

Femtosecond laser-assisted cataract surgery compared with phacoemulsification cataract surgery (FACT): a randomised non-inferiority trial, 1 year outcomes

Running title:

Femtosecond laser vs phacoemulsification cataract surgery

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Contributorship statement:

ACD, JMB, CB, CJD, GSR and MRW conceived and designed the trial; MW was the chief investigator, ACD was the sub-chief investigator and oversaw the trial throughout. MRW, KSB and MN were principal investigators at each centre. KB and CJD had access to raw data, and planned and performed the statistical analysis. RH performed the health economic analysis. All authors contributed to the interpretation of data, drafting of the report and its content. ACD wrote and submitted the final manuscript on behalf of the FACT trial group. All authors approved the final version of the manuscript.

Competing interests:

There are no conflicts of interest to disclose.

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Data sharing:

The trial protocol and statistical analysis plan are available at <https://fundingawards.nihr.ac.uk/award/13/04/46>

Abstract:

Purpose:

To report the 1 year outcomes of a randomised trial comparing femtosecond laser assisted cataract surgery (FLACS) and phacoemulsification cataract surgery (PCS).

Setting:

Moorfields Eye Hospital, New Cross Hospital and Sussex Eye Hospital, UK

Design:

Multicentre, randomised controlled non inferiority trial.

Methods:

311 of 392 (79%) participants allocated to FLACS and 292 of 393 (74%) participants allocated to PCS attended follow-up at 1 year. Postoperative assessments were masked to the allocated intervention. Outcomes included UDVA, CDVA, complications, corneal endothelial cell count and patient reported outcomes measures. ISRCTN77602616.

Results:

Mean UDVA was 0.14 (SD 0.22) for FLACS and 0.17 (0.25) for PCS with difference between treatment arms of -0.03 logMAR (95% CI: -0.06 to 0.01, $p=0.17$). 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, $p=0.11$). 75% of both FLACS (230/307) and PCS (218/290) cases were within $\pm 0.5D$ refractive target, and 95% FLACS (292/307) and 96% PCS (279/290) cases within $\pm 1.0D$. 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 ($p=0.036$) favouring FLACS. The mean cost difference was £167.62 per patient greater for FLACS (95% of iterations between -£14.12 and £341.67).

Conclusions:

PCS is not inferior to FLACS in terms of vision, patient reported health and safety outcomes after one year follow-up. A difference was found for binocular CDVA, which whilst statistically significant, was not clinically important. FLACS is not cost effective.

Introduction.

Cataract is the leading cause of reversible blindness in the world¹ and cataract surgery is one of the most commonly performed operations. Phacoemulsification cataract surgery (PCS) was first introduced over 50 years ago,² and femtosecond laser assisted cataract surgery (FLACS) has been commercially available for almost a decade. Part automation by a computer controlled laser has a number of advantages include more accurate positioning, shape and size of the capsulotomy when compared to a capsulorrhexis³⁻⁵, and less IOL tilt⁶ with fewer higher order aberrations.⁷ Additionally by using a laser to fragment the crystalline lens, less ultrasound energy is subsequently needed for its removal and so there is 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 benefit⁹⁻¹² and the cost of FLACS is significantly more than PCS.

Two large randomised controlled trials have recently been completed, namely the French multicentre FEMCAT trial¹³ and a UK single site trial from St Thomas' Hospital.¹⁴ Both FEMCAT and the St Thomas' Hospital RCT found similar visual and refractive outcomes for FLACS and PCS, and similar complications with the exception of a 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 FEMCAT 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 FACT (Femtosecond laser Assisted Cataract Trial), a large multicentre 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, 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, multicentre, single masked, non-inferiority RCT done at 3 NHS hospitals in the UK to

establish whether FLACS is as good as or better than PCS (ISRCTN.com registry number ISRCTN77602616).¹⁵ All trial centres 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 & Hampstead (06/02/2015, ref: 14/LO/1937). The trial adhered to the tenets of the Declaration of Helsinki.

All patients were screened and recruited from cataract clinics between May 2015 and September 2017. In summary, adults aged 18 years or older with age related cataract with expected postoperative refractive target within ± 0.5 dioptres of emmetropia (ie. good UDVA) were eligible to take part. Full inclusion and exclusion criteria are provided in the protocol <https://fundingawards.nihr.ac.uk/award/13/04/46> . All patients provided written informed consent before trial participation.

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 an independent web based online system (<https://www.sealedenvelope.com>) using treatment centre, surgeon and one or both eyes eligible as minimisation 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. Due to 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 slit-lamp examination by an Ophthalmologist prior to listing for cataract surgery. Patients with one or both eyes eligible were treated identically. All participants had either PCS or FLACS with the Catalys femtosecond laser (Johnson & Johnson Inc, USA) or Ziemer LDV 8 (Ziemer Ophthalmic Systems AG, Switzerland), under

topical or local anaesthesia. Trial surgeons were ophthalmologists who routinely performed cataract surgery at their respective trial centres 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 arcuate keratotomy could be performed using the Catalys laser at the surgeon's discretion. Detailed descriptions of the Catalys^{18,19} and Ziemer Z8^{20,21} usage for FLACS have previously been published. All patients had planned implantation of a monofocal IOL. PCS was performed as per local practice.

Postoperative care including eye drops was as per standard local centre practice for cataract surgery. Where the FLACS treatment could not be performed for whatever reason following randomisation (eg, unable to dock, laser machine fault, etc), the patient underwent PCS.

Outcomes

The trial primary outcome was unaided distance visual acuity (UDVA, ETDRS logMAR chart at a starting distance of 4 metres)²² at 3 months postoperatively, and this outcome has previously been published in addition to intraoperative surgical complications.¹⁶ Outcomes at one year were UDVA in the study eye and binocular UDVA, corrected distance visual acuity (CDVA) in the study eye alone and binocularly. Long term safety measures included postoperative complications²³ and corneal endothelial cell count loss. Refractive outcomes were percentage within 0.5 and 1.0 dioptre of the intended refractive target. Health-related quality of life was measured by the EQ-5D-3 L questionnaire+vision bolt-on question (EQ-5DV)²⁴ at 1 year, patient-reported vision health status using Catquest-9SF²⁵ at 1 year, a Rasch validated instrument.

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. We aimed to recruit at least 808 patients (404 per arm). This sample size was estimated to identify a treatment effect size of one logMAR line UDVA that 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 as about 0.07 logMAR on letter-by-letter scoring.^{26,27} If there is truly no difference in mean logMAR between the two groups, then 432 patients (216 per group) 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 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 since 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 ICC (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. Additionally, 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, participants remained in their randomised treatment group irrespective of the treatment they received. Each continuous outcome measure was analysed using a model containing the baseline value of the outcome, the stratifying variables of centre 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, two-sided 95% confidence intervals, and two-sided p -values are reported for each outcome measure. A two sample test for independent proportions was used to compare rates of any post operative complications. Visual and refractive outcomes are reported using the standardised graphs for reporting the outcomes of intraocular lens surgery.²⁸ Full details on

the statistical analysis are available in the Statistical Analysis Plan <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 over 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 centres and trial CRFs. 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 CRF, FACT costing study, Client Service Receipt Inventory (CSRI)²⁹, EQ-5D 3 level (EQ-5D-3L). QALYs were calculated as the area under the curve³⁰ using the EQ-5D-3L utility values for the UK³¹ at baseline, 3 months, 6 months and 12 months. 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 no. 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 (IDMC) regularly reviewed outcomes by randomisation arm.

Results:

Of the 3448 patients assessed for trial eligibility, we enrolled 785 participants between May 2015 and September 2017 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 dioptres 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 withdrew prior to randomisation and 26 were awaiting randomisation when recruitment closed. Forty major protocol deviations were identified: not receiving treatment according to randomisation (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 of 392 (74%) participants allocated to FLACS and 311 of 393 (79%) participants allocated to PCS attended their follow-up visit at 1 year. Trial participant demographics and baseline characteristics were similar by randomised group and these have previously been published. Of note, 128 of 392 (33%) FLACS cases and 140 of 393 (36%) PCS cases had one or more ocular co-pathologies at baseline. Analysis of toric IOL usage by arm showed 22 toric lens used in the FLACS arm (369 monofocal, 1 data missing), and 19 toric lens in the PCS arm (370 monofocal, 4 data missing). Table 1 shows the postoperative visual and refractive outcomes at 1 year. Borderline statistical significance was met for binocular CDVA with mean difference of -0.02 logMAR (-0.05 to -0.002 , $p=0.036$) favouring 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 standardised graphs for reporting the outcomes of intraocular lens surgery.

Table 2 shows the postoperative complications for each trial arm. Participants may have had more than one event. There was no significant difference in the proportion of patients with any postoperative complication. Table 3 shows the corneal endothelial cell count at one 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 minutes (SD 3.5), with a total time of 20.8 minutes (SD 8.2). In the PCS arm, surgery took 17.8 minutes (SD 8.0). There was no significant difference in the use of anaesthetic 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 to 3 patients in the FLACS arm) at a cost per vial of £8.65.

There were no significant differences between the two 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 to 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 one 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 (one more letter better CDVA) which whilst 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 (PCR) in FACT were low (0.0% for FLACS and 0.5% for PCS) compared to a reported UK benchmark rate of 1.6%.³ Reported PCR rates in the FEMCAT study were 1.4% for FLACS compared to 1.6% for PCS.¹³ In the St Thomas' RCT, PCR rates were significantly higher in PCS (3.0%) compared to 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 and so a meta-analysis is required to investigate for possible differences.

For refractive outcomes at one year, we found 75% of both FLACS and PCS cases were within $\pm 0.5D$ target, and 95% FLACS cases and 96% PCS cases within $\pm 1.0D$ target. The values reported in a recent large EUREQUO analysis of 282,811 cataract surgeries were 73% and 93% eyes being within $\pm 0.5D$ and $\pm 1.0D$ target respectively.³⁴ Comparative values from the recent St Thomas' Hospital single centre RCT with one month follow-up data of FLACS vs PCS were 71% and 77% eyes respectively within $\pm 0.5D$ and 94% and 95% eyes within $\pm 1.0D$.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 YAG laser capsulotomy or retinal tear or retinal detachments. 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 to 17.8 minutes for PCS. However, after including the FLACS laser time which was an additional mean 3.9 minutes, the total FLACS case time was increased to 20.8 minutes. FLACS therefore does not improve theatre productivity, and with the additional logistical movement of the patient from the laser to the operating table clearly impedes theatre 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). As there is no evidence of any additional benefit as a result 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 cost-effectiveness 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 theatres, using two theatres at the same time, and hence having some cost savings on staff that can work across theatres, 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 al³⁵ <https://paperpile.com/c/8y9gDw/RA6M>, 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 across them both. They came to the conclusion that 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.³⁶ similarly 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 healthcare system.¹³

FACT was designed to detect important differences in visual acuity and to minimise possible bias. The trial was publicly funded by the National Institute for Health Research and thought to be representative of the publicly funded NHS in the UK. Due to 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. Loss to follow-up rates at one year were 26% for FLACS and 21% for PCS, compared to 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,¹⁶ there is a possible surgical learning curve effect for FLACS, with all trial surgeons having performed hundreds of PCS cases compared to a minimum of ten FLACS surgeries that were required to meet trial surgeon eligibility. 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 Additionally, if the FLACS learning curve is much higher than the minimum of 10 previous cases in our surgeon inclusion criteria, as 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 the majority of participants were recruited from St Ann's, Moorfields Eye Hospital in comparison to the other centres, and the setup here may not be fully representative of other cataract surgery centres in the UK.

In summary, the one year results of the FACT trial found that PCS is not inferior to FLACS. Both methods are as good in terms of 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 due to the low complication rates and apparent similar efficacy.

References:

1. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5(12):e1221-e1234.
2. Kelman CD. Phaco-emulsification and aspiration. A new technique of cataract removal. A preliminary report. *Am J Ophthalmol*. 1967;64(1):23-35.
3. Friedman NJ, Palanker DV, Schuele G, et al. Femtosecond laser capsulotomy. *Journal of Cataract & Refractive Surgery*. 2011;37(7):1189-1198. doi:10.1016/j.jcrs.2011.04.022
4. Kránitz K, Takacs A, Miháltz K, Kovács I, Knorz MC, Nagy ZZ. Femtosecond laser capsulotomy and manual continuous curvilinear capsulorrhexis parameters and their effects on intraocular lens centration. *J Refract Surg*. 2011;27(8):558-563.
5. Nagy ZZ, Kránitz K, Takacs AI, Miháltz K, Kovács I, Knorz MC. Comparison of intraocular lens decentration parameters after femtosecond and manual capsulotomies. *J Refract Surg*. 2011;27(8):564-569.
6. Kránitz K, Miháltz K, Sándor GL, Takacs A, Knorz MC, Nagy ZZ. Intraocular lens tilt and decentration measured by Scheimpflug camera following manual or femtosecond laser-created continuous circular capsulotomy. *J Refract Surg*. 2012;28(4):259-263.
7. Miháltz K, Knorz MC, Alió JL, et al. Internal aberrations and optical quality after femtosecond laser anterior capsulotomy in cataract surgery. *J Refract Surg*. 2011;27(10):711-716.
8. Abell RG, Kerr NM, Vote BJ. Toward zero effective phacoemulsification time using femtosecond laser pretreatment. *Ophthalmology*. 2013;120(5):942-948.
9. 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.
10. Popovic M, Campos-Möller X, Schlenker MB, Ahmed IIK. Efficacy and Safety of Femtosecond Laser-Assisted Cataract Surgery Compared with Manual Cataract Surgery: A Meta-Analysis of 14 567 Eyes. *Ophthalmology*. 2016;123(10):2113-2126.
11. 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.

12. Day AC, Gore DM, Bunce C, Evans JR. Laser-assisted cataract surgery versus standard ultrasound phacoemulsification cataract surgery. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2016.
13. Schweitzer C, Brezin A, Cochener B, et al. Femtosecond laser-assisted versus phacoemulsification cataract surgery (FEMCAT): a multicentre participant-masked randomised superiority and cost-effectiveness trial. *Lancet*. 2020;395(10219):212-224.
14. Roberts HW, Wagh VK, Sullivan DL, et al. A randomized controlled trial comparing femtosecond laser-assisted cataract surgery versus conventional phacoemulsification surgery. *J Cataract Refract Surg*. 2019;45(1):11-20.
15. Day AC, Burr JM, Bunce C, et al. Randomised, single-masked non-inferiority trial of femtosecond laser-assisted versus manual phacoemulsification cataract surgery for adults with visually significant cataract: the FACT trial protocol. *BMJ Open*. 2015;5(11):e010381.
16. Day AC. FACT 3 Month Paper - pending publication in *Ophthalmology* - accepted - need to add details.
17. NIHR National Institute for Health Research. A Randomised, single masked, non inferiority trial of Femtosecond Laser Assisted vs Manual Phacoemulsification Cataract Surgery for Adults with Visually Significant Cataract: The FACT trial. <https://fundingawards.nihr.ac.uk/award/13/04/46> accessed 10 August 2019.
18. Day AC, Gartry DS, Maurino V, Allan BD, Stevens JD. Efficacy of anterior capsulotomy creation in femtosecond laser-assisted cataract surgery. *J Cataract Refract Surg*. 2014;40(12):2031-2034.
19. Day AC, Lau NM, Stevens JD. Nonpenetrating femtosecond laser intrastromal astigmatic keratotomy in eyes having cataract surgery. *J Cataract Refract Surg*. 2016;42(1):102-109.
20. Pajic B, Cvejic Z, Pajic-Eggspuehler B. Cataract Surgery Performed by High Frequency LDV Z8 Femtosecond Laser: Safety, Efficacy, and Its Physical Properties. *Sensors* . 2017;17(6). doi:10.3390/s17061429
21. Vasquez-Perez A, Simpson A, Nanavaty MA. Femtosecond laser-assisted cataract surgery in a public teaching hospital setting. *BMC Ophthalmol*. 2018;18(1):26.
22. Ferris FL 3rd, Bailey I. Standardizing the measurement of visual acuity for clinical research studies: Guidelines from the Eye Care Technology Forum. *Ophthalmology*. 1996;103(1):181-182.
23. Day AC, Donachie PHJ, Sparrow JM, Johnston RL, Royal College of Ophthalmologists' National Ophthalmology Database. The Royal College of Ophthalmologists' National Ophthalmology Database study of cataract surgery: report 1, visual outcomes and complications. *Eye* . 2015;29(4):552-560.
24. Yang Y, Rowen D, Brazier J, Tsuchiya A, Young T, Longworth L. An exploratory study to test the impact on three "bolt-on" items to the EQ-5D. *Value Health*. 2015;18(1):52-60.
25. Lundström M, Pesudovs K. Catquest-9SF patient outcomes questionnaire: nine-item short-form Rasch-scaled revision of the Catquest questionnaire. *J Cataract Refract Surg*. 2009;35(3):504-513.

26. Elliott DB, Sheridan M. The use of accurate visual acuity measurements in clinical anti-cataract formulation trials. *Ophthalmic Physiol Opt.* 1988;8(4):397-401.
27. Vanden Bosch ME, Wall M. Visual acuity scored by the letter-by-letter or probit methods has lower retest variability than the line assignment method. *Eye* . 1997;11 (Pt 3)(3):411-417.
28. Reinstein DZ, Archer TJ, Srinivasan S, et al. Standard for Reporting Refractive Outcomes of Intraocular Lens–Based Refractive Surgery. *Journal of Refractive Surgery.* 2017;33(4):218-222. doi:10.3928/1081597x-20170302-01
29. Beecham J, Knapp M, Others. Costing psychiatric interventions. *Measuring mental health needs.* 2001;2:200-224.
30. Hunter, R. M., Baio, G., Butt, T., Morris, S., Round, J., & Freemantle, N. An Educational Review of the Statistical Issues in Analysing Utility Data for Cost-Utility Analysis. *PHARMACOECONOMICS.* 2015; 33 (4), 355-366.
31. Dolan P. Modeling valuations for EuroQol health states. *Med Care.* 1997;35:1095 - 108.
32. Leurent B, Gomes M, Faria R, Morris S, Grieve R, Carpenter JR. Sensitivity analysis for not-at-random missing data in trial-based cost-effectiveness analysis: a tutorial. *Pharmacoeconomics* 2018;36:889–901. <https://doi.org/10.1007/s40273-018-0650-5>
33. The Royal College of Ophthalmologists. National Ophthalmology Database Audit. Year 3 Annual Report – The Second Prospective Report of the National Ophthalmology Database Audit. <https://www.nodaudit.org.uk/u/docs/20/avusuryktz/NOD%20Audit%20Annual%20Report%20018.pdf>. Published June 2018. Accessed August 20, 2019.
34. Lundström M, Dickman M, Henry Y, et al. Risk factors for refractive error after cataract surgery: Analysis of 282 811 cataract extractions reported to the European Registry of Quality Outcomes for cataract and refractive surgery. *J Cataract Refract Surg.* 2018;44(4):447-452.
35. Roberts HW, Ni MZ, O’Brart DPS. Financial modelling of femtosecond laser-assisted cataract surgery within the National Health Service using a “hub and spoke” model for the delivery of high-volume cataract surgery. *BMJ Open.* 2017;7(3):e013616.
36. Abell RG, Vote BJ. Cost-effectiveness of femtosecond laser-assisted cataract surgery versus phacoemulsification cataract surgery. *Ophthalmology.* 2014;121(1):10-16.
37. Day AC, Dhallu SK, Maurino V, Wilkins MR. Initial experience using a femtosecond laser cataract surgery system at a UK National Health Service cataract surgery day care centre. *BMJ Open.* 2016;6(7):e012078.

Figure Legends

Figure 1. Consort chart: trial profile

Figure 2: Standardised graphs: PCS arm at 12 months a) Uncorrected distance visual acuity (UDVA), b) UDVA vs corrected distance visual acuity (CDVA), c) Spherical equivalent refraction, d) Refractive cylinder.

Figure 3: Standardised graphs: FLACS arm at 12 months a) Uncorrected distance visual acuity (UDVA), b) UDVA vs corrected distance visual acuity (CDVA), c) Spherical equivalent refraction, d) Refractive cylinder.

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Table 1. Postoperative results for the two 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)	0.17
UDVA logMAR both eyes, mean (SD)	0.05 (0.16)	0.07 (0.20)	-0.03 (-0.05, 0.003)	0.08
CDVA logMAR study eye, mean (SD)	0.003 (0.18)	0.03 (0.23)	-0.03 (-0.06, 0.01)	0.11
CDVA logMAR both eyes, mean (SD)	-0.05 (0.11)	-0.03 (0.17)	-0.02 (-0.05, 0.002)	0.036
Refraction within $\pm 0.5D$ of target, n (%)	230/307 (75)	218/290 (75)	0.99 (0.68, 1.43)	0.94
Refraction within $\pm 1.0D$ of target, n (%)	292/307 (95)	279/290 (96)	0.76 (0.34, 1.69)	0.50
Catquest 9-SF score, mean (SD)	2.94 (1.05)	2.96 (1.09)	0.01 (-0.15, 0.17)	0.91
EQ-5D-3L index score, mean (SD)	0.83 (0.23)	0.82 (0.25)	0.001 (-0.03, 0.03)	0.95
EQ-5D-3L health state VAS, mean (SD)	79 (17)	77 (19)	2.0 (-0.4 to 4.4)	0.11
-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)	-	-

Table 2: Postoperative complications over 1 year

Complication, n(%)	FLACS	PCS
One or more post operative complications [‡]	62	54
Postoperative anterior uveitis	38	33
Macular oedema	9	14
Retinal tear or detachment	2	3
Steroid response ocular hypertension	7	3
Medication allergy or intolerance	4	3
Corneal oedema	8	2
Vitreous to wound	1	1
Posterior vitreous detachment	3	2
Posterior capsule opacification	4	6
Endophthalmitis	0	0

Participants may have had more than one event

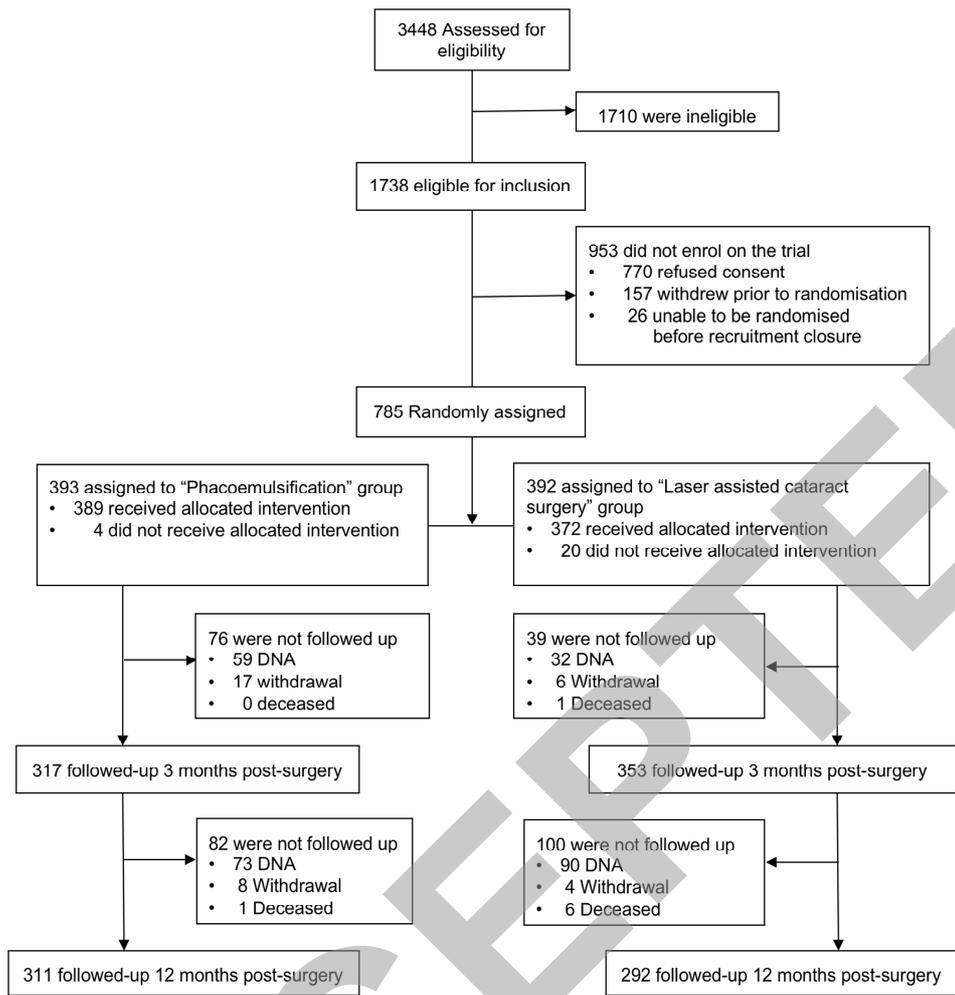
[‡]Difference: not statistically significant

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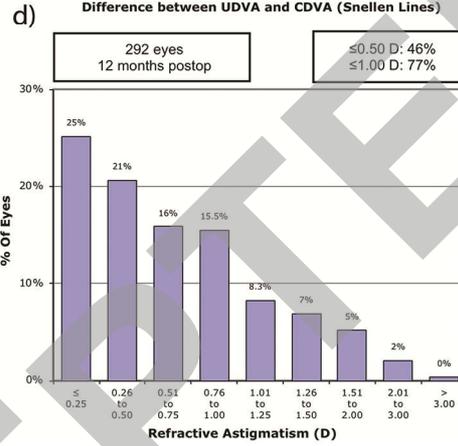
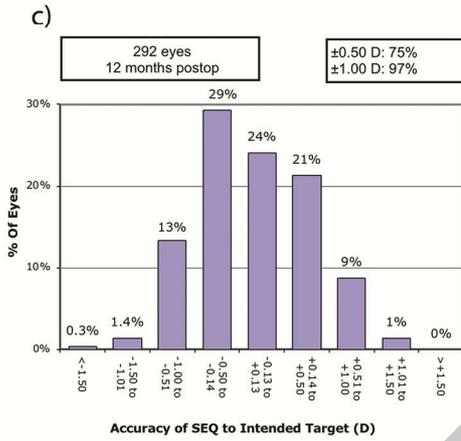
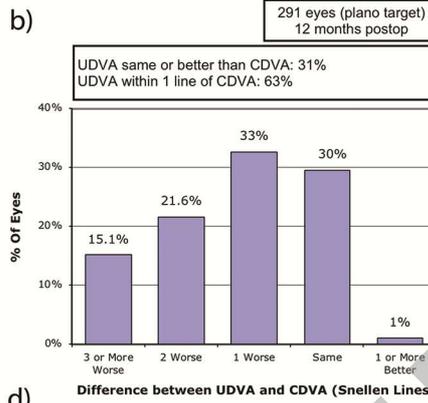
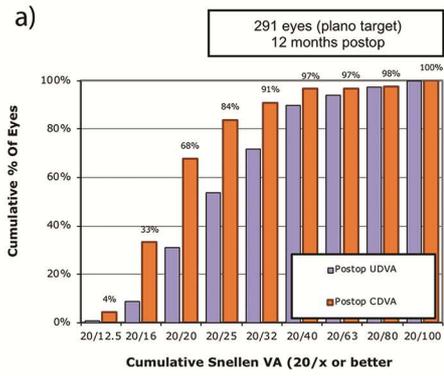
Table 3. Corneal endothelial cell parameters at 1 year

Variable	FLACS n=304	PCS n=284	Effect FLACS-PCS (95% CI)	p value
Corneal endothelial cell count cells/mm ² , mean (SD)	2404 (434)	2413 (406)	-40 (-89 to 8)	0.10
Endothelial cell count loss baseline-final cells/mm ² , mean (SD)	228 (353)	175 (312)	40 (-8 to 89)	0.10

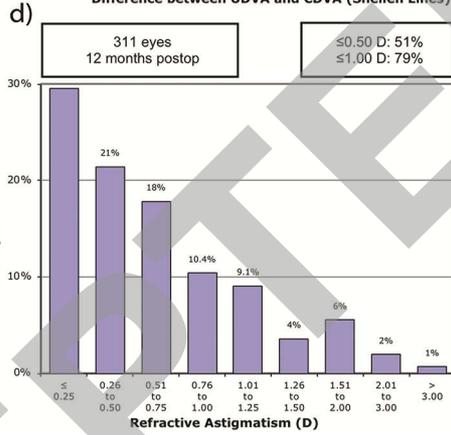
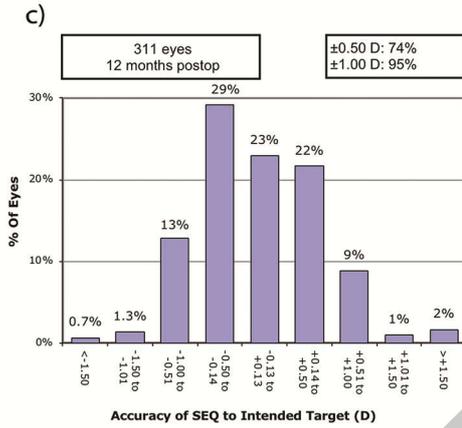
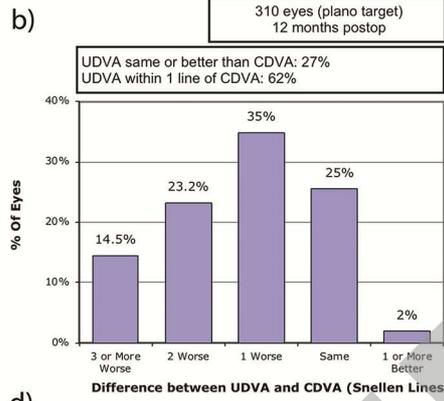
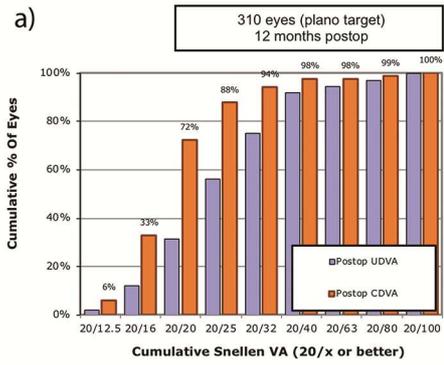
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