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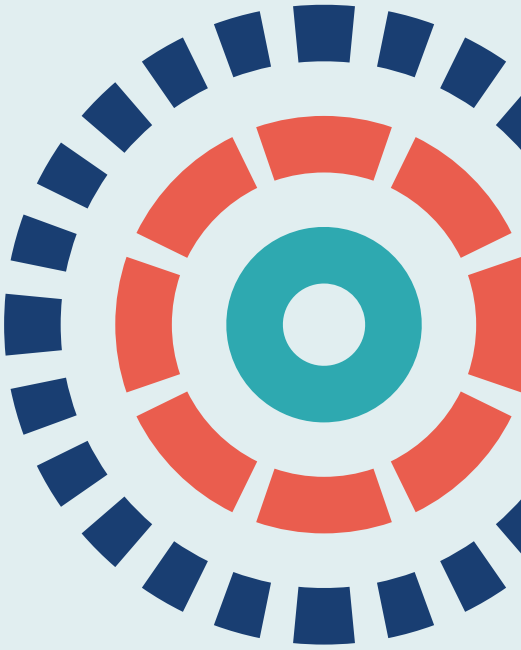

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Femtosecond laser-assisted cataract surgery compared with phacoemulsification: the FACT non-inferiority RCT

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This report

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Abstract

Femtosecond laser-assisted cataract surgery compared with phacoemulsification: the FACT non-inferiority RCT

Alexander C Day[1,2,3*] Jennifer M Burr[4] Kate Bennett[5] Rachael Hunter[5] Catey Bunce[6] Caroline J Doré[5] Mayank A Nanavaty[7] Kamaljit S Balaggan[8] and Mark R Wilkins[1,2]

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Background: Cataract surgery is one of the most common operations. Femtosecond laser-assisted cataract surgery (FLACS) is a technique that automates a number of operative steps.

Objectives: To compare FLACS with phacoemulsification cataract surgery (PCS).

Design: Multicentre, outcome-masked, randomised controlled non-inferiority trial.

Setting: Three collaborating NHS hospitals.

Participants: A total of 785 patients with age-related cataract in one or both eyes were randomised between May 2015 and September 2017.

Intervention: FLACS (n = 392 participants) or PCS (n = 393 participants).

Main outcome measures: The primary outcome was uncorrected distance visual acuity in the study eye after 3 months, expressed as the logarithm of the minimum angle of resolution (logMAR): 0.00 logMAR (or 6/6 if expressed in Snellen) is normal (good visual acuity). Secondary outcomes included corrected distance visual acuity, refractive outcomes (within 0.5 dioptre and 1.0 dioptre of target), safety and patient-reported outcome measures at 3 and 12 months, and resource use. All trial follow-ups were performed by optometrists who were masked to the trial intervention.

Results: A total of 353 (90%) participants allocated to the FLACS arm and 317 (81%) participants allocated to the PCS arm attended follow-up at 3 months. The mean uncorrected distance visual acuity was similar in both treatment arms [0.13 logMAR, standard deviation 0.23 logMAR, for FLACS, vs. 0.14 logMAR, standard deviation 0.27 logMAR, for PCS, with a difference of −0.01 logMAR (95% confidence interval −0.05 to 0.03 logMAR; $p = 0.63$)]. The mean corrected distance visual acuity values were again similar in both treatment arms (−0.01 logMAR, standard deviation 0.19 logMAR FLACS vs. 0.01 logMAR, standard deviation 0.21 logMAR PCS; $p = 0.34$). There were two posterior capsule tears in the PCS arm. There were no significant differences between the treatment arms for

any secondary outcome at 3 months. At 12 months, the mean uncorrected distance visual acuity was 0.14 logMAR (standard deviation 0.22 logMAR) for FLACS and 0.17 logMAR (standard deviation 0.25 logMAR) for PCS, with a difference between the treatment arms of −0.03 logMAR (95% confidence interval −0.06 to 0.01 logMAR; $p = 0.17$). The mean corrected distance visual acuity was 0.003 logMAR (standard deviation 0.18 logMAR) for FLACS and 0.03 logMAR (standard deviation 0.23 logMAR) for PCS, with a difference of −0.03 logMAR (95% confidence interval −0.06 to 0.01 logMAR; $p = 0.11$). There were no significant differences between the arms for any other outcomes, with the exception of the mean binocular corrected distance visual acuity with a difference of −0.02 logMAR (95% confidence interval −0.05 to 0.00 logMAR) ($p = 0.036$), which favoured FLACS. There were no significant differences between the arms for any health, social care or societal costs. For the economic evaluation, the mean cost difference was £167.62 per patient higher for FLACS (95% of iterations between −£14.12 and £341.67) than for PCS. The mean QALY difference (FLACS minus PCS) was 0.001 (95% of iterations between −0.011 and 0.015), which equates to an incremental cost-effectiveness ratio (cost difference divided by QALY difference) of £167,620.

Limitations: Although the measurement of outcomes was carried out by optometrists who were masked to the treatment arm, the participants were not masked.

Conclusions: The evidence suggests that FLACS is not inferior to PCS in terms of vision after 3 months' follow-up, and there were no significant differences in patient-reported health and safety outcomes after 12 months' follow-up. In addition, the statistically significant difference in binocular corrected distance visual acuity was not clinically significant. FLACS is not cost-effective.

Future work: To explore the possible differences in vision in patients without ocular co-pathology.

Trial registration: Current Controlled Trials ISRCTN77602616.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 6. See the NIHR Journals Library website for further project information. Moorfields Eye Charity (grant references GR000233 and GR000449 for the endothelial cell counter and femtosecond laser used).

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List of abbreviations

CDVA	corrected distance visual acuity
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
ETDRS	Early Treatment Diabetic Retinopathy Study
FACT	Femtosecond laser-Assisted Cataract Trial
FEMCAT	FEMtosecond laser-assisted versus phacoemulsification CATaract surgery
FLACS	femtosecond laser-assisted cataract surgery
ICER	incremental cost-effectiveness ratio
IOL	intraocular lens
logMAR	logarithm of the minimum angle of resolution
MICE	multiple imputation by chained equations
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OCT	optical coherence tomography
PCR	posterior capsule rupture
PCS	phacoemulsification cataract surgery
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SD	standard deviation
TSC	Trial Steering Committee
UCL	University College London
UDVA	uncorrected distance visual acuity
WTP	willingness to pay

Plain English summary

Cataract is a condition in which the natural lens inside the eye becomes cloudy, leading to loss of vision. In cataract surgery, the cloudy lens is replaced by a clear, artificial one. The standard surgical method (phacoemulsification) is carried out manually by the surgeon using ultrasound.

Part of the procedure can now be automated using a computer-controlled laser. This is called femtosecond laser-assisted cataract surgery (FLACS). The potential advantages of FLACS include greater precision reproducibility, but this new technique is more expensive than the standard surgery.

We performed a randomised controlled trial comparing the two techniques. We assessed vision, surgical complications, patient-related quality of life and cost-effectiveness at 3 and 12 months.

We found that the outcomes were almost identical for eyesight, quality of life and complications. Overall, the evidence suggests that the new technique is not worth the additional costs.

Scientific summary

Background

Cataract surgery is one of the most commonly performed operations in the Western world, with almost half a million of these operations performed per year in the UK alone. The current standard method, phacoemulsification cataract surgery (PCS) (using ultrasound), was introduced > 50 years ago. An alternative, femtosecond laser-assisted cataract surgery (FLACS), first became commercially available almost 10 years ago. The reported advantages of FLACS include more accurate positioning, more reproducible shape and size of the capsulotomy when compared with a capsulorrhexis, and less intraocular lens tilt with fewer higher-order aberrations. In addition, by using a laser to fragment the crystalline lens, less ultrasound energy is subsequently required to complete its removal, which should result in less endothelial cell loss. Overall, this would be expected to translate to greater safety and better visual outcomes through greater precision and reproducibility.

When they were introduced, laser cataract surgery platforms were marketed as bringing a stepwise improvement in surgical technique and were used as a differentiating factor between cataract surgery providers. The cost of FLACS remains high, which reflects the high development costs. For example, Alcon (Geneva, Switzerland) took over LenSx for US$744M in 2010 and Abbott Medical Optics (Abbott Park, IL, USA) purchased OptiMedica Corp. for up to US$400M in 2013. To date, there are limited high-quality data from randomised controlled trials on outcomes from laser cataract surgery compared with outcomes from the standard technique, with the data that are available being predominantly from large comparative case series. The 2016 Cochrane review of FLACS compared with PCS concluded that there was limited evidence to determine the equivalence or superiority of FLACS, and that large, adequately powered randomised controlled trials were needed (Day AC, Gore DM, Bunce C, Evans JR. Laser-assisted cataract surgery versus standard ultrasound phacoemulsification cataract surgery. *Cochrane Database Syst Rev* 2016;**7**:CD010735). Three meta-analyses have been published; (Chen X, Xiao W, Ye S, Chen W, Liu Y. Efficacy and safety of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification for cataract: a meta-analysis of randomized controlled trials. *Sci Rep* 2015;**5**:13123; Popovic M, Campos-Möller X, Schlenker MB, Ahmed II. Efficacy and safety of femtosecond laser-assisted cataract surgery compared with manual cataract surgery: a meta-analysis of 14 567 eyes. *Ophthalmology* 2016;**123**:2113–26; and Ye Z, Li Z, He S. A meta-analysis comparing postoperative complications and outcomes of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification for cataract. *J Ophthalmol* 2017;**2017**:3849152) one found superior refractive outcomes for FLACS, whereas the others found no statistically significant differences in terms of patient-reported visual, refractive and complications. Two large randomised controlled trials have recently been published: the French FEMCAT (FEMtosecond laser-assisted versus phacoemulsification CATaract surgery) trial, which found no difference in visual or safety measures between FLACS and PCS [Schweitzer C, Brezin A, Cochener B, Monnet D, Germain C, Roseng S, *et al.* Femtosecond laser-assisted versus phacoemulsification cataract surgery (FEMCAT): a multicentre participant-masked randomised superiority and cost-effectiveness trial. *Lancet* 2020;**395**:212–24], and a UK trial from St Thomas' Hospital of 400 eyes (Roberts HW, Wagh VK, Sullivan DL, Hidzheva P, Detesan DI, Heemraz BS, *et al.* A randomized controlled trial comparing femtosecond laser-assisted cataract surgery versus conventional phacoemulsification surgery. *J Cataract Refract Surg* 2019;**45**:11–20) found similar visual outcomes between its arms and a statistically significantly lower posterior capsule tear rate in the FLACS arm.

Objective

The aim of this trial, FACT (Femtosecond laser-Assisted Cataract Trial), is to establish whether FLACS is a cataract surgical technique that is as good as or better than PCS.

Primary outcome

The primary outcome was uncorrected distance visual acuity [measured using a ETDRS (Early Treatment Diabetic Retinopathy Study) logMAR (logarithm of the minimum angle of resolution) chart at a starting distance of 4 m] in the study eye at the 3-month follow-up.

Secondary outcomes

Secondary outcomes were corrected distance visual acuity at 3 months in the study eye, safety measures including intraoperative and postoperative complications and corneal endothelial cell count change and refractive error (spherical equivalent) within 0.5 dioptre and within 1.0 dioptre of intended refractive outcomes. Health-related quality of life was measured at 6 weeks and 3, 6 and 12 months using the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), questionnaire plus the vision bolt-on question and patient-reported vision health status using Catquest-9SF (a Rasch-validated instrument). All trial follow-ups were performed by optometrists who were masked to the trial intervention.

Methods

We designed a pragmatic, randomised controlled non-inferiority trial with participants who were unmasked to treatment allocation across three NHS sites, to compare FLACS with PCS.

All patients were screened and recruited from routine cataract clinics. They were adults aged $\geq$ 18 years with age-related cataract. For a patient to be eligible for participation, the expected postoperative refractive target had to be within $\pm$ 0.5 dioptre of emmetropia (i.e. good distance vision).

Randomisation was carried out using minimisation with a random element, and with treatment centre, surgeon and the number of eyes that as stratification factors. Participants were randomised 1 : 1 to undergo either FLACS or PCS. A secure online service (Sealed Envelope™, Sealed Envelope Ltd, London, UK; www.sealedenvelope.com) provided computer-generated participant identifiers and the trial arm allocations. For participants who required bilateral cataract surgery, the same intervention (namely FLACS or PCS) was offered when the patient returned for their second eye surgery, unless the patient wished otherwise. Owing to the nature of the intervention, surgeon and participant masking was not possible. All trial follow-ups were performed by optometrists who were masked to the trial intervention.

Follow-up

Participants attended a follow-up visit at 3 months post study eye surgery and again at 12 months.

Outcome measures

The primary outcome was uncorrected distance visual acuity (logMAR) at 3 months following surgery on the study eye, measured using a standard ETDRS chart at a starting distance of 4 m. Additional secondary outcome measures included visual acuity outcomes, refractive outcomes, adverse events, health-related quality of life and resource use.

Sample size

We aimed to recruit at least 808 patients (404 per arm). This sample size was estimated to to allow the identification of a treatment effect size of 1 logMAR line uncorrected distance visual acuity, which we thought would be clinically important to patients and ophthalmologists as determined by prior patient and public involvement in the trial design. One logMAR line is 5 letters (each letter is 0.02 logMAR) and the test–retest variability is reported to be about 0.07 logMAR on letter-by-letter scoring. If there is

truly no difference in mean logMAR between the two treatment arms, then 432 patients (216 per arm) would provide 90% power to be sure that a 95% two-sided confidence interval would exclude the non-inferiority limit of 0.1 logMAR, assuming a common standard deviation of 0.32. The standard deviation is from the Royal College of Ophthalmologists' National Ophthalmic Database uncorrected distance visual acuity data.

As patients were clustered within operating surgeons, each patient could not be assumed to generate independent information. To take account of this, the sample size was increased by an inflation factor of 1.59, giving a required sample size of 688 patients (344 per arm). To allow for an anticipated 15% dropout rate (the median age of patients undergoing cataract surgery in the UK is 77 years and many of these patients have significant systemic comorbidities), the total sample size required was 808 patients.

Statistical methods

As detailed in the statistical analysis plan (excluding the health economic evaluation) that was approved before the analyses were carried out, missing outcome data for the primary outcome were imputed using only multiple imputation with chained equations, and the results were combined using Rubin's rules. All secondary outcome analyses were performed on complete cases only. All analysis models included information on the site and on the number of eyes that were eligible as covariates; details about the surgeon were included in the analysis models as random effects. The model for the primary outcome was also adjusted for baseline habitual logMAR visual acuity values, and similar adjustments were made for any continuous secondary outcomes if a baseline value was recorded. Astigmatism at baseline [as measured by keratometry readings from Pentacam® (OCULUS Optikgeräte GmbH, Wetzlar, Germany) corneal topography] was incorporated as an adjustment factor in the analyses of visual acuity outcomes. Adjusted treatment effect estimates, two-sided 95% confidence intervals and two-sided *p*-values were reported for each outcome measure. Further supportive analyses of the primary outcome were carried out, including a per-protocol analysis and complete-case analysis.

Economic evaluation

The aim of the economic evaluation was to conduct a within-trial analysis of the mean incremental cost per quality-adjusted life-year gained by FLACS compared with PCS over 12 months from a health and social care cost perspective. A secondary analysis from a societal cost perspective was also conducted. Given that the primary outcome of the trial was uncorrected distance visual acuity at 3 months, a cost-effectiveness analysis was also conducted for 3 months. Multiple imputation by chained equations and bootstrapping were used to construct cost-effectiveness acceptability curves and cost-effectiveness planes.

Results

Between May 2015 and September 2017, a total of 3448 patients were assessed for eligibility (1710 were excluded because they were ineligible). Of the 1738 patients who were eligible, we recruited 785, of whom 392 were randomly assigned to the FLACS arm and 393 were randomly assigned to the PCS arm. The average age of the patients was 68 years (± 10 years), and more female than male patients were recruited (52% female, 48% male). In total, 70% of all participants were of white ethnicity (black/black British was the second largest ethnic group at 14%). A total of 20% of the participants had undergone previous cataract surgery in one eye. The baseline characteristics of participants were similar in both treatment arms.

A total of 352 out of 392 (90%) participants who were allocated to the FLACS arm and 317 out of 393 (81%) participants who were allocated to the PCS arm attended their follow-up visit 3 months postoperatively. The mean uncorrected distance visual acuity difference between the treatment arms was −0.01 logMAR (95% confidence interval −0.05 to 0.03 logMAR) and the mean corrected distance visual acuity difference was −0.01 logMAR (95% confidence interval −0.05 to 0.02 logMAR). Seventy-one per cent of FLACS and 70% of PCS cases were within ± 0.5 dioptre of the reflective target, and 93% of

FLACS cases and 95% of PCS cases were within ± 1.0 dioptre. There were two posterior capsule tears in the PCS arm and none in the FLACS arm.

A total of 311 out of 392 (79%) participants who were allocated to the FLACS arm and 292 out of 393 (74%) participants who were allocated to the PCS arm attended their follow-up visit at 12 months. The mean uncorrected distance visual acuity difference between treatment arms was −0.03 logMAR (95% confidence interval −0.06 to 0.01 logMAR) and the mean corrected distance visual acuity difference was −0.03 logMAR (95% confidence interval −0.06 to 0.01 logMAR). Seventy-five per cent of both FLACS and PCS cases were within ± 0.5 dioptre refractive target, and 95% of FLACS and 96% of PCS cases were within ± 1.0 dioptre. There were no significant differences between the treatment arms for any other outcome, with the exception of mean binocular corrected distance visual acuity difference of −0.02 logMAR (95% confidence interval −0.05 to 0.00 logMAR; $p = 0.036$) favouring the FLACS arm.

In the FLACS arm, surgery took a mean time of 17.1 minutes (standard deviation 7.4 minutes). The FLACS laser procedure took an additional 3.9 minutes (standard deviation 3.5 minutes), with a total time of 20.8 minutes (standard deviation 8.2 minutes). In the PCS arm, surgery took 17.8 minutes (standard deviation 8.0 minutes). There was no significant difference in the use of anaesthetic drugs or consumables between treatment arms except for VisionBlue® [D.O.R.C. (Dutch Ophthalmic Research Center) (International) B.V., Zuidland, the Netherlands; used for staining the anterior capsule to increase visibility in 43 patients in the PCS arm and in three patients in the FLACS arm] at a cost of £8.65 per vial.

There were no significant differences between the two treatment arms for any health, social care or societal costs. For the economic evaluation, the mean cost difference (FLACS minus conventional phacoemulsification) for the imputed, bootstrapped, adjusted data was £167.62 per patient (95% of iterations between −£14.12 and £341.67). The mean QALY difference (FLACS minus PCS) was 0.001 (95% of iterations between −0.011 and 0.015). This equates to an incremental cost-effectiveness ratio (cost difference divided by QALY difference) of £167,620.

For the threshold analysis from a health and social care cost perspective, assuming that FLACS results in an additional 0.001 QALYs per patient, FLACS needs to cost £138 less than it currently does to potentially be cost-effective at a willingness-to-pay threshold of £30,000 for a QALY gained.

Conclusions

In terms of vision FLACS is not inferior to PCS. There were no clinically important differences in patient-reported health and safety outcomes after 12 months' follow-up. A difference was found for binocular corrected distance visual acuity, which, although statistically significant, was not clinically significant. FLACS was not found to be cost-effective.

Implications for health care

Both FLACS and PCS have similar visual, refractive and safety outcome measures. FLACS is a more expensive technique than PCS and is not cost-effective in its present form.

Recommendations for research

It is possible that FLACS may offer advantages over PCS for patients with certain subtypes of cataract, or for lens replacement surgery using multifocal or other 'premium' intraocular lens, but further research may be required.

Trial registration

This trial is registered as ISRCTN77602616.

Funding

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Chapter 1 Introduction

Cataract surgery is one of the most commonly performed operations in the Western world, with almost half a million procedures performed per year in the UK[3] alone. The current standard method, phacoemulsification cataract surgery (PCS) (using ultrasound), was introduced > 50 years ago.[4]

Complications can affect recovery, and some complications are serious and associated with long-term poor outcomes [e.g. posterior capsule rupture (PCR)/vitreous loss was reported to occur in 1.4% cases in the recent UK National Ophthalmology Database audit for the period 2016–17].[5] Among patients who experience serious outcomes, one-third have complaints about their eye and vision 3.5 years after surgery.[6] One in five patients requires further surgery[7] and they are at a risk of retinal detachment within 3 years that is 15 times higher than in those who do not have further surgery.[8] The surgical learning curve is associated with complications, with a 1.6 to 3.7 times higher risk of PCR for surgeries performed by non-consultant-grade doctors.[9] Other complications, the majority of which are less serious, may mean a longer operation duration and delayed healing, as well as additional appointments and the need to use eye drops. Patients can be devastated when suffering a complication and, because of the importance of vision for daily activities, can find even minor complications very distressing.

Femtosecond laser-assisted cataract surgery (FLACS) first became commercially available almost 10 years ago. The reported advantages include more accurate positioning, the shape and size of the capsulotomy when compared with a capsulorrhexis,[10–12] and less intraocular lens (IOL) tilt[13] with fewer higher-order aberrations.[14] In addition, by using a laser to fragment the crystalline lens, less ultrasound energy is required to complete the lens removal and reductions of 70–96% of effective phacoemulsification time (ultrasound power) have been reported,[15–17] with zero effective phacoemulsification time being possible in 30% of operations in a recent series.[15] This study[15] also reported a 36% lower endothelial cell loss in the laser-assisted procedures than when using manual phacoemulsification.

When introduced, laser cataract surgery platforms were marketed as bringing a stepwise improvement in surgical technique and were used as a differentiating factor between cataract surgery providers.

The timing of FACT (Femtosecond laser-Assisted Cataract Trial) was critical because FLACS was being rapidly adopted worldwide, despite the absence of any randomised controlled trials (RCTs) comparing its safety and efficacy with that of PCS. Although its potential advantages may be attractive to patients and surgeons, laser-assisted surgery is expensive and there are logistical and practical issues that need to be understood. The absence of good evidence for any advantage of laser-assisted surgery was highlighted in a 2013 review article by Trikha *et al.*[18] and also by the National Institute for Health Research (NIHR) Horizon Scanning Centre.[19] The topic was identified as a research priority by the national James Lind Alliance Sight Loss and Vision Priority Setting Partnership (see www.fightforsight.org.uk/sightlosspsp; accessed 1 January 2013).

The 2016 Cochrane review[20] of FLACS compared with PCS concluded that there was limited evidence to determine equivalence or superiority and that large, adequately powered RCTs were needed. Three meta-analyses have been published;[21–23] one found superior refractive outcomes with FLACS,[23] whereas the others[21,22] found no statistically significant differences in terms of patient-reported visual, refractive and complications. Two large RCTs have recently been completed, namely the French

FEMCAT (FEMtosecond laser-assisted versus phacoemulsification CATaract surgery) trial,[24] which found no difference in visual or refractive outcomes or complications between arms, and a UK trial of 400 eyes that found similar visual outcomes between treatment arms and a statistically significantly lower posterior capsule tear rate in the FLACS arm.[25]

Overall, it was thought that the potential advantages of FLACS were broad and would translate to greater safety and better visual outcomes through greater precision and reproducibility. These systems are expensive but costs may potentially be mitigated by greater efficiency (faster surgery), fewer complications, less repeat surgery and better outcomes. At the time of funding FACT, there was already a demand for FLACS among NHS patients, and some NHS trusts, were tendering for FLACS platforms.

Currently, the cost of FLACS still remains high, which reflects the high development costs. For example, Alcon (Geneva, Switzerland) took over LenSx for US$744M in 2010[26] and Abbott Medical Optics (Abbott Park, IL, USA) purchased OptiMedicaCorp. for up to US$400M in 2013.[27]

FACT will answer important questions about the potential introduction of laser cataract surgery platforms into NHS practice, and will also benchmark current surgical standards.

Aims and objectives

The aim of this trial is to determine if FLACS is as good as or better than PCS in NHS cataract surgical units. The proposed advantages were assessed by evaluating the following at 3 and 12 months post surgery:

- visual acuity – uncorrected distance visual acuity (UDVA) (primary outcome at 3 months) and corrected distance visual acuity (CDVA) (secondary outcome) in the study eye, measured using the ETDRS (Early Treatment Diabetic Retinopathy Study) chart at a distance of 4 m
- patient-reported outcome measures – vision health status using Catquest-9SF questionnaires
- ocular complications
- cost-effectiveness.

Chapter 2 Methods

Design and patients

FACT was a pragmatic, multicentre, single-masked, randomised controlled non-inferiority trial carried out at three hospitals in the UK to compare FLACS with PCS.[28] The three trial sites were high-volume NHS day care surgery units (Moorfields at St Ann's Hospital, Tottenham; Sussex Eye Hospital, Brighton; and New Cross Hospital, Wolverhampton). The trial received ethics approval from the National Research Ethics Service Committee London – City Road and Hampstead (6 February 2015, reference 14/LO/1937). The design of the trial is detailed in full in the published protocol,[28,29] and the final version (i.e. version 4.0) is available (https://fundingawards.nihr.ac.uk/award/13/04/46; accessed 5 October 2020). The trial adhered to the tenets of the Declaration of Helsinki.[30]

All patients were screened and recruited from routine cataract clinics between May 2015 and September 2017. In summary, adults aged $\geq$ 18 years with age-related cataract with expected postoperative refractive target within $\pm$ 0.5 dioptre of emmetropia (i.e. good distance vision) were eligible for participation. All patients provided written informed consent before participation. The patient inclusion and exclusion criteria are listed below, and there were no changes to these after trial commencement.

Participant inclusion criteria

- Adults aged $\geq$ 18 years with visually symptomatic cataract in one or both eyes.
- Patients must be willing to attend for follow-ups at 3 and 12 months following surgery in the study eye.
- Patients must be sufficiently fluent in English for informed consent and completion of the health state questionnaires.
- Postoperative intended refractive target in the study eye is within $\pm$ 0.5 dioptre of emmetropia.

Participant exclusion criteria

- Eyes with corneal ring and/or inlay implant(s), or severe corneal opacities, corneal abnormalities, significant corneal oedema or diminished aqueous clarity that are likely to obscure optical coherence tomography (OCT) imaging of the anterior lens capsule.
- Descemetocele with impending corneal rupture.
- Poor pupil dilatation that is expected to require surgical iris manipulation.
- Subluxed crystalline lens.
- Patient unable to give consent or unable to attend follow-up assessment.
- Patient unable to be positioned for surgery.
- Patient scheduled to undergo combined surgery (e.g. cataract and trabeculectomy).
- Any contraindications to cataract surgery.
- Any clinical condition that the investigator considers would make the patient unsuitable for the trial, including pregnancy.

Randomisation and masking

Participants were randomly assigned in a 1 : 1 ratio to undergo FLACS or PCS. Randomisation was performed on the day of surgery using a web-based online system (Sealed Envelope™, Sealed Envelope Ltd, London, UK; www.sealedenvelope.com) that used treatment centre, surgeon and one or both eyes eligible as minimisation stratifiers. For participants who required bilateral cataract surgery, the same intervention (i.e. FLACS or PCS) was offered when the patient returned for their second eye surgery,

unless the patient wished otherwise. When possible, the second eye was operated on within 8 weeks of the first. Owing to the nature of the intervention, surgeon and participant masking was not possible. All trial follow-ups were performed by optometrists who were masked to the trial intervention.

Procedures

All participants underwent dilated slit-lamp examination prior to being listed for cataract surgery by an ophthalmologist. Patients were treated identically whether they had one or two eligible eyes. All participants underwent either PCS or FLACS with the CATALYS® femtosecond laser (Johnson & Johnson Inc., New Brunswick, NJ, USA) or Femto LDV Z8 (Ziemer Ophthalmic Systems AG, Port, Switzerland) while under topical or local anaesthesia. Trial surgeons were ophthalmologists who routinely performed cataract surgery at their trial sites and who had completed at least 10 supervised FLACS operations and had been certified by the CATALYS or Ziemer manufacturer. In FLACS, the laser was used to perform the capsulotomy and lens fragmentation. Laser arcuate keratotomy could be performed using the CATALYS laser at the surgeon's discretion. Detailed descriptions of the use of CATALYS[31,32] and Femto LDV Z8[33,34] for cataract surgery have previously been published. All patients had planned implantation of a monofocal IOL. Standard phacoemulsification was performed as per local practice. Management of astigmatism was at the treating ophthalmologist's discretion. Prior to randomisation, the surgeon indicated if they would use a toric lens if local NHS funding arrangements permitted, a limbal relaxing incision for a PCS patient or an astigmatic keratotomy for a FLACS patient.

Postoperative care, including eye drops, was as per standard unit practice for cataract surgery. If the FLACS laser treatment could not be performed for any reason (e.g. unable to dock, laser machine fault) after a patient was randomised to this arm, the patient underwent PCS.

Follow-up assessments

Patients attended a follow-up visit at 3 and 12 months post surgery to undergo assessment of all end points and to complete all relevant trial questionnaires. If a patient was unable to attend the 3-month visit, they continued to be included in the trial and were encouraged to attend the 12-month follow-up visit. The majority of patients attended a check-up at 6 weeks post surgery (not part of the trial assessments schedule) as a routine part of cataract surgery care. Visual acuity data from this visit were obtained and are reported with the trial results.

Outcomes

The primary outcome was UDVA [measured using a ETDRS logMAR (logarithm of the minimum angle of resolution) chart at a starting distance of 4 m][35] in the study eye at the 3-month follow-up.

Secondary outcomes were CDVA at 3 months in the study eye, safety measures including intraoperative and postoperative complications and corneal endothelial cell count change, and refractive error (spherical equivalent) within 0.5 dioptre and within 1.0 dioptre of intended refractive outcomes. Health-related quality of life was assessed using the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), questionnaire plus the vision bolt-on question[36] at 6 weeks and 3 months, and patient-reported vision health status was assessed using Catquest-9SF[37] (a Rasch-validated instrument) at 6 weeks and 3 months. No changes were made to the trial outcomes after trial commencement.

Outcome measures are detailed in *Table 1* and also in the trial protocol (version 4.0, 27 September 2016). For participants without complete postal questionnaire data, a telephone interview was carried out for additional clarification and the completion of missing items. Staff measuring outcomes were all trained in doing so and masked to the trial arm for trial postoperative assessments, including visual acuity,

TABLE 1 Schedule of assessments

	Time point							
		Baseline	Randomisation	Follow-up				
	Standard pre-assessment	Surgical pre-assessment visit	Randomisation and surgery	Standard non-study post-operation appointment	6 weeks post surgery (postal)	First trial appointment: 3 months post surgery	6 months post surgery (postal)	Second trial appointment: 12 months post surgery
Visit	1	1 or later	2	3		4		5
Medical and ocular history	✗	✗						
Consent for cataract surgery	✗							
Informed consent and eligibility screening		✗						
Identification of study eye		✗						
Visual acuity: UDVA (logMAR), pinhole, with/without glasses (Snellen), each eye	✗			✗				
Visual acuity: UDVA[a] and CDVA[b] (logMAR) each eye and binocular						✗		✗
Visual acuity (logMAR) with usual method of correction			✗[c]					
Subjective refraction						✗		✗
Ocular biometry	✗							
Pentacam® (OCULUS Optikgeräte GmbH, Wetzlar, Germany) corneal topography	✗[d]	✗				✗		✗
OCT[e]	✗[d]	✗[f]		✗[d]		✗		✗

continued

TABLE 1 Schedule of assessments (*continued*)

	Time point							
		Baseline	Randomisation	Follow-up				
Visit	Standard pre-assessment 1	Surgical pre-assessment visit 1 or later	Randomisation and surgery 2	Standard non-study post-operation appointment 3	6 weeks post surgery (postal)	First trial appointment: 3 months post surgery 4	6 months post surgery (postal)	Second trial appointment: 12 months post surgery 5
Inclusion/exclusion criteria		✗						
Catquest-9SF questionnaire		✗			✗	✗	✗	✗
EQ-5D vision bolt-on		✗			✗	✗	✗	✗
Client Service Receipt Inventory[g]		✗				✗	✗	✗
Endothelial cell count measurement	✗[d]	✗[f]				✗		✗
Surgery			✗					
Adverse event collection					✗	✗	✗[h]	✗

a All visual acuity measures used the standard ETDRS logMAR chart at 4 m. At the baseline visit (the usual pre-assessment clinic for cataract surgery), ETDRS was the usual care visual acuity measure and, thus, could be taken prior to consent.
b CDVA using subjective refraction result.
c Current glasses or unaided.
d Some patients would have these tests performed at the standard pre-assessment visit, depending on the site's local procedure for surgical pre-assessment.
e OCT was measured as part of the standard pre-assessment for all patients. OCT was repeated at 3 and 12 months.
f Baseline procedures that should be repeated if surgery is delayed for > 3 months.
g The Client Service Receipt Inventory is a questionnaire for collecting retrospective information about study patients' use of health and social care services, accommodation and living situation, income, employment and benefits.
h Patient-reported complications only.

subjective refraction, corneal measurements and endothelial cell count. After these measures had been completed, complications data were collected by reviewing the patient medical notes (masking to this was not possible). Additional secondary outcomes were collected at 12 months postoperatively, including UDVA, CDVA, patient-reported health, safety outcomes and data for a health economic analysis.

Sample size

FACT was designed as a non-inferiority trial to demonstrate that visual acuity following FLACS is not inferior to that achieved following PCS. The non-inferiority margin was based on a difference in mean UDVA of 0.1 logMAR (5 letters or one line measured using a standard ETDRS chart at a starting distance of 4 m) in the study eye at 3 months, which was considered to be clinically important to patients and ophthalmologists based on prior patient and public input to the trial design.

Interpretation of the trial results is based on the 95% confidence interval (CI) for the difference between FLACS and PCS. If the 95% CI for the difference lies wholly to the left of the non-inferiority margin, then we can conclude that FLACS is not inferior to PCS. If the 95% CI for the difference lies wholly to the left of zero (i.e. the 95% CI excludes zero), then we can conclude that FLACS is superior to PCS. We performed sequential testing of the non-inferiority and superiority hypotheses.

If there is truly no difference in mean logMAR between the two treatment arms, then 432 patients (216 per arm) would provide 90% power to be sure that a 95% two-sided CI would exclude the non-inferiority limit of 0.1 logMAR, assuming a common standard deviation (SD) of 0.32.[38] However, although treatment was delivered to patients individually, each patient could not be assumed to generate independent information because patients were clustered within surgeons. To take account of clustering by surgeon (i.e. the variation between surgeons in the treatment effect) the sample size was increased by an inflation factor:

$$f = 1 + (m - 1) \times \rho. \quad (1)$$

Assuming that a total of 16 surgeons contributed an average cluster size (m) of 50 patients and an estimated intracluster correlation coefficient (ρ) of 0.012 gives an f of 1.59. Having a total of 688 patients (344 per arm) enabled the trial to take account of clustering by surgeon. To allow for an anticipated 15% dropout rate (the median age of patients undergoing cataract surgery in the UK is 77 years[38] and many have significant systemic comorbidities), the total sample size required was 808 patients.

Statistical analysis

All primary and secondary analyses were carried out on an intention-to-treat basis, such that all consented randomised participants who had attended the follow-up visits were included in the analysis set in their allocated treatment group, regardless of the treatment that they received. All analysis models included information on the site and on the number of eyes eligible as covariates; surgeon identifier was included in the analysis models as random effects. The model for the primary outcome was also adjusted for baseline habitual logMAR visual acuity values, and similar adjustments were made for any continuous secondary outcomes if a baseline value was recorded. Astigmatism at baseline (as measured by keratometry readings from Pentacam corneal topography) was incorporated as an adjustment factor in the analyses of visual acuity outcomes. Adjusted treatment effect estimates, two-sided 95% CIs and two-sided *p*-values were reported for each outcome measure.

In a pragmatic clinical trial in a predominantly elderly patient group, some patients are inevitably lost to follow-up. Outcomes for such patients were therefore not fully observed. This could lead to biased estimates and standard errors, which could potentially mask or artificially augment any treatment effect. To reduce any potential impact of bias, multiple imputation by chained equations (MICE) was used to impute data for any missing 3-month follow-up visits. Missing data were assumed to be missing at random conditional on all variables included in the imputation model and so to be independent of the values of the unobserved data themselves.

Enough imputed data were generated that the Monte Carlo error of the treatment effects estimated in the multiple imputation analysis was acceptably small (15 sets). The following (fully observed) variables were included in the imputation model: treatment arm, site, sex, age, ethnicity, astigmatism, prior ocular co-pathology, the number of eyes that were eligible for surgery, ocular complications and intraoperative complications. All available outcomes were included in the imputation model (UDVA, CDVA, central retinal thickness and spherical equivalent refraction index). In addition, postoperative visual acuity at 6 weeks, collected as part of NHS standard care, was included in the multiple imputation model.

For all continuous outcomes, including the primary outcome, of UDVA at 3 months, mixed-effects linear regression models were fitted to estimate the difference in outcomes between the two treatments (FLACS – PCS), together with a two-sided 95% CI, adjusting for baseline habitual logMAR visual acuity and the randomisation stratifiers (centre, surgeon and whether patients had one or two eligible eyes). Surgeon was included in the models as a random effect (random intercept) to account for clustering by surgeons. The effects were estimated using restricted maximum likelihood, and the results were presented using the mean difference with its corresponding 95% CI. For the primary outcome, if the upper end of the 95% CI for the difference between treatment means does not cross the non-inferiority limit of 0.1 logMAR, then FLACS is regarded as non-inferior. If the mean difference is negative and its 95% CI lies wholly to the left of zero, then we can conclude that FLACS cataract surgery is superior to PCS. Further supportive analyses of the primary outcome were also carried out, including a per-protocol analysis and a complete-case analysis. Binary secondary outcomes were analysed using mixed-effects logistic regression models, adjusting for stratification variables as above and baseline values as above.

The study eye is defined as the first eye to undergo cataract surgery and is chosen by the patient in discussion with the surgeon. For patients having surgery on both eyes, the fellow eye will also receive the allocated intervention unless the patient expresses a wish not to receive the same intervention. The fellow eye refers to fellow eyes eligible for trial surgery that received surgery after the study eye and within 3 months of study eye surgery. Note that where both eyes were eligible for surgery, there is no guarantee that the fellow eye received the same intervention as the study eye (as patients could express their wish not to receive the same intervention in the fellow eye). Given the observational nature of data on fellow eyes, outcomes are presented by treatment received and for the subgroup of patients who underwent surgery in the fellow eye within 3 months of surgery in the study eye.

Health economic analysis

The aim of the economic evaluation was to conduct a within-trial analysis of the mean incremental cost per quality-adjusted life-year (QALY) gained by FLACS compared with that gained by PCS over 12 months from a health and social care cost perspective. A secondary analysis from a societal cost perspective was also conducted.

Questionnaires

The following outcome measures were used for the trial-based component of the economic evaluation:

- Study case report form (CRF) – a researcher completed the pro forma that included information on the surgery. It included timings for the FLACS patients and details on anaesthesia, consumables, intraoperative adverse events and postoperative adverse events for patients in both arms.
- FACT costing study – this was a time-and-motion study of a sample of FLACS and PCS surgeries carried out by a trial research associate. This includes specific information on the timings of patient movements and the seniority of staff who were involved in the procedures.
- Client Service Receipt Inventory[39] – this is participant-completed questionnaire asking about health and social care resource use, the impact on employment, out-of-pocket costs and about the use of help from unpaid carers in the past 3 months at baseline and at 3 and 6 months post-surgery follow-up, and over the past 6 months at the 12-month follow-up.
- EQ-5D-3L – this is a five-item, three-level questionnaire, scored from 1 (no problem) to 3 (extreme problems). Value sets corresponding to participants' responses to the items are available from EuroQoL and the paper published by Dolan.[40] These value sets are used to calculate utility scores used in the QALY calculation. The EQ-5D-3L also includes a 100-point visual analogue scale, anchored at 0, the worst health imaginable, and 100, the best health imaginable. Participants mark how they feel on the day that they complete the measure. The vision bolt-on for the EQ-5D-3L was also completed, which has an associated utility tariff.[41]

Costs of FLACS and PCS

The incremental cost of FLACS compared with PCS was calculated using bottom-up microcosting based on data collected from sites and trial CRFs. *Table 2* lists all of the cost components used to cost FLACS and PCS and the details of how this costing was conducted; the costs of the components are based on standardised items used to cost the use of operating theatres.[46] The mean surgery time, including laser, for each patient was calculated using data from the FACT surgery CRF. Observational data were collected for 12 patients (FLACS arm, $n = 7$; PCS arm, $n = 5$) to assess if there were any key differences in how FLACS and PCS were delivered with regard to pre-surgery assessments and staffing, and to determine what model of delivery for FLACS was being used. Staffing levels were those recommended by the Association for Perioperative Practice.[46] Both FLACS and PCS had the same level of staffing except for a health-care assistant for the FLACS during that specific component of the surgery time only.

We conducted a sensitivity analysis to evaluate the impact of using an alternative model of delivery[47] whereby two theatres are used for FLACS at the same time. In this model, the level of staffing is the same, other than only one anaesthetist is needed across the two theatres.

A previous study by Roberts *et al.*[47] found no difference in consumable and anaesthetic costs between FLACS and PCS. As a result, consumables and anaesthetics were costed only if there were any significant differences in their use between the trial arms. The means, SDs and ranges were reported for each component.

Health, social care and societal costs

Health, social care and societal resource use was collected using a modified version of the Client Service Receipt Inventory[39] at baseline and at 3, 6 and 12 months, which asked about the past 3 months at baseline and at 3 and 6 months and about the past 6 months at 12 months. Health and social care resource use was costed using the Personal Social Services Research Unit (PSSRU)[43] and *NHS Reference Costs 2017–2018*[45] (*Table 3*). Private and out-of-pocket costs were assumed to be the same as publicly funded costs given that the quality of data on out-of-pocket costs was poor (this information was missing in the majority of cases). Household adaptations were costed from the PSSRU[43] and NRS Healthcare.[48] Participants were asked the number of hours of unpaid help they received from family and friends each week over the previous 3 or 6 months. This was then multiplied by the number of weeks (13 weeks for 3 months and 26 weeks for 6 months) and the cost per hour or unpaid carer time,

TABLE 2 Methods and sources used to calculate the incremental cost of FLACS vs. PCS

Cost component	Trial data source	Costing source and calculation
Capital cost of laser	Hospital finance data	Annualised per-patient cost, including depreciation in FLACS arm only[42]
Single-use patient interface for FLACS ('click fee')	Hospital finance data	Per-patient cost in FLACS arm only
Maintenance cost of laser	Hospital finance data	Per-patient cost in FLACS arm only
Surgeon training	Professional opinion (Alexander C Day, UCL, personal communication)	PSSRU[43] for surgeon costs
Preparing the patient and theatre before surgery		Assumed to be the same in both arms
Anaesthetist	FACT surgery CRF	Duration of surgery multiplied by the cost of anaesthetist time (from PSSRU)[43]
Anaesthetic drugs	FACT surgery CRF	Costed if different between arms; *British National Formulary*[44]
Nurse cost	FACT surgery CRF for the duration of surgery	Duration of preparation plus duration of surgery multiplied by weighted cost (accounting for different bands from PSSRU[43])
Surgeon	FACT surgery CRF for the duration of surgery	Duration of surgery multiplied by cost from PSSRU[43]
Health-care assistant for laser	FACT surgery CRF for the duration of FLACS laser	In FLACS arm only. Duration of laser multiplied by cost from PSSRU[43]
Consumables	FACT surgery CRF	Costed if different between the two treatment arms; costs from hospital finance data
Cleaning up after theatre		Assumed to be the same in both treatment arms
Recovery of patient		Assumed to be the same in both treatment arms
Medication following surgery	FACT surgery CRF	*British National Formulary*[44]
Adverse events	FACT surgery CRF	*NHS Reference Costs 2017–2018*[45]
Overhead activity	FACT surgery CRF for the duration of surgery	PSSRU[43] for overhead costs

PSSRU, Personal Social Services Research Unit; UCL, University College London.

costed the same as home help, at £28 per hour.[43] Lost earnings were costed as the mean hourly earnings in the UK in 2017/18 of £16.16 per hour.[49]

The means and SDs of each unit cost are reported for complete cases at each follow-up time point. The adjusted total difference in mean costs at 12 months for complete cases across all time points was calculated using linear regression and adjusting for baseline costs, site and number of eligible eyes and with surgeon as a random effect. All costs are reported in 2017/18 Great British pounds.

Quality-adjusted life-years

The primary measure used to calculate QALYs was the EQ-5D-3L. QALYs were calculated as the area under the curve[50] using the EQ-5D-3L utility values for the UK[40] at baseline and at 3, 6 and 12 months for complete cases at each time point. For the FLACS arm compared with the PCS arm, the mean utility values are reported at each time point, and the mean unadjusted QALYs are reported from baseline to 12 months for complete cases. The adjusted total difference in mean QALYs at 12 months for complete cases across all time points was calculated using linear regression, adjusting for baseline utilities, site and the number of eligible eyes and with surgeon as a random effect.

TABLE 3 Health and social care unit costs used in the cost-effectiveness analysis

Resource use	Unit cost (£) (per contact)	Source
GP: surgery	28	PSSRU[43]
GP: home visit	64	PSSRU[43]
GP: telephone	21	PSSRU[43]
Primary care nurse: telephone	9	PSSRU[43]
Primary care nurse: clinic	12	PSSRU[43]
District nurse	49	PSSRU[43]
Occupational therapist: home	99	PSSRU[43]
Occupational therapist: surgery	78	PSSRU[43]
Physiotherapist: home	63	PSSRU[43]
Physiotherapist: surgery	54	PSSRU[43]
Clinical nurse specialist	19	PSSRU[43]
Acute hospital day case	745	PSSRU[43]
Inpatient: one night	626	PSSRU[43]
Inpatient: more than one night	337 (per night)	*NHS Reference Costs 2017–2018*[45]
A&E attendance	160	*NHS Reference Costs 2017–2018*[45]
Outpatient	134	PSSRU[43]
Home help	14	PSSRU[43]
Social worker	31	PSSRU[43]

A&E, accident and emergency; GP, general practitioner.

A recently developed vision bolt-on question increases the sensitivity of the instrument to those populations whose primary condition is vision related.[36] As there is no agreed method for incorporating the vision tariff into QALY calculations, and to maintain consistency with National Institute for Health and Care Excellence (NICE) guidelines,[51] the primary analysis was based on the EQ-5D-3L without the additional vision question. A secondary analysis was conducted to calculate QALYs as the area under the curve using the vision tariff in addition to the EQ-5D-3L tariff to calculate the mean utility values at each time point for FLACS compared with PCS. The adjusted differences for total QALYs at 12 months were also reported.

Missing resource use or utilities data

The primary analysis was intention to treat. Assuming that the data are missing at random, MICE was used to impute missing costs and utilities at 3, 6 and 12 months, with age and ethnicity found to be predictors of missingness. A total of 60% of patients had missing resource use or utilities data for at least one follow-up point, and hence 60 imputed data sets were created.

Incremental cost-effectiveness ratio

The incremental cost-effectiveness ratio (ICER) was defined as the mean incremental cost of FLACS compared with PCS divided by the mean incremental QALYs of FLACS compared with PCS. The mean incremental differences were adjusted for baseline values, site and the number of eligible eyes. To account for the correlation between costs and QALYs, seemingly unrelated regression was used to calculate the numerator and denominator of the ICER. ICERs are reported for total health and social care costs, using the EQ-5D-5L to calculate QALYs in the primary analysis and using total societal costs and the vision bolt-on question to calculate QALYs in secondary analyses. The final results for total

costs and QALYs are based on imputed data, as described above, and the missing at random methodology described in Leurent *et al.*[52] is used for calculating cost-effectiveness acceptability curves (CEACs) using bootstrapping and MICE for 100 draws of each of the 60 imputed data sets for 6000 replications in total.

Cost-effectiveness acceptability curves and cost-effectiveness planes

The CEACs were calculated for each bootstrap imputed analysis to calculate the probability that FLACS is cost-effective compared with PCS at a range of values of willingness to pay (WTP) for a QALY gained. Cost-effectiveness planes have also been reported for each bootstrapped, imputed, analysis.

Secondary and sensitivity analyses

Secondary analyses were conducted (1) using the EQ-5D-3L vision bolt-on to calculate QALYs and (2) to calculate costs from a societal cost perspective.

For sensitivity analyses, we evaluated the impact of an alternative model of FLACS delivery with two theatres, as described above, as well as a threshold analysis to determine how much FLACS would need to cost either to be no longer cost-effective or to be cost-effective.

Patient and public involvement: lay advisory group

Cataract patients and relatives of patients with cataracts were invited from clinics at Moorfields Eye Hospital and formed our lay advisory group, who were consulted on trial design, choice of outcome measures, trial recruitment and treatment acceptability. The lay advisory group contributed directly to the tailored trial information leaflets and consent forms.

As required by the NHS, and by INVOLVE guidelines and UK Clinical Research Collaboration policy, the results of this trial are being communicated to patients via NHS Choices and the findings will be published in open-access media.

Chapter 3 Results

Participant enrolment

Of the 3448 patients assessed, 785 participants were enrolled between May 2015 and September 2017 and 392 were randomly assigned to the FLACS arm and 393 were randomly assigned to the PCS arm (*Figure 1*). Of these 785 participants, 653 were enrolled from Moorfields St Ann's, 100 were enrolled from New Cross Hospital and 32 were enrolled from Sussex Eye Hospital.

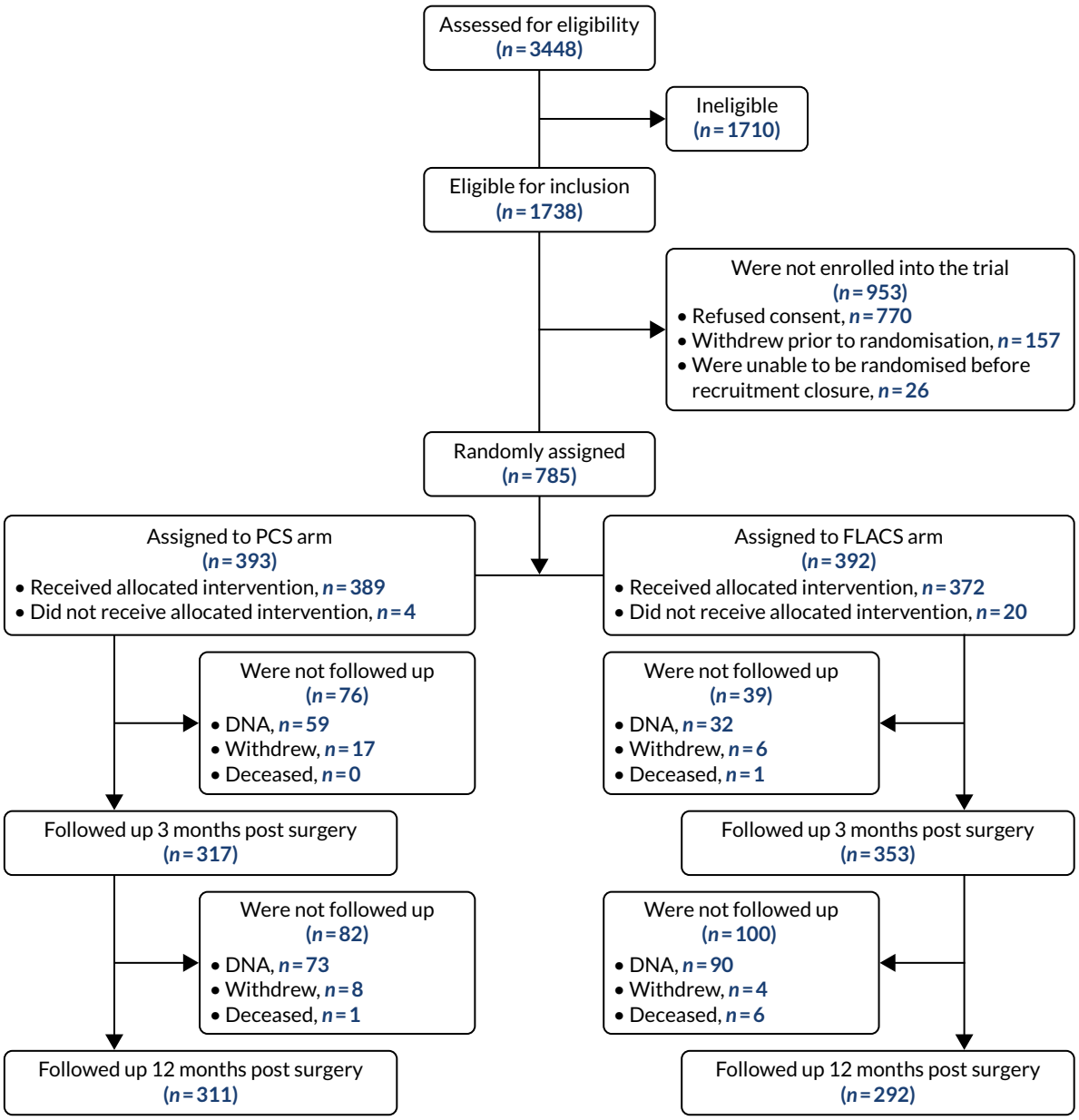

FIGURE 1 The trial profile. DNA, did not attend. Reproduced from Day *et al.*[1,2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

The main reasons participants were excluded ($n = 1710$) were not being sufficiently fluent in English for informed consent and trial questionnaire completion ($n = 564$), postoperative refractive target being outside ± 0.5 dioptre of emmetropia ($n = 180$), having poor pupil dilatation ($n = 176$) and not being willing to attend follow-up ($n = 155$). Of the 1738 patients eligible to participate, 770 declined to take part, 157 withdrew prior to randomisation and 26 were awaiting randomisation at recruitment closure.

Protocol deviations

Forty major protocol deviations were identified: not receiving treatment according to randomisation [25 participants (5.1%): 21 allocated to FLACS and four allocated to PCS]; and not fulfilling refractive target eligibility criteria (15 participants: 10 allocated to FLACS and five allocated to PCS (see *Appendix 1*). Overall, 352 out of 392 (90%) participants allocated to the FLACS arm and 317 out of 393 (81%) participants allocated to the PCS arm attended their follow-up visit at 3 months. *Figure 1* shows the trial profile.

Table 4 shows the trial population baseline characteristics by treatment arm. The participant demographics and preoperative ocular biometric characteristics in both arms were similar.

TABLE 4 Baseline characteristics of participants in the two treatment arms

Characteristic	Treatment arm	
	FLACS ($N = 392$)	PCS ($N = 393$)
Sex (male/female), *n* (%)	182 (46)/210 (54)	192 (49)/201 (51)
Previous cataract surgery (second eye cataract surgery in trial), *n* (%)	82 (21)	72 (18)
Right eye/left eye, *n* (%)	206 (53)/186 (47)	226 (57)/167 (43)
Age (years), mean (SD)	68 (10)	68 (10)
Ethnicity, *n* (%)		
White	281 (72)	272 (69)
Mixed	3 (0.8)	7 (2)
Asian or Asian British	33 (8)	46 (12)
Black or black British	57 (15)	52 (13)
Other ethnic group	18 (5)	15 (4)
Not declared	0 (0)	1 (0.3)
Anterior chamber depth (mm), mean (SD)	3.22 (0.41)	3.21 (0.39)
Axial length (mm), mean (SD)	24.00 (1.49)	23.97 (1.47)
Preoperative corneal astigmatism, *n* (%)		
< 0.75 dioptre	194 (49)	177 (45)
0.75 to < 2.0 dioptre	163 (42)	184 (47)
≥ 2.0 dioptre	34 (8.7)	29 (7.4)
Endothelial cell count (cells/mm^2), mean (SD)	2640 (334)	2604 (348)
Macular thickness (μm), mean (SD)	249 (42)	249 (41)
Ocular co-pathology, *n* (%)	128 (33)	140 (36)
Habitual UDVA logMAR, mean (SD)	0.61 (0.46)	0.68 (0.50)
Catquest-9SF score, mean (SD)	0.62 (1.7)	0.52 (1.7)

TABLE 4 Baseline characteristics of participants in the two treatment arms (*continued*)

Characteristic	Treatment arm	
	FLACS (*N* = 392)	PCS (*N* = 393)
EQ-5D-3L, mean (SD)	0.79 (0.24)	0.78 (0.25)
EQ-5D-3L VAS, mean (SD)	77.8 (18)	77.3 (18)
EQ-5D-3L: vision bolt-on, *n* (%)		
I have no problems seeing	149 (38)	137 (35)
I have some problems seeing	127 (32)	114 (29)
I have extreme problems seeing	6 (1.5)	5 (1.3)
Missing, *n* (%)	110 (28)	137 (35)

VAS, visual analogue scale.

The 3-month outcomes

Overall, 353 out of 392 (90%) participants allocated to the FLACS arm and 317 out of 393 (81%) participants allocated to the PCS arm attended their follow-up visit at 3 months. *Table 5* shows the postoperative results at 3 months by treatment arm for selected outcomes. The trial primary outcome was UDVA (logMAR). Additional outcomes for the study eye and all outcomes for the fellow eye can be found in *Appendix 2*.

TABLE 5 Three-month outcomes in the study eye by treatment arm

Outcome	Treatment arm		FLACS vs. PCS effect (95% CI)	*p*-value
	FLACS (*N* = 392)[a]	PCS (*N* = 393)		
Primary outcome: UDVA logMAR, imputed, mean (SD); *n*	0.13 (0.23); 392	0.14 (0.27); 393	−0.01 (−0.05 to 0.03)	0.63
UDVA logMAR, complete case, mean (SD); *n*	0.13 (0.23); 352	0.14 (0.26); 317	−0.01 (−0.04 to 0.03)	0.70
UDVA logMAR, per protocol, mean (SD); *n*	0.13 (0.22); 334	0.14 (0.26); 317	−0.01 (−0.05 to 0.02)	0.54
CDVA logMAR mean (SD); *n*	−0.01 (0.19); 352	0.01 (0.21); 317	−0.01 (−0.05 to 0.02)	0.34
SE refraction within ± 0.5 dioptre of target, *n* (%)	250/352 (71)	224/316 (71)	1.01 (0.72 to 1.41)	0.95
SE refraction within ± 1.0 dioptre of target, *n* (%)	327/352 (93)	292/316 (92)	1.08 (0.60 to 1.94)	0.80
Change in endothelial cell count (cells/mm^2): mean loss (SD); *n*	242 (416); 345	200 (369); 308	47 (−3 to 97)	0.06
Catquest 9-SF score, mean (SD); *n*	2.30 (1.31); 283	2.27 (1.30); 253	0.07 (−0.13 to 0.28)	0.49
EQ-5D-3L index score, mean (SD); *n*	0.84 (0.23); 351	0.82 (0.25); 323	0.0002 (−0.03 to 0.03)	0.88
I have no problems seeing, *n* (%)	235 (67)	220 (68)	–	–
I have some problems seeing, *n* (%)	114 (32)	100 (31)	–	–
I have extreme problems seeing, *n* (%)	3 (0.9)	3 (0.9)	–	–

SE, standard error.
a In total, 353 FLACS patients were seen at 3 months, but one patient had a missing value for the primary outcome.

Table 6 shows the intraoperative complications in the study eye by treatment arm.

Table 7 shows the postoperative complications in the study eye by treatment arm.

Figures 2 and *3* show the standardised graphs for reporting the outcomes of IOL surgery.[53]

TABLE 6 Three-month intraoperative complications in the study eye by treatment arm

Complication	Treatment arm (*n*)	
	FLACS	PCS
Anterior capsule tear	3	2
Posterior capsule tear with vitreous loss	0	0
Posterior capsule tear with no vitreous loss	0	2
Intraoperative pupil constriction needing intervention	3	1
Zonular dialysis with or without vitreous loss	1	0
Dropped lens fragments	0	0
Suprachoroidal haemorrhage	0	0
Incomplete laser capsulotomy	4	n/a

n/a, not applicable.

TABLE 7 Three-month postoperative complications in the study eye by treatment arm

Complication	Treatment arm, *n* (%)	
	FLACS	PCS
Postoperative anterior uveitis	34 (9.7)	32 (8.2)
Endophthalmitis	0 (0)	0 (0)
Vitreous to wound	1 (0.3)	1 (0.3)
Steroid response ocular hypertension	4 (1.0)	3 (0.8)
Macular oedema	8 (2.0)	7 (1.8)
Retinal tear or detachment	1 (0.3)	1 (0.3)
Medication allergy or intolerance	4 (1.0)	3 (0.8)
Corneal oedema	4 (1.0)	2 (0.5)

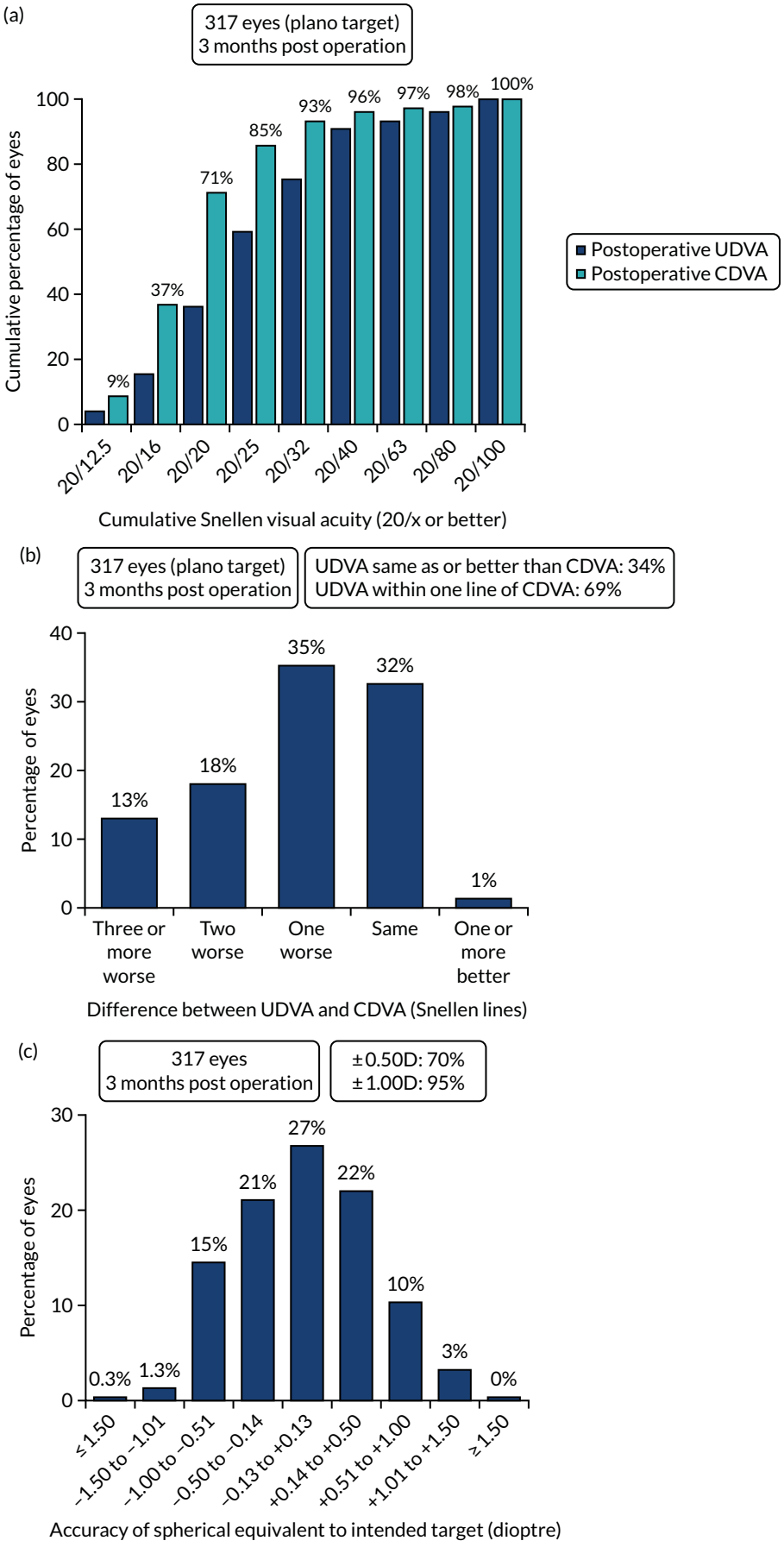

FIGURE 2 Outcomes of IOL surgery: PCS arm. (a) UDVA and CDVA; (b) difference between UDVA and CDVA; (c) accuracy of spherical equivalent refraction to target; and (d) refractive astigmatism. (*continued*)

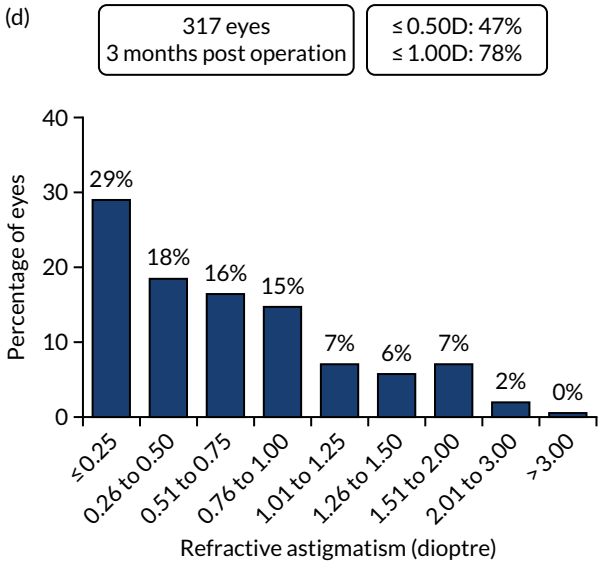

FIGURE 2 Outcomes of IOL surgery: PCS arm. (a) UDVA and CDVA; (b) difference between UDVA and CDVA; (c) accuracy of spherical equivalent refraction to target; and (d) refractive astigmatism.

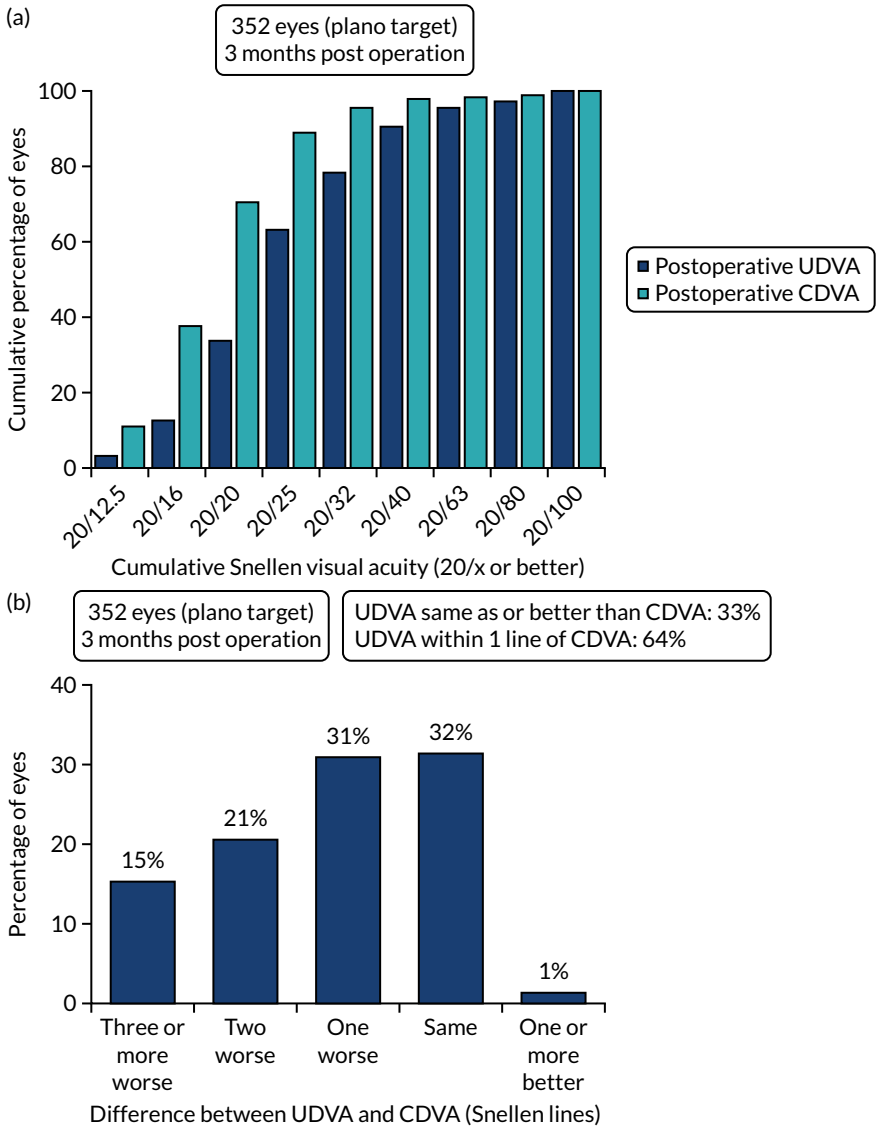

FIGURE 3 Outcomes of IOL surgery: FLACS arm. (a) UDVA; (b) UDVA vs. CDVA; (c) spherical equivalent refraction accuracy; and (d) refractive astigmatism. (*continued*)

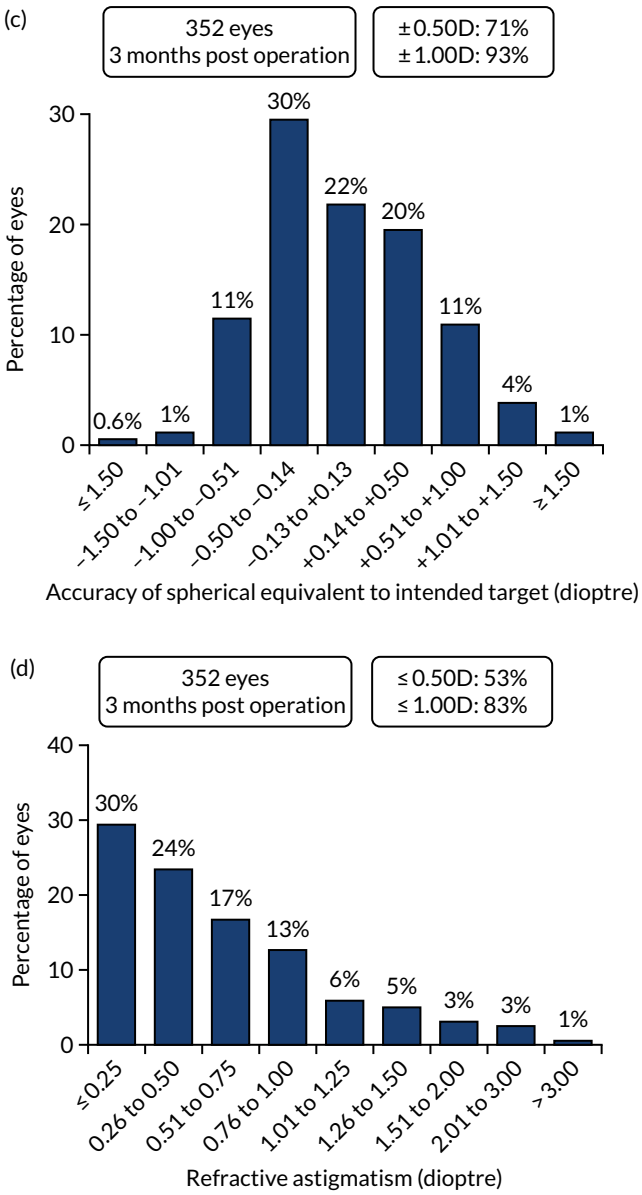

FIGURE 3 Outcomes of IOL surgery: FLACS arm. (a) UDVA; (b) UDVA vs. CDVA; (c) spherical equivalent refraction accuracy; and (d) refractive astigmatism.

The 12-month outcomes

Overall, 311 out of 392 (79%) participants allocated to the FLACS arm and 292 out of 393 (74%) participants allocated to the PCS arm attended their follow-up visit at 12 months.

The analysis of toric IOL use by arm showed that 22 toric lens were used in the FLACS arm (369 monofocal, one with data missing) and 19 toric lens were used in the PCS arm (370 monofocal, four with data missing). *Table 8* shows the postoperative visual and refractive outcomes at 12 months. Borderline statistical significance was met for CDVA both eyes open, with a mean CDVA difference of −0.02 logMAR (95% CI −0.05 to −0.002; $p = 0.036$) favouring the FLACS arm. There were no significant differences between the arms for any other outcome. Additional outcomes for the study eye and all outcomes for the fellow eye can be found in *Appendix 3*.

TABLE 8 The 12-month outcomes in the study eye by treatment arm

Outcome	Treatment arm		FLACS vs. PCS effect (95% CI)	*p*-value
	FLACS (*N* = 311)	PCS (*N* = 292)		
UDVA logMAR, study eye, mean (SD); *n*	0.14 (0.22); 310	0.17 (0.25); 291	−0.03 (−0.06 to 0.01)	0.17
UDVA logMAR, both eyes open, mean (SD); *n*	0.05 (0.16); 310	0.07 (0.20); 292	−0.03 (−0.05 to 0.003)	0.08
CDVA logMAR, study eye, mean (SD); *n*	0.003 (0.18); 311	0.03 (0.23); 292	−0.03 (−0.06 to 0.01)	0.11
CDVA logMAR, both eyes, mean (SD)	−0.05 (0.11); 310	−0.03 (0.17); 291	−0.02 (−0.05 to 0.002)	**0.036**
SE refraction within ± 0.5 dioptre of target, *n* (%)	230/307 (75)	218/290 (75)	0.99 (0.68 to 1.43)	0.94
SE refraction within ± 1.0 dioptre of target, *n* (%)	292/307 (95)	279/290 (96)	0.76 (0.34 to 1.69)	0.50
Catquest 9-SF score, mean (SD); *n*	2.94 (1.05); 318	2.96 (1.09); 300	0.01 (−0.15 to 0.17)	0.91
EQ-5D-3L index score, mean (SD); *n*	0.83 (0.23); 318	0.82 (0.25); 299	0.001 (−0.03 to 0.03)	0.95
I have no problems seeing, *n* (%)	242 (76)	231 (77)	–	–
I have some problems seeing, *n* (%)	70 (22)	62 (21)	–	–
I have extreme problems seeing, *n* (%)	6 (2)	6 (2)	–	–

SE, standard error. Bold text indicates statistical significance.

Figures 4 and *5* show the standardised graphs for reporting the outcomes of IOL surgery.[53]

Table 9 shows the postoperative complications at 12 months.

Table 10 shows the corneal endothelial cell measures at 12 months. There was no significant difference between the arms.

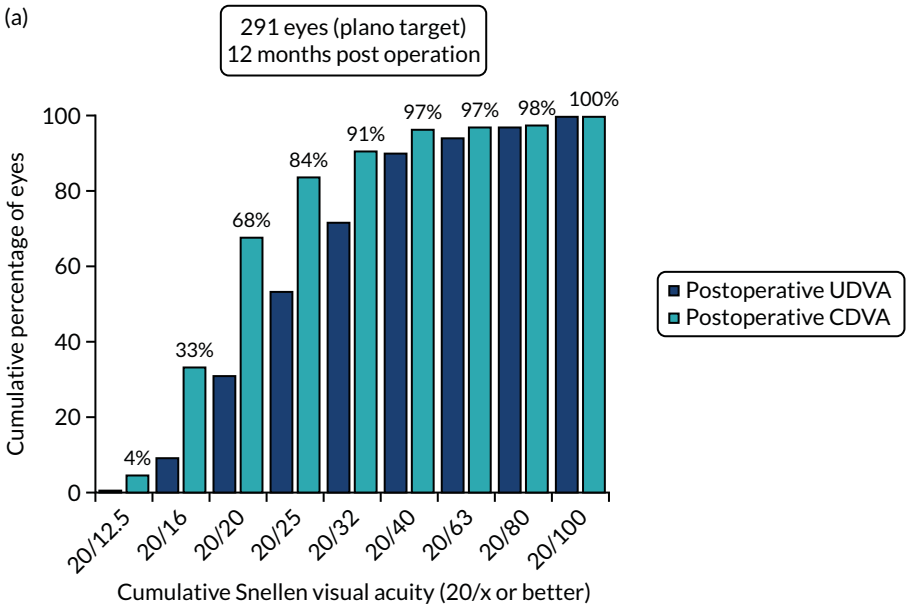

FIGURE 4 Standardised graphs: PCS arm at 12 months. (a) UDVA; (b) UDVA vs. CDVA; (c) spherical equivalent refraction; and (d) refractive cylinder. Reproduced from Day *et al.*[1,2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure. (*continued*)

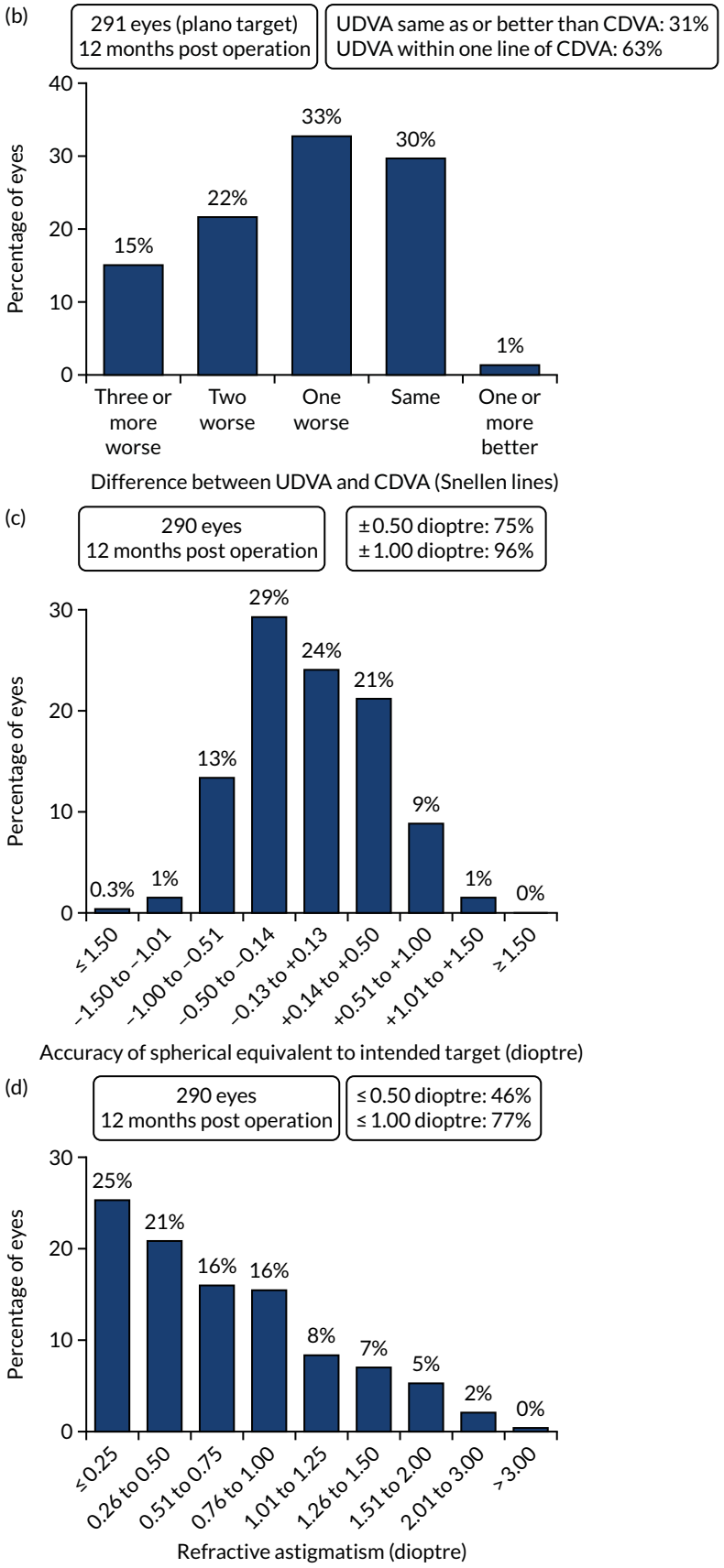

FIGURE 4 Standardised graphs: PCS arm at 12 months. (a) UDVA; (b) UDVA vs. CDVA; (c) spherical equivalent refraction; and (d) refractive cylinder. Reproduced from Day *et al.*[1,2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

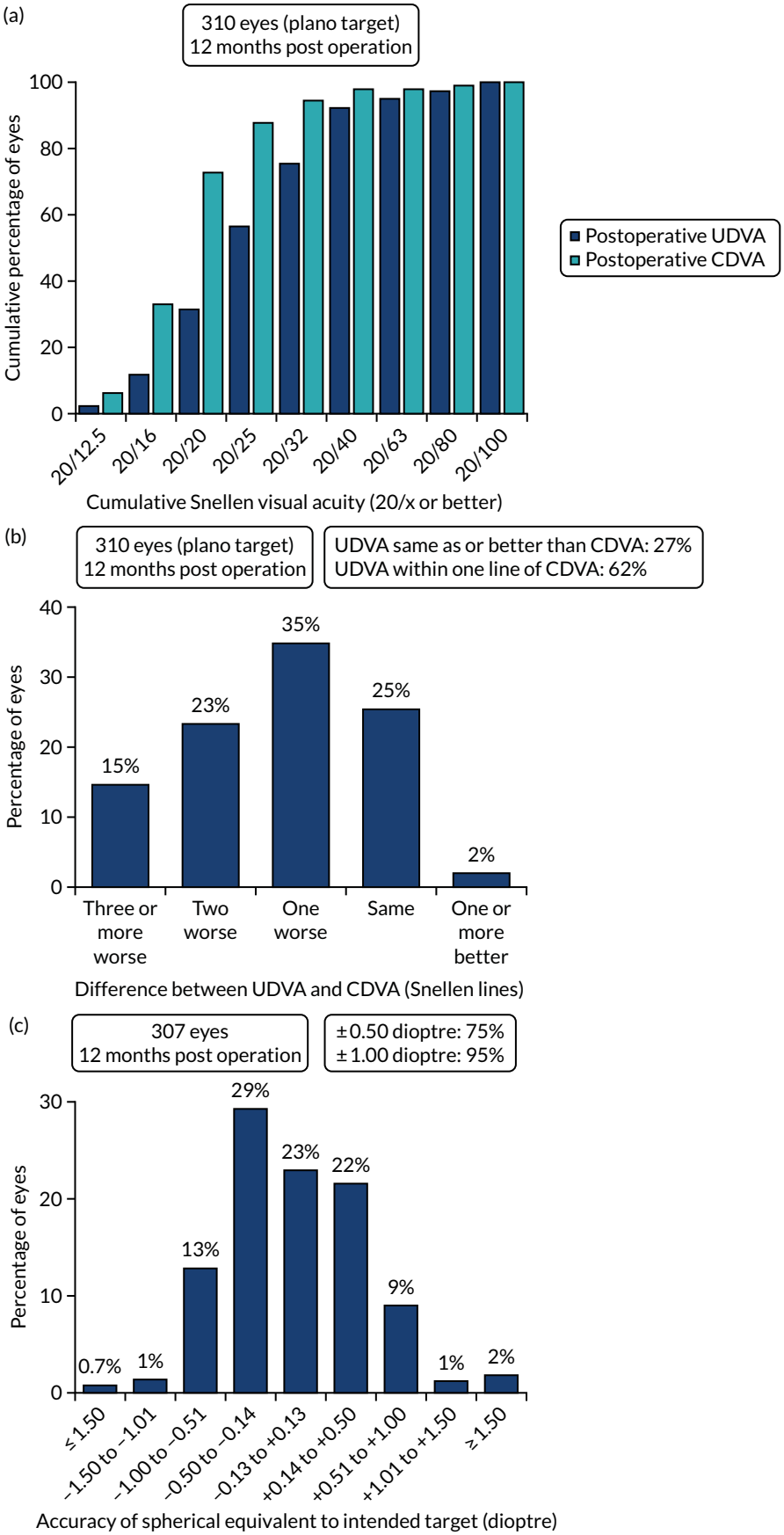

FIGURE 5 Standardised graphs: FLACS arm at 12 months. (a) UDVA; (b) UDVA vs. CDVA; (c) spherical equivalent refraction; and (d) refractive cylinder. Reproduced from Day *et al.*[1,2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure. (*continued*)

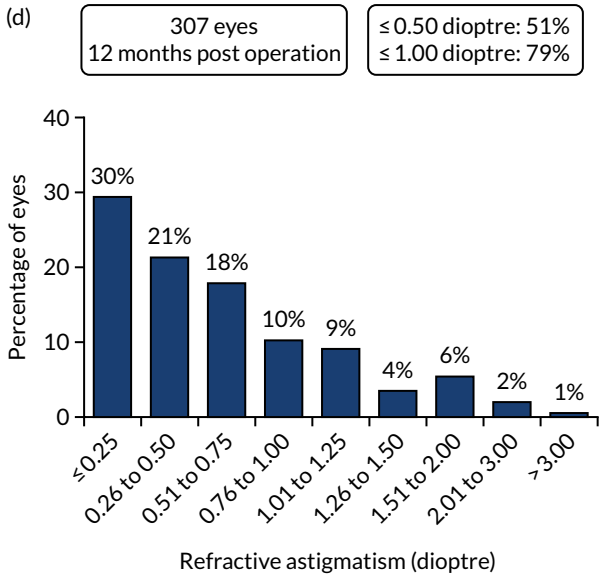

FIGURE 5 Standardised graphs: FLACS arm at 12 months. (a) UDVA; (b) UDVA vs. CDVA; (c) spherical equivalent refraction; and (d) refractive cylinder. Reproduced from Day *et al.*[1,2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

TABLE 9 The 12-month postoperative complications in the study eye by treatment arm

	Treatment arm, *n* (%)	
Complications	**FLACS**	**PCS**
Postoperative anterior uveitis	38 (9.7)	33 (8.4)
Endophthalmitis	0 (0)	0 (0)
Vitreous to wound	1 (0.3)	1 (0.3)
Steroid response ocular hypertension	7 (1.8)	3 (0.8)
Macular oedema	9 (2.3)	14 (3.6)
Posterior vitreous detachment	3 (0.8)	2 (0.5)
Retinal tear or detachment	2 (0.5)	3 (0.8)
Medication allergy or intolerance	4 (1.0)	3 (0.8)
Corneal oedema	8 (2.0)	2 (0.5)
Posterior capsule opacification	4 (1.0)	6 (1.5)

Participants may have had more than one event.
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TABLE 10 The 12-month corneal endothelial cell count in the study eye by treatment arm

Corneal endothelial cell count (cells/mm^2)	Treatment arm, mean (SD); *n*		FLACS vs. PCS effect (95% CI)	*p*-value
	FLACS (*N* = 307)	PCS (*N* = 286)		
Corneal endothelial cell count	2404 (434); 307	2412 (406); 286	40 (–8 to 89)	0.10
Change in endothelial cell count, mean loss	228 (353); 304	175 (312); 284	40 (–8 to 89)	0.10

Health economic results

Cost of the FLACS and PCS interventions

Based on the Association for Perioperative Practice guidance and evidence from the observational study,[46] the following staff were involved in delivering both the FLACS and PCS interventions:

- two nurses (one band 5 and one band 6)
- one operating department practitioner
- one health-care assistant
- one surgeon
- one anaesthetist.

A technician was also present when patients were allocated to the FLACS arm, but only for the duration of the actual FLACS treatment. The total staff and overhead cost per minute was £9.59 per minute in the FLACS arm during the actual FLACS treatment and £9.02 per minute in the FLACS and PCS arms during the time in the operating theatre.

In the FLACS arm, surgery took a mean of 17.1 minutes (SD 7.4 minutes). FLACS laser took an additional 3.9 minutes (SD 3.5 minutes), with a total time of 20.8 minutes (SD 8.2 minutes). In the PCS arm, surgery took 17.8 minutes (SD 8.0 minutes).

At a cost of £232,500 for the machine, and an annual maintenance cost of £16,221, the cost per patient for the machine, annuitising for a 5-year lifespan, is £26 if one assumes that each site sees 3000 patients per year for cataract surgery and 90.5% of patients are able to receive FLACS based on the exclusion criteria seen in the trial. There is also a per-patient cost of £130 for the patient interface, with a total machine cost per patient for FLACS of £156. If an 8-year lifespan is assumed, the cost per patient for the machine is £18, with a total cost per patient of £148 including the patient interface.

There was no significant difference in the use of anaesthetic drugs or consumables between treatment arms except for VisionBlue® [D.O.R.C. (Dutch Ophthalmic Research Center) (International) B.V., Zuidland, the Netherlands; used for staining the anterior capsule to increase visibility, 43 patients in the PCS arm compared with three patients in the FLACS arm] at a cost per vial of £8.65.

Surgeon training for FLACS comprised 10 sessions of using the laser. At a cost per minute of £1.80 for surgeon time and an average time of using the lasert in FLACS of 4 minutes, the total cost of training per surgeon is £70. Given a caseload of approximately 1000 cataracts per year (from professional opinion), the cost of training is very close to zero and hence has been excluded from the total cost.

The average total patient cost of surgery was £363.21 (95% CI £347.65 to £378.77) in the FLACS arm, compared with £174.58 (95% CI £163.24 to £185.92) in the PCS arm (*Table 11*). The analysis is intention to treat, in line with the analysis plan. As a result, it includes 20 patients who were randomised to the FLACS arm but received standard cataract surgery and so are costed as PCS. Five patients had missing surgery data and, therefore, are not included in the analysis. Details on adverse events are also reported in *Table 11*.

Health, social care and societal costs

Complete-case health and social care and societal costs and MICE total costs are reported in *Tables 12* and *13*. There were no significant differences between the two arms in any health and social care or societal costs. For societal costs, missing carer costs were imputed as zero because otherwise the missing data created issues in the analysis, as a patient who was missing data at multiple time points had skewed carer costs. The carer costs should be interpreted with caution as they are calculated from a single question: 'How many hours per week on average did [friends or relatives] help you over the last 3 months?'

Quality-adjusted life-years

There were no significant differences between the FLACS and PCS arms for the complete-case analysis of QALYs (*Table 14*) or for the MICE analysis of QALYs (*Table 15*).

Primary economic evaluation

The primary economic evaluation was a within-trial cost-effectiveness analysis over 12 months from a health and social care cost perspective using the EQ-5D-3L to calculate QALYs and using MICE for missing cost and utility data. Seemingly unrelated regression was used to account for correlation between costs and outcomes, with adjustment for baseline, site and the number of eyes that were eligible.

The mean cost difference (FLACS minus PCS) for the imputed, bootstrapped, adjusted data was £167.62 per patient (95% of iterations between -£14.12 and £341.67). The mean QALY difference (FLACS minus PCS) was 0.001 (95% of iterations between −0.011 and 0.015). This equates to an ICER (cost difference divided by QALY difference) of £167,620. The CEAC and cost-effectiveness planes are reported in *Figures 6* and *7*, respectively. There is a 24% probability that FLACS is cost-effective compared with PCS at a WTP threshold of £20,000 for a QALY gained and 30% probability at a £30,000 WTP threshold. As shown in *Figure 7*, the incremental mean cost of FLACS is greater than that of PCS for 97% of iterations, and in 53% of iterations FLACS has greater incremental mean QALYs.

TABLE 11 Total cost of surgery (£)

	Treatment arm, mean cost (SD)	
Cost	**FLACS ($n = 391$)**	**PCS ($n = 389$)**
Surgery staff cost	199.70 (78.38)	160.95 (72.26)
FLACS machine	146.70 (35.95)	0
Consumables: VisionBlue	0.11 (0.97)	0.90 (2.65)
Adverse events	14.12 (112.06)	8.90 (77.13)
Surgery medication	3.72 (1.41)	3.82 (1.80)
Total per patient	363.21 (156.5)	174.58 (113.78)

TABLE 12 Health and social care costs (£)

Cost	Treatment arm						Adjusted[a] mean difference	95% CI	*p*-value
	FLACS			PCS					
	n	Mean	SD	*n*	Mean	SD			
GP									
Baseline	383	45	61	375	48	57			
3 months	354	28	37	323	31	44			
6 months	265	35	44	242	42	65			
12 months	318	31	40	298	32	46			
Total cost	220	86	84	196	100	124	−0.080	−21.823 to 21.663	0.994
Community nurse									
Baseline	383	6	21	374	10	55			
3 months	353	7	57	323	23	274			
6 months	266	5	14	242	10	49			
12 months	318	8	35	298	6	30			
Total cost	221	21	84	195	20	50	1.637	−8.729 to 12.002	0.748
Occupational therapist									
Baseline	382	14	187	374	3	25			
3 months	353	1	16	323	4	27			
6 months	265	2	18	242	4	36			
12 months	318	3	24	298	5	34			
Total cost	220	6	39	195	11	57	−8.215	−17.578 to 1.147	0.083
Physiotherapist									
Baseline	381	14	127	375	8	48			
3 months	353	9	47	323	8	43			
6 months	265	4	28	242	9	41			
12 months	318	17	155	298	20	96			
Total cost	220	29	96	195	28	82	0.389321	−15.015 to 15.794	0.959
Other community									
Baseline	382	57	482	374	27	247			
3 months	352	8	63	322	38	460			
6 months	263	24	124	240	26	169			
12 months	318	9	72	298	24	198			
Total cost	218	36	123	193	121	716	−70.747	−156.78 to 15.286	0.103
Total community									
Baseline	383	135	589	375	95	283			
3 months	354	53	111	323	103	548			
6 months	266	69	141	243	89	234			
12 months	318	67	189	298	87	236			
Total cost	221	177	253	196	278	773	−89.789	−185.006 to 5.429	0.063

TABLE 12 Health and social care costs (£) (*continued*)

Cost	Treatment arm						Adjusted[a] mean difference	95% CI	*p*-value
	FLACS			PCS					
	n	Mean	SD	*n*	Mean	SD			
A&E									
Baseline	383	18	64	374	9	47			
3 months	354	20	61	323	22	69			
6 months	262	13	62	241	14	61			
12 months	318	14	50	298	15	77			
Total cost	217	41	101	193	45	118	−7.047	−26.578 to 12.48	0.464
Outpatient									
Baseline	383	65	176	374	98	321			
3 months	354	63	270	323	55	179			
6 months	262	63	163	241	68	160			
12 months	318	88	211	298	100	280			
Total cost	217	209	445	193	235	446	−22.879	−110.509 to 64.751	0.596
Inpatient									
Baseline	383	40	320	375	37	236			
3 months	354	72	518	323	45	418			
6 months	265	51	383	243	73	519			
12 months	318	104	757	298	89	422			
Total cost	219	248	1204	195	198	783	97.360	−86.520 to 281.250	0.286
Social care									
Baseline	382	3	44	375	3	34			
3 months	354	5	4	323	11	154			
6 months	267	2	27	244	4	38			
12 months	319	2	24	298	2	18			
Total cost	222	6	45	196	20	201	−16.578	−46.287 to 13.130	0.261
Total NHS and social care									
Baseline	383	262	750	375	289	958			
3 months	354	215	757	323	239	751			
6 months	267	201	495	244	262	743			
12 months	319	365	1444	298	304	641			
Total cost	222	750	1970	196	807	1477	−28.743	−290.488 to 233.002	0.823
MICE NHS and social care									
	n	*Mean*	*SE*	n	*Mean*	*SE*			
3 months (MICE)	383	215	43	375	226	40			
6 months (MICE)	383	196	29	375	210	34			
12 months (MICE)	383	312	60	375	304	37			
Total cost	383	723	88	375	741	74	−10.890	−234.124 to 212.344	0.924

A&E, accident and emergency; GP, general practitioner; SE, standard error.
a Adjusted for baseline costs, site, the number of eyes that were eligible and random surgeon effects.

TABLE 13 Societal costs

Cost	Treatment arm: FLACS *n*	FLACS Mean	FLACS SD	PCS *n*	PCS Mean	PCS SD	Adjusted[a] mean difference	95% CI	*p*-value
Home help private									
Baseline	382	0.69	8.47	375	0.21	2.56			
3 months	354	0.23	2.9	323	0.17	3.06			
6 months	266	0.42	5.5	244	0.25	3.93			
12 months	318	0.2	2.86	298	1.11	14.48			
Total cost	220	0.68	6.88	196	1.92	25.85	−1.75055	−6.19982 to 2.698725	0.425405
Unpaid carers									
Baseline	381	703	3834	373	667	2484			
3 months	353	623	2557	321	761	3799			
6 months	263	448	1857	239	755	2469			
12 months	319	669	3831	298	824	4485			
Total cost	373	1477	5732	357	1878	6911	−559.751	−1394.57 to 275.0671	0.179873
Reducing hours									
Baseline	383	11.18	66.81	375	8.58	54.47			
3 months	354	5.84	40.19	323	5.85	46.31			
6 months	266	0.3	4.95	244					
12 months	319			299	1.08	18.69			
Total cost	221	4.83	41	197	6.32	50.83	−1.41168	−12.1063 to 9.282926	0.787964
All societal									
Baseline	383	711	3830	375	672	2478			
3 months	354	627	2556	323	762	3787			
6 months	267	442	1845	244	740	2446			
12 months	319	669	3831	299	824	4478			
Total cost	374	1480	5726	358	1880	6901	−566.077	−1342.95 to 210.7933	0.146231
MICE all societal costs									
3 months	383	587	131	375	700	193			
6 months	383	337	85	375	824	154			
12 months	383	612	193	375	754	223			
Total cost	383	1537	308	375	2279	423	−761.396	−1783.597 to 260.804	0.144

a Adjusted for baseline costs, site, the number of eyes that were eligible and random surgeon effects.

TABLE 14 Utilities and QALYs

	Treatment arm								
	FLACS			PCS					
EQ-5D	*n*	Mean	SD	*n*	Mean	SD	Adjusted mean difference	95% CI	*p*-value
EQ-5D-3L									
Baseline	380	0.795	0.236	373	0.783	0.25			
6 weeks	280	0.81	0.271	254	0.813	0.253			
3 months	351	0.835	0.23	323	0.822	0.245			
6 months	262	0.824	0.26	234	0.812	0.255			
12 months	318	0.833	0.231	299	0.819	0.253			
QALYs	179	0.825	0.206	143	0.832	0.165	−0.011	−0.037 to 0.016	0.416
EQ-5D-3L vision bolt-on									
Baseline	380	0.769	0.249	373	0.759	0.26			
6 weeks	280	0.801	0.279	254	0.805	0.26			
3 months	351	0.829	0.232	323	0.816	0.25			
6 months	262	0.818	0.265	234	0.805	0.26			
12 months	318	0.828	0.233	299	0.814	0.257			
QALYs	179	0.819	0.209	143	0.826	0.169	−0.012	−0.038 to 0.014	0.360

TABLE 15 Multiple imputation by chained equations utilities and QALYs

	Treatment arm								
	FLACS			PCS					
EQ-5D	*n*	Mean	SD	*n*	Mean	SD	Adjusted mean difference	95% CI	*p*-value
EQ-5D-3L									
6 weeks	380	0.819	0.015	373	0.827	0.014			
3 months	380	0.844	0.012	373	0.835	0.013			
6 months	380	0.828	0.015	373	0.827	0.014			
12 months	380	0.839	0.012	373	0.827	0.014			
QALYs	380	0.815	0.010	373	0.810	0.001	0.0004	−0.022 to 0.023	0.974
EQ-5D-3L vision bolt-on									
6 weeks	380	0.810	0.015	373	0.818	0.014			
3 months	380	0.838	0.013	373	0.830	0.013			
6 months	380	0.822	0.015	373	0.822	0.014			
12 months	380	0.834	0.013	373	0.821	0.015			
QALYs	380	0.811	0.012	373	0.804	0.011	−0.004	−0.0284 to 0.0203	0.744

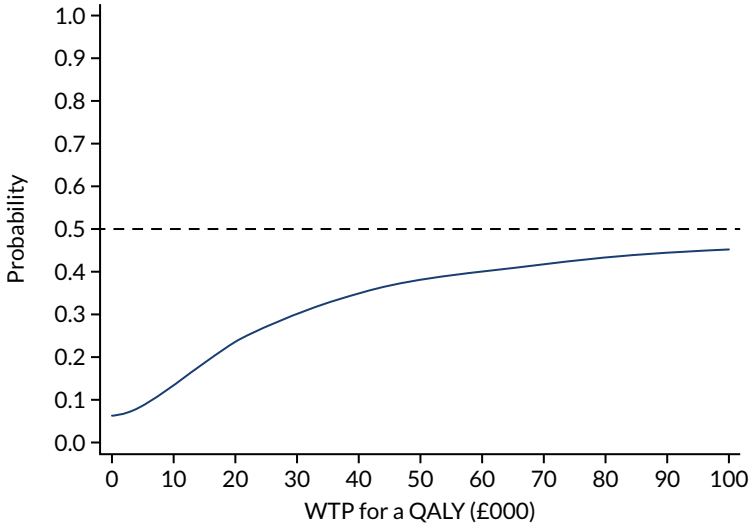

FIGURE 6 Cost-effectiveness acceptability curve of FLACS compared with PCS from a health and social care cost perspective: bootstrapped, adjusted with MICE.

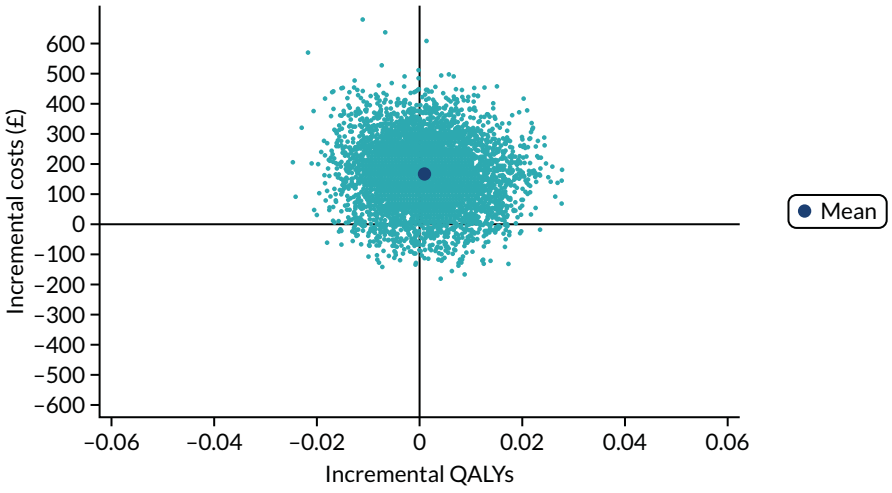

FIGURE 7 Cost-effectiveness plane of FLACS compared with PCS from a health and social care cost perspective: bootstrapped, adjusted with MICE.

Secondary and sensitivity analyses

Using the 3-month data only to calculate cost-effectiveness, in the MICE, bootstrapped and adjusted analysis, FLACS is dominated by PCS (mean cost difference of £171.70, 95% CI £57.59 to £285.80; mean QALY difference of −0.001, 95% CI −0.006 to 0.004).

When the vision bolt-on is included in the MICE, bootstrapped, adjusted results, PCS dominates FLACS, in that there is a mean cost difference of £234.94 (95% of iterations between £56.44 and £455.83) and the mean QALY difference is −0.003 (95% of iterations between −0.016 and 0.011). There is an 11% probability that FLACS is cost-effective compared with PCS at a WTP threshold of £20,000 for a QALY gained and a 16% probability at a £30,000 WTP threshold.

If two theatres are used at the same time, as opposed to just one, in the MICE, bootstrapped, adjusted results the ICER is £149,830, in that there is mean cost difference of £149.83 (95% of iterations between −£31.64 and £232.80) and the mean QALY difference is −0.001 (95% of iterations between −0.011 and 0.015). There is a 26% probability that FLACS is cost-effective compared with PCS at a WTP threshold of £20,000 for a QALY gained and a 32% probability at a £30,000 threshold.

In the societal analysis using MICE for missing data, and with the bootstrapped adjusted results, FLACS dominates PCS, with a mean cost saving of £623.53 per patient (95% of iterations between −£1431.27 and £203.24) and a mean QALY difference of 0.0004 (95% of iterations between −0.013 and 0.015). There is an 87% probability that FLACS is cost-effective compared with PCS at a £20,000 WTP for a QALY gained and an 86% probability at a £30,000 WTP threshold (*Figure 8*). The downwards slope of the CEAC is because of the very small number of additional negative incremental QALYs compared with positive incremental QALYs (50.2% vs. 49.8%, respectively).

For the threshold analysis from a health and social care cost perspective, assuming that FLACS results in an additional 0.001 QALYs per patient, FLACS needs to cost £138 less than it currently does to potentially be cost-effective at a WTP threshold of £30,000 for a QALY gained.

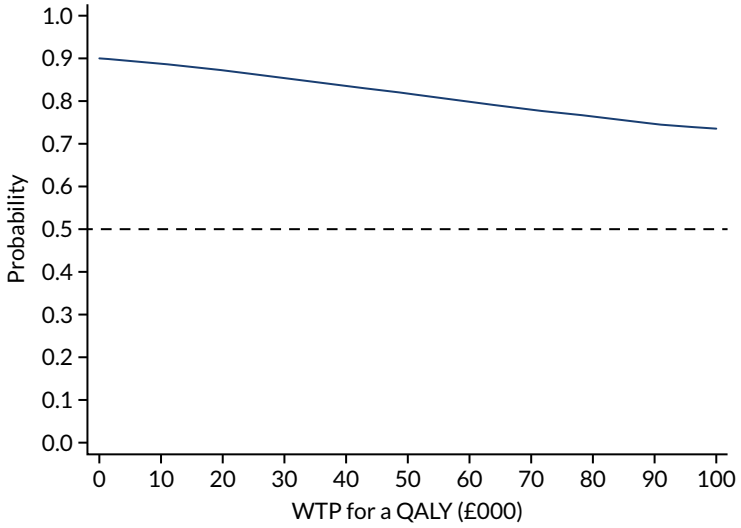

FIGURE 8 Cost-effectiveness acceptability curve of FLACS compared with conventional cataract surgery from a societal cost perspective: bootstrapped, adjusted with MICE.

Chapter 4 Discussion

The result of FACT is that FLACS is not inferior to PCS for UDVA 3 months postoperatively (the primary outcome). In addition, we found no significant difference in any of our secondary outcome measures by treatment arm with follow-up to 12 months, with the exception of binocular CDVA, which, although statistically significant, was not clinically significant.

Overall, our complication rates were lower than or comparable to previously published data from big data sets on cataract surgery outcomes.[38] Specifically, the PCR rates were 0.0% for FLACS and 0.5% for PCS, compared with a reported UK benchmark rate of 2.0%.[38] Reported PCR rates in the FEMCAT study were 1.4% for FLACS compared with 1.6% for PCS.[24] A RCT of 400 eyes of 400 patients from St Thomas' Hospital (London, UK) undergoing either FLACS or PCS found a statistically significantly lower PCR rate in the FLACS than in the PCS arm (0.0% vs. 3.0%).[25] Previously, there had been some concern over possible higher anterior capsule tear rates with FLACS because of the 'postage-stamp' edge pattern following laser capsulotomy creation, with rates of 1.9% reported for laser capsulotomy compared with 0.1% for standard capsulorrhexis in a comparative case series of 1626 surgeries.[54] In our trial, anterior capsule tear rates were 0.8% (3/392) for laser capsulotomy compared with 0.5% (2/393) for standard capsulorrhexis, and this difference did not reach statistical significance. In the St Thomas' laser cataract RCT,[25] the anterior capsule tear rate was 3.0% for FLACS cases and 1.5% for PCS, which did not reach statistical significance. In view of the low event rates of posterior capsule tears and anterior capsule tears, a meta-analysis of RCT outcomes is required to investigate this further.

For refractive outcomes, 75% of both FLACS and PCS cases were within ± 0.5 dioptre target, and 95% of FLACS cases and 96% of PCS cases within ± 1.0 dioptre target at 1 year, compared with 73% and 93% of eyes being within ± 0.5 dioptre and ± 1.0 dioptre target in a recent large EUREQUO (European Registry of Quality Outcomes for Cataract and Refractive Surgery) analysis of 282,811 cataract surgeries.[55] Comparative values from another recent large RCT of FLACS compared with standard PCS were 71% and 77% of eyes, respectively, within ± 0.5 dioptre, and 94% and 95% of eyes, respectively, within ± 1.0 dioptre.[25]

This trial was designed to have adequate power to detect important differences in vision and to minimise possible bias. It was publicly funded and designed to be representative of the publicly funded NHS in the UK. Masking the operating surgeon was not possible because of the surgery methodology, and, although trial participants were not masked to their allocated arm, we do not believe that this was a significant source of bias in the outcome measures. Interestingly, we did observe a small difference in the 3-month follow-up rates for those who underwent FLACS compared with those who underwent PCS, with 90% of FLACS patients attending follow-up compared with 80% of PCS patients. Participants who did not attend were contacted by identical methods to rebook within trial timescales and an additional sensitivity analysis does not suggest a difference in the characteristics of those who were lost to follow-up. A surgical learning curve effect is possible for FLACS, as all trial surgeons had performed hundreds to thousands of PCS compared with a minimum of 10 FLACS to meet trial surgeon eligibility. We have previously published data on the learning curve for FLACS and found that complications attributable to FLACS tend to occur in the first few patients,[56] but correspondence suggests that the learning curve may include the first 100 patients undergoing FLACS.[57] Even if the FLACS learning curve is 100 patients, the complication rate in the FLACS arm is low and so it is difficult to see how this would materially affect our findings. Another limitation is that the majority of patients were recruited from a high-volume cataract day surgery unit (St Ann's, Moorfields Eye Hospital, London, UK) and this may not be fully representative of the set-up in other areas of the UK. Trial recruitment (785 participants) was slightly below the planned 808 total; however, based on the pre-recruitment power calculation, the 95% CI for the difference in visual acuity (95% CI −0.05 to 0.03 logMAR) did not include our non-inferiority margin of 0.1 logMAR that was considered to be appropriate for cataract drug efficacy trials.[58]

FACT was not powered to identify differences in complications such as PCR that happen infrequently, and an additional meta-analysis of the available evidence is required to investigate possible differences in rare events.

FLACS automates cataract surgery steps, including capsulorrhexis, which can typically take < 1 minute to complete. This is a key step in surgical training, and delegating this step to a machine may have an impact on training, potentially affecting surgical cases that are unsuitable for FLACS and, therefore, by definition, technically more complex. In FACT, eligible surgeons were those who had completed 10 or more FLACS cases, and, although the trial was open to surgeons of all grades, we found that, anecdotally, specialist trainees were often not keen to take part as this would give them less experience of all the steps completed by hand in PCS.

The within-trial analysis conducted as part of FACT provides the best evidence that we are aware of to date of the cost-effectiveness of FLACS compared with PCS. Given that FLACS costs £216 more than PCS (£168 when any potential cost benefits from health and social care costs are included) and that the study has found no evidence of any additional benefit as a result of FLACS, there is a low probability that implementing FLACS is cost-effective for the NHS.

Based on the threshold analysis, FLACS would need to cost at least £138 less than it currently does to potentially be cost-effectiveness at a WTP threshold of £30,000 for a QALY gained (£168 if the non-significant difference in QALYs is not included). This cost is very close to that of the FLACS patient user interface. Even with a more efficient use of theatres, using two theatres at the same time, and hence saving some cost on staff that can work across theatres, FLACS has a 26% probability of being cost-effective at the upper NICE WTP threshold of £30,000 per QALY gained. Similar conclusions have been drawn by Roberts *et al.*,[47] who explored how FLACS could be implemented in the NHS so that it is cost neutral, using the model of two theatres functioning in parallel and staff working between the two. They came to the conclusion that either theatres would need to increase their list size by 100% or the cost of the patient interface would need to decrease by 70% for FLACS to approach cost saving. Based on the results of a decision model, Abell *et al.*[59] came to the conclusion that FLACS would need to significantly improve patient outcomes to be cost-effective in an Australian setting. The recent FEMCAT study concluded that FLACS was not cost-effective for the French health-care system.[24]

There was some evidence that FLACS is potentially cost-effective from a societal perspective. However, this result is predicated on the single question about time spent caring for a partner and, hence, should be interpreted with caution. There is a slight possibility that this question captured an impact on patients that is not captured elsewhere in the analysis, but there is limited evidence for this. Any future health economic evaluations in this area should continue to measure the impact on carers but should ensure that this is done using a validated measure of carer time, such as iMTA Valuation of Informal Care Questionnaire (iVICQ),[60] to ensure a more robust analysis. We may have underestimated the FLACS and PCS costs of surgeons for FLACS and PCS as these are based on the PSSRU[44] cost per hour, including overheads, but do not include an adjustment for additional activities conducted outside face-to-face time with patients.

Although the EuroQol-5 Dimensions (EQ-5D) is generally not recommended in trials involving eyes because it has been found to be unreliable at capturing changes in vision,[36] we included the vision bolt-on in an attempt to overcome this. The QALYs for the vision bolt-on are not significantly different from those for the EQ-5D-3L, although the mean is in a different direction (negative mean QALYs for the vision bolt-on compared with positive mean QALYs for the standard EQ-5D-3L). Given the results reported elsewhere in this report, it is unlikely that a condition-specific measure would have detected a change that the EQ-5D-3L and its vision bolt-on have failed to capture. We have not explored the cost-effectiveness for any of the other outcomes in the trial because there were no significant differences between arms and hence these analyses would have provided limited additional information.

Chapter 5 Conclusions

In summary, the results of FACT showed that FLACS is not inferior to PCS. The methods appear to be similar in terms of vision, patient-reported health and safety outcomes after 12 months' follow-up. FLACS is not cost-effective. Additional RCT data and meta-analyses are required to further investigate possible differences between the surgical methods due to the low complication rates and apparently similar efficacy.

Implications for health care

The results of this RCT provide the current best available evidence, to our knowledge, that is generalisable to the UK NHS. We did not find evidence for a change in practice to adopt FLACS in preference to PCS.

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- TSC: chairperson Professor David Spalton, Mr Andrew Elders, Mr Larry Benjamin and Mr Horace Cheung.

Independent members of the Data Monitoring Committee:

- Independent Data Monitoring Committee: chairperson Dr Chris Rogers, Miss Emma Hollick and Professor Augusto Azuara-Blanco.
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Contributions of authors

Alexander C Day (https://orcid.org/0000-0002-2099-8870) led the initial conception and design of the trial, led the writing of the protocol, acquired the funding and ethics approval, had complete involvement and oversight of the trial, provided clinical expertise and was the major contributor to manuscript writing.

Jennifer M Burr (https://orcid.org/0000-0002-9478-738X) contributed to the design of the trial and writing of the protocol. She also helped to acquire the funding and ethics approval, and contributed to the trial oversight and manuscript writing.

Kate Bennett (https://orcid.org/0000-0002-2358-4497) was responsible for the trial statistical analysis and helped with the manuscript writing.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Publications

Day AC, Burr JM, Bennett K, Bunce C, Doré CJ, Rubin GS, *et al.* Femtosecond laser-assisted cataract surgery versus phacoemulsification cataract surgery (FACT): a randomized noninferiority trial. *Ophthalmology* 2020;**127**:1012–19.

Day AC, Burr JM, Bennett K, Doré CJ, Bunce C, Hunter R, *et al.* Femtosecond laser-assisted cataract surgery compared with phacoemulsification cataract surgery: randomized noninferiority trial with 1-year outcomes. *J Cataract Refract Surg* 2020;**46**:1360–7.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Protocol deviations

Tables 16–18 detail the protocol deviations.

TABLE 16 Protocol deviation: participants not fulfilling inclusion criterion of postoperative intended refractive target in the study eye is within ± 0.5 dioptre of emmetropia

Participant identifier	Site	Date of event	Randomised group	Preventative action
FACT049	Moorfields	21 July 2015	FLACS	Eligibility checklist to be completed on day of surgery to ensure criterion is still met
FACT035	Moorfields	7 July 2015	FLACS	Eligibility checklist to be completed on day of surgery to ensure criterion is still met
FACT055	Moorfields	24 July 2016	FLACS	Eligibility checklist to be completed on day of surgery to ensure criterion is still met
FACT080	Moorfields	2 September 2015	FLACS	Trial manager has instructed site to use eligibility checklist to be completed on day of surgery to ensure criterion is still met. Co-ordinator to retrain surgeons and trial team
FACT202	Moorfields	26 January 2016	FLACS	Trial manager has instructed site to use eligibility checklist to be completed on day of surgery to ensure criterion is still met. Co-ordinator to retrain surgeons and trial team
FACT144	Moorfields	15 July 2016	FLACS	At time of randomisation the target was in range but it was noticed in theatre, at the time of surgery, that the lens was out of stock so an alternative strength was used, which took the refractive target out of range Investigators would check the availability of the lens required for FACT patients prior to randomisation
FACT315	Moorfields	24 May 2016	FLACS	
FACT004	Moorfields	27 May 2015	PCS	
FACT124	Moorfields	3 November 2016	PCS	Trial manager has instructed site to use eligibility checklist to be completed on day of surgery to ensure criterion is still met. Co-ordinator to retrain surgeons and trial team
FACT222	Moorfields	1 March 2016	PCS	
FACT371	Wolverhampton	16 June 2016	FLACS	The inclusion/exclusion checklist to be used prior to any patients being randomised in addition to responding to the eligibility questions on sealed envelope
FACT368	Wolverhampton	16 June 2016	FLACS	The inclusion/exclusion checklist to be used prior to any patients being randomised in addition to responding to the eligibility questions on sealed envelope
FACT374	Wolverhampton	16 June 2016	FLACS	The inclusion/exclusion checklist to be used prior to any patients being randomised in addition to responding to the eligibility questions on sealed envelope
FACT336	Wolverhampton	2 June 2016	PCS	The inclusion/exclusion checklist to be used prior to any patients being randomised in addition to responding to the eligibility questions on sealed envelope
FACT372	Wolverhampton	16 June 2016	PCS	

TABLE 17 Protocol deviation: participants not receiving treatment according to randomisation (1)

Participant identifier	Site	Date of event	Randomised group	Preventative action
FACT546	Moorfields	14 October 2016	FLACS	
FACT292	Moorfields	17 May 2016	FLACS	Trial team to be aware of number of patients recruited before the consent process

TABLE 18 Protocol deviation: participants not receiving treatment according to randomisation (2)

Participant identifier	Site	Date of event	Randomised group	Preventative action
FACT528	Moorfields	20 September 2016	FLACS	Equipment: engineer contacted
FACT608	Moorfields	14 December 2016	FLACS	Consider/test patient positioning
FACT118	Moorfields	21 October 2015	FLACS	Equipment failure: randomise individual patients as close to surgery as possible and avoid randomising patients in batches (one after the other). Once laser is complete and is prepared and ready for use, the next participant should be randomised
FACT777	Moorfields	22 September 2017	FLACS	Surgeon aware of the pupil size requirement for laser and will take extra precautions in future when considering patient eligibility
FACT269	Moorfields	26 April 2016	FLACS	Trial team instructed to be aware of and record pupil size of all patients during assessments taken at baseline visit
FACT695	Moorfields	11 May 2017	FLACS	Equipment malfunction: where possible, avoid proceeding with non-allocated treatment. Continue to inform UCL and contact helpdesk for device
FACT597	Moorfields	30 November 2016	FLACS	Equipment: research manager to check with technician that device is fully functioning prior to randomisation
FACT246	Moorfields	1 April 2016	FLACS	Equipment: the device reported as faulty to manufacturer on same day. Laser ready to use on same day
FACT741	Moorfields	14 July 2017	FLACS	Equipment: technician reminded to report technical faults to sponsor on day of occurrence
FACT245	Moorfields	1 April 2016	FLACS	Equipment: the device reported as faulty to manufacturer on same day. Laser ready to use on same day
FACT753	Moorfields	4 August 2017	FLACS	Surgeon was reminded of pupil size eligibility criterion after the study eye could not be lasered because of small pupil size
FACT527	Moorfields	20 September 2016	FLACS	Equipment: NAE reported to CCTU, engineer contacted
FACT482	Wolverhampton	18 August 2016	FLACS	Manual surgery performed
FACT325	Wolverhampton	26 May 2016	FLACS	Equipment: to ensure the laser is working before each randomisation. NAE reported to CCTU. Engineer called, issue now resolved
FACT533	Wolverhampton	29 September 2016	FLACS	Equipment: NAE reported, engineer contacted. Device now working

TABLE 18 Protocol deviation: participants not receiving treatment according to randomisation (2) (*continued*)

Participant identifier	Site	Date of event	Randomised group	Preventative action
FACT327	Wolverhampton	26 May 2016	FLACS	Equipment: NAE reported to CCTU. Engineer called, issue now resolved
FACT326	Wolverhampton	26 May 2016	FLACS	To ensure that the laser is working before each randomisation. NAE reported to CCTU. Engineer called, issue now resolved
FACT471	Brighton	9 August 2016	FLACS	Equipment: NAE reported to CCTU, engineer contacted, device now fixed

CCTU, Comprehensive Clinical Trials Unit; NAE, not available equipment.
Historically, all crossovers from arm B (FLACS) to arm A (PCS) were reported as deviations. However, from the protocol, it is apparent that crossover from arm B to arm A is allowed and, therefore, does not class as a deviation. Page 23 of version 4.0 the protocol states that 'where the laser treatment cannot be performed for whatever reason following randomisation to arm B (e.g. unable to dock, laser machine fault), patient will undergo surgery in accordance with arm A'.

Appendix 2 Full 3-month outcomes

Table 19 shows the number of patients screened by centre and *Table 20* shows the number of patients randomised by centre. *Figure 9* shows the number of patients consented and randomised each month. *Tables 21* and *22* show the baseline characteristics of trial patients by allocated treatment – study eye. *Tables 23* and *24* show the baseline characteristics of trial patients by treatment received – fellow eye. *Table 25* shows the frequency of intraoperative complications by treatment allocated (study eye) or by treatment received (fellow eye), and *Table 26* shows the results of the regression models (adjusted for stratification variables and baseline values) and safety events at 3 months in the study eye. *Table 27* shows the results of the regression models (adjusted for stratification variables) and safety events at 3 months in the fellow eye.

TABLE 19 Number of patients screened but not enrolled, and reasons[a] not enrolled, by centre

Reason for exclusion	Centre (*n*)			Total (*n*)
	MEH	SEH	NCH	
Total patients screened	3213	90	145	3448
Total exclusions	1688	14	8	1710
Reasons for exclusions[a]				
Eyes with corneal ring and/or inlay implant(s), or severe corneal opacities, corneal abnormalities, significant corneal oedema or diminished aqueous clarity that is likely to obscure OCT imaging of the anterior lens capsule	64	0	0	64
Adult, not aged ≥ 18 years with visually symptomatic cataract in one or both eyes	11	0	0	11
Not sufficiently fluent in English for informed consent and completion of the health state questionnaires	561	3	0	564
Postoperative intended refractive target in the study eye is not within ± 0.5 dioptre of emmetropia	180	0	0	180
Descemetocele with impending corneal rupture	0	0	0	0
Poor pupil dilatation that is expected to require surgical iris manipulation	176	0	0	176
Subluxed crystalline lens	2	0	0	2
Patient unable to give consent	97	4	0	101
Patient not willing to attend follow-up 3 and 12 months after cataract surgery in the study eye	152	3	0	155
Patient unable to be positioned for surgery	89	0	0	89
Patient scheduled to undergo combined surgery (e.g. cataract and trabeculectomy)	2	0	0	2
Any contraindications to cataract surgery	30	2	0	32
Any clinical condition that the investigator considers would make the patient unsuitable for the trial, including pregnancy	230	2	8	240
Other	94	0	0	94
Total eligible	**1525**	**76**	**137**	**1738**
Refused consent	706	41	23	770
Total withdrawn prior to randomisation	140	3	14	157
Awaiting randomisation at recruitment closure	26	0	0	26
Randomised	**653**	**32**	**100**	**785**

MEH, St Ann's at Moorfields Eye Hospital; NCH, New Cross Hospital; SHE, Sussex Eye Hospital.
a Only one reason is tabulated for each patient.

TABLE 20 Number of patients randomised by month and centre

Year	Month	Centre (*n*)			Total (*n*)
		MEH	SEH	NCH	
2015	May	5	0	0	5
	June	23	0	0	23
	July	30	0	0	30
	August	19	0	0	19
	September	22	0	0	22
	October	24	0	0	24
	November	32	0	0	32
	December	23	0	0	23
2016	January	27	0	0	27
	February	15	0	0	15
	March	21	3	0	24
	April	30	4	0	34
	May	30	11	15	56
	June	34	4	18	56
	July	26	5	31	62
	August	29	5	18	52
	September	24	0	8	32
	October	24	0	0	24
	November	27	0	10	37
	December	17	0	0	17
2017	January	18	0	0	18
	February	20	0	0	20
	March	21	0	0	21
	April	13	0	0	13
	May	19	0	0	19
	June	27	0	0	27
	July	18	0	0	18
	August	10	0	0	10
	September	25	0	0	25
Total		653	32	100	785

MEH, St Ann's at Moorfields Eye Hospital; NCH, New Cross Hospital; SHE, Sussex Eye Hospital.

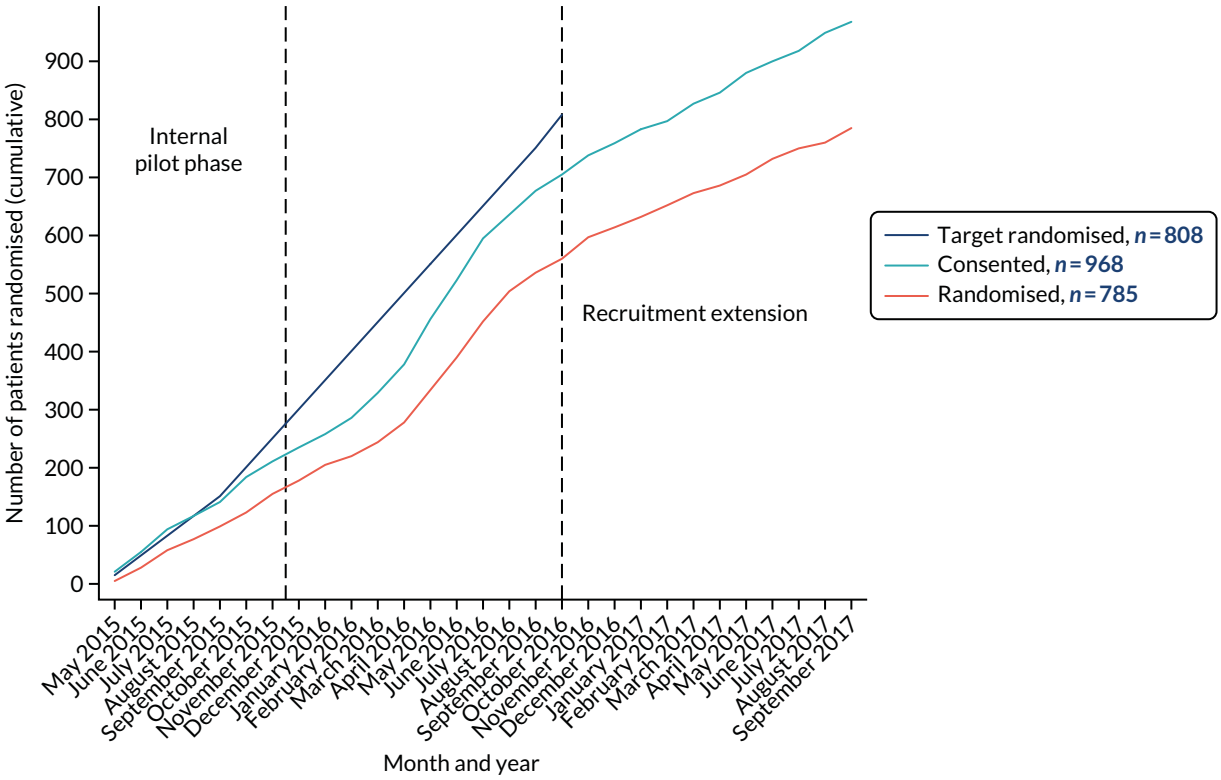

FIGURE 9 Number of patients consented and randomised each month.

TABLE 21 Baseline characteristics of trial patients by allocated treatment: study eye (1)

Characteristic	Category	Treatment arm			
		FLACS (*N* = 392)	Minimum to maximum	PCS (*N* = 393)	Minimum to maximum
Sex, *n* (%)	Male	182 (46)		192 (49)	
	Female	210 (54)		201 (51)	
Age (years), mean (SD)		68.3 (9.8)	31 to 96	68.2 (10.4)	31 to 90
Study eye, *n* (%)	Right	206 (52.6)		226 (57.5)	
	Left	186 (47.4)		167 (42.5)	
Ethnicity, *n* (%)	White	281 (72)		272 (69)	
	Mixed	3 (0.8)		7 (2)	
	Asian or Asian British	33 (8)		46 (12)	
	Black or black British	57 (15)		52 (13)	
	Other ethnic groups	18 (5)		15 (4)	
	Missing	0 (0)		1 (0.3)	
Deviations from randomised treatment allocation (received other treatment), *n* (%)		20 (5.1)		0 (0)	

continued

TABLE 21 Baseline characteristics of trial patients by allocated treatment: study eye (1) (*continued*)

Characteristic	Category	Treatment arm			
		FLACS (*N* = 392)	Minimum to maximum	PCS (*N* = 393)	Minimum to maximum
Stratification variables*, n *(%)					
Eyes eligible for surgery	One eye	166 (42)		167 (43)	
	Both eyes	226 (58)		226 (58)	
Surgeon grade	Consultants	153 (39)		150 (38)	
	Fellows	239 (61)		243 (62)	
Centre[a]	Moorfields	326 (83)		327 (83)	
	Wolverhampton	50 (13)		50 (13)	
	Brighton	16 (4)		16 (4)	
Preoperative astigmatism					
Pentacam data					
Corneal astigmatism,[b] *n* (%)	< 0.75 dioptre	141 (36)		151 (38)	
	0.75 to < 2.0 dioptre	131 (33)		134 (34)	
	≥ 2.0 dioptre	26 (6.6)		22 (5.6)	
	Missing, *n* (%)	94 (24)		86 (22)	
Corneal astigmatism[b] (dioptre)	Mean (SD)	0.94 (0.67)	0 to 3.90	0.92 (0.74)	0 to 6.50
	Missing, *n* (%)	94 (24)		86 (22)	
IOL master					
Corneal astigmatism,[b] *n* (%)	< 0.75 dioptre	194 (49)		177 (45)	
	0.75 to < 2.0 dioptre	163 (42)		184 (47)	
	≥ 2.0 dioptre	34 (8.7)		29 (7.4)	
	Missing, *n* (%)	1 (0.3)		3 (0.8)	
Corneal astigmatism[b] (dioptre)	Mean (SD)	0.92 (0.68)	0 to 3.69	0.95 (0.72)	0 to 6.59
	Missing, *n* (%)	1 (0.3)		3 (0.8)	
Astigmatic keratotomy complete, *n* (%)	Yes	21 (6)		n/a	
	Not planned	349 (89)		n/a	
	Missing	22 (5.6)		n/a	
Axial length (mm)	Mean (SD)	24.00 (1.49)	19.93 to 29.17	23.97 (1.47)	19.00 to 29.34
	Missing, *n* (%)	2 (0.5)		2 (0.5)	
Intended refractive target (dioptre)	Mean (SD)	0.25 (0.14)	0 to 0.88	0.25 (0.14)	0 to 1.25
Intended refractive target (dioptre), *n* (%)	Within ± 0.5 dioptre	381 (97)		384 (98)	
	Within ± 1.0 dioptre	10 (2.6)		4 (1.0)	
	Outside ± 1.0 dioptre	0 (0)		1 (0.3)	
	Missing, *n* (%)	1 (0.3)		4 (1.0)	
Central retinal thickness (μm)	Mean (SD)	249 (42)	140 to 585	249 (41)	118 to 523
	Missing, *n* (%)	33 (8.4)		30 (7.6)	

TABLE 21 Baseline characteristics of trial patients by allocated treatment: study eye (1) (*continued*)

Characteristic	Category	Treatment arm			
		FLACS (*N* = 392)	Minimum to maximum	PCS (*N* = 393)	Minimum to maximum
Anterior chamber depth (µm)	Mean (SD)	3.22 (0.41)	2.12 to 4.36	3.21 (0.39)	2.05 to 4.51
	Missing, *n* (%)	2 (0.5)		2 (0.5)	
Previous cataract surgery (before enrolling in trial), *n* (%)		82 (21)		72 (18)	
Ocular co-pathology,[c] *n* (%)	Present	128 (33)		140 (36)	
	Absent	264 (67)		253 (64)	
Type of ocular co-pathology, *n* (%)	Glaucoma	15 (3.8)		17 (4.3)	
	Diabetic retinopathy	11 (2.8)		8 (2.0)	
	Brunescent or white cataract	16 (4.1)		17 (4.3)	
	No fundal view or vitreous opacities	7 (1.8)		11 (2.8)	
	Pseudoexfoliation or phacodonesis	3 (0.8)		3 (0.8)	
	Previous vitrectomy	21 (5.4)		26 (6.6)	
	Age-related macular degeneration	18 (4.6)		25 (6.4)	
	High myopia (> −6 dioptre)	29 (7.4)		31 (7.9)	
	Amblyopia	7 (1.8)		7 (1.8)	
	Corneal pathology	8 (2.0)		11 (2.8)	
	Other ocular co-pathology	34 (8.7)		35 (8.9)	
	Previous cataract surgery	82 (21)		72 (18)	

n/a, not applicable.
a MEH, St Ann's at Moorfields Eye Hospital (St. Ann's); NCH, The Royal Wolverhampton (New Cross Hospital); SEH, Brighton & Sussex University Hospital (Sussex Eye).
b Absolute values.
c Number of patients with at least one co-pathology.

TABLE 22 Baseline characteristics of trial patients by allocated treatment: study eye (2)

Demographics	Category	Treatment arm			
		FLACS (*N* = 392)	Minimum to maximum	PCS (*N* = 393)	Minimum to maximum
Visual acuity					
Habitual UDVA, logMAR[a]	Mean (SD)	0.61 (0.46)	−0.18 to 2.4	0.68 (0.50)	−0.26 to 2.7
	Missing, *n* (%)	0 (0)		4 (4)	
Safety					
Preoperative corneal endothelial cell count (cells/mm^2)	Mean (SD)	2640 (334)	518 to 3428	2604 (348)	658 to 3387
	Missing, *n* (%)	8 (2.0)		6 (1.5)	
Quality of life					
Catquest-9SF	Mean (SD)	0.62 (1.7)		0.52 (1.7)	
	Missing, *n* (%)	12 (3.1)		19 (4.8)	
EQ-5D-3L health utility	Mean (SD)	0.79 (0.24)		0.78 (0.25)	
	Missing, *n* (%)	12 (3.1)		20 (5.1)	
EQ-5D-3L health state – VAS	Mean (SD)	77.8 (18)		77.3 (18)	
	Missing, *n* (%)	116 (30)		149 (38)	
EQ-5D-3L vision bolt-on, *n* (%)	I have no problems seeing	149 (38)		137 (35)	
	I have some problems seeing	127 (32)		114 (29)	
	I have extreme problems seeing	6 (1.5)		5 (1.3)	
	Missing, *n* (%)	110 (28)		137 (35)	

VAS, visual analogue scale.
a Visual acuity (logMAR) with the patient's usual method of correction (current glasses or unaided).

TABLE 23 Baseline characteristics of trial patients by treatment received: fellow eye (1)

Demographics	Category	Treatment arm			
		FLACS (*N* = 136)	Minimum to maximum	PCS (*N* = 181)	Minimum to maximum
Sex, *n* (%)	Male	61 (44.8)		87 (48.1)	
	Female	75 (55.2)		94 (51.9)	
Age (years), mean (SD)		69.1 (9.0)	43 to 91	70.0 (10.0)	42 to 90
Fellow eye, *n* (%)	Right	58 (42.6)		71 (39.2)	
	Left	78 (57.4)		110 (60.8)	
Ethnicity, *n* (%)	White	88 (64.7)		125 (69.1)	
	Mixed	0 (0)		4 (2.2)	
	Asian or Asian British	15 (11.0)		18 (9.9)	
	Black or black British	22 (16.2)		27 (14.9)	
	Other ethnic group	11 (8.1)		7 (3.9)	

TABLE 23 Baseline characteristics of trial patients by treatment received: fellow eye (1) (*continued*)

Demographics	Category	Treatment arm			
		FLACS (*N* = 136)	Minimum to maximum	PCS (*N* = 181)	Minimum to maximum
Stratification variables,[a] **n *(%)***					
Eyes eligible for surgery[b]	One eye	11 (8.1)		17 (9.4)	
	Both eyes	125 (91.9)		164 (90.6)	
Surgeon grade	Consultants	59 (43.4)		71 (39.2)	
	Fellows	77 (56.6)		110 (60.8)	
Centre	MEH	117 (86.0)		159 (87.8)	
	SEH	10 (7.4)		9 (5.0)	
	NCH	9 (6.6)		13 (7.2)	
Preoperative astigmatism					
Pentacam data					
Corneal astigmatism,[c] *n* (%)	< 0.75 dioptre	85 (62.5)		110 (60.8)	
	0.75 to < 2.0 dioptre	44 (32.4)		60 (33.2)	
	≥ 2.0 dioptre	7 (5.2)		11 (6.1)	
Corneal astigmatism[c] (dioptre)	Mean (SD)	0.87 (0.58)	0 to 2.6	0.96 (0.77)	0.1 to 6.2
	Missing, *n* (%)	31 (22.8)		42 (23.2)	
IOL master					
Corneal astigmatism,[c] *n* (%)	< 0.75 dioptre	61 (45)		76 (42)	
	0.75 to < 2.0 dioptre	64 (47)		90 (50)	
	≥ 2.0 dioptre	11 (8.1)		15 (8.3)	
Corneal astigmatism[c] (dioptre)	Mean (SD)	0.97 (0.65)	0 to 3.47	0.97 (0.73)	0 to 6.06
Astigmatic keratotomy complete	Yes	8 (5.9)		n/a	
	Not planned	128 (94)		n/a	
	Missing *n* (%)	0 (0)		n/a	
Axial length (mm)	Mean (SD)	24.07 (1.56)	19.14 to 28.40	23.78 (1.23)	20.44 to 29.31
Intended refractive target (dioptre)	Mean (SD)	0.34 (0.36)	0 to 2.19	0.30 (0.26)	0.01 to 1.75
Intended refractive target (dioptre), *n* (%)	Within ± 0.5 dioptre	126 (92.6)		170 (93.9)	
	Within ± 1.0 dioptre	2 (1.5)		3 (1.7)	
	Outside ± 1.0 dioptre	8 (5.9)		8 (4.4)	
Central retinal thickness (μm)	Mean (SD)	245.8 (40.3)		247.0 (32.8)	
	Missing, *n* (%)	9 (6.6)		2 (1.1)	
Anterior chamber depth	Mean (SD)	3.22 (0.43)	2.20 to 4.39	3.15 (0.38)	2.00 to 3.99
	Missing, *n* (%)	1 (0.7)		0	

continued

TABLE 23 Baseline characteristics of trial patients by treatment received: fellow eye (1) (*continued*)

Demographics	Category	Treatment arm			
		FLACS (*N* = 136)	Minimum to maximum	PCS (*N* = 181)	Minimum to maximum
Fellow eye surgery					
Fellow eye received the allocated study eye treatment, *n* (%)	Yes	135 (99.3)		165 (91.2)	
	No	1 (0.7)		16 (8.8)	
Time from previous study eye cataract surgery to fellow eye surgery (days)	Median (IQR)	42 (28–63)		42 (28–63)	
Anterior chamber depth (μm)	Mean (SD)	3.22 (0.4)	2.12 to 4.36	3.21 (0.4)	2.05 to 4.51
	Missing, *n* (%)	2 (0.5)		2 (0.5)	
Ocular co-pathology,[d] *n* (%)	Present	47 (34.6)		38 (21.0)	
	Absent	89 (65.4)		143 (79.0)	
Type of ocular co-pathology, *n*	Glaucoma	4 (2.9)		5 (2.8)	
	Diabetic retinopathy	4 (2.9)		4 (2.2)	
	Brunescent or white cataract	3 (2.2)		2 (1.1)	
	No fundal view or vitreous opacities	0 (0)		2 (1.1)	
	Pseudoexfoliation or phacodonesis	1 (0.7)		1 (0.6)	
	Previous vitrectomy	3 (2.2)		1 (0.6)	
	Age-related macular degeneration	9 (6.6)		14 (7.7)	
	High myopia (> −6 dioptre)	17 (12.5)		5 (2.8)	
	Amblyopia	2 (1.5)		1 (0.6)	
	Corneal pathology	4 (2.9)		4 (2.2)	
	Other ocular co-pathology	11 (8.1)		13 (7.2)	

MEH, St Ann's at Moorfields Eye Hospital (St. Ann's); n/a, not appliable; NCH, The Royal Wolverhampton (New Cross Hospital); SEH, Brighton & Sussex University Hospital (Sussex Eye).
a Both eyes have to be eligible and, therefore, we do not present data relating to 'eyes eligible for surgery'.
b In the opinion of the surgeon at the start of the trial.
c Absolute values.
d Number of patients with at least one co-pathology.

TABLE 24 Baseline characteristics of trial patients by treatment received: fellow eye (2)

Characteristic	Category	Treatment arm			
		FLACS (*N* = 136)	Minimum to maximum	PCS (*N* = 181)	Minimum to maximum
Safety					
Preoperative corneal endothelial cell count (cells/mm^2)	Mean (SD)	2664 (291)	970–3166	2593 (394)	676–3244
	Missing, *n* (%)	3 (2.2)		3 (1.7)	
Quality of life					
Catquest-9SF	Mean (SD)	0.36 (1.78)		0.45 (1.68)	
	Missing, *n* (%)	3 (2.2)		7 (3.9)	
EQ-5D-3L health utility	Mean (SD)	0.92 (0.09)		0.92 (0.10)	
	Missing, *n* (%)	35 (25.7)		58 (32.0)	
EQ-5D-3L health state – VAS	Mean (SD)	79.1 (16.0)		77.1 (17.8)	
	Missing, *n* (%)	36 (26.5)		61 (33.7)	
EQ-5D-3L vision bolt-on, *n* (%)	I have no problems seeing	49 (36.0)		62 (34.3)	
	I have some problems seeing	52 (38.2)		58 (32.0)	
	I have extreme problems seeing	0 (0)		3 (1.7)	
	Missing, *n* (%)	35 (25.8)		58 (32.0)	

VAS, visual analogue scale.

TABLE 25 Frequency of intraoperative complications by treatment allocated (study eye) or by treatment received (fellow eye)

Eye	Treatment arm	
	FLACS	PCS
Study eye	**N = *392***	**N = *393***
Intraoperative complications,[a] *n* (%)	11 (2.8)	5 (1.3)
Reported intraoperative complications, *n*		
Anterior capsule tear	3	2
Posterior capsule tear with vitreous loss	0	0
Posterior capsule tear no vitreous loss	0	2
Intraoperative pupil constriction needing intervention	3	1
Dropped lens fragments or nucleus	0	0
Choroidal haemorrhage	0	0
Zonular dialysis	1	0
Failure to dock laser	0	
Aborted or incomplete laser delivery	0	
Incomplete capsulotomy identified in surgery, requiring manual completion	4	
Laser delivery to inappropriate structure of eye	0	

continued

TABLE 25 Frequency of intraoperative complications by treatment allocated (study eye) or by treatment received (fellow eye) (*continued*)

Eye	Treatment arm	
	FLACS	PCS
Fellow eye	**N = *136***	**N = *181***
Intraoperative complications,[a] *n*/*N* (%)	9 (6.6)	2 (1.1)
Anterior capsule tear	3	1
Posterior capsule tear with vitreous loss	1	0
Posterior capsule tear no vitreous loss	1	0
Intraoperative pupil constriction needing intervention	3	0
Dropped lens fragments or nucleus	0	0
Choroidal haemorrhage	0	0
Zonular dialysis	0	1
Failure to dock laser	0	
Aborted or incomplete laser delivery	0	
Incomplete capsulotomy identified in surgery, requiring manual completion	2	
Laser delivery to inappropriate structure of eye	0	

a Number of patients with one or more complications.

TABLE 26 Results of the regression models (adjusted for stratification variables and baseline values) and safety events at 3 months: study eye

	Treatment arm		Effect (FLACS vs. PCS), adjusted coefficient (95% CI)[a] unless stated otherwise	*p*-value
	FLACS (*N* = 392)	PCS (*N* = 393)		
Primary outcome				
UDVA logMAR (imputed), mean (SD); *n*	0.13 (0.23)	0.14 (0.27)	−0.01 (−0.05 to 0.03)	0.63
UDVA logMAR (complete case), mean (SD); *n*	0.13 (0.23); 352	0.14 (0.26); 317	−0.01 (−0.04 to 0.03)	0.70
UDVA logMAR (per protocol), mean (SD); *n*	0.13 (0.22); 334	0.14 (0.26); 317	−0.01 (−0.05 to 0.02)	0.54
Secondary outcomes				
Distance visual acuity				
UDVA logMAR – both eyes open, mean (SD); *n*	0.06 (0.16); 351	0.07 (0.19); 316	−0.01 (−0.03 to 0.02)	0.58
CDVA logMAR, mean (SD); *n*	−0.01 (0.19); 352	0.01 (0.21); 317	−0.01 (−0.05 to 0.02)	0.34
CDVA logMAR – both eyes open, mean (SD); *n*	−0.04 (0.18); 351	−0.04 (0.16); 316	0.00 (−0.02 to 0.03)	0.89
Refractive data				
Achieved refractive target, *n* (%)			Adjusted odds ratio (95% CI)	
Within ± 0.50 dioptre	250/352 (71)	224/316 (71)	1.01 (0.72 to 1.41)	0.95
Within ± 1.00 dioptre	327/352 (93)	292/316 (92)	1.08 (0.60 to 1.94)	0.80

TABLE 26 Results of the regression models (adjusted for stratification variables and baseline values) and safety events at 3 months: study eye (*continued*)

	Treatment arm		Effect (FLACS vs. PCS), adjusted coefficient (95% CI)[a] unless stated otherwise	*p*-value
	FLACS (*N* = 392)	PCS (*N* = 393)		
Quality of life				
Catquest-9SF score, mean (SD); *n*	2.30 (1.31); 283	2.27 (1.30); 253	0.07 (−0.13 to 0.28)	0.49
EQ-5D-3L health utility, mean (SD); *n*	0.84 (0.23); 351	0.82 (0.25); 323	0.002 (−0.03 to 0.03)	0.88
EQ-5D-3L health state – VAS, mean (SD); *n*	79 (17); 353	78 (18); 320	0.61 (−1.70 to 2.92)	0.61
EQ-5D-3L vison bolt-on, *n* (%)				
I have no problems seeing	235 (67)	220 (68)		
I have some problems seeing	114 (32)	100 (31)		
I have extreme problems seeing	3 (0.9)	3 (0.9)		
Safety				
Corneal endothelial cell count (cells/mm^2); adjusted for baseline, mean (SD); *n*	2398 (492); 346	2376 (500); 311	47.3 (−2.66 to 97.2)	0.06
Corneal endothelial cell loss (from baseline) (cells/mm^2), mean (SD); *n*	242 (416); 345	200 (369); 308	47.3 (−2.66 to 97.2)	0.06
Postoperative ocular AEs, patients with at least one event, *n*/*N* (%)	144/392 (36.7)	124/393 (31.6)	0.05 (−0.02 to 0.12)	0.13
Expected ocular AEs,*[b] n *(%)				***0.52***
Postoperative uveitis	34 (9.7)	32 (8.2)		
Endophthalmitis	0	0		
Retinal tear or retinal detachment	1 (0.3)	1 (0.3)		
Elevated intraocular pressure requiring treatment	4 (1.0)	3 (0.8)		
Medication allergy or intolerance	4 (1.0)	3 (0.8)		
Macular oedema	8 (2.0)	7 (1.8)		
Corneal oedema	4 (1.0)	2 (0.5)		
Vitreous to wound	1 (0.3)	1 (0.3)		
Other ocular surgery	1 (0.3)	1 (0.3)		
Unexpected ocular AEs,* n *(%)				***0.06***
Posterior vitreous detachment	3 (0.8)	1 (0.3)		
Cracked/damaged IOL	0	2 (0.5)		
Capsular block	2 (0.5)	0		
Posterior capsule opacification	0	3 (0.8)		
Corneal abrasion	4 (0.8)	1 (0.3)		
Cataract remnant post operation	1 (0.3)	0		
IOL subluxation	1 (0.3)	1 (0.3)		
Other ocular (definitely, possibly or probably related to surgery)	85 (22)	58 (15)		

continued

TABLE 26 Results of the regression models (adjusted for stratification variables and baseline values) and safety events at 3 months: study eye (*continued*)

	Treatment arm		Effect (FLACS vs. PCS), adjusted coefficient (95% CI)[a] unless stated otherwise	*p*-value
	FLACS (*N* = 392)	PCS (*N* = 393)		
Other ocular (unrelated or unlikely to be related to surgery)	91 (23)	75 (19)		
SAEs; patients with at least one event	36 (9)	27 (7)	0.02 (−0.11 to 0.16)	0.24
Exploratory outcomes				
Central retinal thickness (μm), mean (SD); *n*	258 (40.8) 348	264 (51.6) 311	−4.88 (−11.3 to 1.58)	0.14
Spherical equivalent refraction error (dioptre), mean (SD); *n*	−0.22 (0.55) 351	−0.22 (0.54) 316	0.01 (−0.10 to 0.09)	0.89
Corneal astigmatism, *n* (%)			Adjusted odds ratio (from mixed-effects ordinal regression)	0.87
< 0.75 dioptre	136 (35)	133 (34)	1.03 (0.73 to 1.44)	
0.75 to < 2.0 dioptre	113 (29)	112 (29)		
≥ 2.0 dioptre	29 (7.4)	20 (5.1)		
Missing	113 (29)	128 (33)		
Corneal astigmatism (dioptre), mean (SD); *n*	0.96 (0.76); 278	0.94 (0.72); 265	−0.02 (−0.11 to 0.07)	0.68
Refractive astigmatism, *n* (%)			Adjusted odds ratio (from mixed-effects ordinal regression)	0.17
< 0.75 dioptre	187 (48)	149 (38)	0.81 (0.60 to 1.09)	
0.75 to < 2.0 dioptre	151 (39)	156 (40)		
≥ 2.0 dioptre	14 (3.6)	11 (2.8)		
Missing	40 (10)	77 (20)		
Refractive astigmatism (dioptre), mean (SD); *n*	0.72 (0.66); 352	0.76 (0.62); 316		
UDVA 6 weeks post-surgery, logMAR (NHS records), mean (SD); *n*	0.14 (0.20); 384	0.15 (0.23); 384	−0.01 (−0.04 to 0.02)	0.50
Visual acuity outcomes excluding patients with ocular co-pathology at baseline				
UDVA logMAR, mean (SD); *n*	0.11 (0.19); 240	0.10 (0.22); 204	0.01 (−0.03 to 0.05)	0.60
UDVA logMAR – both eyes open, mean (SD); *n*	0.04 (0.14); 239	0.04 (0.15); 204	0.01 (−0.02 to 0.03)	0.68
CDVA logMAR, mean (SD); *n*	−0.04 (0.14); 240	−0.02 (0.17); 204	−0.01 (−0.04 to 0.02)	0.43
CDVA logMAR – both eyes open, mean (SD); *n*	−0.06 (0.14); 239	−0.06 (0.12); 204	0.01 (−0.02 to 0.03)	0.52

VAS, visual analogue scale.
a All efficacy outcomes adjusted for site, the number of eyes that were eligible and random surgeon effects. Primary outcome also adjusted for baseline habitual logMAR visual acuity values.
b Patients may have experienced more than one event.
All visual acuity outcomes also adjusted for baseline astigmatism (Pentacam corneal topography). All secondary outcomes are analysed using complete cases only.

TABLE 27 Results of the regression models adjusted for stratification variables and safety events at 3 months: fellow eye

	Treatment arm		Effect (FLACS vs. PCS), difference (95% CI)	*p*-value
	FLACS (*N* = 136)	PCS (*N* = 181)		
Distance visual acuity				
UDVA logMAR, mean (SD); *n*	0.17 (0.23); 129	0.15 (0.21); 150	−0.03 (−0.08 to 0.02)	0.27
UDVA logMAR – both eyes open, mean (SD); *n*	0.05 (0.17); 129	0.05 (0.17); 150	−0.01 (−0.05 to 0.03)	0.60
CDVA logMAR, mean (SD); *n*	0.001 (0.16); 129	−0.003 (0.15); 150	−0.01 (−0.04 to 0.03)	0.74
CDVA logMAR – both eyes open, mean (SD); *n*	−0.04 (0.20); 129	−0.05 (0.14); 150	−0.01 (−0.05 to 0.03)	0.77
Refractive data				
Achieved refractive target, *n* (%)				
Within ± 0.5 dioptre	84/129 (65)	98/150 (65)	1.01 (0.61 to 1.69)	0.96
Within ± 1.0 dioptre	111/129 (86)	133/150 (89)	1.27 (0.61 to 2.68)	0.53
Safety				
Corneal endothelial cell count (cells/mm^2); adjusted for baseline, mean (SD); *n*	2410 (520); 127	2397 (543); 147	37.8 (−25.8 to 101)	0.24
Corneal endothelial cell loss (from baseline) (cells/mm^2), mean (SD); *n*	251 (437); 126	175 (379); 145	−86.0 (−158 to −13.9)	0.019
Postoperative AEs, patients with at least one event,[a] *n* (%)	18 (13.2)	20 (11.0)	0.02 (−0.05 to 0.09)	0.60
Expected ocular AEs,[b]* n *(%)				***0.57***
Postoperative uveitis	3 (2.2)	6 (3.3)		
Endophthalmitis	0	0		
Vitreous to wound	0	0		
Retinal tear or retinal detachment	0	0		
Elevated intraocular pressure requiring treatment	0	0		
Medication allergy or intolerance	0	0		
Macular oedema	1 (0.7)	2 (1.1)		
Corneal oedema	0	0		
Other ocular surgery	0	0		
Unexpected ocular AEs	***0***	***0***		***0.43***
Posterior vitreous detachment	1 (0.7)	0		
Cracked/damaged IOL	0	0		
Capsular block	0	0		
Posterior capsule opacification	0	0		
Corneal abrasion	1 (0.7)	0		
Cataract remnant post operation	0	1 (0.6)		
IOL subluxation	0	0		

continued

TABLE 27 Results of the regression models adjusted for stratification variables and safety events at 3 months: fellow eye (*continued*)

	Treatment arm		Effect (FLACS vs. PCS), difference (95% CI)	*p*-value
	FLACS (*N* = 136)	PCS (*N* = 181)		
Other ocular (definitely, possibly or probably related to surgery)	5 (3.7)	7 (3.9)		
Other ocular (unrelated or unlikely to be related to surgery)	8 (5.9)	12 (6.6)		
Exploratory outcomes				
Central retinal thickness (μm), mean (SD); *n*	253 (38.8); 127	259 (42.9); 147	3.50 (−3.55 to 10.5)	0.33
Spherical equivalent (dioptre), mean (SD); *n*	−0.34 (0.66); 128	−0.35 (0.61); 150	0.002 (−0.14 to 0.14)	0.98
Corneal astigmatism, *n* (%)			Adjusted odds ratio (from mixed-effects ordinal regression)	
< 0.75 dioptre	46 (34)	59 (33)	0.79 (0.43 to 1.45)	0.44
0.75 to < 2.0 dioptre	37 (27)	49 (27)		
≥ 2.0 dioptre	13 (9.6)	10 (5.5)		
Missing	40 (29)	63 (35)		
Corneal astigmatism (dioptre), mean (SD); *n*	1.00 (0.70); 96	0.89 (0.63); 118	−0.10 (−0.22 to 0.02)	0.11
Refractive astigmatism, *n* (%)			Adjusted odds ratio (from mixed-effects ordinal regression)	
< 0.75 dioptre	66 (49)	73 (40)	1.63 (0.98 to 2.71)	0.06
0.75 to < 2.0 dioptre	55 (40)	68 (38)		
≥ 2.0 dioptre	8 (5.9)	9 (5.0)		
Missing	7 (5)	31 (17)		
Refractive astigmatism (dioptre), mean (SD); *n*	0.29 (0.45); 129	0.39 (0.49); 150	0.11 (−0.01 to 0.22)	0.06
Visual acuity outcomes excluding patients with ocular co-pathology at baseline				
UDVA logMAR, mean (SD); *n*	0.16 (0.21); 84	0.13 (0.19); 121	−0.04 (−0.09 to 0.02)	0.19
UDVA logMAR – both eyes open, mean (SD); *n*	0.03 (0.13); 84	0.03 (0.15); 121	−0.01 (−0.05 to 0.03)	0.49
CDVA logMAR, mean (SD); *n*	−0.03 (0.15); 84	−0.02 (0.18); 121	0.01 (−0.02 to 0.04)	0.57
CDVA logMAR – both eyes open, mean (SD); *n*	−0.07 (0.10); 84	−0.06 (0.12); 121	0.002 (−0.03 to 0.03)	0.92

a Note that this does not include the AEs reported as occurring in both eyes; these are reported with the study eye AEs.
b Patients may have experienced more than one event.

Appendix 3 Full 12-month outcomes

Table 28 shows the results of the regression models for secondary outcomes at 12 months in the study eye and *Table 29* shows the results of the regression models for secondary outcomes at 12 months in the fellow eye.

TABLE 28 Results of the regression models for secondary outcomes at 12 months: study eye

	Treatment arm		Effect (FLACS vs. PCS), adjusted coefficient (95% CI)[a] unless stated otherwise	*p*-value
	FLACS (*N* = 392)	PCS (*N* = 393)		
Secondary outcomes				
Distance visual acuity				
UDVA logMAR, mean (SD); *n*	0.14 (0.22); 310	0.17 (0.25); 291	−0.03 (−0.06 to 0.01)	0.17
UDVA logMAR – both eyes open, mean (SD); *n*	0.05 (0.16); 310	0.07 (0.20); 292	−0.03 (−0.05 to 0.003)	0.08
CDVA logMAR, mean (SD); *n*	0.003 (0.18); 311	0.03 (0.23); 292	−0.03 (−0.06 to 0.01)	0.11
CDVA logMAR – both eyes open, mean (SD); *n*	−0.05 (0.11); 310	−0.03 (0.17); 291	−0.02 (−0.05 to -0.002)	0.036
Refractive data				
Achieved refractive target, *n* (%)			Adjusted odds ratio (95% CI)	
Within ± 0.5 dioptre	230/307 (75)	218/290 (75)	0.99 (0.68 to 1.43)	0.94
Within ± 1.0 dioptre	392/307 (95)	279/290 (96)	0.76 (0.34 to 1.69)	0.50
Quality of life				
Catquest-9SF score, mean (SD); *n*	2.94 (1.05); 318	2.96 (1.09); 300	0.01 (−0.15 to 0.17)	0.91
EQ-5D-3L health utility, mean (SD); *n*	0.83 (0.23); 318	0.82 (0.25); 299	0.001 (−0.03 to 0.03)	0.95
EQ-5D-3L health state – VAS, mean (SD); *n*	79 (17); 318	77 (19); 298	1.99 (−0.46 to 4.44)	0.11
EQ-5D-3L vison bolt-on, *n* (%)				
I have no problems seeing	242 (76)	231 (77)		
I have some problems seeing	70 (22)	62 (21)		
I have extreme problems seeing	6 (2)	6 (2)		
Safety				
Corneal endothelial cell count (cells/mm^2); adjusted for baseline, mean (SD); *n*	2404 (434); 307	2412 (406); 286	40.2 (−8.2 to 88.6)	0.10
Corneal endothelial cell loss (from baseline) (cells/mm^2), mean (SD); *n*	227.6 (353.2); 304	174.6 (312.4); 284	40.2 (−8.2 to 88.6)	0.10
			Difference (95% CI)	
Postoperative ocular AEs, patients with at least one event occurring at any time during the 12-month follow-up period, *n*/*N* (%)	175/392 (44.6)	153/393 (38.9)	0.057 (−0.01 to 0.13)	0.11

continued

TABLE 28 Results of the regression models for secondary outcomes at 12 months: study eye (*continued*)

	Treatment arm		Effect (FLACS vs. PCS), adjusted coefficient (95% CI)[a] unless stated otherwise	*p*-value
	FLACS (*N* = 392)	PCS (*N* = 393)		
Expected ocular AEs,*[b] n *(%)				
Postoperative uveitis	38 (9.7)	33 (8.4)		
Endophthalmitis	0	0		
Vitreous to wound	1 (0.3)	1 (0.3)		
Retinal tear or retinal detachment	2 (0.5)	3 (0.8)		
Elevated intraocular pressure requiring treatment	7 (1.8)	3 (0.8)		
Medication allergy or intolerance	4 (1.0)	3 (0.8)		
Macular oedema	9 (2.3)	14 (3.6)		
Corneal oedema	8 (2.0)	2 (0.5)		
Other ocular surgery	1 (0.3)	1 (0.3)		
Unexpected ocular AEs,* n *(%)				
Posterior vitreous detachment	3 (0.8)	2 (0.5)		
Cracked/damaged IOL	0	2 (0.5)		
Capsular block	2 (0.5)	0		
Posterior capsule opacification	4 (1.0)	6 (1.5)		
Corneal abrasion	4 (1.0)	1 (0.3)		
Cataract remnant post operation	1 (0.3)	0		
IOL subluxation	1 (0.3)	2 (0.5)		
Other ocular (definitely, possibly or probably related to surgery)	95 (24.0)	68 (17.3)		
Other ocular (unrelated or unlikely to be related to surgery)	138 (35.2)	125 (31.8)		
Exploratory outcomes				
Central retinal thickness (μm), mean (SD); *n*	254 (39) 310	257 (52) 291	0.80 (−4.0 to 5.63)	0.75
Spherical equivalent refraction error (dioptre), mean (SD); *n*	−0.19 (0.52) 307	−0.18 (0.48) 290	−0.01 (−0.09 to 0.07)	0.84
Corneal astigmatism *n* (%)			Adjusted odds ratio (from mixed-effects ordinal regression)	
< 0.75 dioptre	108 (28)	90 (23)	0.87 (0.55 to 1.36)	0.53
0.75 to < 2.0 dioptre	74 (19)	75 (19)		
≥ 2.0 dioptre	13 (3.3)	10 (2.5)		
Missing	197 (50)	218 (55)		

TABLE 28 Results of the regression models for secondary outcomes at 12 months: study eye (*continued*)

	Treatment arm		Effect (FLACS vs. PCS), adjusted coefficient (95% CI)[a] unless stated otherwise	*p*-value
	FLACS (*N* = 392)	PCS (*N* = 393)		
Corneal astigmatism (dioptre), mean (SD); *n*	0.81 (0.59); 195	0.88 (0.67); 175	−0.07 (−0.16 to 0.03)	0.17
Refractive astigmatism			Adjusted odds ratio (from mixed-effects ordinal regression)	
< 0.75 dioptre	157 (40)	133 (34)	0.86 (0.63 to 1.18)	0.86
0.75 to < 2.0 dioptre	134 (34)	146 (37)		
≥ 2.0 dioptre	16 (4.1)	11 (2.8)		
Missing	85 (22)	103 (26)		
Refractive astigmatism (dioptre), mean (SD); *n*	0.73 (0.63)	0.79 (0.61)	0.19 (−0.31 to 0.69)	0.46
Visual acuity outcomes excluding patients with ocular co-pathology at baseline				
UDVA logMAR, mean (SD); *n*	0.12 (0.20); 207	0.14 (0.23); 187	−0.01 (−0.05 to 0.03)	0.63
UDVA logMAR – both eyes open, mean (SD); *n*	0.03 (0.13); 207	0.05 (0.15); 188	−0.02 (−0.04 to 0.01)	0.26
CDVA logMAR, mean (SD); *n*	−0.02 (0.15); 208	−0.01 (0.19); 188	−0.004 (−0.04 to 0.03)	0.82
CDVA logMAR – both eyes open, mean (SD); *n*	−0.06 (0.10); 207	−0.06 (0.10); 187	−0.005 (−0.02 to 0.01)	0.63

VAS, visual analogue scale.
a All efficacy outcomes adjusted for site, the number of eyes that were eligible and random surgeon effects. UDVA logMAR also adjusted for baseline habitual logMAR visual acuity values.
b Patients may have experienced more than one event.
All visual acuity outcomes are also adjusted for baseline astigmatism (Pentacam corneal topography).

TABLE 29 Results of the regression models for secondary outcomes at 12 months: fellow eye

	Treatment arm		Effect (FLACS vs. PCS), difference (95% CI)	*p*-value
	FLACS (*N* = 136)	PCS (*N* = 181)		
Distance visual acuity				
UDVA logMAR, mean (SD); *n*	0.18 (0.21); 109	0.16 (0.21); 129	−0.02 (−0.07 to 0.03)	0.42
UDVA logMAR – both eyes open, mean (SD); *n*	0.03 (0.15); 109	0.05 (0.17); 129	0.02 (−0.02 to 0.06)	0.42
CDVA logMAR, mean (SD); *n*	0.01 (0.15); 109	0.003 (0.15); 129	−0.01 (−0.05 to 0.03)	0.53
CDVA logMAR – both eyes open, mean (SD); *n*	−0.05 (0.11); 1109	−0.04 (0.17); 129	0.01 (−0.02 to 0.05)	0.45
Refractive data				
Achieved refractive target, *n* (%)				
Within ± 0.5 dioptre	76/109 (70)	90/127 (71)	1.08 (0.60 to 1.93)	0.81
Within ± 1.0 dioptre	98/109 (90)	115/127 (91)	1.09 (0.45 to 2.64)	0.85
Safety				
Corneal endothelial cell count (cells/mm^2); adjusted for baseline, mean (SD); *n*	2476 (360); 108	2441 (401); 127	28.5 (−38.0 to 94.9)	0.40
Corneal endothelial cell loss (from baseline) (cells/mm^2), mean (SD); *n*	172.6 (249); 107	105.4 (225); 126	−61.0 (−132 to 10.3)	0.09
Postoperative AEs, patients with at least one event occurring at any time during the 12-month follow-up period,[a] *n* (%)	33 (24.3)	32 (17.7)	0.07 (−0.03 to 0.16)	0.16
Expected ocular AEs,[b] n (%)				
Postoperative uveitis	4 (2.9)	6 (3.3)		
Endophthalmitis	0	0		
Vitreous to wound	0	0		
Retinal tear or retinal detachment	0	0		
Elevated intraocular pressure requiring treatment	0	0		
Medication allergy or intolerance	0	0		
Macular oedema	3 (2.2)	2 (1.1)		
Corneal oedema	0	0		
Other ocular surgery	0	0		
Unexpected ocular AEs,* n *(%)				
Posterior vitreous detachment	1 (0.7)	0		
Cracked/damaged IOL	0	0		
Capsular block	0	0		
Posterior capsule opacification	0	0		
Corneal abrasion	1 (0.7)	0		
Cataract remnant post operation	0	1 (0.6)		
IOL subluxation	1 (0.7)	0		

TABLE 29 Results of the regression models for secondary outcomes at 12 months: fellow eye (*continued*)

	Treatment arm		Effect (FLACS vs. PCS), difference (95% CI)	*p*-value
	FLACS (*N* = 136)	PCS (*N* = 181)		
Other ocular (definitely, possibly or probably related to surgery)	7 (5.1)	7 (3.9)		
Other ocular (unrelated or unlikely to be related to surgery)	16 (11.8)	15 (8.3)		
Exploratory outcomes				
Central retinal thickness (μm), mean (SD); *n*	254 (42.9); 109	253 (41.1); 129	−4.47 (−10.4 to 1.50)	0.14
Spherical equivalent (dioptre), mean (SD); *n*	−0.32 (0.60); 109	−0.28 (0.62); 127	0.06 (−0.09 to 0.21)	0.43
Corneal astigmatism, *n* (%)			Adjusted odds ratio (from mixed-effects ordinal regression)	
< 0.75 dioptre	37 (27)	35 (19)	0.44 (−0.35 to 1.23)	0.28
0.75 to < 2.0 dioptre	28 (21)	34 (19)		
≥ 2.0 dioptre	2 (1.5)	6 (3.3)		
Missing	69 (51)	106 (59)		
Corneal astigmatism (dioptre), mean (SD); *n*	0.76 (0.49); 67	0.86 (0.60); 75	0.05 (−0.06 to 0.15)	0.41
Refractive astigmatism			Adjusted odds ratio (from mixed-effects ordinal regression)	
< 0.75 dioptre	53 (39)	58 (32)	1.29 (0.80 to 2.10)	0.30
0.75 to < 2.0 dioptre	50 (37)	61 (34)		
≥ 2.0 dioptre	6 (4.4)	9 (5.0)		
Missing	27 (20)	53 (29)		
Refractive astigmatism (dioptre), mean (SD); *n*	0.37 (0.48); 109	0.38 (0.49); 128	0.10 (−0.11 to 0.13)	0.89
Visual acuity outcomes excluding patients with ocular co-pathology at baseline				
UDVA logMAR, mean (SD); *n*	0.18 (0.21); 73	0.14 (0.19); 103	−0.05 (−0.11 to 0.01)	0.11
UDVA logMAR – both eyes open, mean (SD); *n*	0.03 (0.13); 73	0.03 (0.13); 103	0.007 (−0.03 to 0.04)	0.73
CDVA logMAR, mean (SD); *n*	−0.007 (0.10); 73	−0.02 (0.11); 103	−0.001 (−0.03 to 0.03)	0.93
CDVA logMAR – both eyes open, mean (SD); *n*	−0.06 (0.09); 73	−0.06 (0.09); 103	−0.008 (−0.04 to 0.02)	0.63

a Note that this does not include the AEs reported as occurring in both eyes; these are reported with the study eye AEs.
b Patients may have experienced more than one event.

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