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Augusto Azuara-Blanco , Aaron Carlisle , Matthew O'Donnell , Hari Jayaram , Gus Gazzard , Daniel F.P Larkin , Louisa Wickham , Noemi Lois

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Design and conduct of randomized clinical trials evaluating surgical innovations in ophthalmology: a systematic review.

Augusto Azuara-Blanco PhD FRCOphth,[1] Aaron Carlisle MD,[1,2] Matthew O'Donnell MD,[1] Hari Jayaram MD FRCOphth,[3,4] Gus Gazzard MD FRCOphth, [3,4] Daniel F P Larkin, MD FRCOphth,[5] Louisa Wickham MD FRCOphth,[6] Noemi Lois PhD FRCS(Ed).[7]
[1] Centre for Public Health, Queen's University Belfast, Belfast, UK
[2] Belfast Health and Social Care Trust, Belfast, UK
[3] NIHR Biomedical Research Centre & Glaucoma Service at Moorfields Eye Hospital NHS Foundation Trust, London, UK
[4] Institute of Ophthalmology, University College London, UK
[5] Cornea & External Diseases Service, Moorfields Eye Hospital, London, UK
[6] Vitreo-retinal Service, Moorfields Eye Hospital, London, UK
[7] Wellcome-Wolfson Institute for Experimental Medicine, Queen's University, Belfast, UK

Corresponding author and address for reprints: Professor Augusto Azuara-Blanco Centre for Public Health, ICS-A, Grosvenor Road, Belfast, BT12 6BA, UK. E-mail: a.azuara-blanco@qub.ac.uk.

Short title: Trials evaluating novel surgeries in ophthalmology

ABSTRACT

Purpose: Surgical innovations are necessary to improve patient care. After an initial exploratory phase novel surgical technique should be compared with alternative options or standard care in randomized clinical trials (RCTs). However surgical RCTs have unique methodological challenges. Our study sought to investigate key aspects of the design, conduct and reporting of RCTs of novel surgeries.

Design: Systematic Review

Methods: The protocol was prospectively registered in PROSPERO (CRD42021253297). RCTs evaluating novel surgeries for cataract, vitreoretinal, glaucoma and corneal diseases were included. Medline, EMBASE, Cochrane Library and Clinicaltrials.gov were searched. The search period was January 1, 2016, to June 16, 2021.

Results: Fifty-two ophthalmic surgery RCTs were identified in the fields of glaucoma (n=12), vitreoretinal surgery (n=5) cataract (n=19) and cornea (n=16). A description defining the surgeon's experience or level of expertise was reported in 30 RCTs (57%); and was presented in both, control and intervention groups, in eleven (21%). Specification of number of cases performed in the particular surgical innovation being assessed prior to the trial was reported in 10 RCTs (19%); and an evaluation of quality of the surgical intervention in seven (13%). Prospective trial registration was recorded in 12 RCTs (23%), retrospective registration in 13 (25%) and there was no registration record in the remaining 28 (53%) studies.

Conclusion: Important aspects of the study design such as surgical learning curve, surgeon's previous experience, quality assurance, and trial registration details were often missing in novel ophthalmic surgical procedures. The IDEAL framework aims to improve the quality of study design.

Key words:

Randomized clinical trial, surgery, systematic review

INTRODUCTION

Ophthalmology is a high-volume surgical specialty. For cataract operations alone there are over 10 million surgeries worldwide annually.[1] In common with other areas of surgical practice, novel techniques are constantly introduced in ophthalmology and designed to improve patient outcomes. Cataract, vitreoretinal, glaucoma and corneal surgeries are often complex procedures; their performance requires frequent repetition over time to optimise surgical skills.

When considering the adoption of a novel surgical technique ophthalmologists need to evaluate the best available evidence and critically analyse the surgical options available whilst also considering patients' preferences. Randomized controlled trials (RCTs) provide the foundation for evidence-based medicine and help inform health policy. As such, they are often regarded as the gold standard for comparing the effectiveness of interventions.

The assessment of novel surgical techniques has unique methodological challenges that make evaluation inherently complex.[2-11] Surgical procedures are conducted with an almost infinite set of subtle variations associated with surgeon's skills, team expertise, centre policy and infrastructure, patient's anatomical features and the use of different surgical manoeuvres. The consideration of these variations in intervention delivery at trial design will ensure that any appropriate adjustments can be made during trial design and analysis. Clustering effects refer to the influence of treatment provider, as outcomes observed by the same surgeon or at the same hospital may be more similar than those obtained in patients treated by other health providers.[4,5] In addition, surgical skill are expected to improve over time.[6-10] Further challenges in designing surgical RCTs include achieving masking of surgeons and outcome assessors, appropriate outcome selection, and longer-term monitoring. Communicating to

patients uncertainties about the efficacy of safety of novel technologies also needs special consideration.[11]

Deficiencies in the reported designs, conduct, and analysis of non-ophthalmological surgical RCTs has been previously highlighted.[10] The IDEAL (Idea, Development, Exploration, Assessment, Long-term follow-up) collaboration (https://www.ideal-collaboration.net) has been created to improve the quality of research in surgery, devices, and non-pharmacological interventions.[2, 12, 13] It explains the stages through which surgical innovation evolves, illustrating outcomes that may be achieved at each phase. These evolve through idea (Phase 1), development (Phase 2A), exploration (Phase 2B), assessment (phase 3), and long-term follow-up (phase 4). In the early stage (Phase 1), the focus of the innovation is on explanation and description. During development (Phase 2a), RCT protocols should be prospectively registered and techniques refined through small case series. At the next stage of innovation development (Phase 2B), the RCT aims to investigate the efficacy and safety of the intervention; and at the assessment stage (Phase 3), the objective is to compare the surgical intervention to standard practice. Finally, in long term follow-up (Phase 4,) innovations are monitored for adverse events. The IDEAL collaboration advocates the need for considering the surgical learning curve, quality assurance, surgeon's expertise and preference, and prospective reporting of novel surgical clinical trials. [2, 12, 13]

The aim of this study was to review some key aspects of the design, conduct and reporting of RCTs evaluating novel surgical techniques in ophthalmology according to the IDEAL collaboration domains, specifically in the fields of cataract, cornea, glaucoma and vitreoretinal surgery.

METHODS

This systematic review was carried out in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The detailed study protocol was developed prior to start of the review and registered with the PROSPERO systematic review database (CRD42021253297).

We included RCTs involving patients with cataract, corneal disease, glaucoma, vitreoretinal disease comparing different surgical techniques, with at least one being considered innovative. A surgical technique was 'innovative' according to the opinion of expert ophthalmic surgeons authoring this study. Non-randomized prospective studies, retrospective studies, and case-series were excluded. Any variation of RCT design was eligible, including cluster or crossover. RCTs with multiple publications were reviewed and recorded from the earliest date of publication. We excluded retinal laser and glaucoma laser trials because of the reduced variability and relative lack of technical difficulties compared with other surgical or laser techniques. However, we included novel laser refractive surgery and laser for cataract procedures which may require substantial technical expertise.

Only papers published in indexed medical journals (conference abstracts were excluded) were included, with English as the language of publication. The date of publication was restricted to January 1, 2016, to June 16, 2021 to try to capture recent developments. A qualified librarian was consulted regarding the search strategy. Searches were conducted on CENTRAL on the Cochrane Library, Medline OVID, Embase OVID and Clinical Trials.gov databases. The search strategy is described in Supplementary Figure 1. The list of search terms used is given in Appendix 1.

Searches were conducted by one investigator (MOD) and validated by a second investigator (AC and AAB). Data was extracted for each trial by one investigator (MOD) and data entries were checked by a second investigator (AC and AAB). This methodology used for search strategy and data extraction is efficient and has been validated and proved to be

adequate for the undertaken of systematic reviews, obviating the need for two investigators to conduct these steps independently.[14]

The following information was recorded for each RCT: first author, publication year; total number of patients/eyes, population group (cataract, cornea, glaucoma, vitreoretinal disease), intervention; overall surgeon's experience, and number surgeries performed using the new surgery before the RCT was initiated; surgeon's preference or expertise design (when a particular surgeon is involved performing only one surgical technique if they have the experience to choose either the conventional or the novel surgical technique);[15] learning curve considerations; assessment of fidelity to intended intervention or surgical quality;[16] independent monitoring; declarations on conflict of interest (COI) and funding and registration status of study's protocol.[17-22] Examples of assessment of fidelity would include an analysis of a surgical video by a clinician or automated analysis facilitated by artificial intelligence. We recorded whether the study specifically detailed the "grade" of the professional and their experience with the surgical control and intervention. The grade of the professional was defined as the surgeon's position of responsibility and the overall surgeon's experience was determined if the study specified how experienced the surgeon was in the study. When RCT recorded a protocol registration this was verified. Descriptive statistics were used to analyse the results.

We did not evaluate the other domains of trial design not specific to surgical innovations and not included as domains in the IDEAL collaboration such as randomization, allocation concealment, masking of outcome assessment, attrition or reporting bias.

RESULTS

Our search strategy revealed a total of 1763 records after duplicates were removed. Fifty-two RCTs met the inclusion criteria (Figure 1).[23-75] There were 12 glaucoma, five vitreoretinal,

19 cataract and 16 cornea RCTs. The innovative surgical techniques evaluated in these RCTs are shown in Tables 1-4.

Tables 1-4 describe data on surgeon's experience, reported in 30 RCTs (57%) on cataract (n=14), cornea (n=11), glaucoma (n=4) and vitreoretinal conditions (n=1). The remaining RCTs (n=22) did not provide this information. The recording of the surgeon's experience in both arms of the trial was provided in 11 RCTs (21%), and it was unclear in the remaining 41 (79%). Specification of number of cases performed in the particular surgical innovation prior to the trial participation were recorded in ten RCTs (19%).

In relation to cataract RCTs, trials reported a wide range of surgical experience with the novel intervention, Femto Laser Assisted Cataract Surgery (FLACS), prior to the study. One study reported surgeons practicing 2500 FLACS intervention procedures prior to the study to achieve competency,[40] in contrast other studies reported experience of just two cases.[52]

Surgeon's preference was incorporated in trial design in two RCTs (4%), whereby the surgeon would be allowed to perform their preferred surgical technique.[31, 34]

A formal evaluation of the quality of surgical intervention was conducted in seven studies (13%): three cataract;[31,52,55] two cornea,[26,49] two glaucoma[23,25] and none of the vitreoretinal RCTs. The other 45 studies (87%) did not consider this issue. Study details are included in Tables 1-4.

Descriptions of data management responsibilities were recorded in twenty-five trials (48%) including ten cataract, eight cornea, five glaucoma and two vitreoretinal RCTs. Twenty-seven (51%) trials omitted this aspect.

The declaration on the study's funding was recorded in 43 trials (83%) but omitted in nine (17%). There was manufacture support in 15 trials (29%), government support in 13 trials (25%), charity support in two trials (4%) and no financial support in 22 trials (42%)

Similarly conflict of interests (COI) information was omitted in seven trials (13%);and declared in 45 (87%) of trials.

Concerning trial registration, prospective registration was recorded in twelve trials (23%) (four in each cataract, cornea and glaucoma), and retrospective registration in thirteen trials (25%) (cataract n=4; cornea n=3; glaucoma n=5; vitreoretinal n=1). Information on trial registration was not reported in twenty-seven (52%) RCTs (cataract n=11; cornea n=9; glaucoma n=3; vitreoretinal n=4).

DISCUSSION

This systematic review of RCTs evaluating efficacy and safety of novel surgical procedures in ophthalmology found that important aspects of study design and conduct, such as influence of previous surgeon's experience, learning curve of the new technique, quality assurance/fidelity of the intervention, declaration of potential conflict of interests, and trial registration were often missing.

Surgical trials are difficult to design and conduct and many of the challenges are due to the fact that surgery is a complex intervention and standardizing surgical techniques is not easy. The existence and impact of surgical learning curves, where a surgeon's expertise increases throughout the course of a trial, should be considered when a trial is evaluating new interventions. Our study found that the "learning curve" was reported in a minority of RCTs. Number of prior cases performed prior to the undertaking of the new surgery in the trial were recorded in only ten studies (19%). Surgeons' overall experience in standard and intervention arms of the RCT was frequently omitted.

Potential solutions to reduce the influence of the "learning curve" when evaluating new surgical procedures include statistical adjustments or the use of an expertise-based design that consists of surgeons that will perform only one intervention in which they have expertise. Expertise-based design will enhance the validity, applicability, feasibility, and ethical integrity of RCTs in surgery, but this particular design was not used in any of the ophthalmic trials.[15] Alternative valid strategies include selecting surgeons who have attained a specified level of training experience in the novel technique, or who have documented their expertise is at the plateau of the learning curve.

An important consideration is clustering, where variation in outcomes may be smaller between patients treated by the same surgeon or center than patients treated by different surgeons or centers.[16] Clustering can be adjusted statistically or by stratifying

randomization, but this issue was not addressed or properly reported in ophthalmic surgical trials.[16]

The evaluation of the quality or fidelity of the surgical interventions (Tables 1-4), was not reported in most RCTs (87%). With the possibility of video-recording now widely available we suggest that at least a proportion of the interventions could be assessed by trial management committees.

All human studies should be registered in international publicly accessible databases for accountability, research integrity, and clinical governance. Protocol registration has several advantages: it ensures patient and public access to information about ongoing trials, and reduction of redundant RCTs with same purpose. Registration promotes adherence to internationally agreed-upon ethical standards and prevents the modification of primary endpoints during the interim analyses according to the results. It ensures the trial is done and analysed as originally planned, thus, permitting investigators to increase the quality of research design and reliability of the scientific evidence. Only 12 trials (23%) were registered prospectively; this warrants an urgent need for chief investigators, research organisations, journal editors, and grant-awarding bodies to take a more active role in enforcing prospective trial registration.

The deficiencies in trial design and conduct found in our study have also been reported in RCTs in other surgical areas.[10, 76] Among 388 trials of surgical interventions (not including ophthalmology) Robinson et al found that most trials (78.0%) did not control for surgeon experience, and only 4.4% assess the quality of the intervention. Registration was done in 62.4% of trials, a higher rate than the observed in ophthalmology trials.

Ophthalmic surgery is very equipment-dependent and thus it is important that clinicians, researchers and industry collaborate successfully. Reflecting the mutual dependence of surgical device manufacturers and eye surgeons in innovation, we found a high proportion of

trials for which there was manufacturer's financial support. However description of funding, sponsorship and potential conflicts of interest were still missing in a substantial proportion of trials.

A possible limitation of this review is the definition of surgical innovation and the specification of novel interventions proposed by our small group of experts. But a different or wider criteria to select innovations is unlikely to change the main findings of this study. Another limitation is the lack of risk of bias assessment which is common practice in systematic reviews of RTCs. However we wanted to focus this study on specific aspects of surgical trials design and conduct.

The IDEAL collaboration was initiated in 2009 with the aim of promoting the safe, transparent, and efficient introduction and evaluation of surgical innovation (Figure 2). The IDEAL collaboration reported clear guidance regarding the features of studies at each development phase in the surgical innovation evolution. IDEAL has been increasingly accepted in other surgical specialties but is still not mentioned in ophthalmic studies. A core outcome set (COS) for evaluating new surgical procedures and devices has been developed recently, although no patients with eye diseases or ophthalmic surgeons were involved.[77] Useful next steps to improve the quality and consistency of evaluation of surgical innovation include the implementation of recommendations of the IDEAL collaboration in ophthalmology trials. The IDEAL guidelines advise surgical innovators, methodologists and device manufacturers in the practical application of the IDEAL framework by clarifying the essential outcomes to measure throughout the innovation life cycle.

In conclusion, this systematic review RCTs evaluating surgical innovations in ophthalmology have important deficiencies in the reporting of their design and conduct. The IDEAL guidelines provide an appropriate template for improving current standards.

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There are no competing interests.

Table of contents statement
Our systematic review investigated key aspects of the design, conduct and reporting of randomized clinical trials (RCTs) of novel surgeries. Fifty-two ophthalmic RCTs evaluating surgical innovations were identified in the fields of glaucoma, vitreoretinal surgery, cataract, and cornea. Key aspects of the study design and reporting such as surgical learning curve, surgeon's previous experience, quality assurance, and trial registration were often missing. The IDEAL framework aims to improve the quality of trials of innovative surgeries.

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Legends for Figures

Figure 1. PRISMA flow diagram describing the process leading to the identification of included trials.

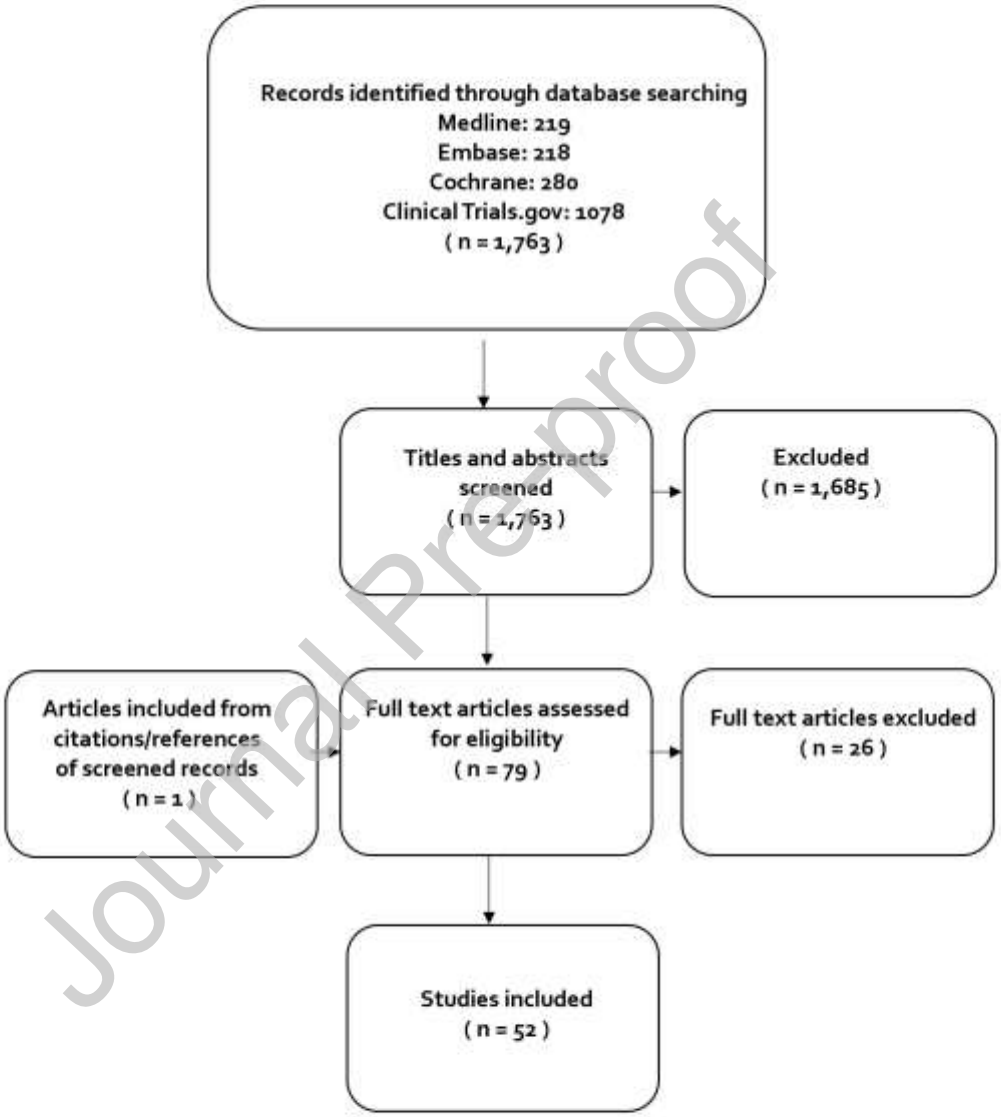

Figure 2. Description of different stages of surgical innovation according to the IDEAL collaboration.

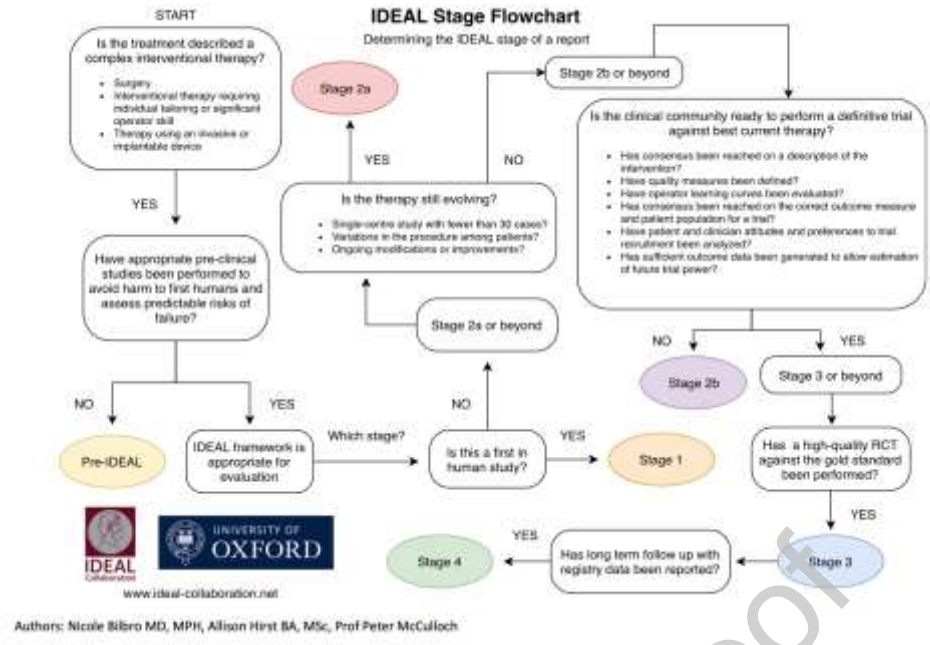

Table 1 Glaucoma trials evaluating surgical innovations.

Study first author, year	Eyes: cases + controls	Innovation	Control group	Surgeon's overall surgical experience	Specific training in novel technique	Specification of number of cases done prior to RCT	Quality assessment of intervention	Data management	Financial disclosure	Funding support	Registration status
Gonzalez-Rodriguez, 2016 [38]	63	Ex-PRESS	Trabeculectomy	NR	NR	NR	No	NR	Yes	Industry	Retrospective
Vold, 2016 [71]	505	Phacoemulsification + CyPass Microstent	Phacoemulsification	NR	NR	NR	No	NR	Yes	Industry	Prospective
El Sayed, 2017 [37]	62	Glaucolight illuminated microcatheter assisted trabeculotomy (250-360°)	Standard rigid probe trabeculotomy (140-180°)	NR	NR	NR	No	NR	No	No	None
Arimura, 2018 [65]	64	Ex-PRESS	Trabeculectomy	NR	NR	NR	No	NR	Yes	Industry	Prospective
Samuelson, 2019 [58]	505	Phacoemulsification + iStent *inject* (2 in 98%)	Phacoemulsification	NR	NR	NR	No	Yes	Yes	Industry	Retrospective
Samuelson, Chang, 2019 [59]	556	Phacoemulsification + Hydrus Microstent	Phacoemulsification	Yes	Yes	NR	No	Yes	Yes	Industry	Retrospective
Ahmed, 2020 [23]	152	Hydrus Microstent (1)	iStent (2)	Yes	Yes	+/ - 100 Hydrus	Yes	Yes	Yes	Industry	Retrospective

Chen, 2020 [27]	32	Phacoemulsification + Micro-bypass stent	Phacoemulsification	NR	NR	NR	No	NR	Yes	Public fundi ng	Retrospective
Doraira j, 2020 [33]	42	Phacoemulsification + Kahook Dual Blade	Phacoemulsification + iStent	Yes	NR	NR	No	Yes	Yes	Industry	Prospective
Griesh aber, 2020 [39]	32	Incision technique for canaloplasty: vertical cut-down incision	Canaloplasty with classic scleral flap dissection	NR	NR	NR	No	NR	Yes	No	None
Baker, 2021[25]	527	Ab-externo MicroShunt	Trabeculectomy	Yes	NR	NR	Yes	Yes	Yes	Industry	Prospective
Shokoohi-Rad, 2021[57]	63	Phacoemulsification + visco-goniosynechialysis + goniotomy	Phacoemulsification + visco-goniosynechialysis	NR	NR	NR	No	NR	Yes	No	None

[1]NR = not reported.

Table 2 Retina trials evaluating surgical innovations.

Study First Author, Year	**Eyes: cases + controls**	**Innovation**	**Control group**	**Surgeon's overall surgical experience**	**Specific training in novel technique**	**Specification of number of cases done prior to RCT**	**Quality assessment of intervention**	**Data management**	**Financial disclosure**	**Funding support**	**Registration status**
Mitsui et al, 2016 [50]	74	27 Gauge Vitrectomy	25 Gauge Vitrectomy	NR	NR	NR	No	Yes	No	No	None
Rastogi, 2018 [54]	20	25 Gauge Vitrectomy	20 Gauge Vitrectomy	NR	NR	NR	No	NR	No	No	None
Romano, 2016 [56]	30	27 Gauge Vitrectomy	25 Gauge Vitrectomy	NR	NR	NR	No	NR	Yes	Industry	None
Sborgia, 2019 [60]	92	27 Gauge Vitrectomy	25 Gauge Vitrectomy	Yes	NR	NR	No	NR	Yes	No	None
Susskind, 2016 [67]	39	25 Gauge Vitrectomy	20 Gauge Vitrectomy	NR	NR	NR	No	Yes	No	No	None

Table 3 Cataract trials evaluating surgical innovations.

Study: First author, year	**Eyes: cases + controls**	**Innovation**	**Control group**	**Surgeon's overall surgical experience**	**Specific training in novel technique**	**Specification of number of cases done prior to RCT**	**Quality assessment of intervention**	**Data management**	**Financial disclosure**	**Funding support**	**Registration status**

Chen, 2019 [28]	94	FLACS	Phacoemulsification	NR	NR	NR	No	NR	Yes	Public funding	Retrospective
Chlasta-Twardzik, 2019 [29]	87	FLACS	Phacoemulsification	Yes	NR	NR	No	NR	Yes	Public funding	None
Day, 2020 [31]	785	FLACS	Phacoemulsification	Yes	Yes	Yes - >10	Yes	Yes	Yes	Public funding	Prospective
Dzhaber, 2020 [36]	134	FLACS	Phacoemulsification	NR	NR	NR	No	Yes	Yes	Charity	Prospective
Hida, 2017 [40]	400	FLACS	Phacoemulsification	Yes	Yes	yes - 2500	No	NR	Yes	No	None
Khan, 2017 [44]	50	FLACS	Phacoemulsification	NR	NR	NR	No	NR	No	No	None
Khodabakhsh, 2018 [45]	100	FLACS	Phacoemulsification	Yes	NR	NR	No	Yes	Yes	Industry	None
Krarup, 2019 [46]	216	FLACS	Phacoemulsification	Yes	NR	NR	No	Yes	Yes	No	None
Lanchulvev, 2019 [47]	101	MiLOOP	Phacoemulsification	Yes	NR	NR	No	Yes	Yes	Industry	Prospective
Mursch-Edlmayr, 2017 [52]	100	FLACS	Phacoemulsification	Yes	NR	NR	Yes	NR	Yes	Industry	None
Roberts, 2018 [55]	400	FLACS	Phacoemulsification	Yes	Yes	Yes - 30	Yes	Yes	Yes	Industry	Prospective
Schojai, 2017 [61]	56	FLACS	Phacoemulsification	NR	NR	NR	No	NR	Yes	No	Retrospective
Schroeter, 2021 [62]	130	FLACS	Phacoemulsification	Yes	NR	NR	No	NR	Yes	No	None
Schweitzer, 2020 [63]	1476	FLACS	Phacoemulsification	Yes	Yes	Yes - 20 flacs	No	Yes	Yes	Industry	Retrospective
Ferreira, 2018 [68]	600	FLACS	Phacoemulsification	Yes	NR	NR	No	Yes	Yes	No	None
Uy , 2017 [69]	62	FLACS	Phacoemulsification	Yes	NR	NR	No	Yes	Yes	Industry	None
Vasavada, 2019 [70]	182	FLACS	Phacoemulsification	NR	NR	NR	No	NR	Yes	No	Retrospective
Yu-AY, 2016 [72]	39	FLACS	Phacoemulsification	Yes	NR	NR	No	NR	Yes	Public funding	Retrospective
Yu-Chi Liu, , 2019 [10]	70	FLACS	Phacoemulsification	Yes	NR	NR	No	Yes	Yes	Public funding	None

Table 4 Cornea trials evaluating surgical innovations.

Study: First author, year	Eyes: cases + controls	Innovation	Control group	Surgeon's overall surgical experience	Specific training in novel technique	Specification of number of cases done prior to RCT	Quality assessment of intervention	Data management	Financial disclosure	Funding support	Registration status
Ang, 2019 [24]	140	SMILE	Femtosecond LASIK	Yes	Yes	50 (SMILE)	No	Yes	Yes	Public funding	Prospective
Chamberlain, 2019 [26]	50	UT-DSAEK	DSAEK	Yes	Not reported/unclear	Not reported/unclear	Yes	Yes	Yes	Public funding	Retrospective
Damgaard, 2018 [30]	140	SMILE	Femtosecond LASIK	Yes	Not reported/unclear	Not reported/unclear	No	Yes	No	No	Prospective
Dickman, 2016 [32]	66	UT-DSAEK	DSAEK	Yes	Not reported/unclear	200 DSAEK	No	Yes	Yes	Public funding	None
Dunker, 2020 [34]	54	UT-DSAEK	DMEK	Yes	Yes	25 DMEK & 100 + DSAEK	No	NR	Yes	Public funding	Prospective
Kanellopoulos, 2018 [41]	44	SMILE	Femtosecond LASIK	Not reported/unclear	Not reported/unclear	Not reported/unclear	No	NR	Yes	No	None
Kanellopoulos, 2019 [42]	42	SMILE	Femtosecond LASIK	Not reported/unclear	Not reported/unclear	Not reported/unclear	No	Yes	No	No	None
Khalifa, 2017 [43]	107	SMILE	Femtosecond LASIK	Yes	Yes	Not reported/unclear	No	NR	Yes	Industry	None
Liu, 2016 [48]	197	SMILE	Femtosecond LASIK	Yes	Yes	200 SMILE	No	NR	Yes	Public funding	None
Matsou, 2021 [49]	56	UT-DSAEK	DSAEK	Yes	Yes	100 DMEK & 350 DSAEK	Yes	Yes	Yes	Charity	Retrospective
Mohamed, 2016 [51]	26	Non-DMEK	DSAEK	Not reported/unclear	Not reported/unclear	Not reported/unclear	No	NR	No	No	None
Qian, 2020 [53]	96	SMILE	Femtosecond LASIK	Not reported/unclear	Not reported/unclear	Not reported/unclear	No	NR	No	No	None
Seitz, 2017 [64]	60	Non-contact excimer laser Penetrating keratoplasty	Femtosecond Laser Trephination	Not reported/unclear	Not reported/unclear	Not reported/unclear	No	NR	Yes	No	None
Simons,2019 [66]	64	UT-DSAEK	DSAEK	Yes	Not reported/unclear	Not reported/unclear	No	Yes	Yes	Public funding	Retrospective
Liu, 2020 [74]	48	SMILE	Femtosecond LASIK	Yes	Not reported/unclear	Not reported/unclear	No	Yes	Yes	No	Prospective
Zhang, 2018 [75]	215	Femtosecond LASIK	SMILE	Yes	Not reported/unclear	Not reported/unclear	No	NR	Yes	No	None