EUnetHTA Joint Action 3 2016-2020

Relative effectiveness assessment of Femtosecond laser-assisted cataract surgery (FLACS) compared to standard cataract surgery

Project ID: ***OTCA07***

Project description and planning

Regione Emilia-Romagna (RER), Italy

Gesundheit Österreich GmbH (GÖG), Austria

Version Log

Version number	Date	Modification	Reason for the modification
V1	15/09/2017	First draft sent to co-authors	
V2	20/10/2017	Integration of comments and suggestions from co-authors	Review by co-authors
V3	20/12/17	Draft sent to dedicated reviewers	
V4	19/01/2018	Integration of comments and suggestions from dedicated reviewers	Review by dedicated reviewers
V4	19/01/2018	Draft sent to external experts	
V5	13/02/2018	Final version	Integration of comments and suggestions from scoping e-meeting with assessment team and experts and from fact check from one manufacturer Integration of results of ratings of importance of outcomes via GRADEpro

CONTENTS

List of tables

1 Project organisation

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Regione Emilia-Romagna – RER	Author	Italy	•Develop the first draft of EUnetHTA project plan •Perform the literature search & study selection •Carry out the assessment (extraction, analysis, synthesis and interpretation of findings) •Send 1st draft to dedicated reviewers and 2nd draft to external experts, compile feedback from reviewers and perform changes according to reviewer's comments •Send 2nd draft to manufacturers for fact check. •Prepare final assessment and write a final summary of the assessment
2.	Gesundheit Österreich GmbH - GÖG	Co-Author	Austria	• Collaboration in the development of the EUnetHTA project plan • Check, provide input and approve all steps (e.g. collaboration in literature selection, data extraction, assessment of risk of bias). • Check, provide input and approve content of all domains. Discussion of conclusions, which will be agreed upon. • Review draft assessment, propose amendments where necessary and provide written feedback.
3.	Belgian Health Care Knowledge Centre - KCE	Dedicated Reviewer	Belgium	• Review draft project plan, propose amendments where necessary and provide written feedback. • Rate the relevance of outcomes (GRADE method) • Review 1st draft assessment, propose amendments where necessary and provide written feedback.
4.	Basque Office for Health Technology Assessment - Osteba	Dedicated Reviewer	Spain	• Review draft project plan, propose amendments where

				necessary and provide written feedback. • Rate the relevance of outcomes (GRADE method) • Review 1st draft assessment, propose amendments where necessary and provide written feedback.
5.	Health Service of Canary Islands - SESCS Fundación Canaria de Investigación Sanitaria - FUNCANIS	Dedicated Reviewer	Spain	• Review draft project plan, propose amendments where necessary and provide written feedback. • Rate the relevance of outcomes (GRADE method) • Review 1st draft assessment, propose amendments where necessary and provide written feedback.
6.	Agency for Health Quality and Assessment of Catalonia - AQuAS	Dedicated Reviewer	Spain	• Review draft project plan, propose amendments where necessary and provide written feedback. • Rate the relevance of outcomes (GRADE method) • Review 1st draft assessment, propose amendments where necessary and provide written feedback.
7.	State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania - VASPVT	Observer	Lithuania	• Review draft project plan, propose amendments where necessary and provide written feedback. • Rate the relevance of outcomes (GRADE method) • Review 1st draft assessment, propose amendments where necessary and provide written feedback.
Contributors				
8.	Dr. Marco Vecchi Azienda Usl di Reggio Emilia - Italy	External expert	Italy	Review and provide input to draft project plan. Rate the relevance of outcomes (GRADE method) Review and provide written feedback to 2nd draft assessment
9.	Prof. Gianmaria Cavallini + Dr. Tommaso Verdina Azienda Ospedaliero Universitaria di Modena, Italy	External expert	Italy	Review and provide input to draft project plan. Rate the relevance of outcomes (GRADE method) Review and provide written feedback to 2nd draft assessment
10.	TBD	Medical Editor	-	-
11.	Health Information and Quality Authority - HIQA	Project Manager	Ireland	Project Management throughout the project.

1.2 Project stakeholders

Table 1-2: Project stakeholders

Organisation	Role in the project
Ziemer Ophthalmic Systems AG – Femto LDV Z8	Manufacturer – None (Did not respond to request)
Abbott Medical Optics Inc. (J&J) - Catalys Precision laser system	Manufacturer – None (Did not respond to request)
Alcon (Novartis) - LenSx Laser System	Manufacturer – fact check of project plan and 2nd draft assessment; submission template
Bausch + Lomb– Victus femtosecond laser platform	Manufacturer – None (Did not respond to request)
Lensar (PDL BioPharma) – Lensar laser system	Manufacturer - fact check of 2nd draft assessment; submission template
Patient/consumer representative groups	None (No group available)

1.3 Milestones and Deliverables

Table 1-3: Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**01/09/2017**	**26/10/2018**
Scoping phase	20/12/2017	30/01/2018
Identification of manufacturer(s) and external experts; identification of patients	15/09/2017	12/02/2018
Scoping and development of draft Project Plan incl. preliminary PICO	15/09/2017	30/10/2017
Consultation of draft Project Plan with co-authors and transfer to new template	15/09/2017	19/10/2017
Managing DOICUs on behalf of EUnetHTA partners and finalising assessment team	15/10/2017	18/01//2018
Consultation of draft Project Plan with dedicated reviewers	21/12/2017	19/01/2018
Consultation of draft Project Plan with external experts	19/01/2018	25/01/2018
Internal Scoping e-meeting with the assessment team and external experts	25/01/2018	
Confirmation of list of outcomes and ratings of importance of outcomes (via GRADEpro)	**26/01/2018**	**12/02/2018**
Send the preliminary PICO for comments and the request for the completion of the Submission file template to manufacturer	23/01/2018	30/01/2018
Fact check by manufacturer	23/01/2018	02/02/2018
Amendment of draft Project Plan & final Project Plan available	29/01/2018	13/02/2018
Completion of Submission file template by manufacturer + Clarifying further questions concerning draft Submission file)	23/01/2018	20/02/2018
Assessment phase	14/02/2018	21/09/2018
Writing first draft rapid assessment	14/02/2018	23/05/2018
Review by dedicated reviewer(s)	24/5/2018	06/06/2018
Writing second draft rapid assessment	07/06/2018	04/07/2018

Review by ≥ 2 external experts and fact check by manufacturers	05/07/2018	02/08/2018
RELAUNCH OF LITERATURE SEARCH AND UPADATING	**16/07/2018**	**31/08/2018**
Writing third draft rapid assessment	03/09/2018	21/09/2018
Medical editing	24/09/2018	05/10/2018
Writing of fourth version of rapid assessment	08/10/2018	22/10/2018
Formatting	23/10/2018	26/10/2018
Final version of rapid assessment		**week from 22/10/2018 - to 26/102018**

2 Project Outline

2.1 Project Objectives

The rationale of this assessment is to collaboratively produce structured (rapid) core HTA information on femtosecond laser-assisted cataract surgery (FLACS). In addition, the aim is to apply this collaboratively produced assessment in the national or regional context.

Table 2-1: Project objectives

	List of project objectives	Indicator (and target)
1.	To jointly produce health technology assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of health technologies.	Production of 1 (rapid) collaborative relative effectiveness assessment for femtosecond laser-assisted cataract surgery (FLACS)
2.	To apply this collaboratively produced assessment into local (e.g. regional or national) context.	Production of ≥2 local (e.g. national or regional) reports based on the collaboratively produced assessment.

This rapid assessment addresses the research question whether femtosecond laser-assisted cataract surgery (FLACS) in adult patients affected by cataract is more effective and/or safer than standard cataract surgery.

This topic was chosen based on a request from local decision makers who commissioned the authors' agency to carry out an HTA on FLACS in adult patients affected by cataract. The topic resulted relevant to other partnering agencies that joined in a collaborative assessment team.

The relevance of the topic lies in the fact that the technology is presently intensely marketed in both public and private institutions, but not yet widely introduced in the public sector and could have a heavy organisational and economic impact on services for patients needing cataract surgery.

2.2 Project Method and Scope

2.2.1 Approach and Method

Table 2-2: Project approach and method

Project approach and method
International guidelines, Up-to-date [1] and a general search for relevant studies will be performed in order to fulfill information requested by "Health problem and current use" of FLACS (CUR) domain [2]. The selection of assessment elements will be based on The HTA Core Model® for Rapid Relative Effectiveness Assessment Version 4.2 [2]. Four high quality systematic reviews recently published in 2016 [3–6] were found to be available and will constitute the starting point for this assessment. The most recent high quality systematic review of effectiveness of FLACS vs standard care [3] which includes only Randomized Clinical Trials (RCTs) would constitute the basis for setting and updating the search for RCTs to answer questions on effectiveness and safety (EFF and SAF). The other three systematic reviews [4–6], which include also observational studies, would constitute the basis for setting the search for non randomised controlled studies to answer questions on SAF related to long term outcomes (i.e. surgical re-intervention at 6 months).

The short version of the Medical Devices Evidence Submission template will be sent to all identified manufacturers of the technology under assessment. Manufacturers will be asked to submit non-confidential evidence, focusing on the technical characteristics and current use of the technology.

The evidence provided will be used in addition to the literature identified by the literature search for the "Description and technical characteristics" of FLACS (TEC) domain [2].

The database specific search strategies will be used to identify RCTs and non-randomized controlled studies for "Clinical Effectiveness" (EFF) and "Safety" (SAF) domains [2].
A plan for information retrieval will be created including sources and search terms for locating domain specific information, inclusion/exclusion criteria for studies or other information, in terms of content, methods and quality of the studies to be included. The information unit will be the study: data for multiple reports of the same study will be combined in a single data for the "Summary of findings" table.

Two authors will carry out the study selection process, independently, in accordance with previously defined PICO question. This process will be checked by co-authors. Disagreement will be discussed and resolved between authors. Since eligible studies may have been reported in several articles, firstly a link between articles reporting the same study will be performed and secondly, data from each article will be extracted to determine which studies are eligible for inclusion. A PRISMA flow chart reporting the studies selection process will be created.

The data extraction process will be performed by one author and reviewed by another author. This process will be checked by co-authors. Data collection form including information listed in the Preliminary evidence table (*Table 2-4*) will be used, tracking with a unique ID to each article and to each study included, providing the link between multiple articles from the same study. Disagreement or consensus between reviewers on the eligibility of each study will be tracked in the data collection form.

Quality assessment tools: according to Cochrane's Handbook, the assessment of evidence quality will be performed focusing mainly on "risk of bias" of the included studies.
For quality assessment of RCTs the Cochrane risk of bias tool (RoB 2.0 tool) [7] and the AMSTAR instrument for systematic reviews will be used as recommended by the EUnetHTA guideline "Internal validity of RCTs" [8].
The EUnetHTA guideline "Internal validity of non-randomised studies on interventions" [9] and ROBINS will be used for non-randomised controlled trials/studies.

The level of confidence/certainty in the body of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [10].

External experts as well as authors and dedicated reviewers have been involved in selecting outcomes of interest and in grading the importance of each identified outcome.
Relevant subgroup analyses will be assessed especially for the most important outcomes.

A "Summary of findings" table will be created using GRADE Pro tool [11]. Quantitative analysis methods with meta-analysis where possible will be used for SAF and EFF domains [12].
Descriptive analysis of information will be performed for other domains.

Table 2-3: Planned literature search strategy

Literature search strategy
A systematic review of the scientific literature will be performed according to the Cochrane Handbook methodology - Version 5.1.0 [12]. The Systematic Review production tool (RevMan 5.3.5) will be also used [13] for data extraction, risk of bias representation and SoF tables. As four high quality systematic reviews have been published in 2016 [3–6] the systematic search will have January 2016 as a starting date, and the strategy will combine the search strategies of all 4 recent systematic reviews. The systematic search of the scientific literature - starting January 2016 - will be performed in the following databases y: - 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. Search of ongoing clinical trials and research projects: - Clinicaltrials.gov, - International ClinicalTrials Registry Platform (ICTRP), - UK Clinical Trials gateway, - EU Clinical Trials Register (EU CTR). The search strategy developed for all databases will be 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*)) As several ongoing RCTs registered on dedicated databases (clinicaltrial.gov) are potentially relevant to this assessment, the literature search will be re-launched after completion of the second draft to check for additional studies eligible for inclusion. Should such studies be identified, they will be analyzed and their results reported and discussed against main results of the REA. A list of ongoing studies will also be included in the REA, reporting their research question, planned number of patients' enrolment, intervention and comparator, outcomes and expected date of completion.

Table 2-4: Plan for data extraction

Planned data extraction
Evidence tables for data extraction will be created according to the Cochrane Handbook for Systematic Reviews of Interventions [12], http://www.cochrane.org/training/cochrane-handbook, chapter 7.5, "Data collection forms". In the heading of the table the title of the review, the revision date (or version number) and the name (or ID) of the author that complete the table will be included. Information about data that will be extracted from the included studies are shown below: Author Year of publication Article ID Study ID (used in RevMan) Study Registration number (Registry identifier) Country/ies of recruitment Data collection period Funding sources Intervention (FLACS – all available brand) Comparator (standard cataract surgery technique) Study design (RCT/non-randomised controlled studies) Number of patients Inclusion criteria Exclusion criteria Number of patients in intervention group Number of patients in comparator group Patients age (mean/range) Patient sex (%) **Risk of Bias RCTs** Random sequence generation (selection bias) Allocation concealment (selection bias) Blinding of participants and personnel (performance bias) Blinding of outcome assessment (detection bias) Incomplete outcome data (attrition bias) Selective reporting (reporting bias) Risk of Bias non-randomised controlled trials/studies Bias due to confounding Bias in selection of participants into the study Bias in measurement of interventions Bias due to departures from intended interventions Bias due to missing data Bias in measurement of outcomes Bias in selection of the reported result

Overall bias

Outcomes

Primary outcome

Other outcomes

Results

Safety

Anterior capsular tear

Posterior capsular tear (PCR)

Vitreous loss

Cystoid macular oedema (within 90 days)

Elevated intraocular pressure (IOP) (1 day to 1 week after surgery)

Endothelial cells loss

Central corneal thickness

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 months; 6 months)

Surgical re-intervention (within 6 months)

Secondary cataract (24 months)

Effectiveness

Corrected distance visual acuity (CDVA) (1 month; 6 months after surgery)

Uncorrected distance visual acuity (UDVA) (1 month; 6 months after surgery)

Refractive outcomes

Vision-related quality of life as measured by any validated questionnaire

Patient reported outcome measures (PROMs)

Other outcomes

Patient satisfaction

Procedural time

Resource use

For safety and clinical effectiveness assessment, the unit of analysis will be the eye, whenever outcomes relate uniquely to the eye (e.g. vitreous loss; corrected distance visual acuity). For patient reported outcomes, quality of life and patient satisfaction the unit of analysis will be the patient.

2.2.2 Project Scope

The EUnetHTA Guidelines, available at http://www.eunethta.eu/eunethta-guidelines, will be consulted throughout the assessment process.

The Project Scope was discussed during the scoping e-meeting, attended by the assessment team and external experts. During the meeting, it was agreed to adopt the GRADE approach in order to finalize the list of outcomes and rate the importance of each outcome.

The list of outcomes that resulted from the e-meeting was circulated among the *panelists* (assessment team and external experts) via the use of GRADEpro (*https://gradepro.org/)* .During a *brainstorming* phase, panelists reviewed the outcomes, added comments and/or added outcomes. The final list of outcomes was then circulated to the panelists, who were asked to rate the importance of each outcome, according to a 1 to 9 point scale ("1" meaning the lowest importance and "9" meaning the highest importance). After completion of the rating round the median of the votes was computed and each outcome was assigned a rate of importance: “critical” (median between 7 and 9); “important” (median from 4 to 6) and “not important” (median from 1 to 3). In Table 2-5 ratings of importance are reported for each outcome.

Summary of Findings tables will be completed only for outcomes rated as “critical” and “important”, while for outcomes rated as “not important” results will be reported and commented in main text.

Table 2-5: Project Scope: PICO (please see HTA Core Model® for rapid REA)

Description	**Project Scope**
Population	• The target disease is age-related cataract. (ICD-9 366.1; ICD-10 H25; MeSH terms “cataract”) • The target population is adult patients (>18 years) of any gender, affected by cataract and for which the 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”) The intended use of the technology is surgical treatment of age-related cataract. Sub-populations: Subgroup analyses are planned for LOCS type and sub-exfoliation Rationale: According to current American and European guidelines [14,15], the cataract surgery should be considered for all the adult patients affected by age-related cataract that could benefit in terms of health-related quality of life. Specifically, and contrary to previous guidelines, the NICE guidelines 2017 states that restricting referral to cataract surgery on the basis of visual acuity thresholds is inappropriate [16]
Intervention	• Cataract surgery assisted by femtosecond laser (FLACS) 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. The name of the products included in the assessment (and relative manufacturers) are: LenSx Laser System (Alcon), Catalys Precision laser system (Abbott), Victus femtosecond laser platform (Bausch & Lomb), Lensar laser system (Lensar) and Femto LDV Z8 (Ziemer).
Comparison	• Standard cataract surgery

<table>
<tr><td></td><td>Rationale: comparator has been identified from guidelines mentioned above i.e. European and American guidelines [14–16].</td></tr>
<tr><td>Outcomes</td><td>The claimed benefits are related to the ultrashort duration of laser pulses that should minimise the damage to adjacent tissues. In particular, by reducing the phacoemulsification times and the intraocular fluid flow it could decrease the corneal endothelial loss. Moreover, reproducible incisions and accurately centred and circular capsulotomies may reduce postoperative refractions issues and allow long-term intraocular lens centration. At the same time, use of resources and logistic issues might be considered to determine the organizational impact of FLACS[16].

Safety:

<table>
<tr><th></th><th>Rate of Importance</th></tr>
<tr><td>Intraoperative complications</td><td></td></tr>
<tr><td>Anterior capsular tear</td><td>8.5 (6-9) “critical”</td></tr>
<tr><td>Posterior capsular tear (PCR)</td><td>8.5 (7-9) “critical”</td></tr>
<tr><td>Vitreous loss</td><td>7.5 (3-9) “critical”</td></tr>
<tr><td>Post operative complications</td><td></td></tr>
<tr><td>Elevated Intraocular Pressure (1 day - 1 week)</td><td>6.0 (3-9) “important”</td></tr>
<tr><td>Endothelial cells loss</td><td>6.5 (4-9) “important”</td></tr>
<tr><td>Central corneal thickness</td><td>5.0 (3-8) “important”</td></tr>
<tr><td>Iridocyclitis</td><td>7.0 (3-8) “critical”</td></tr>
<tr><td>Cystoid macular oedema (within 90 days)</td><td>8.0 (3-9) “critical”</td></tr>
<tr><td>Infections (within 90 days)</td><td>8.0 (3-9) “critical”</td></tr>
<tr><td>Corneal endothelial decompensation (within 90 days)</td><td>8.0 (5-9) “critical”</td></tr>
<tr><td>Surgically induced astigmatism</td><td>6.0 (6-8) “important”</td></tr>
<tr><td>Retinal detachment</td><td>8.0 (7-9) “critical”</td></tr>
<tr><td>Posterior capsule opacification</td><td>8.0 (7-8) “critical”</td></tr>
<tr><td>Visual acuity loss post cataract surgery (1 month;6 months)</td><td>8.0 (6-9) “critical”</td></tr>
<tr><td>Surgical re-intervention (within 6 months)</td><td>8.0 (3-9) “critical”</td></tr>
<tr><td>Secondary cataract (24 months)</td><td>8.0 (3-9) “critical”</td></tr>
<tr><td></td><td></td></tr>
</table>

Clinical effectiveness:

<table>
<tr><th></th><th>Rate of Importance</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>
<tr><td></td><td></td></tr>
</table>

Other outcomes:

<table>
<tr><th></th><th>Rate of Importance</th></tr>
<tr><td>Patient satisfaction</td><td>5.5 (4-8) “important”</td></tr>
<tr><td>Procedural time</td><td>5.0 (2-8) “important”</td></tr>
<tr><td>Resource use</td><td>6.0 (2-9) “important”</td></tr>
</table>
</td></tr>
<tr><td>Study design</td><td>• Safety of FLACS: randomised controlled clinical trials; non randomised controlled studies (for safety outcomes at ≥ 6 months follow up)
• Clinical effectiveness of FLACS: randomised controlled clinical trials.</td></tr>
</table>

	• **Other outcomes:** randomised controlled clinical trials and non-randomised controlled studies.

PLANNED SUMMARY OF FINDINGS

FLACS compared to Standard cataract surgery for cataract surgery in terms of safety

Patient or population: adult people with age-related cataract
Setting:
Intervention: FLACS
Comparison: Standard cataract surgery

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens	Level of Importance of outcome
		Without FLACS	**With FLACS**	**Difference**			
Anterior capsular tear № of participants: (studies)					-		
Posterior capsular tear № of participants: (studies)					-		
Vitreous loss № of participants: (studies)							
Cystoid macular oedema (within 90 days) № of participants: (studies)					-		
Elevated intraocular pressure (IOP) (1 day to 1 week after surgery) № of participants: (studies)					-		
Infections (within 90 days) № of participants: (studies)					-		
Corneal Endothelial Decompensation (within 90 days) № of participants: (studies)					-		
Endothelial cell loss № of participants: (studies)							
Central corneal thickness № of participants: (studies)							
Idrocyclitis № of participants: (studies)							

FLACS compared to Standard cataract surgery for cataract surgery in terms of safety

Patient or population: adult people with age-related cataract
Setting:
Intervention: FLACS
Comparison: Standard cataract surgery

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens	Level of Importance of outcome
		Without FLACS	**With FLACS**	**Difference**			
Retinal detachment № of participants: (studies)					-		
Posterior capsule opacification № of participants: (studies)					-		
Surgically induced astigmatism № of participants: (studies)							
Visual acuity loss post cataract surgery № of participants: (studies)					-		
Surgical re-intervention (within 6 months) № of participants: (studies)					-		
Secondary cataract (24 months) № of participants: (studies)							

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

FLACS compared to Standard cataract surgery for cataract surgery in terms of clinical effectiveness

Patient or population: adult people with aged-related cataract
Setting:
Intervention: FLACS
Comparison: Standard cataract surgery

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens	Level of Importance of outcome
		Without FLACS	**With FLACS**	**Difference**			
Corrected distance visual acuity (CDVA) (1 month; 6 months after surgery) № of participants: (studies)					-		
Uncorrected distance visual acuity (UDVA) (1 month; 6 months after surgery) № of participants: (studies)					-		
Patient reported outcome measures (PROMs) № of participants: (studies)					-		
Refractive outcomes № of participants: (studies)					-		
Vision-related quality of life as measured by any validated questionnaire № of participants: (studies)					-		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

FLACS compared to Standard cataract surgery for cataract surgery in terms of other outcomes

Patient or population: adult people with age related cataract
Setting:
Intervention: FLACS
Comparison: Standard cataract surgery

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens	Level of Importance of outcome
		Without FLACS	**With FLACS**	**Difference**			
Patient satisfaction № of participants: (studies							
Total duration of procedure № of participants: (studies)					-		
Resource use № of participants: (studies)					-		

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

3 Communication and collaboration

Table 3-1: Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	To internally discuss and reach consensus on the scoping.	25/01/2018	E-meeting	Author(s), co-author(s), dedicated reviewers, observers, project manager, external experts
	Selection of outcomes and rating of importance of outcomes	26/01/2012 – 12/02/2018	GRADEpro Software	Author(s), Co-author(s), dedicated reviewer(s), external experts
First draft of the rapid assessment	*To discuss comments of dedicated reviewers*	*[TBC]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers*
Second draft of the rapid assessment	*To discuss comments from ≥ 2 external experts and manufacturers*	*[TBC]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers; external experts, manufacturers*

3.3 Dissemination plan

The final rapid assessment will be published on the EUnetHTA website: http://www.eunethta.eu/joint-assessments.

All stakeholders and contributors are informed about the publication of the final assessment by the project manager.
Findings will be proposed for publication/presentation in relevant journals, conferences and databases.

3.4 Collaboration with stakeholders

Collaboration with manufacturer(s)

There will be a review of the preliminary PICO and a fact check of the 2nd draft project plan and the 2nd draft assessment by all manufacturer(s) willing to get involved.

Manufacturers will be asked to complete the submission file by manufacturers for other technologies (short version).

Collaboration with other stakeholders

Patients' involvement has been sought through contact with Ireland's patients' associations and EURORDIS.

3.5 Collaboration with EUnetHTA WPs

For the individual rapid assessment, some collaboration with other WPs is planned: WP7 [Implementation] will be informed of the project, in order to prepare activities to improve national uptake of the final assessment. Feedback on the WP4 REA process will be asked from the involved parties by WP6 [Quality Management], and this information will be processed by WP6 to improve the quality of the process and output.

3.6 Conflict of interest and confidentiality management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised “Declaration of Interest and Confidentiality Undertaking” (DOICU) statement.

Authors, co-authors and dedicated reviewers who declare a conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in other assessments.

For external experts, patients or other stakeholders involved, conflict of interest declarations are collected regarding the topic. External experts or patients who declare conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in other assessments.

Manufacturer(s) will sign a Confidentiality Undertaking (CU) form regarding the specific project.

4 References

1 Jacobs D, Trobe J, Libman H. Cataract in adults - UpToDate. Up-to-date. 2017.https://www.uptodate.com/contents/cataract-in-adults (accessed 28 Jun2017).

2 EUnetHTA. Joint Action on HTA 2012 - 2015 HTA Core Model for Rapid Relative Effectiveness Assessments 4.2. Published Online First: 2015.http://meka.thl.fi/htacore/model/HTACoreModel_ForRapidREAs4.2.pdf

3 Day AC, Gore DM, Bunce C, *et al.* Laser-assisted cataract surgery versus standard ultrasound phacoemulsification cataract surgery. Cochrane Database Syst. Rev. 2016. doi:10.1002/14651858.CD010735.pub2

4 Popovic M, Campos-Möller X, Schlenker MB, *et al.* Efficacy and Safety of Femtosecond Laser-Assisted Cataract Surgery Compared with Manual Cataract Surgery: A Meta-Analysis of 14 567 Eyes. In: *Ophthalmology*. 2016. doi:10.1016/j.ophtha.2016.07.005

5 Qian D-W, Guo H-K, Jin S-L, *et al.* Femtosecond laser capsulotomy versus manual capsulotomy: a Meta-analysis. *Int J Ophthalmol* 2016;**9**:453–8. doi:10.18240/ijo.2016.03.23

6 Chen X, Chen K, He J, *et al.* Comparing the Curative Effects between Femtosecond Laser-Assisted Cataract Surgery and Conventional Phacoemulsification Surgery: A Meta-Analysis. *PLoS One* 2016;**11**:e0152088. doi:10.1371/journal.pone.0152088

7 Higgins J, Sterne J, Savović J, *et al.* Cochrane Collaboration risk of bias tool (RoB 2.0 tool). *Cochrane Methods Cochrane Database Syst Rev* Published Online First: 2016. doi:dx.doi.org/10.1002/14651858.CD201601

8 EUNETHA. Internal Validity of Randomized Controlled Trials. 2015. https://5026.makemeweb.net/outputs/internal-validity-randomised-controlled-trials

9 EUNETHA. Internal validity of non-randomised studies (NRS) on interventions. 2015. http://www.eunethta.eu/outputs/publication-ja2-methodological-guideline-internal-validity-non-randomised-studies-nrs-interv

10 The GRADE working group. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. 2013. http://gdt.guidelinedevelopment.org/app/handbook/handbook.html#h.qmsmbyw3yxsl

11 The GRADE working group. GRADE Pro GDT. 2015.https://gradepro.org/

12 Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions Ver. 5.1.0. 2011. http://handbook-5-1.cochrane.org/ (accessed 30 Aug2017).

13 Cochrane Collaboration. Review Manager 5.3. 2014.http://community.cochrane.org/tools/review-production-tools/revman-5

14 AAO PPP Cataract/Anterior Segment Panel HC for QEC. Cataract in the Adult Eye PPP - 2016 - American Academy of Ophthalmology. 2016. https://www.aao.org/preferred-practice-pattern/cataract-in-adult-eye-ppp-2016 (accessed 24 May2017).

15 Lundström M, Barry P, Henry Y, *et al.* Evidence-based guidelines for cataract surgery: Guidelines based on data in the European Registry of Quality Outcomes for Cataract and Refractive Surgery database. J. Cataract Refract. Surg. 2012. doi:10.1016/j.jcrs.2012.03.006

16 National Institute for Health and Care Excellence. Cataracts in adults: management 26 October: 2017. httpss://www.nice.org.uk/guidance/ng77/resources/cataracts-in-adults-management-pdf-1837639266757

5 Appendix A

5.1 Selected Assessment Elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessment elements contained in the 'Model for Rapid Relative Effectiveness Assessment'. Additionally, assessment elements from other HTA Core Model Applications (for medical and surgical interventions, for diagnostic technologies or for screening) have been screened and included/ merged with the existing questions if deemed relevant.

Table 5-1: Selected Assessment Elements

ID	Topic	Topic Issue	Relevance in this assessment [**Yes – critical**, **Yes** or **No**]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology					
B0001	Features of the technology and comparators	What is the technology and the comparator(s)?	YES - critical	M	What is FLACS and the standard cataract surgery?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking? [This assessment element can be placed either in the TEC OR in the CUR domain]	YES - critical	M	For which indications have the different types of FLACS received marketing authorisation or CE marking?
B0002	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparator(s)?	YES - - critical	M	What is the claimed benefit of FLACS in relation to the standard cataract surgery?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	YES	NM	What is the phase of development and implementation of FLACS and standard cataract surgery?
B0004	Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?	YES - critical	M	Who administers FLACS and the standard cataract surgery and in what context and level of care are they provided?
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	YES - critical	NM	What kind of special premises are needed to use FLACS and the standard cataract surgery?
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	YES - critical	NM	What equipment and supplies (including maintenance resources) are needed to use FLACS and the standard cataract surgery?
E0001	Resource utilisation	What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?	YES	NM	What types of resources are used when using the different types of FLACS and standard cataract surgery?
A0021	Regulatory Status	What is the reimbursement status of the technology?	YES	NM	What is the reimbursement status of FLACS in the different EU countries?

ID	Topic	Topic Issue	Relevance in this assessment [Yes – critical, Yes or No]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
		[This assessment element can be placed either in the TEC OR in the CUR domain]			
Health problem and current use of technology					
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?	YES - critical	M	What is the type of cataract in the scope of this assessment?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	YES - critical	NM	What are the known risk factors for the cataract?
A0004	Target Condition	What is the natural course of the disease or health condition?	YES - critical	M	What is the natural course of the cataract?
A0005	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	YES	M	What are the symptoms and the burden of the cataract for the patient?
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	YES	NM	What are the consequences of the cataract for the society?
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	YES - critical	M	How is the cataract currently diagnosed according to published guidelines and in practice?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	YES - critical	M	How is the cataract currently managed according to published guidelines and in practice?
A0007	Target Population	What is the target population in this assessment?	YES - critical	M	What is the target population in this assessment?
A0023	Target Population	How many people belong to the target population?	YES	M	How many people belong to the target population?
A0011	Utilisation	How much are the technologies utilised?	YES	M	How much are the Femtosecond Lasers (FLACS) utilised?
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	NO	M	The condition is not mortality related
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	YES - critical	M	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	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	YES - critical	M	How does intervention with FLACS compare to standard cataract surgery in terms of refractive outcomes?
D0011	Function	What is the effect of the technology on patients' body functions?	NO	M	Addressed in D0005

ID	Topic	Topic Issue	Relevance in this assessment [**Yes – critical**, **Yes** or **No**]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
D0016	Function	How does the use of technology affect activities of daily living?	NO	NM	Addressed in D0005 + D0012
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	YES	M	How does intervention with FLACS compare to standard cataract surgery in terms of patient reported outcomes and general quality of life)?
D0013	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	YES - critical	M	What is the effect of FLACS compared to standard cataract surgery on disease-specific quality of life?
D0017	Patient satisfaction	Were patients satisfied with the technology?	YES	NM	How does intervention with FLACS compare to standard cataract surgery in terms of patient satisfaction?
Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	YES - critical	M	How safe is FLACS compared to standard cataract surgery in terms of intraoperative and postoperative complications?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	NO	NM	Dosage is not an issue applicable to this technology.
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	YES	M	How safe is FLACS compared to the standard cataract surgery over time or in diffferent settings of use?
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	YES - critical	M	What are the susceptible patient groups that are more likely to be harmed through the use of FLACS?
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	YES - critical	NM	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	Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	YES	M for medical devices NM for screening and diagnostics	What kind of data/records and/or registry is needed to monitor the use of FLACS and the standard cataract surgery

5.2 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
Equity of access issues	
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
The comparator is widely available.	
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
The new intervention requires substantial additional resources.	
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