IQWiG

ThemenCheck Medizin

Cataract[1]

Does surgery with the femtosecond laser offer advantages over other procedures for people affected?

Health technology assessment commissioned by IQWiG

EXTRACT OF HTA REPORT

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Patient involvement

Patients were consulted as part of the report preparation process. The aim of the consultation was to obtain information on the following topics: the impact of the disease on life and daily activities and how the patient copes with it, treatment preferences including treatment goals, and experiences and concerns about treatment. Five people took part in the consultation; they were not involved in the report preparation. The authors of the report would like to thank them for their participation.

The Institute for Quality and Efficiency in Health Care (IQWiG) was responsible for coordinating the project, conducting information retrieval for the domains “Benefit

assessment“ and “Health economic evaluation”, and preparing the easy-to-understand summary (HTA kompakt).

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A13 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

Publisher's comment

What is the background of the HTA report?

Insured persons and other interested individuals are invited to propose topics for the assessment of medical procedures and technologies through "ThemenCheck Medizin" (Topic Check Medicine) to the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). The assessment is done in the form of a comprehensive Health Technology Assessment (HTA) report. Comprehensive HTA reports include an assessment of medical benefit and health economics as well as an investigation of ethical, social, legal, and organizational aspects of a technology.

In a 2-step selection procedure, which also involves the public, up to 5 new topics are selected each year from among all submitted proposals. According to the legal mandate, these topics are supposed to be of particular relevance to patients [1]. IQWiG then commissions external teams of scientists to investigate the topics in accordance with IQWiG methods, and it publishes the HTA reports.

In September 2022, IQWiG commissioned a team of scientists from the Institute of General Practice and Evidence-based Health Services Research at the Medical University of Graz together with Gesundheit Österreich GmbH to work on the selected topic "HT22-04: Cataracts: Does femtosecond laser surgery offer advantages for patients compared to other procedures?". The team consisted of methodologists experienced in generating HTA reports, experts with knowledge and experience in health economic, ethical, social, legal, and organizational topics as well as an ophthalmologist.

Why is the HTA report important?

A cataract is an eye disorder in which one or both eye lenses become cloudy. As a result, visual acuity deteriorates, and vision becomes increasingly hazy and blurred. Some people only have slight impairments, while others lose their visual acuity quickly. In most cases, both eyes are affected. However, the disorder can progress more quickly in one eye over the other.

Cataracts usually develop in people over the age of 50. The risk increases with age: around 20 out of 100 people between the ages of 65 and 74 have a cataract. Among those aged 74 years and older, it's more than 50 out of 100. Approximately 90% of all those affected have so-called age-related cataracts (senile cataracts) [2].

There are indications that UV light from the sun and smoking, for example, increase the risk. In addition, people with diabetes are more frequently affected. A cataract can also be caused

by inflammation or injury to the eye. In addition, eye surgery and long-term use of certain medications (e.g. cortisone) can lead to cataracts.

Some people can compensate for the loss of vision temporarily or even long-term with eyeglasses or contact lenses. There are no drugs for treating cataracts.

Surgery is the only effective treatment option. This involves removing the cloudy lens and replacing it with a new, artificial lens. During surgery, the lens capsule surrounding the lens remains in the eye. At the beginning of the surgery, a small incision is made at the edge of the cornea. The membrane surrounding the lens is then opened at the front. The nucleus and cortex of the lens are broken down using ultrasound and aspirated through a small incision (phacoemulsification). A plastic lens is then inserted into the capsule. This procedure is the standard procedure in Germany.

Some physicians offer laser-assisted surgery as an alternative. In this procedure, a femtosecond laser is used to make the incision and the lens is broken down with the laser as well. The surgery is then continued as in the standard procedure.

Femtosecond laser surgery for cataracts is often advertised by claiming that capsulotomy with the femtosecond laser is more precise and that less ultrasound energy is required due to the fragmentation of the lens. This is said to lead to fewer complications, better healing and better results (e.g. [3-5]).

Concerns of those proposing the topic

Those proposing the topic also report that laser-assisted cataract surgery is offered at various sites in Germany. Against this background, they ask whether the laser-assisted procedure has advantages over other surgical procedures.

Objective of the HTA report

To answer the suggesting party's question, the commissioned team of scientists took the different perspectives of an HTA report to investigate whether people with cataracts can expect an advantage from laser-assisted cataract surgery compared to the standard surgery. This would be the case, for example, if it were proven that patients operated on with the laser-assisted procedure have better visual acuity at a distance than patients operated on with the standard procedure. There would also be a benefit if the laser-assisted procedure resulted in fewer complications during or after the surgery or if the vision-related quality of life improved.

Which questions are answered – and which are not?

Benefit assessment

The authors of the report analysed the results of a total of 35 studies in which 7189 eyes of 5510 patients were treated with one of the two surgical techniques. The mean age of those

affected was 57 to 73 years and the majority had age-related cataracts without other eye disorders. In the randomized controlled trials (RCTs), the main outcomes analysed were visual acuity (eyesight), achievement of the desired visual acuity after surgery (refractive accuracy), and complications during or after surgery.

The results can be easily summarized: The studies show neither advantages nor disadvantages of laser-assisted surgery compared to the standard procedure. Rather, both methods are similarly effective: The visual acuity of the study participants was usually back to normal 1 to 12 months after the surgery, regardless of the surgical method used. The quality of life also improved with both procedures. There were also no differences in terms of safety: complications such as inflammation, swelling, or injury to the lens capsule were rare with both procedures.

In 30 of the 35 studies evaluated, the risk of bias was rated as high across outcomes, mainly due to inaccurate description of randomization and/or masking of group allocation. In 5 of the 35 studies, the outcome-specific risk of bias was low at least for the outcomes of visual acuity and intraoperative complications. These included the 3 studies with the largest number of patients included. In addition, the authors of the report found 9 ongoing studies with a total of 1196 planned cases.

The authors of the report identified 3 completed studies without published results. The latter were rather small studies, with 136, 132 and 71 participants respectively. Queries to those responsible for these 3 studies remained unanswered. Due to the large number of published RCTs with numerous patients included, it cannot be assumed that unpublished data can significantly influence the results of the present report.

Health Economics

The team of scientists reports that it was difficult to determine the costs of the two surgical procedures. One of the reasons for this is that there are very different forms of billing for laser-assisted surgery, which is offered in Germany as an Individual Health Care Service (Individuelle Gesundheitsleistung, IGeL for short), and none of the parties contacted were able to provide general information. The cost range of around €900 to €1000 for standard cataract surgery and €700 to €2100 for laser-assisted surgery can therefore only serve as a rough guide. It should also be noted that laser-assisted surgery incurs additional material costs. This includes, for example, the cost of the patient interface, a disposable product designed to ensure a stable connection between the eye and the optical laser system. Despite intensive efforts, the authors of the report were unable to quantify the exact material costs. Overall, however, laser-assisted surgery appears to be up to twice as expensive as the standard procedure.

While the costs for the standard surgery are largely covered by statutory health insurance, (additional) costs are incurred for the laser-assisted procedure, which must be borne by the affected individuals themselves.

The report also presents two studies – one from France and one from the UK – which analyse the cost-benefit ratio for standard and laser-assisted surgery. Based on these studies on cost-effectiveness, the authors of the report arrive at the conclusion that laser-assisted surgery cannot be assumed to be cost-effective for the German health care system either – given higher costs and identical results.

Further aspects

From an ethical perspective, the team of scientists points out that a therapeutic indication for cataract surgery only exists once the cataract significantly impairs the affected person's daily life. In order to limit the period of impairment for those affected, the waiting time for cataract surgery should be kept as short as possible. Likewise, to obtain the informed consent of those affected to an operation, detailed and comprehensible information must be provided. This concerns not only the advantages and disadvantages of various treatment options, but also information on the costs of the surgical procedures.

Summarized conclusion from IQWiG's perspective

Regardless of the surgical method, cataract surgery is a safe and effective procedure. However, laser-assisted surgery is advertised as causing less trauma and being more precise and, compared to standard surgery, leading to fewer complications and better results. Often there is no mention of the fact that this supposed superiority of laser-assisted surgery is not proven by study results: Randomized and controlled studies show no differences between standard and laser-assisted surgery for the outcomes of visual acuity, refraction, vision-related quality of life, or intraoperative and postoperative complications.

When deciding on a surgical procedure for cataracts, objective counselling and information for those affected is important for informed decision-making. This is all the more true as patients who opt for laser-assisted surgery have to bear at least part of the costs themselves. In this context, the possible costs for laser-assisted and standard surgery should also be presented transparently – as opposed to the current situation.

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HTA key statements

Research question of the HTA report

The aims of this investigation are to

- assess the benefit of femtosecond laser-assisted cataract surgery compared to standard cataract surgery in adults with diagnosed cataracts with regard to patient-relevant outcomes,

- determine costs (intervention costs),

- assess cost effectiveness as well as

- review ethical, social, legal, and organizational aspects associated with femtosecond laser-assisted cataract surgery.

Conclusion of the HTA report

The benefit assessment identified 36 randomized controlled trials comparing femtosecond laser-assisted cataract surgery versus standard manual cataract surgery, of which 35 studies provided results for the benefit assessment. A total of 7189 eyes of 5510 patients were treated with one of the two surgical techniques in these studies. The mean age of the participants was 57 to 73 years, and the majority had age-related cataracts.

All commercially available laser systems (VICTUS Femtosecond Laser Platform, CATALYS Precision Laser System, LenSx Laser System, LENSAR Laser System, Ziemer FEMTO LDV 8) were investigated in the randomized controlled trials, with the LenSx Laser System from Alcon being the most frequently investigated system. In the randomized controlled trials, the outcomes mainly analysed were visual acuity, refractive accuracy, and intraoperative or postoperative complications. The study duration was mostly between 1 and 18 months. Four randomized controlled trials only reported results obtained immediately after the procedure.

Overall, the randomized controlled trials included show that cataract surgery is safe and effective regardless of the surgical method chosen. Both in the intervention groups with femtosecond laser-assisted cataract surgery and in the control groups with standard manual cataract surgery, few intraoperative and postoperative complications occurred during the course of the study. Both the measured values of visual acuity (sharpness of vision) and those of refraction are almost within the normal range with both surgical techniques after a follow-up period of 1 to a maximum of 12 months.

The results of the individual randomized controlled trials comparing femtosecond laser-assisted cataract surgery versus standard cataract surgery are very homogeneous. Overall, the

metaanalyses carried out did not reveal any statistically significant differences between the two surgical techniques for the outcomes of visual acuity, refractive accuracy, and intraoperative or postoperative complications. With regard to vision-related quality of life, there is also no difference between femtosecond laser-assisted cataract surgery and standard cataract surgery.

Thus, there is no hint, indication, or proof of an added benefit of femtosecond laser-assisted cataract surgery compared to standard manual cataract surgery for the investigated outcomes of visual acuity, refractive accuracy, and vision-related quality of life. At the same time, there is also no proof, indication, or hint of lesser or greater damage from femtosecond laser-assisted cataract surgery compared to standard manual cataract surgery.

The costs of both procedures for standard cataract surgery in Germany in an outpatient setting are around €900 to €1000, and for surgery using a femtosecond laser they are estimated to range from €700 to €2100. The 2 health economic evaluations conducted for the UK and French health care systems conclude that, from the payers' perspective, the femtosecond laser procedure is unlikely to very unlikely to be cost-effective compared to the standard procedure. Considering the results of the benefit assessment of the present report and given the difference in intervention costs, a similar result can be assumed for Germany.

Although the benefit assessment shows neither an added benefit nor a reduced potential for harm of femtosecond laser-assisted cataract surgery compared to the standard procedure, it is sometimes advertised as more precise or safer. Objective counselling and information in this regard by the attending physicians are therefore of great importance for the informed decision-making of those affected, especially in view of the fact that patients who opt for femtosecond laser-assisted cataract surgery have to bear at least part of the costs themselves. The legal uncertainty regarding the billable procedure codes in this context has been clarified by a ruling of the German Federal Court of Justice, according to which only charging the lower-priced laser surcharge is permissible if there is no independent medical indication. Public investment in the more expensive femtosecond laser-assisted cataract surgery is not in line with the principle of distributive justice given the lack of added benefit. In addition, the increased use of environmentally harmful consumables in femtosecond laser-assisted cataract surgery must be viewed critically, irrespective of the cost coverage. Since femtosecond laser-assisted cataract surgery is not an option for people with certain medical conditions or anatomical characteristics, it would have to be ensured that, even if femtosecond laser-assisted cataract surgery were to be used more and more, the medical skills required for the standard procedure (e.g. manual capsulotomy) would continue to be available to a sufficient extent to guarantee the care of these individuals.

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
BMG	Bundesministerium für Gesundheit (Federal Ministry of Health)
DRG	Diagnosis-Related-Groups
EBM	Einheitlicher Bewertungsmaßstab (German Uniform Assessment Standard)
EUnetHTA	European Network for Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
FLACS	femtosecond laser-assisted cataract surgery
GOÄ	Gebührenordnung für Ärzte (German Medical Fee Schedule)
HTA	Health technology assessment
ICD	International Classification of Diseases
IFA	Informationsstelle für Arzneispezialitäten (Information Centre for Specialised Medicines)
IGeL	Individuelle Gesundheitsleistung (Individual Health Care Service)
IOL	intraocular lens
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MDR	Medical Device Regulation
MPDG	Medizinprodukterecht-Durchführungsgesetz (Medical Device Implementation Act)
NICE	National Institute for Health and Care Excellence
OCT	optical coherence tomography
QoL	health-related quality of life
RCT	Randomized controlled trial
SAE	Serious adverse event
SGB V	Sozialgesetzbuch – Fünftes Buch – gesetzliche Krankenversicherung (Social Code Book V, Statutory Health Insurance (SGB V))
SHI	statutory health insurance
SR	systematic review

HTA overview

1 Background

1.1 Health policy background and commission

According to §139b (5) of Social Code Book V, Statutory Health Insurance (SGB V), statutory health insurance members, and other interested people may suggest topics for the scientific assessment of medical interventions and technologies to the Institute for Quality and Efficiency in Health Care (IQWiG). The topics for these health technology assessment (HTA) reports can be submitted on the ThemenCheck Medizin ("topic check medicine") website.

ThemenCheck Medizin aims to promote the involvement of the public in evidence-based medicine and answer questions which are particularly relevant in patient care.

Once yearly, IQWiG, in collaboration with patient representatives and members of the public, selects up to 5 topics on which HTA reports are to be prepared. IQWiG then commissions external experts to investigate the research question. The results prepared by the external experts and a publisher's comment by IQWiG are then published in the form of an HTA report.

IQWiG disseminates HTA reports to German institutions, for instance those deciding about health care services and structures. The HTA report will be made available to the professional community through the ThemenCheck Medizin website (www.iqwig.de). In addition, a lay summary of the results of the HTA report will be published under the title "HTA compact: The most important points clearly explained". This is done to ensure that the results of HTA reports will impact patient care.

1.2 Medical background

A cataract (ICD-10: H25, H26, H28, Q12) is a clouding of the lens of the eye that affects vision, especially visual acuity (Latin: visus), and is the most common cause of blindness worldwide [6]. It can affect one eye or both eyes [7,8]. In most cases, the disorder occurs in both eyes, but often progresses faster in one eye than the other [9]. Clinical symptoms of cataracts include a slow and painless deterioration of vision, an increase in glare sensitivity, a slowed adaptability of the eye to different lighting conditions, seeing in shades of grey, disturbed colour vision, or ultimately a total loss of visual acuity [6]. In addition, the increasingly impaired visual acuity can represent a considerable psychological burden for those affected [10].

To diagnose a cataract, a detailed medical history is first taken, vision impairment is measured (e.g., using Snellen eye charts) and a comprehensive ophthalmological examination is carried

out, in which various parameters are checked: visual acuity, degree of anisometropia (unequal vision in the eyes) after measurement of refraction, sensitivity to glare, pupil function, position and mobility of the eyes, intraocular pressure. A biomicroscopic examination of the anterior and middle sections of the eye using a slit lamp is also performed [6,7,11,12]. Various methods are used to quantify the extent of lens opacity, such as Scheimpflug photography (density measurement of lens opacity using a rapidly rotating combination of a slit light and a Scheimpflug camera) or the Lens Opacities Classification System II (focussing a light slit on the lens and comparing the lens density with four standard photographs) [6,11].

In addition to age-related cataract (senile cataract; Latin: cataracta senilis; ICD-10: H25), which occurs in around 90% of all cases, a distinction is made between other forms of cataract: complicated cataract (ICD-10: H26.2; e.g. after uveitis, longstanding retinal detachment), traumatic cataract (ICD-10: H26.1; after injuries to the eye), radiation cataract (ICD-10: H26.8; due to radiation such as infrared radiation or X-rays), cataract associated with systemic diseases (ICD-10: H28; e.g. diabetes mellitus, myotonia), or drug-induced cataract (ICD-10: H26.3; e.g. due to steroids, narcotics) [6,12]. Less than 1 percent of all cataracts are congenital (ICD-10: Q12) [6].

In 2013, the prevalence of cataracts in Germany was around 4.8 million (6% of the total population). Cataracts usually only develop in people over the age of 50 [9,13]. The risk of developing cataracts increases with each decade from the age of 40 [11]. In the 52 to 64 age group, 50% of the population have cataracts without noticing any visual impairment themselves. Among those aged 65 to 75, well over 90% are affected, half of whom notice impaired vision from the age of 75 [9,12,14]. Women are usually affected earlier or more severely by cataracts than men [6,11].

Lifestyle factors, such as smoking and high alcohol consumption, are associated with an increased risk of developing age-related cataracts [7-9,11]. In addition, radiation (e.g. UV light, x-rays), injuries to the eye (e.g. penetration of foreign bodies, bruises) and the use of medication over a longer period of time (e.g. cortisone) can promote the development of cataracts [9,11,15]. Observational studies show that there is a link between diabetes, obesity, or hypertension and an increased risk of developing cataracts [11]. Having a family history of cataracts and myopia are also risk factors [11].

The natural course of the disease can progress quickly or slowly depending on where the lens of the eye is clouded [9]. If left untreated, the patient's visual acuity continuously deteriorates and blindness may result [16,17].

1.2.1 Cataract therapy

The progressive loss of vision can be compensated for temporarily or, in the case of some affected people, even long-term with eyeglasses or contact lenses. There is no drug treatment

for cataracts [9]. [9]. Cataract surgery is the only way to regain the best possible visual acuity for those affected [16]. A therapeutic indication for cataract surgery exists if there are significant cataract-related impairments or risks to the patient's everyday life (professional, private, fitness to drive) or compelling medical reasons (e.g. narrow angle situation, lens swelling after trauma) [18].

The standard procedure in cataract surgery starts by manually opening the cornea and the lens capsule (incision or capsulorhexis). An ultrasound probe is then used to break up and aspirate the clouded lens (phacoemulsification) before a new artificial lens, known as an intraocular lens (IOL), is inserted [11,14,18,19]. The size, shape and position of the capsulorhexis, which is one of the most critical steps in the entire procedure, is controlled by the physician performing the procedure by pulling and grasping the capsular tissue freehand [19].

Cataract surgery takes around 20 minutes [17] and is performed on an outpatient basis, provided there are no medical or social contraindications [18]. The aim of cataract surgery is to improve visual acuity (sharpness of vision) at a distance (distances over 1 metre). Visual acuity is determined using eye charts, whereby the value for visual acuity at a distance can be determined without optical aids (uncorrected distance visual acuity) or with eyeglass correction (corrected distance visual acuity or best-corrected visual acuity) [20]. An improvement in visual acuity can usually be seen just a few hours after surgery. However, it can take several weeks or months to achieve optimal visual acuity. For this reason, eyeglasses should only be refitted after some time. The inserted artificial lens cannot wear out or become cloudy, which is why the visual acuity achieved should not change over the years. In 25 to 40 out of 100 people, however, the remaining lens capsule may become cloudy in the months or years following the operation (secondary cataract), which can impair visual acuity again [9]. Postoperative checks are carried out on the first day after surgery, followed by further checks several times in the first few days and at longer intervals in the following 2 months, depending on how the surgery went, as well as once a year to check for the development of a secondary cataract [12,18].

Cataract surgery is one of the most frequently performed surgical procedures worldwide and its technique has remained essentially unchanged since the introduction of phacoemulsification towards the end of the 1960s [19]; it has only evolved into today's small incision technique with incision widths of 1.4 to 1.6 mm through the implantation of foldable intraocular lenses.

In contrast to the standard procedure, femtosecond laser-assisted cataract surgery (FLACS), which has been in use since 2009, involves the use of a femtosecond laser to make the incision, perform the capsulotomy (opening of the capsule) and fragment the lens [8,11,19]. First, a so-called patient interface is attached to the patient's eye. It ensures a stable connection

between the eye and the optical system, prevents eye movements, and facilitates the precise transmission of laser energy. The physician performing the surgery then uses an imaging system to analyse the anterior segment of the eye and plans the position and depth of the incision so that the artificial lens can be placed correctly. The laser system generates pulses of highly focused infrared light (wavelength 1053 nm) with an ultra-short duration between 10 and 15 femtoseconds. This is how the incisions are made, the lens capsule of the eye is opened and the lens fragmented. The femtosecond laser thus generates continuous, anterior capsule incisions. The higher precision of these capsule incisions compared to the standard procedure is considered a potential advantage. Crushing and softening the lens using the laser is intended to facilitate its liquefaction (emulsification) and removal. Three-dimensional corneal cutting, guided by diagnostic imaging, creates multiplanar, self-sealing incisions, which are intended to increase the safety and efficiency of cataract surgery [19]. To complete the procedure, conventional manual phacoemulsification (liquefaction of the lens using ultrasound, aspiration of the lens and insertion of the artificial lens) is used [8,19]. On average, it takes about 2.5 minutes from the moment the eye is aspirated until the laser application is completed [21].

Currently, five femtosecond laser systems specifically designed for cataract surgery are approved and commercially available around the world (see) [19,22,23]. The individual laser systems differ in terms of their patient interface and imaging system [15,19]. The patient interfaces are disposable products and can be divided into contact (applanating) and non-contact (non-applanating) versions (see Table 1). Most FLACS systems use optical coherence tomography (OCT) as an imaging system. Only the LENSAR system uses 3-dimensional confocal structural illumination (a so-called ray-tracing reconstruction) [19]. Depending on the FLACS system, surgeons can use different fragmentation patterns to reduce the ultrasound energy required to liquefy the lens (phaco energy) [19].

Depending on the type of laser system, the FLACS application can be performed in the same operating theatre where the subsequent phacoemulsification and IOL implantation is performed, or it may require a separate room. If the FLACS system has an integrated bed, for example, it can be used in a separate clean room that does not necessarily have to be sterile. In this case, patients have to be transported between the separate room of the FLACS system and the operating theatre for the subsequent steps of the surgical procedure after the FLACS application [19].

Table 1: Overview of approved and commercially available femtosecond laser systems

Model	Manufacturer/country	Type of patient interface	Imaging system	Integrated bed	Mobile system on castors
CATALYS Precision Laser System	Johnson & Johnson[a]/United States	No contact, liquid optics	OCT	Yes	No
LenSx Laser System	Alcon/United States	Contact, curved lens	OCT	No	No
LenSx Laser System	Lensar/United States	No contact, liquid optics	3D CSI	No	Yes
VICTUS	Bausch & Lomb/United States	No contact, liquid optics	OCT	Yes	No
FEMTO LDV Z8	Ziemer Group/Switzerland	No contact, liquid optics	OCT	No	Yes

[a]: Until 2017: Abbott Medical Optics.
3D CSI: 3-dimensional confocal structural illumination; OCT: optical coherence tomography

The potential benefits of a FLACS system compared to the standard procedure include reduced corneal endothelial loss due to shorter phacoemulsification times and low ultrasound exposure [8,11,19,24,25]. As a result, FLACS application may be gentler and therefore more suitable for patients with corneal endothelial problems, e.g. corneal dystrophy [26]. Corneal incisions can be performed with extreme precision using femtosecond lasers [8,11,19] and the multiplanar, self-sealing incisions are said to promote better wound healing [19]. The capsulotomy performed by the femtosecond laser is precisely centred and highly accurate in terms of diameter, positioning and shape [8,11,15,19,22]. A maximally precise capsulotomy leads to an optimal position of the IOL, which is crucial for visual acuity [26]. Since the centring of the capsulorhexis is particularly important for toric and multifocal intraocular lenses, the precision of FLACS could be important for the implantation of premium intraocular lenses [19]. FLACS could enable reliable capsulotomies in difficult initial situations, e.g. very shallow anterior chamber or advanced cataracts [15].

The potential benefits of a FLACS system are offset by the high costs of purchasing and maintaining the laser (including employing a laser technician) and the additional space required [8,15,26].

1.3 Health services situation

Cataract surgeries in general are among the most frequently performed surgeries. The frequency in Germany is estimated at between 700,000 and 900,000 surgeries per year [17,27-29]. No information is available on the frequency of FLACS use compared to standard cataract surgery.

The costs of standard cataract surgery are covered by statutory health insurance [27,30]. The use of FLACS generally incurs costs that must be borne by the patients themselves [31]. Reimbursement may be possible through private health insurance; however, cost coverage is not guaranteed in this case either. While ophthalmologists often charge for the use of FLACS via the German Medical Fee Schedule (GOÄ) as "intraoperative radiation treatment" (GOÄ No. 5855), private health insurance companies often only accept the billing of a laser surcharge according to GOÄ No. 441, which is associated with significantly lower costs [32]. The issue of FLACS reimbursement by private health insurance companies has led to several court cases in the past, with varying outcomes [33-35].

The acquisition costs of a femtosecond laser for providers amount to several 100,000 euros [36,37]. Devices from various manufacturers with different technical specifications are available in Germany [29] (see Table 1). Formally, physicians with specialist ophthalmology training are not required to undergo any further training for them to be able to offer FLACS. Device-specific training is usually offered by the manufacturers [38].

1.4 Concerns of those proposing the topic

Those proposing the topic report that femtosecond laser-assisted cataract surgery is offered at various sites in Germany. Against this background, they ask whether a new procedure that uses the femtosecond laser to make the incision and fragment the lens might be more accurate and gentler for those affected.

1.5 Testimonials from those affected as an additional source of information

To supplement the introduction to the disorder, IQWiG provides individual testimonials from patients and/or their relatives. The anonymized testimonials can allow insights into how individuals experience the disorder and how they deal with its consequences. In this way, they can help to better understand the perspectives of those affected.

The testimonials summarize interviews and are published on the IQWiG website www.gesundheitsinformation.de. They are not representative, and statements in the testimonials do not constitute IQWiG recommendations.

For more information on the methodology of the testimonials, please refer to IQWiG's methods paper [39].

The testimonials are available at:

https://www.gesundheitsinformation.de/wie-schlecht-meine-augen-waren-habe-ich-erst-nach-der-op-gemerkt.html

2 Research questions

The aims of this investigation are to

- assess the benefit of femtosecond laser-assisted cataract surgery compared to standard cataract surgery in adults with diagnosed cataracts with regard to patient-relevant outcomes,
- determine costs (intervention costs),
- assess cost effectiveness as well as
- review ethical, social, legal, and organizational aspects associated with femtosecond laser-assisted cataract surgery.

3 Methods

This HTA report is prepared on the basis of General Methods 6.1 [39].

3.1 Methods – benefit assessment

The target population of the benefit assessment consisted of adult patients (age ≥ 18 years) with diagnosed cataracts (ICD-10: H25, H26, H28, Q12) in one or both eyes for whom surgical treatment to remove the cataract and insert an intraocular lens is indicated. Femtosecond laser-assisted cataract surgery (FLACS) was the experimental intervention.

Only femtosecond laser systems with market approval were investigated.

These include

- CATALYS Precision Laser System (Johnson & Johnson Vision, United States),
- VICTUS Femtosecond Laser Platform (Bausch & Lomb GmbH, United States),
- LENSAR Laser System (Lensar, United States),
- FEMTO LDV Z8 (Ziemer, Switzerland), and
- LenSx Laser System (Alcon, United States)

Standard cataract surgery (manual incision and capsulorhexis with subsequent phacoemulsification and insertion of an artificial lens) was used as the comparator intervention.

The following patient-relevant outcomes were taken into account in the investigation:

- Morbidity such as
  - (Best) corrected distance visual acuity

  - Uncorrected distance visual acuity
  - Refractive accuracy
- Vision-related quality of life
- Intraoperative complications such as
  - Capsular rupture
  - Vitreous prolapse
- Postoperative complications such as
  - Retinal detachment
  - Infection
  - Posterior capsule opacification
  - Corneal endothelial decompensation
  - Cystoid macular oedema
  - Increased intraocular pressure
- Other non-ocular adverse events (AEs)
- Study discontinuations due to adverse events

Subjective outcomes, e.g. vision-related quality of life, were only considered if they were surveyed using valid measuring instruments, e.g. validated scales.

Endothelial cell count, duration of surgery and patient satisfaction with the treatment were also analysed. However, (greater) benefit could not be derived based on these outcomes alone.

Only randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions regarding the study duration.

In parallel to the preparation of the HTA report protocol, a search for systematic reviews was conducted in the MEDLINE databases (which includes the Cochrane Database of Systematic Reviews) and the HTA database as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

It was ascertained whether at least 1 high-quality, current systematic review existed whose information retrieval was a suitable basis for the assessment (hereinafter: basic SR).

If that was the case, a 2nd step followed, where a supplementary search was conducted for studies for the time period not covered by the basic SR(s). Otherwise, the search for studies was carried out without time restriction.

A systematic literature search for studies was conducted in the following databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials.

In addition, the following information sources and search techniques were taken into account: trial registries, manufacturer queries, the screening of reference lists, documents made available from hearing procedures, and author queries.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables. To assess the qualitative certainty of results, risk of bias criteria across outcomes and outcome-specific risk of bias criteria were assessed, and the risk of bias was rated as high or low in each case. The results of the individual studies were described according to outcomes.

In addition to the comparison of the individual studies' results, metaanalyses and sensitivity analyses were conducted and effect modifiers investigated, provided that the methodological prerequisites had been met.

For each outcome, a conclusion was drawn regarding the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: there was either proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter was the case if either no data were available or the available data did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn.

Subsequently, an assessment of benefit and harm was carried out across outcomes.

To conduct metaanalyses, results from at least 2 studies involving a comparable intervention and control intervention were required for the same outcome with comparable survey instruments. If results for an outcome were surveyed using multiple instruments, the study results were compared taking into account validity, informative value, and comparability. The estimated effects and confidence intervals from the studies were summarized in metaanalyses using forest plots. The calculation was performed using the Cochrane Collaboration Review Manager software, Review Manager 5.4. If the measures of dispersion required for a metaanalysis were not available in the publications, these were supplemented as far as possible using a conservative approach with the largest measure of dispersion for the intervention or control group from the other studies.

3.2 Methods – health economic assessment

To calculate intervention costs, the average resources required directly when performing the experimental and comparator intervention were estimated. For this purpose, in addition to the experimental and comparator interventions, the services directly associated with the intervention were taken into account. For the services provided, wherever possible, the relevant regulated or negotiated prices were applied, e.g. from the database of the Information Centre for Specialized Medicines (IFA), the German Uniform Assessment Standard (Einheitlicher Bewertungsmaßstab, EBM), the Diagnosis-Related-Groups (DRG) catalogue or similar suitable listings from the pension insurance or the Federal Statistical Office. Reimbursable costs were listed separately from non-reimbursable costs.

The systematic overview of health economic studies included searching for cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses in German or English. The systematic literature search was carried out in the MEDLINE and Embase databases and in the HTA database. In addition, the following information sources and search techniques were taken into account: the screening of reference lists, documents made available from hearing procedures, and author queries. The identified references were selected by 1 person, with a 2nd person doing quality assurance. The data extraction into standardized tables as well as the evaluation of the report quality and the assessment of the transferability of the results – both based on predefined criteria – were carried out by one person each. The results of the individual studies were comparatively described as part of the information synthesis.

3.3 Methods – ethical aspects

For the analysis of ethical aspects, scoping searches were conducted in the following information sources:

- Ethics in Medicine (ETHMED)
- Social Sciences Citation Index (SSCI)
- MEDLINE
- Laws, regulations, or guidelines
- Interest-dependent sources of information, e.g. Websites of interest representatives

Additionally, the following documents were checked for potential ethical arguments and aspects:

- Studies included in the benefit assessment
- Studies included in the health economic assessment
- The protocol for documenting the discussion with the surveyed affected people

As an additional source of information, the reflective thoughts method, i.e. reflection informed by the authors' knowledge regarding potential ethical arguments and aspects, was applied [40].

One reviewer screened the sources from all information sources employed for the scoping searches or all other documents for statements on ethical arguments and aspects of the technology to be investigated. A 2nd person assured the quality of the result. The analysis and presentation of results was based on the collection of questions on the ethical domain of the HTA Core Model of the European Network for Health Technology Assessment (EUnetHTA) [41].

3.4 Methods – social, legal, and organizational aspects

For the analysis of social, legal, and organizational aspects, scoping searches were conducted in the following information sources:

- Social Sciences Citation Index (SSCI)
- MEDLINE
- Laws, regulations, or guidelines
- Interest-dependent sources of information, e.g. Websites of interest representatives

Additionally, the following documents were checked for potential social, legal, and/or organizational arguments and aspects:

- Studies included in the benefit assessment
- Studies included in the health economic assessment
- The protocol for documenting the discussion with the surveyed affected people

As an additional source of information, the reflective thoughts method, i.e. reflection informed by the authors' knowledge regarding potential ethical and social arguments and aspects, was applied [40].

One reviewer screened the information from all sources employed in the scoping searches or all other documents for statements on social, legal, and organizational arguments and aspects of the technology to be investigated. A 2nd person assured the quality of the result.

The preparation of information on social aspects was based on the conceptual framework proposed by Mozygemba 2016 [42]; in addition, the checklist from the HTA Core Model of EUnetHTA [41] was examined. The preparation of information on legal aspects was based on the guidelines developed by Brönneke 2016 [43] for identifying legal aspects, while the

information on organizational aspects was based on the grid proposed by Perleth 2014 [44] for assessing the organizational consequences of examination and treatment methods.

3.5 Interviews with affected people

In order to gain an impression of how patients (or their relatives) experience the disease, what treatment experiences they have had, and what they would like from treatment, 5 patients were involved during the preparation of the preliminary HTA report. The interviews were conducted in the form of individual interviews by telephone or web meeting using a structured interview guide (see Section A11 of the full report). The interview recordings were transcribed and processed in tabular form (see section A12 of the full report). The results of the interviews were used to process the ethical, social, legal, and organizational aspects and were incorporated into the cross-domain presentation of results using an extended logical model based on INTEGRATE-HTA [45].

4 Results: Benefit assessment

4.1 Results of the comprehensive information retrieval

No systematic reviews were rated as being current and of high quality, and none were included for the identification of primary studies.

The information retrieval resulted in 36 RCTs relevant for the research question. No planned studies and 9 ongoing studies were identified. Furthermore, 3 completed studies without reported results were found. The author queries about these studies remained unanswered.

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search was conducted on 27 January 2023.

Table 2: Study pool of the benefit assessment

Study	Available documents	
	Full publication (in scientific journals)	**Registry entry / Result report from trial registries**
Bascaran 2018	Yes [46]	Yes [47] / No
Chee 2021	Yes [48]	Yes [49] / No
Conrad-Hengerer 2013	Yes [50]	No
Conrad-Hengerer 2014	Yes [51]	No
Conrad-Hengerer 2015	Yes [52]	No
Donnenfeld 2018	Yes [53]	No
Dzhaber 2020	Yes [54,55]	Yes [56] / No
FACT 2021	Yes [25,57-59]	Yes [60] / No
FEMCAT 2020	Yes [61]	Yes [62] / No
Ferreira 2018	Yes [63]	No
Filkorn 2012	Yes [64]	No
Hansen 2020	Yes [65]	Yes [66] / No
Hida 2014	Yes [67]	No
Kovacs 2014	Yes [68]	No
Kránitz 2012	Yes [69]	No
Krarup 2019	Yes [70]	No
Liu 2021	Yes [71]	Yes [72] / No
Makombo 2016	Yes [73]	No
Mastropasqua 2014a	Yes [74]	No
Mastropasqua 2014b	Yes [75]	No
Mursch-Edlmayr 2017	Yes [76]	No
Nagy 2011	Yes [77]	No
Nagy 2014	Yes [78]	No
NCT01069172 2014	No	Yes [79] / No
NCT02403206 2018	No	Yes [80] / No
Oka 2021	Yes [81]	Yes [82] / No
Pajic 2017	Yes [83]	Yes [84] / No
Reddy 2013	Yes [85]	Yes [86] / No
Roberts 2019	Yes [87-89]	Yes [90] / No
Schargus 2015	Yes [91]	No
Schargus 2020	Yes [92]	Yes [93] / No
Schröter 2021	Yes [94]	No
Takács 2012	Yes [95]	No
Vasavada 2019	Yes [96]	Yes [97] / No
Vasavada 2023	Yes [98]	Yes [99] /No
Yu 2015	Yes [100]	Yes [101] / No

4.2 Characteristics of the studies included in the assessment

All 36 included RCTs investigated FLACS compared to standard manual cataract surgery, with 25 RCTs having a parallel study design, while 11 RCTs were intra-individual studies in which one eye of a patient was randomly assigned to the FLACS group and the other eye to the control group with standard cataract surgery. The following different laser systems were used in the RCTs.

- 16 RCTs investigated the Alcon LenSx Laser System [55,64,65,67-69,73,74,77,78,80,81,88,95,96,98]
- 9 RCTs investigated the Johnson & Johnson CATALYS Precision Laser System [50-53,61,63,79,91,92]
- 4 RCTs investigated the Bausch & Lomb VICTUS Laser Platform [46,48,76,85]
- 3 RCTs investigated Ziemer FEMTO LDV Z8 Laser System [71,83,94]
- 2 RCTs investigated the LENSAR Laser System [70,100]
- 1 RCT investigated the LenSx Laser System and the LENSAR Laser System in 2 intervention groups [75]
- 1 RCT investigated the CATALYS Precision Laser System or the Ziemer FEMTO LDV Z8 Laser System depending on the study centre [58]

In 19 RCTs, corneal incisions were performed manually in the FLACS groups, and in a further 16 RCTs they were performed using a laser. 1 RCT (Mastropasqua 2014b [75]) had 2 intervention groups with FLACS that differed both in the laser system used and in the way the corneal incisions were performed. In all RCTs, capsulotomy and lens fragmentation were performed by laser in the FLACS groups. In the control groups of the RCTs, these steps were performed manually by the surgeon in accordance with standard cataract surgery. All further steps of cataract surgery (phacoemulsification and insertion of the artificial lens) were performed manually in all study groups.

A total of 7268 eyes from 5589 patients were included in the 36 RCTs. The number of participants in the individual RCTs ranged from 34 to 907.

Nine RCTs included only patients with age-related cataracts, 1 RCT (NCT02403206 2018 [80]) included only patients with white intumescent cataracts – a form of cataract with liquefaction of the cortex and a sometimes hard nucleus. None of the other 26 RCTs imposed any restrictions regarding the type of cataract. The mean age of the study participants was between 57 and 73 years. Patients of all sexes were included in the studies, with the proportion of women ranging from 26% to 92%. The severity of the cataract, where reported, was indicated using the Lens Opacities Classification System III (LOCS III) and was mostly grade

2 to 3. People with other eye disorders were mostly excluded from the studies. Only 1 RCT (FACT 2021 [58]) stated that around 35% of participants had other eye disorders in addition to cataracts. Follow-up duration in the included RCTs ranged mostly from 1 to 18 months. Four RCTs only reported results obtained immediately after the procedure.

4.3 Overview of patient-relevant outcomes

From 35 studies, it was possible to extract data on patient-relevant outcomes. One RCT (Kovács 2014 [68]) reported only postoperative complications (posterior capsule opacification) but the results were presented in a form that was not usable for the benefit assessment. Table 3 presents an overview of the data available on patient-relevant outcomes from the included studies. Results on the outcome of visual acuity, determined using eye charts and presented as uncorrected distance visual acuity, and/or on the outcome of (best) corrected distance visual acuity, were reported in 24 of the 36 RCTs; in 2 further studies (Bascaran 2018 [46], Conrad-Hengerer 2013 [50]) no results were reported despite a planned survey. Results on the outcome of refractive accuracy (dioptres) were reported in 16 of the 36 RCTs, although these were not usable for the benefit assessment in 2 studies (Kránitz 2012 [69], Vasavada 2023 [98]). In Bascaran 2018 [46] and Pajic 2017 [83], no results on refractive accuracy were reported despite a planned survey. Two RCTs (FACT 2021 [58], Roberts 2019 [88]) reported results on vision-related quality of life and general quality of life that could be used for the benefit assessment. In a 3rd RCT (FEMCAT 2020 [61]), the vision-related quality of life was defined as a secondary outcome, however, no results usable for the benefit assessment were reported. Results on the outcome of intraoperative complications were reported in 17 of the 36 RCTs. In addition to information on the total number of patients with intraoperative complications, some RCTs primarily reported results on anterior or posterior capsular ruptures and vitreous prolapses. Results on the outcome of postoperative complications were reported in 25 of the 36 RCTs, but these were not usable for the benefit assessment in 2 RCTs (Chee 2021 [48], Kovács 2014 [68]). Results on (serious) adverse events in general were reported in 4 RCTs as part of the trial registry entries. No data are available on study discontinuations due to adverse events. Table 3 below provides an overview of the patient-relevant outcomes in the individual RCTs.

Table 3: Matrix of patient-relevant outcomes

Study	Outcomes															
	Morbidity			QoL	Intraoperative complications			Postoperative complications							Adverse events	
	(Best) corrected distance visual acuity	Uncorrected distance visual acuity	Refractive accuracy	Vision-related quality of life	Capsular rupture	Vitreous prolapse	Other intraoperative complication	Retinal detachment	Posterior capsule opacification	Corneal endothelial decompensation	Macular/corneal oedema	Increased intraocular pressure	Infections	Other postoperative complications	Study discontinuations due to AEs	Other non-ocular (serious) AEs
Bascaran 2018	x	x	x	–	●	–	●	–	–	–	–	–	–	●	–	–
Chee 2021	●	–	–	–	●	–	●	–	–	–	–	–	–	○	–	–
Conrad-Hengerer 2013	X	–	–	–	●	–	●	–	–	–	●		–	–	–	–
Conrad-Hengerer 2014	–	–	–	–	–	–	●	–	–	–	●	●	–	–	–	–
Conrad-Hengerer 2015	●	●	●	–	●	–	●	–	–	–	●	●	–	–	–	–
Donnenfeld 2018	●	●	●	–	–	–	–	–	–	–	–	–	–	–	–	–
Dzhaber 2020	●	●	●	–	●	–	●	●	–	–	●	–	●	●	–	–
FACT 2021	●	●	●	●	●	●	●	●	●	–	●	–	●	●	–	–
FEMCAT 2020	●	●	●	○	●	●	–	●	–	–	●	–	●	●	–	–

Study	Outcomes															
	Morbidity			QoL	Intraoperative complications			Postoperative complications							Adverse events	
	(Best) corrected distance visual acuity	Uncorrected distance visual acuity	Refractive accuracy	Vision-related quality of life	Capsular rupture	Vitreous prolapse	Other intraoperative complication	Retinal detachment	Posterior capsule opacification	Corneal endothelial decompensation	Macular/corneal oedema	Increased intraocular pressure	Infections	Other postoperative complications	Study discontinuations due to AEs	Other non-ocular (serious) AEs
Ferreira 2018	–	–	–	–	–	–	–	–	–	–	–	–	–	●	–	–
Filkorn 2012	●	–	●	–	–	–	–	–	–	–	–	–	–	–	–	–
Hansen 2020	●	●	–	–	●	●	–	–	–	–	●	–	–	–	–	–
Hida 2014	–	–	●	–		–	●	–	–	–	–	–	–	–	–	–
Kovács 2014	–	–	–	–	–	–	–	–	○	–	–	–	–	–	–	–
Kránitz 2012	●	●	○	–	–	–	–	–	–	–	–	–	–	–	–	–
Krarup 2019	●	●	●	–	●	–	●	●	–	–	–	–	–	●	–	–
Liu 2021	●	●	●	–	–	–	●	–	●	–	●	x	–	–	–	–
Makombo 2016	●	●	–	–	–	–	–	–	–	–	–	–	–	●	–	–
Mastropasqua 2014a	●	●	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Mastropasqua 2014b	●	●	●	–	–	–	●	–	–	–	–	–	–	●	–	–

Study	Outcomes															
	Morbidity			QoL	Intraoperative complications			Postoperative complications							Adverse events	
	(Best) corrected distance visual acuity	Uncorrected distance visual acuity	Refractive accuracy	Vision-related quality of life	Capsular rupture	Vitreous prolapse	Other intraoperative complication	Retinal detachment	Posterior capsule opacification	Corneal endothelial decompensation	Macular/corneal oedema	Increased intraocular pressure	Infections	Other postoperative complications	Study discontinuations due to AEs	Other non-ocular (serious) AEs
Mursch-Edlmayr 2017	●	–	–	–	●	–	●	–	–	–	–	–	–	●	–	–
Nagy 2011	–	–	●	–	–	–	●	–	–	–	–	–	–	●	–	–
Nagy 2014	–	–	–	–	–	–	●	–	–	–	–	–	–	●	–	–
NCT01069172 2014	–	–	–	–	–	–	●	–	–	–	–	●	–	●	–	●
NCT02403206 2018	–	–	–	–	●	●	●	●	–	–	–	●	–	●	–	●
Oka 2021	●	–	–	–	–	–	●	–	●	–	●	–	–	●	–	●
Pajic 2017	●	x	x	–	–	–	●	–	–	–	●	●	–	–	–	●
Reddy 2013	–	–	–	–	●	–	●	–	–	–	–	–	–	–	–	–
Roberts 2019	●	●	●	●	●	●	●	–	●	–	–	–	–	●	–	–
Schargus 2015	●	–	–		●	–	–	–	–	–	●	●	–	●	–	–
Schargus 2020	●	–	–	–	–	–	●	–	–	–	–	–	–	●	–	–
Schröter 2021	●	–	●	–	–	–	–	–	–	–	–	–	–	–	–	x

Study	Outcomes															
	Morbidity			QoL	Intraoperative complications			Postoperative complications							Adverse events	
	(Best) corrected distance visual acuity	Uncorrected distance visual acuity	Refractive accuracy	Vision-related quality of life	Capsular rupture	Vitreous prolapse	Other intraoperative complication	Retinal detachment	Posterior capsule opacification	Corneal endothelial decompensation	Macular/corneal oedema	Increased intraocular pressure	Infections	Other postoperative complications	Study discontinuations due to AEs	Other non-ocular (serious) AEs
Takács 2012	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Vasavada 2019	○	●	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Vasavada 2023	●	●	○	–	–	–	●	–	–	–	–	–	–	–	–	–
Yu 2015	●	–	●	–	●	–	●	–	●	–	–	●	–	●	–	–

●: Data were reported and usable.
○: Data were reported but unusable for the benefit assessment.
x: Data were not reported despite the collection of these data being pre-specified.
-: No data were reported (no further information). / The outcome was not surveyed.

AE: adverse event; QoL: health-related quality of life

4.4 Assessment of the risk of bias of the results

The risk of bias was rated as low across outcomes for 6 studies (Chee 2021, Dzaber 2020, FACT 2021, FEMCAT 2020, Roberts 2019, Vasavada 2023) and high for the remaining 30 studies. The high risk of bias assessment was based in most cases on an unclear description of the randomization method and/or masking of group allocation, in addition, in the majority of studies, it remained unclear whether reporting was independent of the results, as no study protocol was available. In 33 out of 36 studies, the participants were not blinded in terms of the intervention.

In 5 studies with low risk of bias across outcomes, the outcome-specific risk of bias for the following patient-relevant outcomes was also assessed as low: visual acuity, refractive accuracy, intraoperative and postoperative complications in FACT 2021, FEMCAT 2020 and Roberts 2019, visual acuity, intraoperative and postoperative complications in Chee 2021, and visual acuity and intraoperative complications in Vasavada 2023. The outcome-specific risk of bias for the results on visual acuity, refractive accuracy, intraoperative and postoperative complications was assessed as high for the Dzaber 2020 study, as the intention-to-treat (ITT) principle was not adequately implemented. The outcome-specific risk of bias for the results on vision-related quality of life was assessed as high for the FACT 2021 and Roberts 2019 studies, as the outcome scorers were not blinded and subjectivity of the outcome assessment cannot be ruled out.

4.5 Results on patient-relevant outcomes

Table 4 below provides a preliminary summarized overview of the effects reported for each patient-relevant outcome in the 36 included studies. The results for the patient-relevant outcomes are presented descriptively below in sections 4.5.1 to 4.5.6. Detailed results are presented in the appendix in Section A3.3 of the full report.

Table 4: Overview of effects with regard to patient-relevant outcomes at the individual study level

Study	Outcomes															
	Morbidity			QoL	Intraoperative complications			Postoperative complications							AEs	
	(Best) corrected distance visual acuity	Uncorrected distance visual acuity	Refractive accuracy	Vision-related quality of life	Capsular rupture	Vitreous prolapse	Other intraoperative complication	Retinal detachment	Posterior capsule opacification	Corneal endothelial decompensation	Macular/corneal oedema	Increased intraocular pressure	Infections	Other postoperative complications	Study discontinuations due to AEs	Other non-ocular (serious) AEs
Bascaran 2018	x	x	x	–	↔	–	↔	–	–	–	–	–	–	↔	–	–
Chee 2021	↔	–	–	–	↔	–	↔	–	–	–	–	–	–	○	–	–
Conrad-Hengerer 2013	x	–	–	–	↔	–	↔	–	–	–	↔	↔	–	–	–	–
Conrad-Hengerer 2014	–	–	–	–	–	–	↔	–	–	–	↔	↔	–	–	–	–
Conrad-Hengerer 2015	↔	↔	↔	–	↔	–	↔	–	–	–	↔	↔	–	–	–	–
Donnenfeld 2018	↔	↔	↔	–	–	–	–	–	–	–	–	–	–	–	–	–
Dzhaber 2020	↔	↔	↔	–	↔		↔	↔		–	↔	–	↔	↔	–	–
FACT 2021	↔	↔	↔	↔	↔	↔	↔	↔	↔	–	↔	–	↔	↔	–	–
FEMCAT 2020	↔	↔	↔	○	↔	↔	–	↔	–	–	↔	–	↔	↔	–	–
Ferreira 2018	–	–	–	–	–	–	–	–	–	–	–	–	–	↔	–	–
Filkorn 2012	↔	–	↔	–	–	–	–	–	–	–	–	–	–	–	–	–
Hansen 2020	↔	↔	–	–	↗	↔	–	–	–	–	↔	–	–	–	–	–
Hida 2014	–	–	↔	–	–	–	↔	–	–	–	–	–	–	–	–	–
Kovacs 2014	–	–	–	–	–	–	–	–	○	–	–	–	–	–	–	–
Kránitz 2012	↑	↔	○	–	–	–	–	–	–	–	–	–	–	–	–	–
Krarup 2019	↔	↔	↔	–	↔	–	↔	↔	–	–	–	–	–	↔	–	–

Study	Outcomes															
	Morbidity			QoL	Intraoperative complications			Postoperative complications							AEs	
	(Best) corrected distance visual acuity	Uncorrected distance visual acuity	Refractive accuracy	Vision-related quality of life	Capsular rupture	Vitreous prolapse	Other intraoperative complication	Retinal detachment	Posterior capsule opacification	Corneal endothelial decompensation	Macular/corneal oedema	Increased intraocular pressure	Infections	Other postoperative complications	Study discontinuations due to AEs	Other non-ocular (serious) AEs
Liu 2021	↕	↕	↕	–	–	–	↕	–	↕	–	↕	x	–	–	–	–
Makombo 2016	↕	↕	–	–	–	–	–	–	–	–	–	–	–	↕	–	–
Mastropasqua 2014a	↕	↕	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Mastropasqua 2014b	↕	↕	↑	–	–	–	↕	–	–	–	–	–	–	↕	–	–
Mursch-Edlmayr 2017	↕	–	–	–	↕	–	↕	–	–	–	–	–	–	↑[a]	–	–
Nagy 2011	–	–	↕	–	–	–	↕	–	–	–	–	–	–	↕	–	–
Nagy 2014	–	–	–	–	–	–	↕	–	–	–	–	–	–	↕	–	–
NCT01069172 2014	–	–	–	–	–	–	↕	–	–	–	–	↘	–	↕	–	↕
NCT02403206 2018	–	–	–	–	↕	↕	↕	↕	–	–	–	↕	–	↕	–	↕
Oka 2021	↕	–	–	–	–	–	↕	–	↕	–	↕	–	–	↕	–	↕
Pajic 2017	↕	x	x	–	–	–	↕	–	–	–	↕	↕	–	–	–	↕
Reddy 2013	–	–	–	–	↕	–	↘	–	–	–	–	–	–	–	–	–
Roberts 2019	↕	↕	↕	↕	↕	↕	↕	–	↕	–	–	–	–	↕	–	–
Schargus 2015	↕	–	–	–	↕	–	–	–	–	–	↕	↕	–	↕	–	–
Schargus 2020	↕	–	–	–	–	–	↕	–	–	–	–	–	–	↕	–	–
Schröter 2021	↕	–	↕	–	–	–	–	–	–	–	–	–	–	–	–	x
Takács 2012	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Vasavada 2019	o	↕	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Study	Outcomes														
	Morbidity			QoL	Intraoperative complications			Postoperative complications						AEs	
	(Best) corrected distance visual acuity	Uncorrected distance visual acuity	Refractive accuracy	Vision-related quality of life	Capsular rupture	Vitreous prolapse	Other intraoperative complication	Retinal detachment	Posterior capsule opacification	Corneal endothelial decompensation	Macular/corneal oedema	Increased intraocular pressure	Infections	Other postoperative complications	Study discontinuations due to AEs	Other non-ocular (serious) AEs
Vasavada 2023	↔	↔	○	–	–	–	↔	–	–	–	–	–	–	–	–	–
Yu 2015	↔	–	↑	–	↔	–	↔	–	↔	–	–	↔	–	↔	–	–

↑: Statistically significant effect in favour of the intervention.
↓: Statistically significant effect in favour of the control.
↗: Numerical notable difference in favour of the intervention without indication of significance.
↘: Numerical notable difference in favour of the control without indication of significance.
↔: No statistically significant difference.
○ Data were reported but not usable for the benefit assessment.
x: Data were not reported despite the collection of these data being pre-specified.
-: No data reported.

a: Subconjunctival haemorrhages.
AE: adverse event; QoL: health-related quality of life

4.5.1 Results on visual acuity – (best) corrected distance visual acuity, uncorrected distance visual acuity

In all RCTs with reported results, both FLACS and standard cataract surgery led to a statistically significant and clinically relevant improvement in visual acuity.

In 23 RCTs, results on (best)corrected distance visual acuity were reported that could be used for the benefit assessment. Metaanalyses after 1 month (logMAR: -0.0; 95% CI [-0.1; 0.0]; p = 0.22; number of eyes evaluated (A) = 2213) and after 3 months (logMAR: 0.00; 95% CI [-0.01; 0.01]; p = 0.43; A = 3048) revealed no statistically significant differences in (best) corrected distance visual acuity between FLACS and standard manual cataract surgery. However, a metaanalysis of the study results after ≥ 6 months showed a very small statistically

significant advantage for FLACS compared to standard cataract surgery (logMAR: -0.01; 95% CI [-0.02; -0.0]; p = 0.03; A = 1940), which is not perceptible for the patients (relevant change for values ≥ 0.1 logMAR). A relevance assessment (Hedges' g) resulted in a standardized mean difference (SMD) of -0.12; 95% CI [-0.21; -0.03]. Since the confidence interval (CI) was not outside the irrelevance range of −0.2 to 0.2, it cannot be inferred that the effect is relevant.

Results on uncorrected distance visual acuity were reported in 15 RCTs. Here, metaanalyses after 1 month (logMAR: -0.02; 95%-CI [-0.04; 0.01]; p = 0.22; A = 1892), after 3 months (logMAR: -0.00; 95%-CI [-0.02; 0.01]; p = 0.75; A = 2718) and also after ≥ 6 months (logMAR: -0.04; 95%-CI [-0.10; 0.02]; p = 0.21; A = 1562) showed no statistically significant differences between FLACS and standard manual cataract surgery.

For the (best) corrected distance visual acuity after a follow-up period of 6 months or more, despite a statistically significant difference in the metaanalysis, due to the lack of relevance, there is no hint, indication, or proof of an added benefit of FLACS compared to standard cataract surgery. For the (best) corrected distance visual acuity at earlier measurement points as well as for the uncorrected distance visual acuity at all measurement points, there is also no hint, indication, or proof of an added benefit of FLACS compared to standard manual cataract surgery.

Overall, for the outcome of visual acuity, there is also no hint, indication, or proof of an added benefit of FLACS compared to standard manual cataract surgery.

4.5.2 Results on refractive accuracy

In all RCTs with reported results, both FLACS and standard cataract surgery led to a statistically significant and clinically relevant improvement in refraction. In 8 RCTs, results on the absolute error of the spherical equivalent, i.e. the deviation from the targeted refractive outcome in dioptres, were reported that could be used for the benefit assessment. Metaanalyses after 1 month (-0.05 dioptres; 95% CI [-0.11; -0.00]; p = 0.05; A = 905) and after ≥ 3 months (-0.07 dioptres; 95% CI [-0.19; 0.04]; p = 0.22; A = 1980) revealed no statistically significant differences in absolute error between FLACS and standard manual cataract surgery. 4 RCTs also reported the proportion of patients with a deviation of ± 0.5 or ± 1.0 dioptres from the desired refractive target value. Here, the respective metaanalysis showed no statistically significant difference in the proportion of patients at the end of each study (± 0.5 dioptres: RR: 1.00; 95% CI [0.96; 1.05]; p = 0.85; A = 2215 or ± 1.0 dioptres: RR: 0.98; 95% CI [0.96; 1.00]; p = 0.13; A = 2215). In addition, 10 RCTs provided results on the spherical equivalent (dioptres) at the end of the study. Here, 1 RCT (Mastropasqua 2014b) reported a statistically significant lower number of dioptres in the two FLACS groups compared to the group with standard cataract surgery. All other RCTs reported no statistically significant differences in spherical equivalent between the study groups.

Overall, for the outcome of refractive accuracy, there is no hint, indication, or proof of an added benefit of FLACS compared to standard manual cataract surgery.

4.5.3 Results on vision-related quality of life

Results on vision-related quality of life were reported in 3 RCTs (FACT 2021, FEMCAT 2020 and Roberts 2019), whereby only the data from 2 RCTs were usable for the benefit assessment. In both RCTs, there were statistically significant improvements in vision-related quality of life in both study groups over the course of the study. However, there was no statistically significant difference between FLACS and standard cataract surgery after 1 month (Roberts 2019) or after 3 and 12 months (FACT 2021) in the cataract-specific quality of life recorded with the Cat-PROM5 or Catquest-9-SF questionnaire. In the FEMCAT 2020 study, it was only reported that cataract surgery led to a relevant improvement in vision-related quality of life – recorded with the Visual Function 14 questionnaire – in both study groups after 3 and 12 months, but with no difference between the two techniques (FLACS versus standard cataract surgery). In addition to the vision-related quality of life, the general quality of life was also recorded in 2 RCTs using the EQ-5D-3L questionnaire. In both studies, there was a slight improvement in quality of life in both the FLACS and standard manual cataract surgery groups over the course of the study, although there was no data on statistical significance. A metaanalysis of the group difference after 12 months showed no difference between FLACS and standard cataract surgery (0.01 points; 95% CI [-0.01; 0.03), p = 0.16; A = 851).

Overall, for the outcome of vision-related quality of life, there is no hint, indication, or proof of an added benefit of FLACS compared to standard manual cataract surgery.

4.5.4 Results on intraoperative complications

Data on intraoperative complications are available from a total of 25 studies. They included either details about individual complications, such as capsular rupture or vitreous prolapse, and/or about the total number of intraoperative complications. Four RCTs explicitly reported serious intraoperative complications as part of the SAE recording. Of these, two RCTs (Oka 2021, Pajic 2017) found no serious intraoperative complications. The other two studies (NCT01069172 2014, NCT02403206 2018) reported individual serious intraoperative complications, but there was no difference between FLACS and standard cataract surgery. Overall, intraoperative complications were rare in most RCTs in all study groups (0 to 5%). Only one RCT (Reddy 2013) showed a higher incidence of mild intraoperative complications (29%). There were no differences between FLACS and standard cataract surgery either in individual specific complications or in the total number of intraoperative complications. Metaanalyses on capsular rupture (RR: 0.82; 95% CI [0.53; 1.27]; p = 0.38; A = 4333) or on all intraoperative complications (RR: 0.91; 95% CI [0.45; 1.85]; p = 0.79; A = 3231) showed no statistically significant group differences.

Overall, for the outcome of intraoperative complications, there is no hint, indication, or proof of greater harm from FLACS compared to standard manual cataract surgery.

4.5.5 Results on postoperative complications

Data on postoperative complications that are usable for the benefit assessment are available from a total of 24 studies. They included either details about individual complications, such as macular/corneal oedema, increased intraocular pressure or posterior capsule opacification, and/or the total number of postoperative complications. Four RCTs explicitly reported serious postoperative complications as part of the SAE recording. Of these, two RCTs (Oka 2021, Pajic 2017) found no serious postoperative complications. The other two studies (NCT01069172 2014, NCT02403206 2018) reported individual serious postoperative complications, but there was no difference between FLACS and standard cataract surgery. The rates of postoperative complications in the individual RCTs ranged from 0 to about 30%. Short-term minor subconjunctival haemorrhages were reported in 4 RCTs and occurred more frequently with FLACS than with standard cataract surgery (14% versus 1%). However, there were no differences between FLACS and standard cataract surgery with regard to any other specific complications reported and the total number of postoperative complications. A metaanalysis of all postoperative complications during the course of the study revealed no statistically significant group difference (RR: 0.94; 95% CI [0.41; 2.16]; p = 0.89; A = 1941) There was also no statistically significant difference between FLACS and standard cataract surgery for surgically induced astigmatism, a problem caused by the healing process of the incisions made during cataract surgery.

Overall, for the outcome of postoperative complications, there is no hint, indication, or proof of greater or lesser harm from FLACS compared to standard manual cataract surgery.

4.5.6 Results on other non-ocular adverse events

Results on (serious) non-ocular AEs were reported in 4 RCTs as part of the trial registry entries. In 2 RCTs (NCT01069172 2014, Pajic 2017), no non-ocular SAEs occurred during the course of the study. In 1 study (NCT02403206 2018), there was 1 myocardial infarction in the FLACS group but no SAEs in the standard cataract surgery group. In Oka 2021 with crossover design, 2 SAEs (epilepsy and chondrocalcinosis) were reported during the course of the study. One non-serious non-ocular AE (herpes zoster and hypertensive episode respectively) was reported in each of 2 RCTs (Oka 2021, Pajic 2017). None of the included RCTs contained information on study discontinuations due to AEs

Overall, for the outcome of non-ocular adverse events, there is no hint, indication, or proof of greater or lesser harm from FLACS compared to standard manual cataract surgery.

4.6 Results on other reported outcomes

In 18 RCTs, the change in endothelial cell count as a result of the procedure was included as an outcome because one potential advantage of FLACS compared to standard cataract surgery may be less corneal endothelial loss due to shorter phacoemulsification times and low ultrasound exposure. However, 11 of the 18 RCTs showed no statistically significant difference in endothelial cell loss between FLACS and standard cataract surgery at the end of each study. In 6 RCTs (Chee 2021, Conrad-Hengener 2013, Krarup 2019, Liu 2021, Takacs 2012, Vasavada 2023), endothelial cell loss was statistically significantly lower in the FLACS group than in the control group during the course of the study, while in 1 RCT (FEMCAT 2020) it was statistically significantly higher in the FLACS group than in the control group. The duration of phacoemulsification was assessed in 9 RCTs, with no overall difference found between the surgical procedures. Detailed results on other reported outcomes are presented in the appendix in Section A3.4 of the full report.

4.7 Overall evaluation of results

4.7.1 Evidence map

The following Table 5 shows the evidence map regarding patient-relevant outcomes.

Table 5: Evidence map regarding patient-relevant outcomes

Patients with cataracts	Outcomes																
	Morbidity			QoL	Intraoperative complications			Postoperative complications								Adverse events	
	Visual acuity		Refractive accuracy	Vision-related quality of life	Capsular rupture	Vitreous prolapse	Other intraoperative complication	Retinal detachment	Posterior capsule opacification	Corneal endothelial decompensation	Macular/corneal oedema	Increased intraocular pressure	Infections	Other postoperative complications	Study discontinuations due to AEs	Other non-ocular (serious) AEs
	(Best) corrected distance visual acuity	Uncorrected distance visual acuity														
FLACS vs. standard manual cataract surgery	⇔		⇔	⇔	⇔	⇔	⇔	⇔	⇔	–	⇔	⇔	⇔	⇔	–	⇔
	⇔	⇔														

⇗: Hint of (greater) benefit or hint of lesser harm.
⇔: No hint, indication, or proof; homogeneous result.
-: No data reported.

AE: adverse event; FLACS: femtosecond laser-assisted cataract surgery; QoL: health-related quality of life; vs: versus

4.7.2 Assessment of the volume of unpublished data

For the comparison of FLACS versus standard manual cataract surgery, 12 RCTs with unpublished data were identified. These are 3 completed RCTs without publication or without information on study results in the trial registry and 9 ongoing studies (see Section A3.1.4 of the full report) Author queries for the 3 completed studies with 136, 132 and 71 participants respectively remained unanswered. However, due to the large number of RCTs already published and patients examined in these studies, the lack of data is not expected to have a decisive influence on the certainty of conclusions regarding the comparison of FLACS versus standard cataract surgery. It is also not assumed that the results of the ongoing studies will significantly influence the current benefit conclusion. Overall, this does not result in any restriction of the currently available certainty of conclusions regarding the comparison between FLACS and standard cataract surgery.

4.7.3 Weighing of benefits versus harms

A total of 36 RCTs with 5589 patients were included for the comparison between FLACS and standard manual cataract surgery, whereby results from 35 studies with 5510 patients could be used for the benefit assessment. In all RCTs, both FLACS and standard manual cataract surgery achieved statistically significant and clinically relevant improvements in the visual acuity of patients with cataracts. Intraoperative and postoperative complications were rare in both groups in all studies. In the comparison between the groups, however, there was no hint, indication, or proof of an added benefit of FLACS compared to standard manual cataract surgery for any of the outcomes surveyed (visual acuity, refractive accuracy, vision-related quality of life). At the same time, with regard to intraoperative or postoperative complications, such as capsular rupture, vitreous prolapse or macular/corneal oedema, there is no proof, indication, or hint of lesser or greater damage from FLACS compared to standard manual cataract surgery.

5 Results: Health economic evaluation

5.1 Intervention costs

Cataract surgery is usually performed on an outpatient basis. While standard cataract surgery is covered by statutory health insurance, surgery with the femtosecond laser incurs (additional) costs that must be borne by the private individual and are generally not reimbursable. In consultation with various medical experts, attempts were made to identify the average resource consumption and costs of the two processes via a list of potential procedure codes according to the German Uniform Assessment Standard (Einheitlicher Bewertungsmaßstab, EBM) and the German Medical Fee Schedule (Gebührenordnung für Ärzte, GOÄ). It proved challenging to provide a complete overview of the typical or average billable procedure codes, so the results are intended primarily for guidance. However, there

is also a range of costs because different increase factors can be applied in the case of billing according to GOÄ and the billing of material costs is sometimes defined differently depending on the health insurance agreements or cannot be easily quantified. Overall, with all these uncertainties, the research results in a total cost of around €700 to €2100 (plus material costs) for FLACS and around €900 to €1000 for standard cataract surgery.

In the two health-economic evaluations (FACT 2021, FEMCAT 2020; see Section 5.2), the costs of the two cataract operations in the British (FACT) and French (FEMCAT) health care systems were calculated using a microcosting approach. In the FEMCAT study (university hospital setting), the costs were €1260 (standard deviation [SD]: €182) for FLACS and €636 (SD: €69) for standard surgery.[2] In the FACT study (day clinic setting), the costs were €482 (SD: €208) for FLACS and €232 (SD: €151) for standard surgery.[3] In absolute terms, this shows noticeable cost differences between the health care systems and a varying degree of dispersion, which may also be due to the different settings. However, what all costs have in common – both for the two studies and for Germany – is that FLACS is significantly more expensive than the standard procedure, whereby the cost difference can easily amount to 2 times the standard costs.

5.2 Systematic review of health economic evaluations

5.2.1 Results of the information retrieval

The various research steps identified a total of 2 relevant studies: FACT 2021 [57,58,102], and FEMCAT 2020 [61]. The search strategies for bibliographic databases are found in the appendix.

Table 6: Study pool of the health economic assessment

Study	Available documents [reference]
FACT 2021	Hunter 2019 [102] (study protocol) Day 2020 [57] Day 2021 [58]
FEMCAT 2020	Schweitzer 2020 [61]

5.2.2 Characteristics of the studies included in the assessment

Both studies are accompanying health economic evaluations (the associated RCTs are included in the study pool for the benefit assessment). In each case, they compare FLACS with standard

[2] See Schweitzer 2020 [61], Supplementary Appendix Table S4, figures adjusted for inflation to the year 2022 and rounded to whole €.

[3] See Day 2021 [58], Table 11, figures currency-converted and inflation-adjusted to the year 2022 and rounded to whole €.

cataract surgery; in the FEMCAT study, a sham laser procedure is also used for this group. Both studies were commissioned by the public sector and lasted 12 months. FACT was carried out in 3 large day clinics, while FEMCAT was carried out in 5 university clinics. FEMCAT is a cost-effectiveness analysis that calculates the incremental costs per additional patient with successful treatment from the perspective of the public payers in the health care system as an outcome. FACT is a cost-utility analysis that calculates the incremental costs per QALY gained by the intervention as an outcome, also from the perspective of the public payers in the health care system, whereby here the costs are also considered from the perspective of society in a scenario analysis.

5.2.3 Results of health economic evaluations

The FEMCAT study concludes that the total costs for FLACS were slightly higher than for standard cataract surgery, while at the same time the number of patients with successful treatment was slightly lower. This result does not change in the univariate sensitivity analyses, in which individual cost parameters were varied[4]. The probabilistic sensitivity analysis also arrives at a probability of (only) 7% that FLACS is to be seen as a cost-effective intervention – assuming a willingness to pay €16,750 per patient with successful treatment[5].

The FACT study calculates costs of around €220,000[6] per additional QALY gained from the payer perspective if FLACS is performed instead of the standard operation. In the calculations, FLACS is therefore not only slightly more expensive in terms of total costs, but also results in a slightly higher gain in QALYs. In 2 of the 3 univariate sensitivity analyses (variation in the benefit parameters[7]), however, the result is reversed and standard cataract surgery becomes dominant again. However, when using 2 operating theatres (instead of 1) with FLACS, the cost-benefit ratio drops to around € 200,000[8]. Assuming a willingness to pay of €40,000;[9] per QALY, the probabilistic sensitivity analysis indicates a 30% probability that FLACS is actually cost-effective.

In the scenario analysis including the societal perspective, however, the team of authors of the FACT study calculates a result in which FLACS is actually cost-effective with a significantly higher probability of 86%. This is largely due to the results of a survey of the study participants, asking how much unpaid help they had to accept from family and friends in the last 3 or 6

[4] For details see Table 50 in the full report.

[5] This willingness to pay was assumed by the team of authors of the study on the basis of the estimated maximum amount (based on the French medical reimbursement schedule) for the treatment of a serious perioperative ophthalmological complication.

[6] Currency-converted and inflation-adjusted to the year 2022, rounded to €1000.

[7] For details see Table 50 in the full report.

[8] Currency-converted and inflation-adjusted to the year 2022, rounded to €1000.

[9] Currency-converted and inflation-adjusted to the year 2022, rounded to €1000.

months (depending on the follow-up time point). The authors of the study concede, however, that this result would need to be corroborated by further studies and better validated measurements (which should not be based on a single question). In view of the results of the benefit assessment in this report – and also according to the assessment of the clinical expert involved in the report – a difference in the amount of care required is not readily comprehensible in terms of content.

In the quality assessment, which is based on the criteria of the CHEERS statement [103] using a pre-defined list of questions, both studies largely perform well. The transferability of the study results to Germany is limited in detail by differences in procedure code schedules and cost structures (see also Section 5.1); in addition, FEMCAT was conducted exclusively in university hospitals, for example. Overall, the direction of the results can be assumed to be transferable, so it is likely that FLACS is not cost-effective in the German health care system from a payer perspective (and with a similar willingness to pay) either.

6 Results: Ethical, social, legal and organizational aspects

6.1 Results on ethical aspects

The identification of ethical aspects and arguments was guided by the "4 principles" formulated by Beauchamp and Childress. These 4 principles are on an equal footing with each other and are "beneficence", "respect for autonomy", "nonmaleficence" and "justice". The two authors emphasize that ethical medical practice should always be guided by these four principles.

In the 4-principle approach of Beauchamp and Childress, "beneficence" means an obligation to do good and to maintain a balance between benefit and risk. The aspects "physician’s responsibility" and "waiting time" were assigned to the principle "beneficence". It is described that objective counselling by the doctor is important. This is particularly important when it comes to the use of new technologies, which are sometimes heavily advertised [104]. The loss of visual acuity has far-reaching effects on an individual's social participation (interviews with those affected and [105]). One publication emphasizes that performing cataract surgeries tends to keep affected individuals in the workforce. Accordingly, in addition to individual benefits, there are also societal advantages in terms of socioeconomic impacts on economic productivity [106]. A therapeutic indication for cataract surgery only exists once there are significant impairments to the daily life of the affected person. The waiting time for cataract surgery should therefore be kept as short as possible. Several factors that could change as a result of the increased use of FLACS could in turn have an impact on the waiting time for cataract surgery: the availability of the two surgical procedures, the potential expectations of patients, the quality of information provided by the attending physician and the risk of loss of expertise ("downskilling") regarding the standard procedure.

In Beauchamp and Childress' approach, the principle "respecting autonomy" means that individual decisions must be respected and that the ability to make autonomous decisions must be promoted. The aspects of "informed consent", "information by the physician" and "decision for or against the technology under evaluation" were assigned to the principle "autonomy". Each surgical procedure has advantages and disadvantages that may be more or less relevant for the affected person. The surveyed affected people noted that they felt that the standard therapy method achieved good and safe results. For this reason, one affected person was not willing to pay money for a FLACS procedure. For informed consent, it is necessary that the affected person receives detailed information and understands it. The interviews with those affected revealed that it is important for the physician to provide comprehensive information in order to gain an overview of the various treatment methods. Trust in the attending physician is also rated as important. Furthermore, it was noted in the survey of those affected that the individual decision for or against a particular therapy method is also guided by financial aspects. Not every affected person wants to pay the additional costs themselves in order to be able to take advantage of a certain treatment procedure that is not covered by statutory health insurance (SHI).

The principle "nonmaleficence" stipulates the obligation to avoid harm. The aspect "safety" was assigned to this principle. As the experience of the person performing the surgery increases, the procedure becomes safer and fewer complications occur with FLACS [107,108]. On the other hand, increased use of FLACS for the standard procedure could potentially lead to a risk of so-called “downskilling” regarding the standard procedure, i.e. key skills such as capsulotomy and nucleus processing are being taken away from the operating person by the laser with the result that the surgeon loses manual skills – such as performing a capsulotomy. This could negatively impact the safety of individuals who opt for the standard procedure or for whom only the standard procedure is an option (assessment by the team of authors).

Three aspects were identified in the principle of "justice" – i.e. the obligation to distribute advantages and disadvantages fairly – namely: "distribution of financial resources", "consumable materials – climate aspect" and "superiority of the procedure". In the context of the distribution of financial resources, it should be noted that treatment using the FLACS procedure is currently not reimbursed by the SHI in Germany. Should this situation change, criteria would have to be defined as to who – and under what circumstances – can benefit from such treatment. It should be noted at this point that there is currently no advantage of FLACS over the standard procedure for any of the analysed efficacy or safety outcomes (see Section 4). A public investment in the more expensive FLACS procedure would therefore contradict the aspect of a fair distribution of financial resources. In addition to the costs of purchasing and maintaining the device, the FLACS procedure also incurs costs for consumable materials (interface) [37]. These consumable materials also represent an increase in environmentally harmful consumables. In summary, the results of the benefit assessment,

financial aspects and environmental aspects therefore suggest an unequal distribution of benefits versus harms in the FLACS procedure compared to the standard procedure.

6.2 Results on social aspects

As part of the research on social aspects, six relevant topics were identified, namely "quality of life", "patient satisfaction", "people who are more frequently affected by cataracts", "discrimination versus contraindication", "competence and experience of the person performing the surgery" and "socio-economic effects and remaining in the workforce".

Cataract surgery – regardless of the procedure – generally leads to an improvement in the quality of life of those affected (interviews with affected people and [109]). The benefit assessment shows that there are only a few RCTs (2) that compared the respective effects of the two cataract surgery methods on quality of life. However, the two RCTs identified showed no significant differences in quality of life between the two procedures. The benefit assessment did not identify any RCTs that compared patient satisfaction with the FLACS procedure versus with the standard procedure (benefit assessment and [110]). However, the team of authors considers it important and desirable to record more of the perspectives of those affected.

Certain groups of people, for example those with a low socioeconomic status, lower level of education or poorer nutrition, have a higher risk of developing cataracts [111]. In order to decide in favour of or against a treatment option, information must be understood and the advantages and disadvantages weighed up. People with a low level of education may find this difficult. The person providing information must give comprehensive and comprehensible advice in order to obtain the informed consent of the affected person.

The literature describes that treatment using FLACS is not possible in the case of certain anatomical conditions or diseases [112-114]. If the FLACS procedure becomes the primary treatment of choice in the future, care must also be ensured for those for whom this procedure is not an option. With regard to the competence and experience of the person performing the surgery, one publication points out that surgeons would not always favour the FLACS procedure for themselves [115]. The study did not investigate why the surgeons surveyed made this decision.

6.3 Results on legal aspects

Surgical lasers are Class IIb medical devices and manufacturers must comply with the relevant regulations in accordance with the Medical Device Regulation (MDR) and the Medical Device Implementation Act (MPDG) [116,117]. The additional costs for FLACS are not covered by the SHI, so patients have to bear these costs themselves or, if applicable, can have them reimbursed by private insurance. In recent years, there has been uncertainty regarding the

procedure codes to be used. The laser treatment was billed as an independent medical service by treating physicians, but private health insurance companies only authorized the reimbursement of a laser surcharge associated with significantly lower costs (the laser treatment as an independent service is billed at around €400 via GOÄ No. 5855 and can amount to more than around €1000 if the highest rate of increase is applied; the laser surcharge is billed at around €70 via GOÄ No. 441 [118]). In October 2021, a ruling by the German Federal Court of Justice confirmed that charging for the use of a laser as an independent medical service is not permissible in the case of FLACS if there is no independent medical indication [119,120].

6.4 Results on organizational aspects

Cataract surgeries can be performed by ophthalmologists using both the standard procedure and FLACS; no additional training is required for laser use. Similarly, both surgical procedures can be performed in private practice as well as on an outpatient basis in hospitals. Nevertheless, there are aspects relevant to care: A possible loss of expertise ("downskilling") among ophthalmologists due to the increased use of the femtosecond laser is critically discussed in the literature [37]. In addition, due to the high acquisition costs of surgical lasers, it is to be expected that an increased focus on FLACS would concentrate the care of patients requiring cataract surgery more on specialized centres. In addition, FLACS is dependent on manufacturer-specific products due to the additional consumables (interface) required.

7 Summary of results

As part of the scoping phase for this HTA report, an initial logical model was created based on INTEGRATE-HTA [45]. It is intended to graphically illustrate all relevant health technology assessment aspects and includes aspects such as population, intervention, comparative intervention and (patient-relevant) outcomes as well as a range of contextual and implementation factors addressing for example epidemiology, politics, legal system or ethics. After reviewing the evidence, this model was revised into an extended model that provides an overview of all key findings from the domains of benefit assessment, health economic aspects, ethical aspects and social, legal and organizational aspects and thus places them in context with each other (see Figure 1).

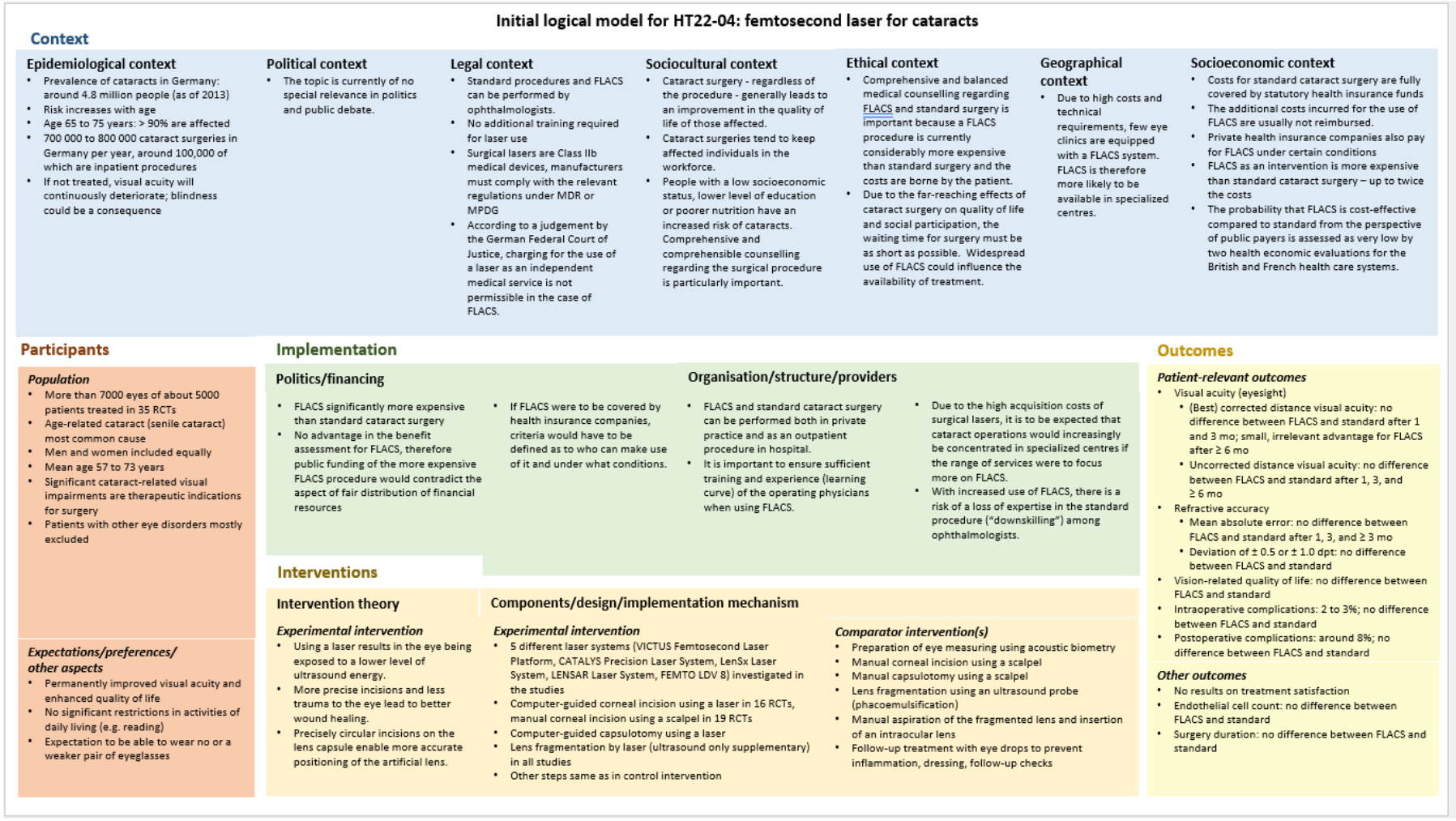

Figure 1: Initial logical model for HT22-04: femtosecond laser for cataracts

8 Discussion

8.1 HTA report compared with other publications

As part of the orientating search, 8 systematic reviews relevant to the topic were identified, 3 of which were published within the last 5 years [19,121,122].

In 2018, a rapid assessment HTA report was published as part of the European Network for Health Technology Assessment (EUnetHTA) Joint Action 3 Plan comparing FLACS versus standard cataract surgery in patients with age-related cataract [19]. Although the focus was on age-related cataracts, RCTs were also included that, due to the inclusion criteria, also included people with cataracts of other causes. A total of 21 studies were included in the analyses, of which 17 RCTs are also included in this HTA report. The remaining 4 studies [123-126] were not included in this HTA report due to the lack of report-relevant results, the publication language or the questionable study design. Overall, based on low to very low GRADE evidence, FLACS showed comparable efficacy and safety compared to standard cataract surgery. The authors therefore conclude that there is no clinically relevant difference in efficacy and safety between the two cataract surgery techniques, but that FLACS incurs higher costs. Results from relevant, more recent RCTs with larger numbers of participants [58,61,88] were, however, not yet available for the EUnetHTA report.

Kolb 2020 [121] also analysed the efficacy and safety of FLACS compared to standard cataract surgery in a systematic review involving 73 studies including 25 RCTs and 48 observational studies. Of these 25 RCTs from Kolb 2020, 6 studies [124-129] are not included in the present HTA report because of doubts about an adequate study design, because the study population (patients with Fuchs endothelial dystrophy) did not meet the inclusion criteria, or because no patient-relevant outcomes were reported. Metaanalyses were conducted jointly for RCTs and observational studies. Overall, there were short-term advantages in visual acuity and refraction as well as less endothelial cell loss for FLACS compared to standard cataract surgery, but in the medium term no differences between the two techniques were found regarding the outcomes. The results of the two RCTs FACT 2021 [58] and FEMCAT 2020 [61] were also not included in this review.

The systematic review by Wang 2019 [122] focussed on intraoperative and postoperative complications in FLACS compared to standard cataract surgery. English-language publications (RCTs and non-randomized controlled trials) with reported results on selected complications of cataract surgery, such as capsular rupture, incomplete capsulotomy, vitreous prolapse, macular or corneal oedema, or increased intraocular pressure, were included. Eight studies, 4 of which were small RCTs, were included in the analyses. Three of the RCTs were also included in this HTA report, the 4th RCT [130] was not included due to the reported outcomes (morphological data). The meta-analyses by Wang 2019 showed statistically significantly

higher rates for some complications, such as incomplete capsulotomy, anterior capsule rupture, or macular or corneal oedema, when using FLACS. For other complications, however, there was no difference compared to standard cataract surgery. The results are based primarily on the data from 2 of the included non-randomized studies. In summary, the authors conclude that FLACS does not lead to an improvement in intraoperative and postoperative complications compared to standard cataract surgery.

8.2 HTA report compared with guidelines

There is currently no valid guideline for the management of cataracts in German-speaking countries. International guidelines on cataracts come from NICE in the UK, the American Academy of Ophthalmology (AAO) and the Ministry of Health of British Columbia (BC), Canada, and were last updated between 2017 and 2021. Given the publication dates, the recommendations or statements in the guidelines on the use of FLACS are mostly based on older studies. Results from more recent RCTs from the present HTA report have therefore not been considered.

The 2017 NICE guideline "Cataracts in adults: management (NG77)" [8], recommends in its guidance on surgical technique for cataracts with regard to FLACS that it should only be used in clinical trials comparing FLACS with conventional cataract surgery, and only if data on resource consumption are also collected. The guidelines commission justified its decision on the grounds that there is no evidence to suggest a difference between FLACS and standard cataract surgery. The overall quality of the evidence was assessed as low in 2017. No advantage of FLACS in terms of visual acuity or complication rates could be shown, which is why the guideline commission judged the regular use of FLACS to be inappropriate. However, it was also pointed out that results from 2 large RCTs (FACT 2021 [58] and FEMCAT 2020 [61]) were not yet available.

The AAO 2021 guideline [11] states that FLACS can improve the circularity and centring of the capsulorhexis as well as the precision of corneal cuts, and that it can also reduce the amount of ultrasound energy needed during cataract surgery. However, the technology is not considered to be cost-effective. In addition, the overall risk profile does not show any superiority over standard cataract surgery. These statements are based on data from a systematic review with 73 studies (observational studies and RCTs) from 2020 [121] as well as the FEMCAT 2020 study [61] and the European registry evaluation of FLACS from 2016 [131].

The BC 2021 guideline [132], on the other hand, only states in the section "Controversies in care" that FLACS is an option in the context of cataract surgery that is not covered by public insurance and is only offered in a few centres. Also, there is little high-quality evidence that FLACS could improve healing time, refractive outcome, or complication rates. The guideline does not contain any information on the underlying evidence.

8.3 Critical reflection on the approach used

The HTA report was not restricted with regard to the population, yet mostly patients with age-related cataracts participated in the RCTs comparing FLACS versus standard cataract surgery. Moreover, the studies included almost exclusively patients without any other eye disorders. Only one RCT (FACT 2021) reported that around 35% of the study participants had ocular comorbidities such as glaucoma, diabetic retinopathy, age-related macular degeneration or severe myopia. Results for this subgroup were not reported. There are currently no studies available with patients with another specific cause of cataract or with certain comorbidities. Therefore, it remains unclear overall whether FLACS offers advantages over standard cataract surgery for a specific patient group.

The included studies investigated all 5 approved and commercially available laser systems. The RCTs spanned 11 years (2010 to 2021), during which time the laser systems underwent continuous advancement. This technological advancement of the laser systems was not taken into account in the metaanalyses. It can be assumed, however, that this had little to no influence, as current large RCTs (FACT 2021 and FEMCAT 2020) with state-of-the-art laser systems showed results comparable to those of RCTs from the 2010s that may have used older laser technologies. Similarly, the results of the metaanalyses did not show any trends in one direction or the other depending on the publication years of the RCTs. Subgroup analyses of the individual laser systems were not possible due to the small number of RCTs with comparable outcomes. Since the individual RCTs also show largely homogeneous results across all measurement points and methods for the comparison of FLACS versus standard cataract surgery, no significant influence of the laser system and the technical specifications and advancement is to be assumed.

Besides analysing existing literature, SHI routine data, relevant legal documents and medical guidelines, the relevant remuneration catalogues (EBM, GOÄ) were used and medical experts were consulted to present the intervention costs in Germany. However, presenting the typical or average billable procedure codes and their valuation in euros proved difficult. Furthermore, not all codes were quantifiable. All in all, only a range of costs could be provided.

9 Conclusion

The benefit assessment identified 36 randomized controlled trials comparing femtosecond laser-assisted cataract surgery versus standard manual cataract surgery, of which 35 studies provided results for the benefit assessment. A total of 7189 eyes of 5510 patients were treated with one of the two surgical techniques in these studies. The mean age of the participants was 57 to 73 years, and the majority had age-related cataracts.

All commercially available laser systems (VICTUS Femtosecond Laser Platform, CATALYS Precision Laser System, LenSx Laser System, LENSAR Laser System, Ziemer FEMTO LDV 8) were

investigated in the randomized controlled trials, with the LenSx Laser System from Alcon being the most frequently investigated system. In the randomized controlled trials, the outcomes mainly analysed were visual acuity, refractive accuracy, and intraoperative or postoperative complications. The study duration was mostly between 1 and 18 months. Four randomized controlled trials only reported results obtained immediately after the procedure.

Overall, the randomized controlled trials included show that cataract surgery is safe and effective regardless of the surgical method chosen. Both in the intervention groups with femtosecond laser-assisted cataract surgery and in the control groups with standard manual cataract surgery, few intraoperative and postoperative complications occurred during the course of the study. Both the measured values of visual acuity (sharpness of vision) and those of refraction are almost within the normal range with both surgical techniques after a follow-up period of 1 to a maximum of 12 months.

The results of the individual randomized controlled trials comparing femtosecond laser-assisted cataract surgery versus standard cataract surgery are very homogeneous. Overall, the metaanalyses carried out did not reveal any statistically significant differences between the two surgical techniques for the outcomes of visual acuity, refractive accuracy, and intraoperative or postoperative complications. With regard to vision-related quality of life, there is also no difference between femtosecond laser-assisted cataract surgery and standard cataract surgery.

Thus, there is no hint, indication, or proof of an added benefit of femtosecond laser-assisted cataract surgery compared to standard manual cataract surgery for the investigated outcomes of visual acuity, refractive accuracy, and vision-related quality of life. At the same time, there is also no proof, indication, or hint of lesser or greater damage from femtosecond laser-assisted cataract surgery compared to standard manual cataract surgery.

The costs of both procedures for standard cataract surgery in Germany in an outpatient setting are around €900 to €1000, and for surgery using a femtosecond laser they are estimated to range from €700 to €2100. The 2 health economic evaluations conducted for the UK and French health care systems conclude that, from the payers' perspective, the femtosecond laser procedure is unlikely to very unlikely to be cost-effective compared to the standard procedure. Considering the results of the benefit assessment of the present report and given the difference in intervention costs, a similar result can be assumed for Germany.

Although the benefit assessment shows neither an added benefit nor a reduced potential for harm of femtosecond laser-assisted cataract surgery compared to the standard procedure, it is sometimes advertised as more precise or safer. Objective counselling and information in this regard by the attending physicians are therefore of great importance for the informed decision-making of those affected, especially in view of the fact that patients who opt for

femtosecond laser-assisted cataract surgery have to bear at least part of the costs themselves. The legal uncertainty regarding the billable procedure codes in this context has been clarified by a ruling of the German Federal Court of Justice, according to which only charging the lower-priced laser surcharge is permissible if there is no independent medical indication. Public investment in the more expensive femtosecond laser-assisted cataract surgery is not in line with the principle of distributive justice given the lack of added benefit. In addition, the increased use of environmentally harmful consumables in femtosecond laser-assisted cataract surgery must be viewed critically, irrespective of the cost coverage. Since femtosecond laser-assisted cataract surgery is not an option for people with certain medical conditions or anatomical characteristics, it would have to be ensured that, even if femtosecond laser-assisted cataract surgery were to be used more and more, the medical skills required for the standard procedure (e.g. manual capsulotomy) would continue to be available to a sufficient extent to guarantee the care of these individuals.

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Please see full HTA report for the full reference list.

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The full HTA report (German version) is published under
https://www.iqwig.de/sich-einbringen/themencheck-medizin/berichte/ht22-04.html

Appendix A – Topics of the EUnetHTA Core Model

The European Network for Health Technology Assessment (EUnetHTA) is a network of European HTA agencies. EUnetHTA promotes the exchange of HTA information between its members and developed the core model [41] for this purpose. IQWiG is also a member of the network.

In order to make it easier for readers of this HTA report to find information on the superordinate domains of the EUnetHTA Core Model, Table 7 indicates where the relevant information can be found. The original names of the domains of the core model are used to describe the topics.

Table 7: Domains of the EUnetHTA Core Model

EUnetHTA domain	**Information in chapters and sections of the HTA report**
Health problem and current use of the technology (CUR)	**Background** Chapter 1
Description and technical characteristics of technology (TEC)	
Safety (SAF)	**Benefit assessment** Section 3.1; Chapter 4
Clinical effectiveness (EFF)	
Costs and economic evaluation (ECO)	**Health economic evaluation** Section 3.2; Chapter 5
Ethical analysis (ETH)	**Ethical aspects** Section 3.3; Section 6.1
Patients and social aspects (SOC)	**Social aspects** Section 3.4; Section 6.2
Legal aspects (LEG)	**Legal aspects** Section 3.4; Section 6.3
Organizational aspects (ORG)	**Organizational aspects** Section 3.4; Section 6.4

Appendix B – Search strategies

B.1 – Search strategies for the benefit assessment

B.1.1 – Searches in bibliographic databases

Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to November 22, 2022

The following filter was adopted:

- Systematic review: Wong [133] – High specificity strategy

#	Searches
1	exp Cataract/ or exp Cataract Extraction/
2	cataract*.ti,ab.
3	or/1-2
4	(femtosecond* or (femto* adj6 second*) or (laser adj1 assisted)).mp.
5	and/3-4
6	Cochrane database of systematic reviews.jn.
7	(search or MEDLINE or systematic review).tw.
8	meta analysis.pt.
9	or/6-8
10	9 not (exp animals/ not humans.sh.)
11	and/5,10
12	11 and (english or german or multilingual or undetermined).lg.
13	..l/ 12 yr=2015-Current

2. International HTA Database

Search interface: INAHTA

#	Searches
1	"Cataract"[mhe]
2	"Cataract Extraction"[mhe]
3	(cataract*)[Title] OR (cataract*)[abs]
4	#3 OR #2 OR #1
5	(femtosecond* OR (femto* AND second*) OR (laser* AND assisted*))
6	#5 AND #4
7	* FROM 2015 TO 2022
8	#7 AND #6

Search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to January 27, 2023

The following filter was adopted:

- RCT: Lefebvre [134]– Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)

#	Searches
1	exp Cataract/ or exp Cataract Extraction/
2	cataract*.ti,ab.
3	or/1-2
4	(exp Laser Therapy/ or exp Lasers/) and exp Cataract Extraction/
5	(femtosecond* adj1 laser*).ti,ab.
6	(laser* adj1 assisted*).ti,ab.
7	or/4-6
8	randomized controlled trial.pt.
9	controlled clinical trial.pt.
10	(randomized or placebo or randomly or trial or groups).ab.
11	drug therapy.fs.
12	or/8-11
13	12 not (exp animals/ not humans.sh.)
14	and/3,7,13
15	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
16	hi.fs. or case report.mp.
17	or/15-16
18	14 not 17
19	18 and (english or german or multilingual or undetermined).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2023 January 27

The following filter was adopted:

- RCT: Wong [133] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	exp cataract/ or exp cataract extraction/
2	cataract*.ti,ab.
3	or/1-2
4	exp femtosecond laser/
5	exp cataract extraction/ and laser surgery/
6	(femtosecond* adj1 laser*).ti,ab.
7	(laser* adj1 assisted*).ti,ab.
8	or/4-7
9	(random* or double-blind*).tw.
10	placebo*.mp.
11	or/9-10
12	and/3,8,11
13	12 not medline.cr.
14	13 not (exp animal/ not exp human/)
15	14 not (Conference Abstract or Conference Review or Editorial).pt.
16	15 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 1 of 12, January 2023

#	Searches
#1	[mh "Cataract"] or [mh "Cataract Extraction"]
#2	cataract*:ti,ab
#3	#1 or #2

#	Searches
#4	([mh "Laser Therapy"] or [mh "Lasers"]) and [mh "Cataract Extraction"]
#5	(femtosecond* NEAR/1 laser*):ti,ab
#6	(laser* NEAR/1 assisted*):ti,ab
#7	#4 or #5 or #6
#8	#3 and #7
#9	#8 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#10	#9 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
#11	#10 in Trials

B.1.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Expert Search

Search strategy
cataract AND (femtosecond OR laser assisted)

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Standard Search

Search strategy
cataract AND (femtosecond OR laser assisted)

B.2 – Search strategies for the health economic evaluation

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to January 31, 2023

The following filter was adopted:

- Glanville [135] – Emory University (Grady)

#	Searches
1	exp Cataract/ or exp Cataract Extraction/
2	cataract*.ti,ab.
3	or/1-2
4	(exp Laser Therapy/ or exp Lasers/) and exp Cataract Extraction/
5	(femtosecond* adj1 laser*).ti,ab.
6	(laser* adj1 assisted*).ti,ab.
7	or/4-6
8	(economic$ or cost$).ti.
9	cost benefit analysis/
10	treatment outcome/ and ec.fs.
11	or/8-10
12	11 not ((animals/ not humans/) or letter.pt.)
13	and/3,7,12
14	13 not (comment or editorial).pt.
15	14 and (english or german or multilingual or undetermined).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2023 January 31

The following filter was adopted:

- Glanville [135] – Embase G

#	Searches
1	exp cataract/ or exp cataract extraction/
2	cataract*.ti,ab.
3	or/1-2
4	exp femtosecond laser/

#	Searches
5	exp cataract extraction/ and laser surgery/
6	(femtosecond* adj1 laser*).ti,ab.
7	(laser* adj1 assisted*).ti,ab.
8	or/4-7
9	(Cost adj effectiveness).ab.
10	(Cost adj effectiveness).ti.
11	(Life adj years).ab.
12	(Life adj year).ab.
13	Qaly.ab.
14	(Cost or costs).ab. and Controlled Study/
15	(Cost and costs).ab.
16	or/9-15
17	and/3,8,16
18	17 not medline.cr.
19	18 not (exp animal/ not exp human/)
20	19 not (Conference Abstract or Conference Review or Editorial).pt.
21	20 and (english or german).lg.

3. International HTA Database

Search interface: INAHTA

#	Searches
1	Cataract[mhe]
2	Cataract Extraction[mhe]
3	(cataract*)[Title] OR (cataract*)[abs]
4	#3 OR #2 OR #1
5	Laser Therapy[mhe]
6	Lasers[mhe]
7	#6 OR #5
8	#7 AND #2
9	(femtosecond* AND laser*)[Title] OR (femtosecond* AND laser*)[abs]
10	((laser* AND assisted*))[Title] OR ((laser* AND assisted*))[abs]
11	#10 OR #9 OR #8
12	#11 AND #4