Authorisation status yes/no/ ongoing | Verbatim wording of the (anticipated) indication(s) | Specified contra-indications | Date of approval (include expiry date for country of assessment) | Launched yes/no If not, include date of launch | Approval number (if available) |
|---|---|---|---|---|---|---|---|---|
| | | | | of full and partial thickness single-plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure. | | | | |
| Victus | European Union | CE mark delivered through LGA INTERCERT ZERTIFIZIERUNGSGESELLSCHAFT MBH | yes | Not available | Not available | Not available | yes | Not available |
| Victus | US | FDA | yes | - the creation of a corneal flap in patients undergoing LASIK surgery or other treatment requiring initial lamellar resection of the cornea.<br>- for anterior capsulotomy during cataract surgery.<br>- the creation of cuts / incisions in the cornea in patients undergoing cataract surgery or other ophthalmic treatment requiring cuts / incisions in the cornea. | Not available | July 2012 | yes | K120426 |

**Abbreviations:** FDA (Food and Drug Administration); US (United States); GmbH (Gesellschaft mit beschränkter Haftung)

Sources: FDA, company website. Submission Template

### Table A 30 - Summary of (reimbursement) recommendations in European countries for the technology

| Country and issuing organisation e.g. G-BA, NICE | Summary of (reimbursement) recommendations and restrictions | Annual number of FLACS procedures performed in the country |
|---|---|---|
| NICE - England | Only use femtosecond laser-assisted | Hospital episode data do not provide a |

| Country and issuing organisation e.g. G-BA, NICE | Summary of (reimbursement) recommendations and restrictions | Annual number of FLACS procedures performed in the country |
|---|---|---|
| | cataract surgery as part of a randomised controlled trial that includes collection of resource use data, comparing femtosecond laser-assisted cataract surgery with ultrasound phacoemulsification. This is a recommendation from the NICE cataracts in adult guideline. It is not a mandatory recommendation. https://www.nice.org.uk/guidance/ng77/chapter/Recommendations#surgical-timing-and-technique Hospital episode data do not provide a breakdown at this level | breakdown at this level |
| ZIN - Netherlands | 2016: legal dispute between patient and health insurance company. Final advice = do not reimburse due to insufficient data about effectiveness. | Unknown |
| IQWiG - Germany | Costs for cataract surgeries are generally reimbursed by the statutory health insurance. The additional costs arising from FLACS have to be covered by the patients.<br>Most private health insurance companies cover the total costs of FLACS. | Overall, about 800.000 cataract surgeries are carried out in Germany. The exact number of FLACS performed is not publicly available. |
| RER - Italy | Currently only one FLACS platform available in a teaching hospital, costs sustained with funds from private foundation. No additional costs for regional health services nor for patients, but provision of femtosecond laser-assisted cataract surgery restricted until funds run out. | Not available annually. In RER about 150 surgical intervention with FLACS to date |
| GÖG - Austria | In general, cataract surgeries are performed in hospitals (hospital department, or day clinic); only few cases are extramural. In hospitals we have a kind of DRG system. In this system only, the hospital stay with cataract surgery is covered, no matter the method, and there is no differentiation between "Femtosecond laser-assisted cataract surgery (FLACS)" and "standard ultrasound phacoemulsification cataract surgery" or others. Therefore, we have no figures for FLACS | Hospital data do not provide a breakdown on different methods of cataract surgery, therefore no figures for this. |
| Belgium | In Belgium there is a fixed reimbursement per eye for cataract surgery, no matter the technique used. It is 500 to 700€ per eye, depending upon the type of lens implanted. This does not cover the total cost so even with standard surgery there is an significant patient co-payment. However, many hospitalisation insurances cover up to 100% depending upon the type of insurance. For the use of Femtosecond there is again an addi- | Not available |

| Country and issuing organisation e.g. G-BA, NICE | Summary of (reimbursement) recommendations and restrictions | Annual number of FLACS procedures performed in the country |
|---|---|---|
| | tional price of about 650 € on top of the price of the standard surgery. Before the intervention a price is set for a specific customer, and since most ophthalmologists in Belgium have chosen not to be 'conventioned' they are free to determine the price. Some websites advertise average prices. See, among others, these two (in Dutch):<br><br>https://www.focus-eye-clinic.com/praktisch/tarieven-ingrepen/<br><br>https://www.oogkliniek.be/cataractheelkunde/ | |
| MOH SI - Slovenia | This technology is used by some individuals in private practice | Funds for implementing this technology are not provided by the healthcare fund. Therefore, we do not have data on the total number of all operations in Slovenia at the annual level. |
| SNHTA | Cataract surgery is generally reimbursed by the obligatory health insurance. There is a national tariff which is not specified with regard to a specific technique, but which is most probably based on costs for conventional surgery. Besides, there are different cantonal flat-rate tariffs. FLACS has not yet been submitted to an assessment or specific tarification process. | We have no access to data on the use of FLACS in Switzerland |
| Spain | In general, cataract surgery is covered in common services portfolio of NHS. A specific method is not detailed. The method to be used depends on the criteria of the surgeon and the availability of specific technique (manual or FLACS). | At least 6 hospitals in Spain (La Paz, Reina Sofía, Vall d'Hebron, La Fe, Elche, Lozano Blesa) have the technology. No data on the use of FLACS are provided. |
| | | |

Sources: EUnetHTA partner organizations.

# APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

| | | |
|---|---|---|
| **1** | **Ethical** | |
| 1.1 | Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues? | Yes |
| | The technology is expensive and would not be installed in all community hospitals. This could lead to inequity of access. | |
| 1.2 | Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant? | No |
| | | |
| **2** | **Organisational** | |
| 2.1 | Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes? | Yes |
| | Operating room, facilities would need adjustment to accommodate the technology. Operating room staff and surgeons would need specific training. | |
| 2.2 | Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant? | No |
| | | |
| **3** | **Social** | |
| 3.1 | Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues? | No |
| | | |
| 3.2 | Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant? | No |
| | | |
| **4** | **Legal** | |
| 4.1 | Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues? | No |
| | | |
| 4.2 | Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant? | No |
| | | |

**For the purpose of transparency, a separate document with comments on the 2nd draft assessment from external experts and the /manufacturer(s) (fact check), as well as responses from authors, is available on the EUnetHTA website.**

# APPENDIX 4

**ASACIR (Asociación Española de Afectados por la Cirugía Refractiva) mails showing the patient perspective regarding FLACS - EUnetHTA assessment**

**First mail -25/7/2018- (an article was added to the mail with the following link)**

Our position in general is:

ASACIR is in favor of the development of preventive and non-surgical treatments for cataracts, such as eye drops lanosterol, which will be probably approved in 2021 for humans (this year has been approved for animals use, and is already marketed and applied), among other compounds. We consider that, spending money in such an expensive procedure does not make sense, when standard phacoemulsification works just as well or better (according to our knowledge as patients and according to ophthalmologist and scientific disseminator Rubén Pascual, for example), and when the possible long-term benefits of the new surgical technology may perhaps become obsolete in a few years with the rise of pharmacological treatments, capable, probably, of preventing cataracts, which we think is the objective that should be raised by our National Health System. We link below some studies related mainly to lanosterol for cataracts. While eliminating a developed nuclear cataract might not be possible, it is possible to prevent this cataract to be developed. The lanosterol is a compound which is naturally present in the eye.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4930773/
https://www.ncbi.nlm.nih.gov/pubmed/26946708
https://www.ncbi.nlm.nih.gov/pubmed/29916249
https://www.ncbi.nlm.nih.gov/pubmed/26200341
https://www.ncbi.nlm.nih.gov/pubmed/26398599
https://www.ncbi.nlm.nih.gov/pubmed/26200338
https://www.ncbi.nlm.nih.gov/pubmed/26542559
https://www.ncbi.nlm.nih.gov/pubmed/26308894
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4784074/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4725592/
https://www.ncbi.nlm.nih.gov/pubmed/27648776

We also link two articles written by the ophthalmologist Rubén Puascual on femtofaco, where he explains that this is a technique still to be perfected, at patients expense. This is a technique that does not present great advantages and presents quite a few inconveniences, related to: price, different rooms use, the suction ring, the energy released, the indication limitations and calculation errors. The first article is introductory to the technique and the second is the truly interesting one.

https://ocularis.es/cirugia-de-catarata-con-laser-femtosegundo-i/
https://ocularis.es/cirugia-de-catarata-con-laser-femtosegundo-ii/

In relation to the suction ring, which is also used in LASIK and LASIK with femtosecond, it has been proven to cause posterior vitreous detachments (PVD) and rhegmatogenous retinal detachment (RRD). The RRD rate 1 year after LASIK in myopia of up to 10 diopters (with less than 5 diopters on average) is around 9 out of 10,000, that is, about 13 times higher than the average annual rate of RRD in normal eyes of non-operated myopic, with no limit of diopters or age, and which is around 7 out of every 100,000 myopic. In addition, the substantial increase in risk extends, to a lesser extent, at least during the following 4 years (5 years after surgery). And if we just refer to those who undergone an operation with myopia magna (of more than 6 diopters), the rates of RRD get multiplied. With conventional LASIK (with blade), the RRD occurs in about 0.62% of operated (0.36% of the eyes), that is, in 1 of every 161 operated with myopia magna (and about 1 in each 278 eyes). The rate may be even higher with femtosecond LASIK, due to the longer application time of the suction ring and its' probably higher percentage of posterior vitreous detachments (up to 85% of PVD or worsening of previous PVD, according to a study), although I have not found studies on this, that compare the RRD. In any case, PVD is very frequent after LASIK in eyes with myopia magna, from 6 diopters (with rates of more than 2 in 10 eyes -between

4 and 6 out of 10 operated-), and frequent in eyes with low myopia of up to 3 diopters and a half (1 in 50 eyes, about 1 in 25 operated). And around 16% of RRDs are bilateral (in both eyes).

https://www.ncbi.nlm.nih.gov/pubmed/22218710

The suction ring can also cause other very serious pathologies of the posterior pole, as indicated in the systematic review that we enclose. If refractive surgeons always reported complications, we would have much more information about it.

We also consider that there are other basic technologies that are much more necessary and should be available in hospitals, such as endothelial cell counting machines, for example, or intraocular lenses with customized asphericity for cataract surgery, or lenses that allow to optimize night vision for all people and, especially, in those with oblate or hyperprolate corneas (either naturally or as a result of refractive surgery), which would improve road safety, traffic accident prevention and collisions with pedestrians, or solving many problems of night blindness and blinding glare by halos and flashes.

We also claim the provision of all hospitals with other basic services, such as the recognition and optical treatment service with qualified personnel (and not just nurses), and, in general, the training and specific budget allocation to deal with the problem and the requirements generated by refractive surgeries, such as chronic pain, suicide prevention, diagnosis and treatment of neurological problems, dry eye, corneal pathologies such as ectasia or edema and visual problems, including in the portfolio of services adaptation of scleral lenses and the lenses themselves, plasma enriched in growth factors and other specialized products for severe dry eye, artificial tears without preservatives, etc. The State is civil responsibility subsidiary, and in the absence of effective regulation, the physicians are taking advantage of a lack of controls and regulation, they systematically fraud by not correctly reporting and disregarding their clients with problems, to which they do not even measure real and complete refractive results.

**Second mail**

The truth is that the problems suffered by those affected by refractive surgery, in relation to cataract surgery, are neither solved by introducing the femtofaco, nor can be prevented with femtofaco. This is because these problems are derived from the implantation of trifocal, bifocal, extended-range or accommodative lenses and toric lenses, which give many visual and disabling problems, as well as the possible existence of refractive surgery with previous laser, which advances cataract surgery 10 years on average, difficulting to calculate the refractive power of the lenses to be implanted (so the patient remains with significant refractive error) and generates a possible large increase in spherical corneal aberration that is not corrected optimally or sufficiently with the spherical lenses covered by the National Health System for cataract surgery (lenses that may not solve night vision problems prior to cataract surgery), as well as the possible existence of a previous refractive surgery with phakic lenses, which forces to extract those lenses, for which a large corneal incision is required (because the lenses enter folded but leave in deployed) that can lead to astigmatism and increases many other risks. In addition, the LASIK suction ring, femtoLASIK and Relex SMILE, and, to a lesser extent, the laser shock waves, both with LASIK / femtoLASIK and with PRK and other surface surgeries, often generate annoying floaters due to condensation of vitreous proteins and partial or total posterior vitreous detachments (the latter due to the suction ring), a problem that could be aggravated to a greater extent when using a suction ring in femtofaco, especially if the ring is applied for many seconds or a lot of pressure. This is the real problem we have, very summarized and simplified.

**Second mail structured for an easier read**

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- the possible existence of refractive surgery with previous laser,

  which
    - advances cataract surgery 10 years on average, difficulting to calculate the refractive power of the lenses to be implanted (so the patient remains with significant refractive error) and
    - generates a possible large increase in spherical corneal aberration, not corrected optimally or sufficiently with the spherical lenses covered by the National Health System for cataract surgery (lenses that may not solve night vision problems prior to cataract surgery),
- the possible existence of previous refractive surgery with phakic lenses, which forces to extract those lenses, for which a large corneal incision is required (because the lenses enter folded but leave in deployed)

  that can lead
    - to astigmatism and increases many other risks.

In addition,
- the LASIK suction ring,
- femtoLASIK
- Relex SMILE, and
- to a lesser extent, the laser shock waves, both with LASIK / femtoLASIK and with *wavefront-guided photorefractive keratectomy* (PRK) and
- other surface surgeries,

often generate
- annoying floaters due to condensation of vitreous proteins and
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a problem that could be aggravated to a greater extent when using a suction ring in femtofaco, especially if the ring is applied for many seconds or a lot of pressure.

**Third mail**

We want to thank you for transferring our opinions to the European FLACS evaluation group, and we are pleased that the group will finally collect them and publish them in the main document and in an annex. Likewise, we want to thank the European group for their desire and willingness to agree on the document with us.

In general, the re-draft document is correct. But it has a lack or a misunderstanding, perhaps, in part, because we do not express ourselves with enough clarity, because of the rush, and the document only mentions the suction ring last and in exclusive relationship with the people who are operated on with refractive surgery, and whose problems could be aggravated when using the femtofaco. However, although that part is correct, that is not what we wanted to say, exactly.

We think that the use of the suction ring, in addition to being more uncomfortable for the patient (this inconvenience is added to the change of room in the middle of the surgery), can be problematic in general, by increasing the risks for everyone, depending on the time of application of the ring and the pressure with which it is applied, and we have provided a major scientific review that we think sufficiently supports the probable causal relationship between the suction ring (applied in LASIK, but extrapolated to any ring of suction) and posterior vitreous detachment, the appearance of floaters, rhegmatogenous retina detachment and other possible pathologies of the posterior segment of the eye. Perhaps, the fact that we added that study as an attached file, could have contributed to the fact that it went unnoticed. The reference is (we attach the document again, and we recommend reading the complete body of the study, and not just the Abstract or the conclusions, often excessively complacent, in our opinion):

Alireza Mirshahi, MD, and Holger Baatz, MD (July-August 2009). «Posterior Segment Complications of Laser in situ Keratomileusis (LASIK)». Survey of Ophthalmology 54 (4): 435.

On the other hand, we would also like to emphasize in the main document the ethical dimension we see in the matter in question, in relation to our observation that femtofaco is a technique that is yet to be perfected, which probably requires many years and many continuous technological innovations that should be progressively bought to the industry and implemented in all hospitals, and which requires a period of learning by surgeons, and all that at the expense of patients, who are the ones who undergo clinical experimentation and the learning curve of each new technique (with longer application times of the suction ring, for example, which increases the risks), what seems ethically questionable to us, and especially when we do not expect any significant net benefit and relevant of this technique in a long-term and that justifies such a choice. Therefore, the problem is not only scientific and economic-political, but also ethical.

In short, we think that there are not enough scientific, practical, economic, and much less ethical arguments to justify the introduction of femtofaco in national health systems. And we do know that there are clear economic interests on the part of a very influential industry (at least in Spain) and with quite aggressive commercial policies.