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Femtosecond laser–assisted cataract surgery compared with phacoemulsification cataract surgery: randomized noninferiority trial with 1-year outcomes

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Purpose: To report the 1-year outcomes of a randomized trial comparing femtosecond laser–assisted cataract surgery (FLACS) and phacoemulsification cataract surgery (PCS).

Setting: Moorfields Eye Hospital, New Cross Hospital, and Sussex Eye Hospital, United Kingdom.

Design: Multicenter, randomized controlled noninferiority trial.

Methods: Patients undergoing cataract surgery were randomized to FLACS or PCS. Postoperative assessments were masked. Outcomes included uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), complications, corneal endothelial cell count, and patient-reported outcomes measures.

Results: The study enrolled 785 participants. A total of 311 of 392 (79%) participants were allocated to FLACS and 292 of 393 (74%) participants were allocated to PCS attended follow-up at 1 year. Mean UDVA was 0.14 (SD = 0.22) for FLACS and 0.17 (0.25) for PCS with difference of −0.03 logarithm of the minimum angle of resolution (logMAR) (95%, −0.06 to 0.01, P = .17). Mean CDVA was 0.003 (0.18) for FLACS and 0.03 (0.23) for PCS with difference of −0.03 logMAR (95% CI, −0.06 to 0.01, P = .11); 75% of both FLACS (230/307) and PCS (218/290) cases were within ±0.5 diopters (D) refractive target, and 292 (95%) of 307 eyes of FLACS and 279 (96%) of 290 eyes of PCS groups were within ±1.0 D. There were no significant differences between arms for all other outcomes with the exception of binocular CDVA mean difference −0.02 (−0.05 to 0.002) logMAR (P = .036) favoring FLACS. Mean cost difference was £167.62 per patient greater for FLACS (95% iterations between −£14.12 and £341.67).

Conclusions: PCS is not inferior to FLACS regarding vision, patient-reported health, and safety outcomes after 1-year follow-up. A difference was found for binocular CDVA, which, although statistically significant, was not clinically important. FLACS was not cost-effective.

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Cataract is the leading cause of reversible blindness in the world, and cataract surgery is one of the most commonly performed operations.[1] Phacoemulsification cataract surgery (PCS) was first introduced more than 50 years ago, and femtosecond laser–assisted cataract surgery (FLACS) has been commercially available for almost a decade.[2] Part automation by a computer-controlled laser has a number of advantages, including more accurate positioning, shape, and size of the capsulotomy when compared with a capsulorhexis and less intraocular lens (IOL) tilt with fewer higher-order

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aberrations.[3–7] In addition, by using a laser to fragment the crystalline lens, less ultrasound energy is subsequently needed for its removal and, thus, lower endothelial cell loss.[8] This increased level of precision would be expected to translate to better visual outcomes and higher safety; however, studies have shown no real benefit, and the cost of FLACS is significantly more than PCS.[9–12]

Two large randomized controlled trials (RCTs) have recently been completed, the French multicenter FEMCAT trial and a U.K. single-site trial from St. Thomas' Hospital.[13,14] Both FEMCAT and the St. Thomas' Hospital RCTs found similar visual and refractive outcomes for FLACS and PCS and similar complications with the exception of higher posterior capsule rupture rates in the PCS arm of the St. Thomas' trial. The St. Thomas' Hospital trial published data with 1 month follow-up and the FEMCAT trial with 3 months follow-up, and longer-term data are needed to investigate for other potential differences, such as posterior capsule opacification rates.

We report the 1-year outcomes of the Femtosecond Laser–Assisted Cataract Trial (FACT), a large multicenter RCT that was designed to establish whether FLACS is as good as or better than PCS.[15] The 3-month outcomes of FACT have previously been reported, and no difference was found for visual acuity, refractive outcomes, or safety outcomes by trial allocation arm.[16]

METHODS

Design and Patients

The trial methodology has previously been published.[15–17] In brief, FACT was a pragmatic, multicenter, single-masked, noninferiority RCT performed at 3 NHS hospitals in the United Kingdom to establish whether FLACS is as good as or better than PCS (ISRCTN.com registry number ISRCTN77602616).[15] All trial centers were high-volume NHS day care surgery units (Moorfields at St Ann's Hospital, Tottenham, London; Sussex Eye Hospital, Brighton; and New Cross Hospital, Wolverhampton). The trial received ethical approval by the NRES Committee London City Road and Hampstead (February 6, 2015, ref: 14/LO/1937). The trial adhered to the tenets of the Declaration of Helsinki. All patients provided written informed consent before trial participation.

All patients were screened and recruited from cataract clinics between May 2015 and September 2017. Eligibility criteria were adults aged 18 years or older with age-related cataract with expected postoperative refractive target within ±0.5 diopter (D) of emmetropia (ie, good uncorrected distance visual acuity [UDVA]). Full inclusion and exclusion criteria are provided in the protocol at https://fundingawards.nihr.ac.uk/award/13/04/46.

Randomization and Masking

Participants were randomly assigned in a 1:1 ratio to undergo FLACS or PCS. Randomization was performed on the day of surgery using an independent web-based online system (https://www.sealedenvelope.com) using treatment center, surgeon, and 1 or both eyes eligible as minimization stratifiers. For participants who required bilateral cataract surgery, the same intervention (FLACS or PCS) was offered when the patient returned for second-eye surgery, unless the patient wished otherwise. Because of the nature of the intervention, surgeon and participant masking was not possible. All trial follow-up was performed by optometrists masked to the trial intervention.

Procedures

All participants underwent dilated slitlamp examination by an ophthalmologist prior to listing for cataract surgery. Patients with 1 or both eyes eligible were treated identically. All participants had either PCS or FLACS with the Catalys femtosecond laser (Johnson & Johnson, Inc.) or LDV Z8 (Ziemer Ophthalmic Systems AG), under topical or local anesthesia. Trial surgeons were ophthalmologists who routinely performed cataract surgery at their respective trial centers who had completed at least 10 supervised FLACS operations and had been certified by the FLACS. For FLACS cases, the laser was used to perform the capsulotomy and lens fragmentation. Management of astigmatism was at the treating surgeon's discretion, and femtosecond laser–assisted arcuate keratotomy could be performed using the Catalys laser at the surgeon's discretion. Detailed descriptions of the Catalys and Ziemer LDV Z8 usage for FLACS have previously been published.[18–21] All patients had planned implantation of a monofocal IOL. PCS was performed as per local practice.

Postoperative care including eyedrops was as per standard local center practice for cataract surgery. Where the FLACS treatment could not be performed for whatever reason after randomization (eg, unable to dock and laser machine fault), the patient underwent PCS.

Outcomes

The trial primary outcome was UDVA (Early Treatment Diabetic Retinopathy Study logarithm of the minimum angle of resolution [logMAR] chart at a starting distance of 4 m) at 3 months postoperatively, and this outcome has previously been published in addition to intraoperative surgical complications.[16,22] Outcomes at 1 year were UDVA in the study eye and binocular UDVA and corrected distance visual acuity (CDVA) in the study eye alone and binocularly. Long-term safety measures included postoperative complications and corneal endothelial cell count loss.[23] Refractive outcomes were percentage within ±0.5 D and 1.0 D of the intended refractive target. Health-related quality of life was measured by the EQ-5D-3L questionnaire + vision bolt-on question (EQ-5DV) at 1 year, and patient-reported vision health status was assessed using Catquest-9SF at 1 year, a Rasch-validated instrument.[24,25]

For participants with incomplete questionnaire data, telephone interviews were conducted for clarification and completion of missing items. All staff performing outcome measures were trained in their collection and masked to trial arm for trial postoperative assessments including visual acuity, subjective refraction, corneal measurements, and endothelial cell count. After these measures had been completed, complications data were collected by patient medical notes review.

Sample Size and Statistical Analysis

The primary outcome of FACT was UDVA at 3 months postoperatively. The study aimed to recruit at least 808 patients (404 per arm). This sample size was estimated to identify a treatment effect size of 1 logMAR line UDVA that was believed to be clinically important to patients and ophthalmologists as determined by previous 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 as about 0.07 logMAR on letter-by-letter scoring.[26,27] If there is truly no difference in mean logMAR between the 2 groups, then 432 patients (216 per group) would provide 90% power to be sure that a 95% 2-sided CI would exclude the noninferiority limit of 0.1 logMAR, assuming a common SD of 0.32. The SD is from the Royal College of Ophthalmologists' National Ophthalmic Database UDVA data.[23] Although each treatment is delivered on an individual patient basis, each patient cannot be assumed to generate independent information because they will be clustered within surgeons. To take account of this clustering effect by surgeon, the sample size was increased by an inflation factor $f = 1 + (m - 1) \times p$. Assuming a total of 16 surgeons contribute an average cluster size (m) of 50 patients and an estimate intraclass correlation coefficient (p) of 0.012, this gives an f of 1.59. A total of 688 patients (344 per group) allowed the trial to take account of clustering by surgeon. In addition, to allow for an estimated 15% dropout rate, the total sample size required was 808 patients.

An intention-to-treat analysis was used for all primary and secondary outcomes, and participants remained in their randomized treatment group irrespective of the treatment they received. Each continuous outcome measure was analyzed using a model

containing the baseline value of the outcome, the stratifying variables of center, and number of eyes eligible. Surgeon was included in the model as a random effect. Astigmatism at baseline (as measured by keratometry readings from Pentacam corneal topography) was included as a covariate for visual acuity outcomes. A logistic regression model was used for the proportion of patients achieving their refractive target. Adjusted treatment effect estimates, 2-sided 95% confidence intervals, and 2-sided *P* values are reported for each outcome measure. A 2-sample test for independent proportions was used to compare rates of any postoperative complications. Visual and refractive outcomes are reported using the standardized graphs for reporting the outcomes of IOL surgery.[28] Full details on the statistical analysis are available in the Statistical Analysis Plan at https://fundingawards.nihr.ac.uk/award/13/04/46.

Economic Evaluation

The aim of the economic evaluation was to perform a within-trial analysis of the mean incremental cost per quality-adjusted life-year (QALY) gained of FLACS compared with PCS more than 12 months from a health and social care cost perspective. The cost of FLACS and PCS were calculated using a bottom–up micro-costing based on data collected from centers and trial corneal resistance factors. A full description of all outcomes and analysis are provided in the health economic analysis plan. The following outcomes were used for the trial-based component of the economic evaluation: surgery corneal resistance factor, FACT costing study, Client Service Receipt Inventory, and EQ-5D 3 level (EQ-5D-3L). QALYs were calculated as the area under the curve using the ED-5D-3L utility values for the United Kingdom at baseline, 3 months, 6 months, and 12 months.[29–31] Multiple imputation using chained equations was used to impute missing cost and utility data at each time point. Seemingly unrelated regression was used to account for correlation between costs and outcomes, with adjustment for baseline, site, and number of eyes eligible. The probability of cost-effectiveness was calculated from bootstrapped, imputed, adjusted results.[32] Full details on the economic evaluation are available at https://fundingawards.nihr.ac.uk/award/13/04/46.

Trial Oversight

An independent trial steering committee provided oversight of the trial to safeguard the interests of participants, and an independent data monitoring committee regularly reviewed outcomes by randomization arm.

RESULTS

Of the 3448 patients assessed for trial eligibility, 785 participants between May 2015 and September 2017 were enrolled and randomly assigned: 392 to FLACS and 393 to PCS (Figure 1). The main reasons for exclusion (1710) were not sufficiently fluent in English for informed consent and trial questionnaire completion (564), postoperative refractive target outside ±0.5 D emmetropia (180), poor pupil dilation (176), and not willing to attend for follow-up (155). Of the 1738 eligible patients, 770 declined to take part, 157

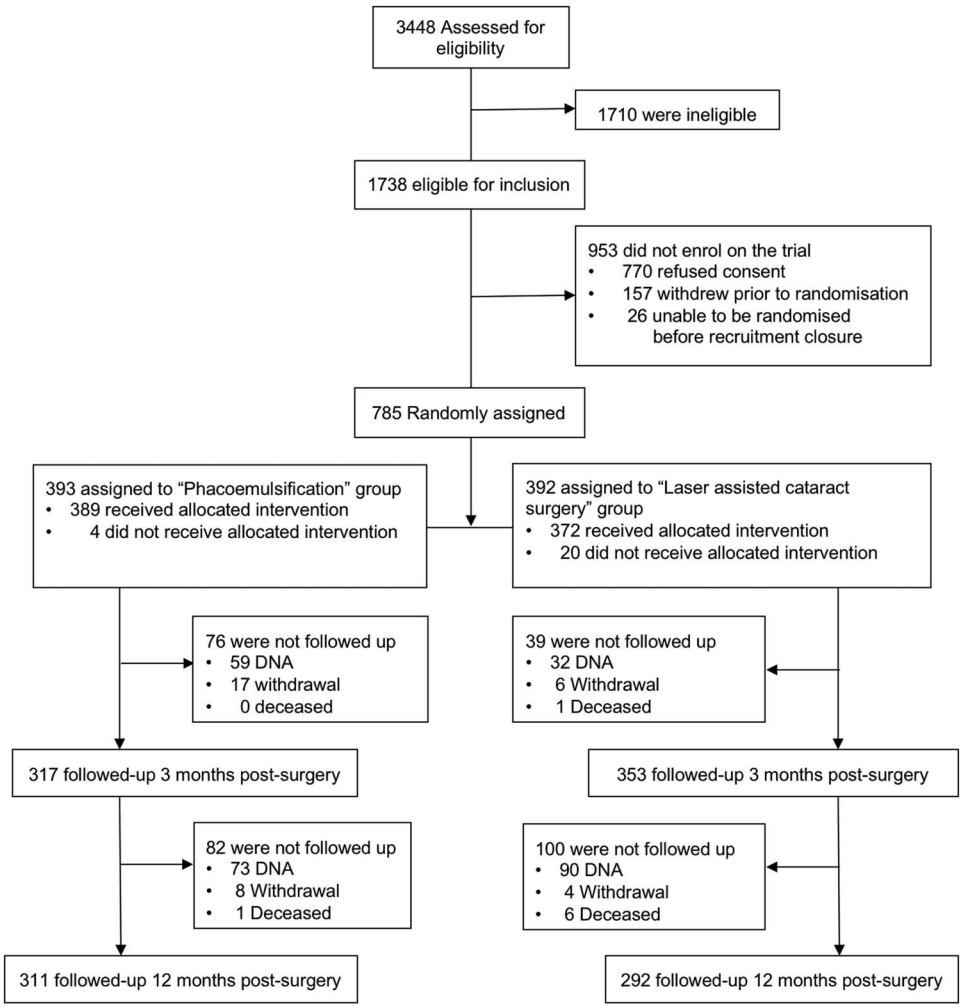

Figure 1. Consort chart: trial profile. DNA = did not attend.

Table 1. Postoperative results for the 2 treatment arms at 1 year.

Variable	FLACS	PCS	Effect FLACS–PCS (95% CI)	*P* Value
UDVA logMAR study eye, mean (SD)	0.14 (0.22)	0.17 (0.25)	−0.03 (−0.06, 0.01)	.17
UDVA logMAR both eyes, mean (SD)	0.05 (0.16)	0.07 (0.20)	−0.03 (−0.05, 0.003)	.08
CDVA logMAR study eye, mean (SD)	0.003 (0.18)	0.03 (0.23)	−0.03 (−0.06, 0.01)	.11
CDVA logMAR both eyes, mean (SD)	−0.05 (0.11)	−0.03 (0.17)	−0.02 (−0.05, 0.002)	.036
Refraction within ±0.5D of target, n (%)	230/307 (75)	218/290 (75)	0.99 (0.68, 1.43)	.94
Refraction within ±1.0D of target, n (%)	292/307 (95)	279/290 (96)	0.76 (0.34, 1.69)	.50
Catquest 9-SF score, mean (SD)	2.94 (1.05)	2.96 (1.09)	0.01 (−0.15, 0.17)	.91
EQ-5D-3L index score, mean (SD)	0.83 (0.23)	0.82 (0.25)	0.001 (−0.03, 0.03)	.95
EQ-5D-3L health state VAS, mean (SD)	79 (17)	77 (19)	2.0 (−0.4 to 4.4)	.11
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)	—	—

CDVA = corrected distance visual acuity; FLACS = femtosecond laser–assisted cataract surgery; PCS = phacoemulsification cataract surgery; UCDVA = uncorrected distance visual acuity; VAS = visual analog scale

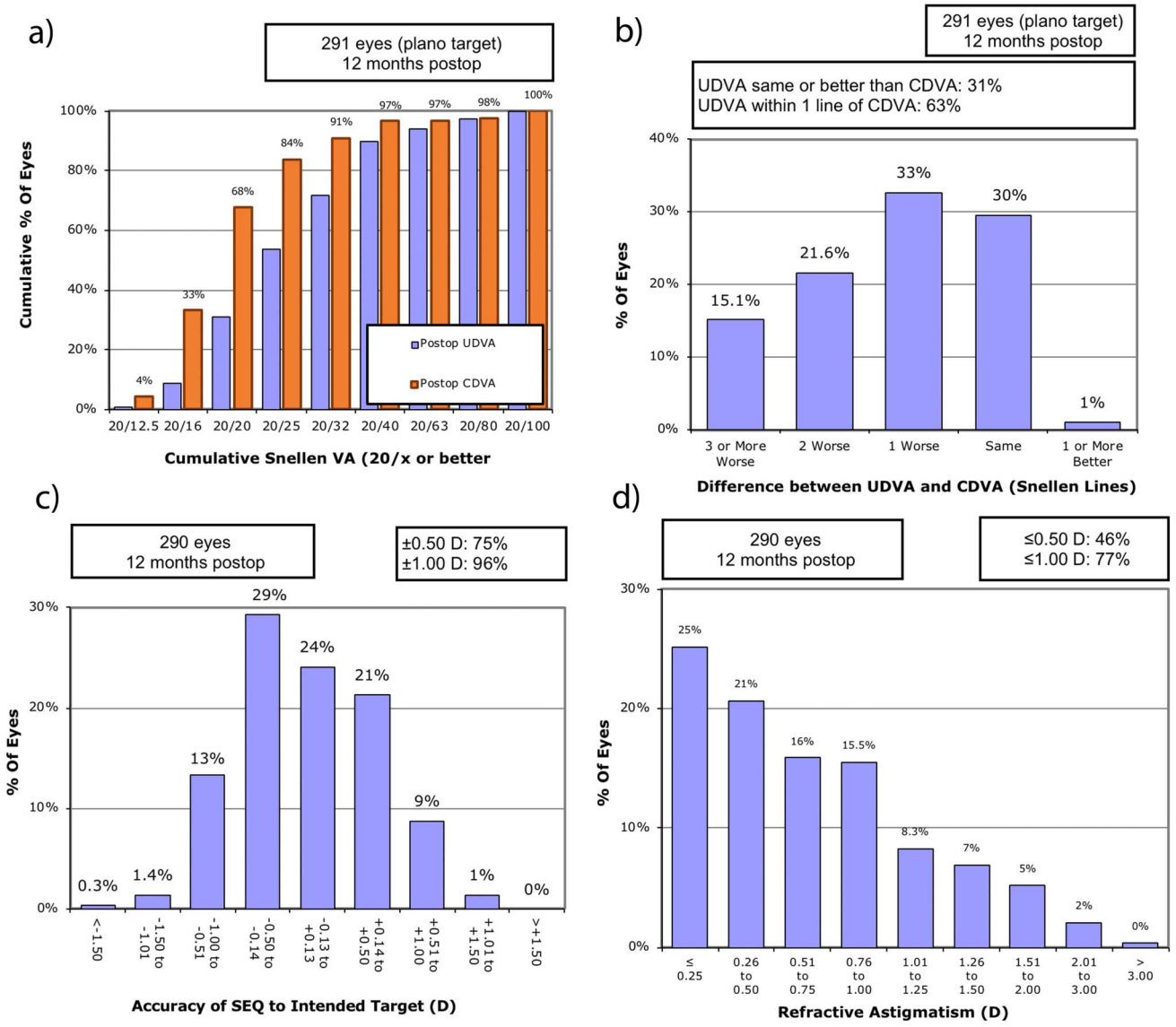

Figure 2. Standardized graphs: PCS arm at 12 months. *A*: UDVA. *B*: UDVA vs CDVA. *C*: Spherical equivalent refraction. *D*: Refractive cylinder (CDVA = corrected distance visual acuity; PCS = phacoemulsification cataract surgery; SEQ = spherical equivalent; UDVA = uncorrected distance visual acuity).

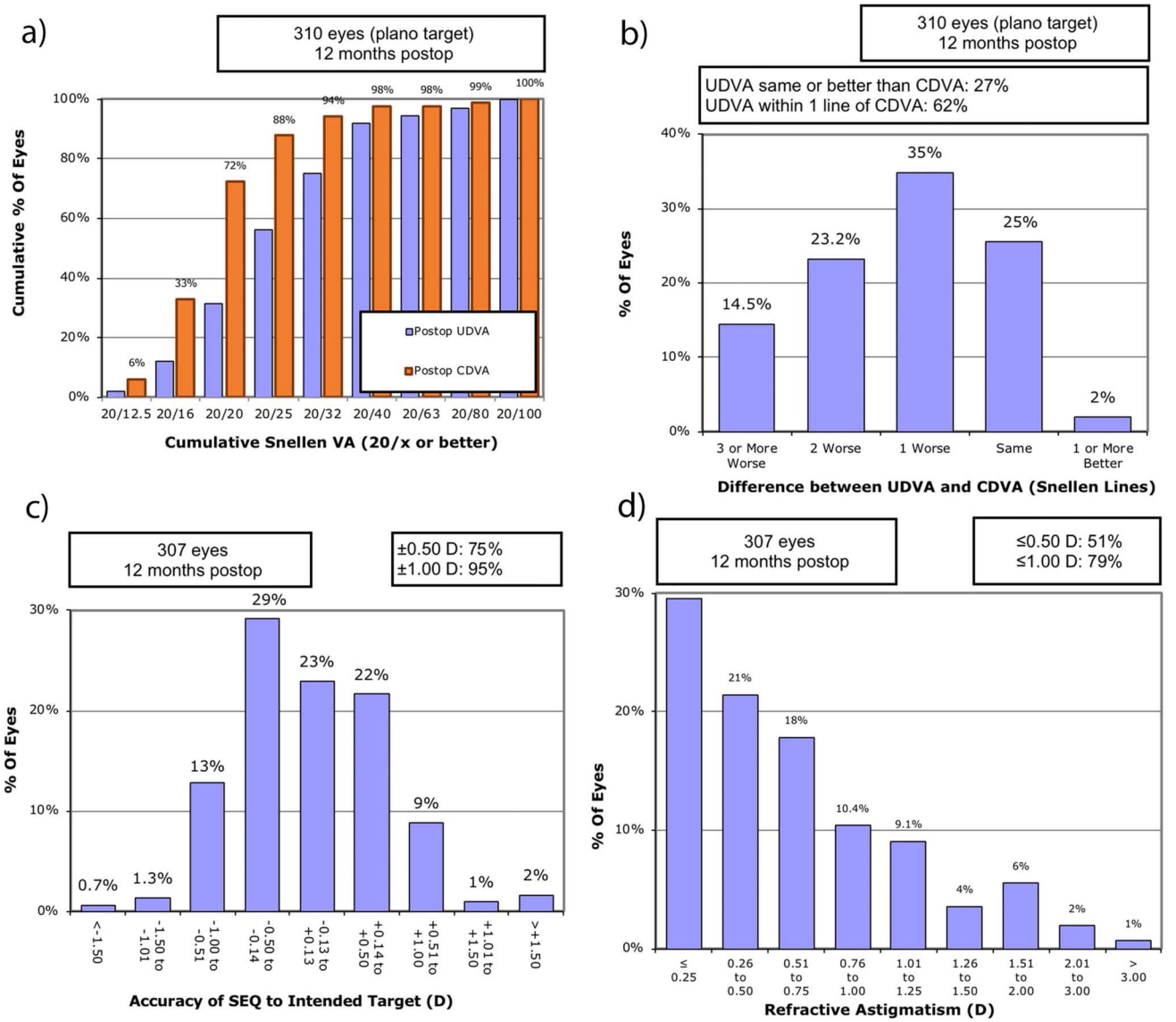

Figure 3. Standardized graphs: FLACS arm at 12 months. *A*: UDVA. *B*: UDVA vs CDVA. *C*: Spherical equivalent refraction. *D*: Refractive cylinder (CDVA = corrected distance visual acuity; FLACS = femtosecond laser–assisted cataract surgery; PCS = phacoemulsification cataract surgery; SEQ = spherical equivalent; UDVA = uncorrected distance visual acuity).

withdrew prior to randomization, and 26 were awaiting randomization when recruitment closed. Forty major protocol deviations were identified: not receiving treatment according to randomization (25 participants [5.1%]: 21 allocated to FLACS and 4 allocated to PCS) and not fulfilling refractive target eligibility criteria (15 participants: 10 allocated to FLACS and 5 allocated to PCS).

Overall, 292 (74%) of 392 participants allocated to FLACS and 311 (79%) of 393 participants allocated to PCS attended their follow-up visit at 1 year. Trial participant demographics and baseline characteristics were similar by randomized group, and these have previously been published. Of note, 128 (33%) of 392 FLACS cases and 140 (36%) of 393 PCS cases had 1 or more ocular copathologies at baseline. Analysis of toric IOL usage by arm showed 22 toric IOLs used in the FLACS arm (369 monofocal and 1 data missing) and 19 toric IOLs in the PCS arm (370 monofocal and 4 data missing). Table 1 summarizes the postoperative visual and refractive outcomes at 1 year. Borderline statistical significance was met for binocular CDVA with a mean difference of −0.02 logMAR (−0.05 to −0.002, $P = .036$) favoring the FLACS arm. There were no significant differences between arms for all other outcomes. A sensitivity analysis investigating UDVA differences by laser platform used showed similar effects. Figures 2 and 3 show the standardized graphs for reporting the outcomes of IOL surgery.

Table 2 tabulates the postoperative complications for each trial arm. Participants might have had more than 1 event. There was no significant difference in the proportion of patients with any postoperative complication. Table 3 summarizes the corneal endothelial cell count at 1 year, and again, there was no significant difference by trial arm.

In the FLACS arm, surgery took a mean time of 17.1 minutes (SD = 7.4). FLACS laser took an additional 3.9

Table 2. Postoperative complications over 1 year.

Complication, n (%)	FLACS n = 391	PCS n = 389
1> postoperative complications*	62 (15.9)	54 (13.9)
Postoperative anterior uveitis	38 (9.7)	33 (8.5)
Macular edema	9 (2.3)	14 (3.6)
Retinal tear or detachment	2 (0.5)	3 (0.8)
Steroid response ocular hypertension	7 (1.8)	3 (0.8)
Medication allergy or intolerance	4 (1.0)	3 (0.8)
Corneal edema	8 (2.0)	2 (0.5)
Vitreous to wound	1 (0.3)	1 (0.3)
Posterior vitreous detachment	3 (0.8)	2 (0.5)
Posterior capsule opacification	4 (1.0)	6 (1.5)
Endophthalmitis	0 (0)	0 (0)

FLACS = femtosecond laser–assisted cataract surgery; PCS = phacoemulsification cataract surgery
Participants might have had more than 1 event.
*Difference 2.0%, 95% CI (−3.0 to 7.0), P = .44.

minutes (3.5), with a total time of 20.8 minutes (8.2). In the PCS arm, surgery took 17.8 minutes (8.0). There was no significant difference in the use of anesthetic drugs or consumables between trial arms except for Vision Blue (used for staining the anterior capsule to increase visibility, 43 patients in the PCS arm compared with 3 patients in the FLACS arm) at a cost per vial of £8.65.

There were no significant differences between the 2 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 ICER (cost difference divided by QALY difference) of £167,620. There was a 24% probability that FLACS is cost-effective compared with PCS at a £20,000 willingness to pay for a QALY gained and 30% probability at a £30,000 willingness to pay threshold.

DISCUSSION

At 1-year follow-up, FLACS had similar visual outcomes and complication rates to PCS. Overall, there were no significant differences for any outcome measures with the exception of binocular CDVA, with a difference of −0.02 logMAR (1-more-letter better CDVA), which, although statistically significant, was not clinically important.

We have previously published the FACT trial 3-month outcomes, which found no significant difference between trial arms for the primary and all secondary outcome measures at this time point.[16] Of note, the posterior capsule rupture rates (PCRs) in FACT were low (0.0% for FLACS and 0.5% for PCS) compared with a reported U.K. benchmark rate of 1.6%.[3] Reported PCR rates in the FEMCAT study were 1.4% for FLACS compared with 1.6% for PCS.[13] In the St Thomas' RCT, PCR rates were significantly higher in PCS (3.0%) compared with FLACS (0.0%), and this just met statistical significance. None of these large RCTs were powered to identify differences in PCR or other complication rates, so a meta-analysis is required to investigate for possible differences.

For refractive outcomes at 1 year, we found 75% of both FLACS and PCS cases were within ±0.5 D target and 95% FLACS cases and 96% PCS cases within ±1.0 D target. The values reported in a recent large EUREQUO analysis of 282,811 cataract surgeries were 73% and 93% eyes being within ±0.5 D and ±1.0 D target, respectively.[34] Comparative values from the recent St Thomas' Hospital single-center RCT with 1-month follow-up data of FLACS vs PCS were 71% and 77% eyes within ±0.5 D and 94% and 95% eyes within ±1.0 D, respectively.[14]

With a trial follow-up duration of 1 year, FACT also captures information on long-term complications of cataract surgery such as posterior capsule opacification requiring Nd:YAG laser capsulotomy or retinal tear or retinal detachments. Nd:YAG capsulotomy rates by trial arm were low, being 1.0% for FLACS and 1.5% for PCS at 1 year. Retinal tear or retinal detachment rates were also low as expected, being 0.5% for FLACS and 0.8% for PCS.

We found that FLACS arm surgery took a mean time of 17.1 minutes compared with 17.8 minutes for PCS. However, after including the FLACS laser time, which was an additional mean of 3.9 minutes, the total FLACS case time increased to 20.8 minutes. FLACS, therefore, does not improve theater productivity, and with the additional logistical movement of the patient from the laser to the operating table clearly impedes theater productivity in its current form. The economic evaluation found that FLACS costs £216 more than PCS (£168 when any potential cost benefits from health and social care costs are included). Because there is no evidence of any additional benefit of FLACS, there is a low probability that implementing it would be cost-effective. Based on the threshold analysis, FLACS would need to cost at least £138 less than it currently does to potentially be

Table 3. Corneal endothelial cell parameters at 1 year.

Variable	FLACS (n = 304)	PCS (n = 284)	Effect FLACS-PCS 95% CI	*P* Value
Corneal ECC cells/mm^2, mean (SD)	2404 (434)	2413 (406)	−40 (−89 to 8)	.10
ECC loss baseline-final cells/mm^2, mean (SD)	228 (353)	175 (312)	40 (−8 to 89)	.10

ECC = endothelial cell count; FLACS = femtosecond laser–assisted cataract surgery; PCS = phacoemulsification cataract surgery

cost-effective at a £30,000 willingness to pay for a QALY gained. This cost is very close to that of the FLACS patient interface that needs to be purchased for each new patient. Even with a more efficient use of theaters, using 2 theaters at the same time, and hence having some cost savings on staff that can work across theaters, FLACS has a 26% probability of being cost-effective at the upper NICE threshold of £30 000 per QALY gained. Similar conclusions have been drawn by Roberts et al., who explored how FLACS could be implemented in the NHS so that it is cost-neutral, using the model of 2 theaters functioning in parallel and staff working across them both.[35] They came to the conclusion that theaters 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. came to similar conclusion that FLACS would need to significantly improve patient outcomes to be cost-effective in an Australian setting.[36] The recent FEMCAT study concluded that FLACS was not cost-effective for the French healthcare system.[13]

FACT was designed to detect important differences in visual acuity and to minimize possible bias. The trial was publicly funded by the National Institute for Health Research and believed to be representative of the publicly funded NHS in the United Kingdom. Because of the nature of FLACS, surgeon masking was not possible, and although participants were not masked to their allocated arm, visual acuity outcomes were assessed by a masked optometrist, so we do not believe this to be a significant source of bias in the outcome measures. The rates of loss to follow-up at 1 year were 26% for FLACS and 21% for PCS, compared with 10% for FLACS and 19% for PCS at 3 months follow-up. Participants who did not attend were contacted by identical methods to rebook within trial time scales. An additional sensitivity analysis did not suggest a difference in the characteristics of those who were lost to follow-up. As previously discussed, there is a possible surgical learning curve effect for FLACS, with all trial surgeons having performed hundreds of PCS cases compared with a minimum of 10 FLACS surgeries that were required to meet trial surgeon eligibility.[16] We have previously published data on the FLACS learning curve, and this found that complications attributable to laser cataract surgery tended to occur in the first few cases.[37] In addition, if the FLACS learning curve is much higher than the minimum of 10 previous cases in our surgeon inclusion criteria, because we found the complication rate for FLACS to be low, it is difficult to see how this would materially affect our findings. Another limitation of FACT is that most participants were recruited from St Ann's Moorfields Eye Hospital in comparison with the other centers, and the setup here might not be fully representative of other cataract surgery centers in the United Kingdom.

In summary, the 1-year results of the FACT trial found that PCS is not inferior to FLACS. Both methods are good for vision, patient-reported health, and safety outcomes. FLACS is not cost-effective. Further RCTs and meta-analysis are needed to investigate possible differences between the surgical methods because of the low complication rates and apparent similar efficacy.

FACT Trial Group Collaborators

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