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Active-fluidics versus gravity-fluidics system in phacoemulsification for age-related cataract (AGSPC): study protocol for a prospective, randomized, double-blind, controlled clinical trial.

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Abstract

Introduction: The active-fluidics system is a new perfusion system of phacoemulsification that automatically detects and maintains stable intraocular pressure at the set value. This trial is designed to compare the efficacy, visual outcomes, safety and patient's subjective perceptions of cataract surgery with the active-fluidics system and gravity-fluidics system.

Methods and analysis: This trial will recruit 110 age-related cataract patients at the Chinese People's Liberation Army General Hospital and they will be randomly assigned to the active-fluidics group and gravity-fluidics group in a ratio of 1:1 to have phacoemulsification. Patients will be followed up at one day, one week, one month and three months postoperatively. The primary outcomes are the cumulative dissipated energy and best corrected visual acuity. Secondary outcomes include: estimated fluid usage, total aspiration time, pain scores, intraocular pressure, the corneal endothelium counts, retinal thickness, macular superficial vessel density, scores of the Cat-PROM 5 questionnaire and the complication rates. The data will be independently analysed by the statistical team, who will be masked for the allocation information as participants are.

Ethics and dissemination: This study was approved by the Ethics Committee of Chinese People's Liberation Army (PLA) General Hospital with approval No. S2021-

068-01. All the results will be published in peer-reviewed journals and used for scholarly communications or technical guidance. Protocol version 1.0.
Trial registration: Chinese Clinical Trial Registry, ChiCTR2100044409. Registered on 18 March 2021.
Keywords: Cataract, Phacoemulsification, Active-fluidics system, Gravity-fluidics system, Randomized controlled trial
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Article summary

Strengths and limitations of this study：
► This study is a prospective, randomized, double-blind, controlled clinical trial.
► Aiming at figuring out whether there are differences in efficacy, visual outcomes, safety and patient's subjective perceptions between the active-fluidics system and gravity-fluidics system when they are applied in phacoemulsification.
► Targeted to age-related cataract patients, who occupy a large part of the blind.
► It is the first comprehensive study aiming at clinical outcomes between the two systems with a sample size this large.
► The trial is conducted in only one hospital in Chinese subjects, which may limit its generalisability.

INTRODUCTION

Cataract has been the leading cause of vision impairment around the world, and according to statistics for 2020, 45.5% of the 33.6 million blind people over the age of 50 worldwide were cataract[1-3]. It could lead to vision loss, glare, diplopia, secondary glaucoma, and even uveitis due to cortical liquefaction. Surgery is currently the only effective way to cure it, and as a common operation in ophthalmology, cataract surgery is estimated to be over 20 million cases performed each year[4-6]. Phacoemulsification, which takes the advantage of ultrasound energy to emulsify nucleus and aspirate cortex of the lens, has fewer complications and faster recovery, making it the mainstream surgery method in the past few decades[4, 7].

In the cataract surgery, surgeons are not only faced with the challenge of capsulorhexis and posterior capsule protection, but also with fluctuating anterior chamber and surge after blocking[8-11]. During the period of phaco and aspiration, once the tip is occluded, the vacuum in the aspiration lines will rise rapidly, and when the blockage is lifted, the accumulated negative pressure will take away the intraocular fluid abruptly, making the anterior chamber shallow or even collapsed if the fluid is not replenished in time[8, 12, 13]. The flow and speed of irrigation fluid are determined by the bottle height under the gravity-fluidics system, and to relieve anterior chamber fluctuation, doctors often set the bottle higher to increase the pressure in this case[8, 14]. However, high pressure could easily damage intraocular tissues such as the cornea, iris and optic nerve, and induce pain or discomfort to the patient[13]. To address this paradox, the active-fluidics system is created, which monitors intraocular pressure at all times, compresses or decompresses the balanced salt solution (BSS) fluid bag with two metal plates and adjusts the perfusion flow in time to maintain intraocular

pressure[13, 15]. This feature will conduce to maintain a stable anterior chamber, and improve surgical safety theoretically.

Several studies have reported the successful application of the active-fluidics system in cataract surgery and compared it with the gravity-fluidics system. In a study simulating the anterior chamber by an acrylic chamber, Nicoli et al. [16] reported that both the active-fluidics and gravity-fluidics system were effective in maintaining the target intraocular pressure (IOP) in the absence of aspiration flow. But the measured IOP would deviate from the target in gravity-fluidics system when the aspiration flow is activated, where the active-fluidics system always matched it closely. The same advantage of anterior chamber stability was also observed by Sharif-Kashani et al. [12], who reported a smaller occlusion break surge in active-fluidics system. However, there are no published studies on the anterior chamber stability during phacoemulsification.

There have also been studies comparing the cumulative dissipated energy (CDE) of the two systems, which is an important indicator for assessing the extent of damage from cataract surgery[17-19]. Some studies have reported that the active-fluidics system conserved CDE, but the results were different, with a variation of 19% to 40%[15, 20-22]. It might be related to the surgical techniques, incorporating the severity of the patients' condition[21, 23]. However, Malik et al. [18] have reported that no significant difference existed in CDE between the two systems with the same phaco tip. These controversies make us can't help thinking whether this kind of advantage exists in active-fluidics system and how much of it. Moreover, most comparisons were based on two different phacoemulsification systems like Centurion® and Infiniti®, which prevents us from really knowing whether the differences are also confounding factors from the devices. In addition, many studies have focused on intraoperative parameters, little attention have been paid to clinical outcomes postoperatively, which are of great meanings. Therefore, an RCT is badly needed to verify whether there are differences in intraoperative parameters, postoperative results, ocular tissue damage and patients' subjective discomfort between the two systems when applied to phacoemulsification.

METHODS AND ANALYSIS

Trial design

The AGSPC (Active-fluidics versus gravity-fluidics system in phacoemulsification for age-related cataract) study is a prospective, double-blind, single-centre, randomised controlled clinical trial. Enrolled patients will be randomly assigned to adopt the active-fluidics system (active-fluidics group) or the gravity-fluidics system (gravity-fluidics group) for phacoemulsification in a ratio of 1 to 1. The main objective of this trial is to assess whether there are differences in efficacy, visual outcomes, safety and patient's subjective perceptions between the active-fluidics system and gravity-fluidics system when they are applied in phacoemulsification. The flow chart of the trial design is shown in Figure 1.

Study setting

This study will be conducted at the Chinese PLA General Hospital, a tertiary hospital in Beijing, China. The recruitment, surgery and follow-up will all take place here. For

patients who are eligible for our inclusion, a dedicated investigator will communicate with them about the specifics and obtain their informed consent. This study does not involve the collection or study of any biological specimens.

Eligibility criteria

Age-related cataract will be diagnosed by the same senior ophthalmologist through slit lamp. Those who meet all the following criteria are eligible to be recruited: (1) age-related cataract patients, whose nuclear colour (NC) and nuclear opalescence (NO) are scored as 2.0 - 4.9 according to The Lens Opacities Classification System Ⅲ (LOCS Ⅲ) [24]; (2) the best corrected visual acuity (BCVA) is better than 0.1 (Snellen equivalent 20/200) preoperatively; (3) aged between 50 and 90 years; (4) with good health, no intraocular surgery history; (5) informed consent is signed by the participant who is capable of accomplishing the whole follow-up process; (6) all examinations before the operation are done with enough quality; (7) phacoemulsification is successfully performed without conversion to other surgical methods due to intraoperative adverse events; (8) no history of long-term ocular medication use.

Exclusion criteria include: (1) unable to undergo the cataract surgery with good cooperation; (2) the correlation between previous history of trauma or surgery and the lesion of the lens cannot be ruled out; (3) the combination of other eye diseases that may affect BCVA or ocular blood circulation, such as corneal disease, glaucoma, endophthalmitis, macular degeneration, diabetic retinopathy, retinal vascular obstruction, retinal detachment, etc.; (4) incomplete follow-up information, with more than one missing visit; (5) participating in other clinical trials.

Recruitment

Recruiting is aimed at patients with age-related cataracts who consults ophthalmologists in the Chinese PLA General Hospital and decides to have operation here. An ophthalmologist (YL) will be assigned to accomplish the recruitment. There will not be any additional recruitments for the amounts of patients here will be sufficient.

Sample size

The sample size calculation is based on a randomised controlled study comparing the changes in retinal microcirculation after phacoemulsification under the active-fluidics and gravity-fluidics system of Centurion® [22]. In its results, CDE of active-fluidics group and gravity-fluidics group is 4.82 ± 2.16 versus 6.28 ± 2.92. Based on their data, a simple size of 100 will be enough to achieve $\alpha=0.05$, power=0.8 in a two-sided test. As the drop-out rate is estimated to be 10%, 110 participants are certified finally.

Randomisation

Throughout the whole trial, only one randomisation method will be used, which will be done at a randomisation website (www.sealedenvelope.com). The block effect will be applied to achieve equal subjects between groups. As two groups will be established without stratification factors, the block size will be set small (n=2) to maintain balance. Then it will create a blocked randomisation list and generate unique randomisation codes. Patients will be allocated in the order of their agreement to be recruited, and the randomisation process will be adhered strictly. Information about the randomisation will be kept by a dedicated investigator (ZY) who is also responsible for the

confidentiality. The codes will be employed to reduce randomisation bias at the same time. The original allocation sequence data will be put in an opaque envelope in a locked drawer to prevent any possible tampering.

Blinding and unblinding

All the trial participants and researchers responsible for data analysis will be blinded to the assignment and treatment during the whole procedure. The surgeon and nurses will be masked before the operation. In addition, the doctor responsible for follow-up will also be masked.

If any serious complications that will threaten the vision or life of the participants happens, procedure for unblinding will be performed. When there is a need to withdraw from the trial midway through due to irresistible factors, the same procession will be considered. Otherwise, the unblinding will not be carried out until the end of the trial.

Interventions

All patients will receive comprehensive ophthalmic examinations preoperatively, including slit lamp, IOP measurement, fundus check, visual quality, biometry measurement and B ultrasound. The cataract surgery patient-reported outcome measures questionnaire (Cat-PROM5) should be completed at the same time.

The procedures of phacoemulsification consist that: a 2.2 mm clear corneal incision at 10 o'clock, injection of viscoelastic (medical sodium hyaluronate gel, Iviz®, Bausch + Lomb, New York, USA) into the anterior chamber, circular tearing of the capsule (diameter at 5.0-5.5 mm), cortical-cleaving hydrodissection, aspiration of the nucleus and residual cortex, polishing of the posterior capsule, injection of viscoelastic again, implantation of a foldable intraocular lens (IOL) in the capsule, aspiration of the remaining viscoelastic and corneal incision closure with BSS. Patients randomly allocated to the active-fluidics group will have standard phacoemulsification under CENTURION® Vision System (Centurion®) (Alcon Laboratories, Texas, USA) with active-fluidics system. The target IOP will be set at 50 mmHg, then the aspiration flow rate and vacuum level will be set at 45 cc/min and 450 mmHg respectively. The gravity-fluidics group will have the same operation under Centurion® with gravity-fluidics system. The bottle height will be put at 90 cm, and the aspiration flow rate and vacuum level will be set at 45 cc/min and 450 mmHg, too. An experienced ophthalmologist (ZHL) will perform all the surgeries on enrolled participants and both the active-fluidics system and the gravity-fluidics system will be prepared in advance.

The prescription in the perioperative period will be the same for both groups if no other adverse events occur, which includes that: (1) the broad-spectrum antibiotic - 0.5% Levofloxacin Eye Drops (Cravit®; Santen Pharmaceutical, Osaka, Japan), four times a day (qid) from three days before the surgery; (2) 0.5% Tropicamide, 0.5% Phenylephrine Eye Drops (Mydrin®; Santen Pharmaceutical, Osaka, Japan), three times before the surgery to dilate the pupil; (3) 0.4% Oxybuprocaine Hydrochloride Eye Drops (Benoxil®; Santen Pharmaceutical, Osaka, Japan), three times before the surgery for anesthesia; (4) 0.3% Tobramycin, 0.1% Dexamethasone Combination Eye Ointment (Tobradex®; Alcon, Fort Worth, Texas, USA) immediately after surgery; (5) 0.5% Levofloxacin Eye Drops (Cravit®; Santen Pharmaceutical, Osaka, Japan), qid, for seven days from the first day after the surgery; (6) 0.3% Tobramycin and 0.1%

Dexamethasone Combination Eye Drops (Tobradex®; Alcon, Fort Worth, Texas, USA) qid for seven days, then reduce to twice a day (bid) for the next seven days from the first day after the surgery; (7) 1% Pranoprofen Eye Drops (Pranopulin®; Senju Pharmaceutical, hyogo-ken, Japan), qid, for seven days, then bid, for the next seven days from the first day after the surgery.

If complications, such as a rupture of the posterior capsule or a fall of nucleus into the vitreous cavity, occur during the surgery, or if the zonules are too weak to undergo phacoemulsification, an alternative surgical approach could be applied instead. When the post-operative follow-up reveals a damage in the cornea, drugs to promote corneal repair could be supplemented.

Outcomes

The primary outcomes of our study include: (1) the CDE, which will be presented at the parameters panel of Centurion®; (2) the postoperative BVCA, measured at each follow-up.

Secondary outcomes include the following items: (1) estimated fluid usage (EFU) and total aspiration time (TAT), which will also be obtained from the panel; (2) IOP by non-contact ocular tonometer; (3) the corneal endothelial cells counted by non-contact specular microscope; (4) retinal thickness measured by optical coherence tomography (OCT); (5) macular superficial vessel density measured by optical coherence tomography angiography (OCTA); (6) pain scores during the surgery valued by Wong-Baker Faces Pain Rating Scale; (7) scores of the Cat-PROM 5 questionnaire; (8) the complication rates.

All participants will be followed up at one day, one week, one month and three months after the operation. The corresponding dates for each item are listed in Figure 2.

Data collection

The following items will be assessed or employed after the operation: (1) BCVA, which is supposed to be the first examination item at each follow-up. An objective refraction will be measured by the autorefractor (KR-800, Topcon, Japan) in the first place, then a manifest refraction with standard illumination will be conducted. The Standard Logarithmic Visual Acuity Chart (Chinese Standards GB 11533-2011) will be applied to evaluate visual acuity in a distance of 5 m without pupil dilation, and all the results will be recorded in decimal. (2) Non-contact tonometry, which is supposed to be carried out between 2 to 4 pm. A Full Auto Tonometer (TX-20P, Canon, Japan) will be adopted to measure the IOP. The measurement will be repeated three times and the average value will be taken as the final result for recording. (3) Slit-lamp biomicroscopy, a device to detect whether the inflammation or any complication exists. All the uncomfortable complaints and adverse events will be fully documented. (4) Corneal specular microscopy. The focus will be put on the centre of the cornea and the participant will be requested to blink several times before taking the picture. Forty adjacent corneal endothelial cells will be counted and analysed in the corneal specular microscope (SP·3000P, Topcon, Japan). (5) OCT and OCTA. The retinal thickness and superficial blood flow density of macular will be measured by a same device (CIRRUS HD-OCT 5000, Carl Zeiss, Germany) in modes of macular cube 512×128, optic disc

cube 200×200 and angiography 6×6 mm respectively. The data of vessel density will be analysed by the software (Carl Zeiss Meditec Review Software 10.0.0.14618) automatically. All the scanning will be conducted in the afternoon in a dark room, centring on the macular fovea or optic disc, and the signal strength is required to be greater than or equal to six. The average values of three valid scanning will be recorded finally. (6) Questionnaires and scales. A brief self-report questionnaire: Cat-PROM5 is selected to assess the effect of cataract and cataract surgery on a patient's vision and life. Its reliability and effectiveness have been tested before[25, 26]. The Wong-Baker Faces Pain Rating Scale will be used to evaluate the level of pain during the phacoemulsification. There are six levels of pain with different corresponding expressions from smile to sorrow to tears. Patients will be asked to make a choice according to their feelings immediately after the operation.

All the examiners will be trained before the start of the trial and stick to a standardised procedure. Every examination will be performed by the same doctor throughout the whole trial.

Data management {19}

The personal information of participants is as confidential as their trial data and medical history. Each participant will be coded with an identity and only the investigator responsible for randomization will be able to decode it at the end of the trial. Data managers will be unaware of the allocation throughout the whole process. All of the raw data will be sealed as soon as the recording is completed, and the electronic files will be kept in a separate computer with a password. There will be separate trainings for those involved in data management. Two individual researchers will input the data separately to the analysis software, any discrepancies will be verified by a third manager. The data collected during these processes will be limited to define clinical characteristics and the datasets will be available from the corresponding author after the trial concludes.

Strategies to promote adherence

This trial will recruit residents living in the local area or nearby cities. They will be aware prior to the enrolment that the study contains four times of follow-up in three months. All researchers will be available to offer assistance and answer questions where there is a need.

The protocol of this study will be made available to every investigator involved. As the intervention is a one-off event, compliance is focused on patients receiving the correct treatment group. The person responsible for randomisation will check the patient's identification code before the operation, and then the first assistant surgeon (YG) will be informed of the grouping to ensure a correct intervention.

Statistical methods

Continuous variables that conform to a normal distribution will be recorded as mean ± standard deviation (SD), and those that do not conform to a normal distribution will be recorded as median with interquartile range (IQR). Categorical variables will be presented as whole numbers and percentages. The data will be analysed by the statistical team (HYL et al.) independently. To assess the balance between the two groups, baseline characteristics will be compared firstly. Then, results from both groups

at the same follow-up timepoint will be compared to verify whether differences exist. The group t-test will be used for continuous variables that conform to a normal distribution with a uniform variance, while the t' test will be applied when the variance is not uniform. The Mann Whitney U-test will be used for continuous variables that do not conform to a normal distribution, and the Chi-square test or Fisher's exact test for all categorical variables. IBM SPSS Statistics 26.0 (SPSS Inc., Chicago, IL, USA) will be selected as the statistical analysis software, and all tests will be two-sided, with $P < 0.05$ as the threshold. This study will not involve the interim analysis. When there are missing values, the multiple imputation and sensitivity analysis will be performed.

Oversight and monitoring

The steering committee (SC) accountable for the whole study will be established, and it will obtain the authority to direct the conduction, specify the rules and modify the protocol. It will be composed of the principal investigator (PI), researchers, data analysts and a monitoring group. The monitoring group will be appointed and qualified by the SC and be responsible for monitoring investigators' compliance with protocols as well as the protection of participants' interests.

Ethics and dissemination

This study was approved by the Ethics Committee of Chinese People's Liberation Army (PLA) General Hospital with approval No. S2021-068-01. All the results will be published in peer-reviewed journals and used for scholarly communications or technical guidance.

Discussion

The vision loss caused by cataract is a huge burden on society and families, fortunately, it is curable [2, 27]. Actually, researches on cataract surgery have not ceased in the past decades in the pursuit of better results [28-30]. Therefore, studies are badly needed to verify whether updates in the surgical systems do lead to better outcomes. The active-fluidics system has been put into use for many years, but it is not yet widespread [15, 21, 31]. Most of the researches on it are laboratory studies, or focusing on intra-operative parameters, there are few studies on the results and injuries of the surgery [12, 16, 18, 32]. In order to fully evaluate changes brought by the phacoemulsification with active-fluidics system, we need to take more items into account. To our knowledge, this AGSPC study is the first comprehensive study aiming at clinical outcomes between the two systems in the same machine with a sample size this large.

Achieving good visual acuity is the ultimate goal of cataract surgery, and the degree of damage brought by phacoemulsification to the cornea is an important factor influencing post-operative vision[33]. Reducing the intraoperative damage is essential to the corneal endothelium as it is non-regenerative [33, 34]. The advantages of the active-fluidics system in reducing CDE have been reported, and it remains to be further explored whether it will lead to a reduction in corneal endothelial damage[11, 18]. Observation of retinal thickness, particularly macular thickness, by OCT can help to figure out whether lesions such as macular edema presents after cataract surgery and to develop targeted treatment early[35, 36]. Assessment of changes in retinal nerve fiber layer thickness is also an important indicator to evaluate the effect of intraoperative

perfusion pressure on the optic nerve[37, 38].

The interest in retinal blood flow has begun in the last few years. Thanks to the advent of OCTA, which helps to visualise and analyse the retinal vasculature in a non-invasive way and allows quantitative calculation of vessel density with the aid of specific software[39]. Changes in the microcirculation of the retina may be an early stage of some diseases but relevant mechanism has not been studied in sufficient detail[40-42]. It is not yet clear whether there is a correlation between perfusion pressure, CDE and vessel density, between changes in blood flow and changes in retinal thickness or macular edema. Our study will devote to analyse the clinical significance of changes in vessel density after cataract surgery and whether there is a difference in the effect of surgery on blood flow under the two systems.

The assessment and analysis of the patient's subjective perception is another feature and strength of our study. When using an active-fluidics system, the target IOP could be set at an appropriate level to avoid causing pains or discomfort and to promote intraoperative cooperation[13, 22]. But whether this theoretical advantage exists has not been reported. A subjective pain scale will be selected and scored by each patient, and the results obtained from both systems will be compared and analysed in order to draw reliable conclusions.

This article describes a rigorously designed randomized controlled clinical trial in order to compare the active-fluidics versus gravity-fluidics system for performing cataract surgery. The structural changes in the eyes after cataract surgery will be fully studied and the evidence-based data will also provide a basis and reference for future work and treatment. The limitation of this trial is that, as a single centre study, we will collect data of one surgeon to reduce the bias. It may result in our findings being different from others and unrepresentative, and it is what we will be working towards in the future.

Trial status

Recruitment for this trial started in March 2021, and is planned to be completed in March 2022. The process might be interrupted or extended due to the COVID-19 pandemic.

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Author Contributions

ZHL is the principal investigator and lead the organization of the whole study. ZY contributed a lot in the trial design and supervision. YL drafted the first manuscript and HYL reviewed it. WQC, YG and TJM paid efforts in the conduction of the trial. All authors read and approved the final version of this protocol for publication.

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Competing interests

The authors declare that they have no competing interests.

Patient and public involvement

Patients and the public were involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Parental consent obtained.

Provenance and peer review

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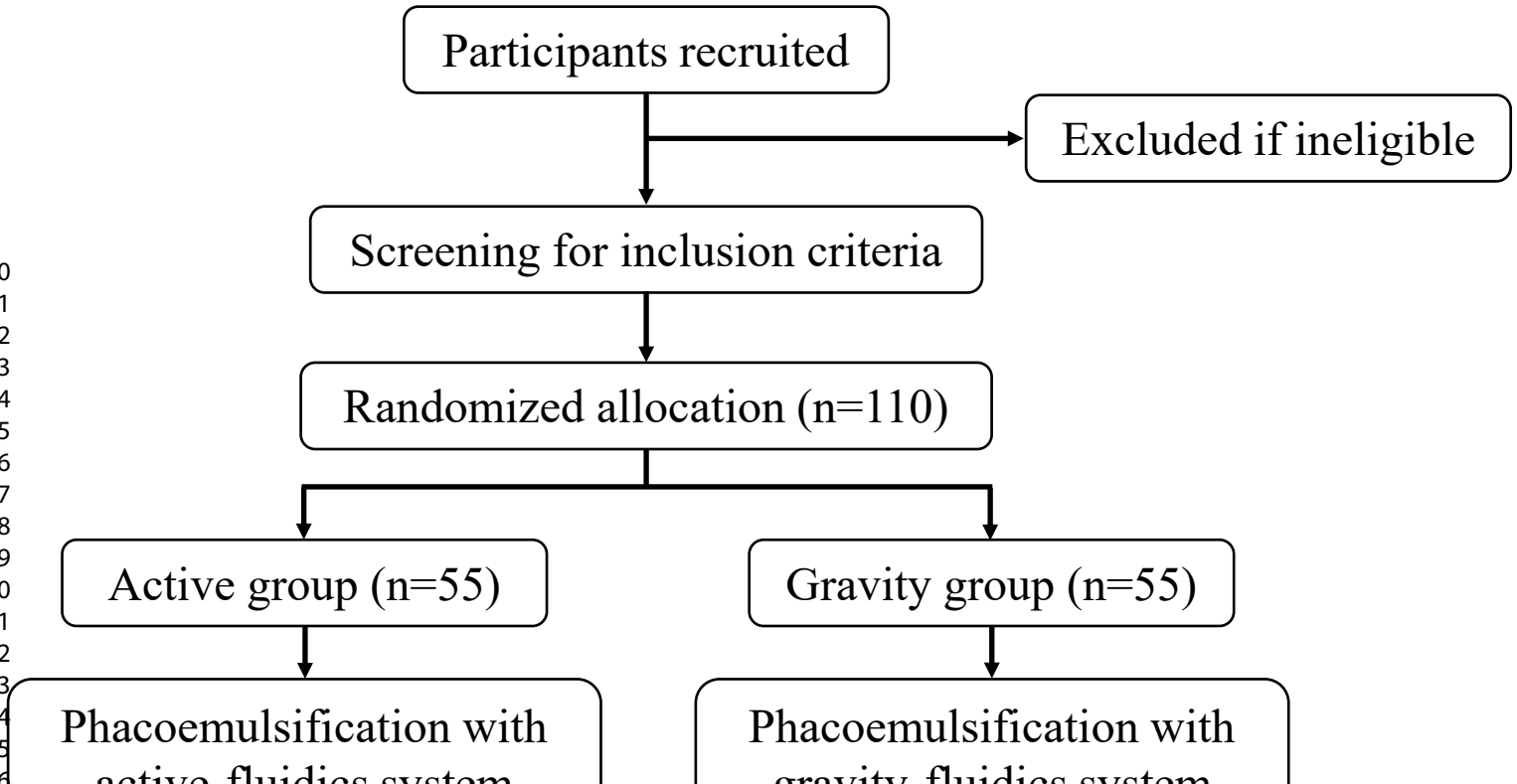
Figure 1. Flow chart of the trial design.
Figure 2. Timeline and data collection schedule for the AGSPC study.


Participants recruited
Excluded if ineligible
Screening for inclusion criteria
Randomized allocation (n=110)
Active group (n=55)
Gravity group (n=55)
Phacoemulsification with active-fluidics system
Phacoemulsification with gravity-fluidics system
Follow-up at 1d, 1w, 1m, 3m postoperatively
Statistical analysis
Draw conclusion

	Baseline	Operation	Follow-up			
			1d	1w	1m	3m
Pick-up information:						
Demographics	×					
NC	×					
NO	×					
Biometry measurement	×					
Medical history	×					
Informed consent	×					
Allocation		×				
Outcomes:						
Adverse events		←	—	—	—	→
Efficacy						
CDE		×				
EFU		×				
TAT		×				
Effects						
BCVA	×		×	×	×	×
Subjective perceptions						
Pain scores		×				
Cat-PROM 5	×				×	
Safety						
Slit lamp biomicroscopy	×					
IOP	×		×	×	×	×
Corneal endothelial cells	×		×	×	×	×
Retinal thickness			×	×	×	×
Vessel density			×	×	×	×

NC, nuclear colour; NO, nuclear opalescence; CDE, cumulative dissipated energy; EFU, estimated fluid usage; TAT, total aspiration time; BCVA, best corrected visual acuity; Cat-PROM 5, cataract surgery patient-reported outcome measures questionnaire; IOP, intraocular pressure; 1d, one day; 1w, one week; 1m, one month; 3m, three months.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	9
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	1,9

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3

Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3-4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4

Methods:			
Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4-5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4-5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4-5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5

Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-7
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7-8

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7-8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7-8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7-8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7-8

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7-8
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	8
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	4,7-8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	10

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	5,7
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	7-8
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	7-8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	4,7-8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	4,10
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	4

BMJ Open

Active-fluidics versus gravity-fluidics system in phacoemulsification for age-related cataract (AGSPC): study protocol for a prospective, randomized, double-blind, controlled clinical trial.

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Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology, Surgery
Keywords:	Cataract and refractive surgery < OPHTHALMOLOGY, Ophthalmology < SURGERY, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

Active-fluidics versus gravity-fluidics system in phacoemulsification for age-related cataract (AGSPC): study protocol for a prospective, randomized, double-blind, controlled clinical trial.

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Abstract

Introduction: The active-fluidics system is a new irrigation system of phacoemulsification that automatically detects and maintains stable intraocular pressure at the set value. This trial is designed to compare the efficacy, visual outcomes, safety and patient's subjective perceptions of cataract surgery with the active-fluidics system and gravity-fluidics system.

Methods and analysis: This trial will recruit 110 age-related cataract patients at the Chinese People's Liberation Army (PLA) General Hospital (Beijing, China) and they will be randomly assigned to the active-fluidics group and gravity-fluidics group in a ratio of 1:1 to have phacoemulsification. Patients will be followed up at one day, one week, one month and three months postoperatively. The primary outcomes are the cumulative dissipated energy and best corrected visual acuity. Secondary outcomes include: estimated fluid usage, U/S time, total aspiration time, intraocular pressure, the corneal endothelium parameters, retinal thickness, macular superficial vessel density, pain scores, scores of the Cat-PROM 5 questionnaire and the complication rates. The data will be independently analysed by the statistical team, who will be masked for the allocation information as participants are.

Ethics and dissemination: This study was approved by the Ethics Committee of Chinese PLA General Hospital with approval No. S2021-068-01. Informed consent will

be obtained from each participant. All the results will be published in peer-reviewed journals and used for scholarly communication or technical guidance. Protocol version 1.0.

Trial registration: Chinese Clinical Trial Registry, ChiCTR2100044409. Registered on 18 March 2021.

Keywords: Cataract, Phacoemulsification, Active-fluidics system, Gravity-fluidics system, Randomized controlled trial

Word count: 3967

Article summary

Strengths and limitations of this study：

► This study is a prospective, randomized, double-blind, controlled clinical trial.

► First comprehensive study aiming at comparison of clinical outcomes between the active-fluidics system and gravity-fluidics system with a sample size like this volume.

► Same phacoemulsifier, phaco tip and operator will increase credibility and minimize bias significantly.

► The follow-up period is not sufficient to observe long-term outcomes.

► Its generalisability may be limited by the data collected from only one surgeon.

INTRODUCTION

Cataract has been the leading cause of vision impairment around the world, and according to statistics for 2020, 45.5% of the 33.6 million blind people over the age of 50 worldwide were cataract[1-3]. It could lead to vision loss, glare, diplopia, secondary glaucoma, and even uveitis due to cortical liquefaction. Surgery is currently the only effective way to cure it, and as a common operation in ophthalmology, cataract surgery is estimated to be over 20 million cases performed each year[4-6]. Phacoemulsification, which takes the advantage of ultrasound energy to emulsify nucleus and aspirate cortex of the lens, has fewer complications and faster recovery, making it the mainstream surgery method in the past few decades[4, 7].

In the cataract surgery, surgeons are not only faced with the challenge of capsulorhexis and posterior capsule protection, but also with fluctuating anterior chamber and surge after blocking[8-11]. During the period of phaco and aspiration, once the tip is occluded, the vacuum in the aspiration lines will rise rapidly, and when the blockage is lifted, the accumulated negative pressure will take away the intraocular fluid abruptly, making the anterior chamber shallow or even collapsed if the fluid is not replenished in time[8, 12, 13]. The flow and speed of irrigation fluid are determined by the bottle height under the gravity-fluidics system, and to relieve anterior chamber fluctuation, doctors often set the bottle higher to increase the pressure in this case[8, 14]. However, high pressure could easily damage intraocular tissues such as the cornea, iris and optic nerve, and induce pain or discomfort to the patient[13]. To address this paradox, the active-fluidics system is created, which monitors intraocular pressure at all times, compresses or decompresses the balanced salt solution (BSS) fluid bag with two metal plates and adjusts the perfusion flow in time to maintain intraocular pressure[13, 15]. This feature will conduce to maintain a stable anterior chamber, and

improve surgical safety theoretically.

Several studies have reported the successful application of the active-fluidics system in cataract surgery and compared it with the gravity-fluidics system. In a study simulating the anterior chamber by an acrylic chamber, Nicoli et al. [16] reported that both the active-fluidics and gravity-fluidics system were effective in maintaining the target intraocular pressure (IOP) in the absence of aspiration flow. But the measured IOP would deviate from the target in gravity-fluidics system when the aspiration flow is activated, where the active-fluidics system always matches it closely. The same advantage of anterior chamber stability was also observed by Sharif-Kashani et al. [12], who reported a smaller occlusion break surge in active-fluidics system. However, there are no published studies on the anterior chamber stability during phacoemulsification.

There have also been studies comparing the cumulative dissipated energy (CDE) of the two systems, which is an important indicator for assessing the extent of damage from cataract surgery[17-19]. Some studies have reported that the active-fluidics system conserved CDE, but the results were different, with a variation of 19% to 40%[15, 20-22]. It might be related to the surgical techniques, incorporating the severity of the patients' condition[21, 23]. However, Malik et al. [18] have reported that no significant difference existed in CDE between the two systems with the same phaco tip. These controversies make us consider whether this kind of advantage exists in active-fluidics system and how much of it. Moreover, most comparisons were based on different phacoemulsifiers, which prevents us from really knowing whether the differences are also confounding factors from the devices. In addition, many studies have focused on intraoperative parameters, very little attention paid to clinical outcomes postoperatively, which are of great meanings. Therefore, an RCT is badly needed to verify whether there are differences in intraoperative parameters, postoperative results, ocular tissue damage and patients' subjective discomfort between the two systems in phacoemulsification.

METHODS AND ANALYSIS

Trial design

The AGSPC (Active-fluidics versus gravity-fluidics system in phacoemulsification for age-related cataract) study is a prospective, double-blind, single-centre, randomized controlled clinical trial. Enrolled patients will be randomly assigned to adopt the active-fluidics system (active-fluidics group) or the gravity-fluidics system (gravity-fluidics group) for phacoemulsification in a ratio of 1 to 1. The main objective of this trial is to assess whether there are differences in efficacy, visual outcomes, safety and patient's subjective perceptions between the active-fluidics system and gravity-fluidics system when they are applied in phacoemulsification. The flow chart of the trial design is shown in Figure 1.

Study setting

This study will be conducted at the Chinese PLA General Hospital, a tertiary hospital in Beijing, China. The recruitment, surgery and follow-up will all take place here. For patients who are eligible for our inclusion, a dedicated investigator will communicate with them about the specifics and obtain their informed consent. This study does not

involve the collection or study of any biological specimens.

Eligibility criteria

Age-related cataract will be diagnosed by the same senior ophthalmologist through slit lamp. Those who meet all the following criteria are eligible to be recruited: (1) age-related cataract patients, whose nuclear colour (NC) and nuclear opalescence (NO) are scored as 2.0 - 4.9 according to The Lens Opacities Classification System Ⅲ (LOCS Ⅲ) [24]; (2) the best corrected visual acuity (BCVA) is better than 0.1 (Snellen equivalent 20/200) preoperatively; (3) aged between 50 and 90 years; (4) with good health, no intraocular surgery history; (5) informed consent is signed by the participant who is capable of accomplishing the whole follow-up process; (6) all examinations before the operation are done with high quality; (7) phacoemulsification is successfully performed without conversion to other surgical methods due to intraoperative adverse events; (8) no history of long-term ocular medication use.

Exclusion criteria include: (1) unable to undergo the cataract surgery with good cooperation; (2) the correlation between previous history of trauma or surgery and the lesion of the lens cannot be ruled out; (3) the combination of other eye diseases that may affect BCVA or ocular blood circulation, such as corneal disease, glaucoma, endophthalmitis, macular degeneration, diabetic retinopathy, retinal vascular obstruction, retinal detachment, etc.; (4) incomplete follow-up information, with more than one missing visit; (5) participating in other clinical trials.

Recruitment

Recruiting is aimed at patients with age-related cataracts who consults ophthalmologists in the Chinese PLA General Hospital and decides to have operation here. An ophthalmologist (YL) will be assigned to accomplish the recruitment. No extra recruitment is needed in other medical centres as the amounts of patients here will be sufficient.

Sample size

The sample size calculation is based on a randomized controlled study comparing the changes in retinal microcirculation after phacoemulsification with the active-fluidics and gravity-fluidics system [22]. In its results, CDE of active-fluidics group and gravity-fluidics group is 4.82 ± 2.16 versus 6.28 ± 2.92. Based on their data, a simple size of 100 will be adequate to achieve α=0.05, power=0.8 in a two-sided test. As the drop-out rate is estimated to be 10%, 110 participants are certified finally.

Randomization

Throughout the whole trial, only one randomization method will be used, which will be done at a randomization website (www.sealedenvelope.com). The block effect will be applied to achieve equal subjects between groups. As two groups will be established without stratification factors, the block size will be set small (n=2) to maintain balance. Then it will create a blocked randomization list and generate unique randomization codes. Patients will be allocated in the order of their recruitment sequence, and the randomization process will be adhered strictly. Information about the randomization will be kept by a dedicated investigator (ZY) who is also responsible for the confidentiality. The codes will be employed to reduce randomization bias. The original allocation sequence data will be put in an opaque envelope in a locked drawer to prevent

tampering.

Blinding and unblinding

All the trial participants and researchers responsible for data analysis will be blinded to the assignment and treatment during the whole procedure. The surgeon and nurses will be masked before the operation. In addition, the doctor responsible for follow-up will also be masked.

In the case of any serious complications that will threaten the vision or life of the participants happen, procedure for unblinding will be performed. When there is a need to withdraw from the trial midway through due to irresistible factors, the same procession will be considered. Otherwise, the unblinding will not be carried out until the end of the trial.

Interventions

All patients will receive comprehensive ophthalmic examinations preoperatively, including slit lamp, IOP measurement, fundus check, visual quality, biometry measurement and B ultrasound. The cataract surgery patient-reported outcome measures questionnaire (Cat-PROM5) should be completed at the same time.

The procedures of phacoemulsification consist that: a 2.2 mm clear corneal incision at 10 o'clock, injection of viscoelastic (medical sodium hyaluronate gel, Iviz®, Bausch + Lomb, New York, USA) into the anterior chamber, circular tearing of the capsule (diameter at 5.0-5.5 mm), cortical-cleaving hydrodissection, aspiration of the nucleus and residual cortex, polishing of the posterior capsule, injection of viscoelastic again, implantation of a foldable intraocular lens (IOL) in the capsule, aspiration of the remaining viscoelastic and corneal incision closure with BSS. Patients randomly allocated to the active-fluidics group will have standard phacoemulsification under CENTURION® Vision System (Centurion®) (Alcon Laboratories, Texas, USA) with active-fluidics system and Intrepid balanced tip. The target IOP will be set at 50 mmHg, then the aspiration flow rate and vacuum level will be set at 45 cc/min and 450 mmHg respectively. The gravity-fluidics group will have the same operation under Centurion® with gravity-fluidics system and Intrepid balanced tip. The bottle height will be put at 90 cm, and the aspiration flow rate and vacuum level will be set at 45 cc/min and 450 mmHg, too. An experienced ophthalmologist (ZHL) will perform all the surgeries on enrolled participants and both the active-fluidics system and the gravity-fluidics system will be prepared in advance.

The prescription in the perioperative period will be the same for both groups, which includes that: (1) the broad-spectrum antibiotic - 0.5% Levofloxacin Eye Drops (Cravit®; Santen Pharmaceutical, Osaka, Japan), four times a day (qid) from three days before the surgery; (2) 0.5% Tropicamide, 0.5% Phenylephrine Eye Drops (Mydrin®; Santen Pharmaceutical, Osaka, Japan), three times before the surgery to dilate the pupil; (3) 0.4% Oxybuprocaine Hydrochloride Eye Drops (Benoxil®; Santen Pharmaceutical, Osaka, Japan), three times before the surgery for anesthesia; (4) 0.3% Tobramycin, 0.1% Dexamethasone Combination Eye Ointment (Tobradex®; Alcon, Fort Worth, Texas, USA) immediately after surgery; (5) 0.5% Levofloxacin Eye Drops (Cravit®; Santen Pharmaceutical, Osaka, Japan), qid, for seven days from the first day after the surgery; (6) 0.3% Tobramycin and 0.1% Dexamethasone Combination Eye Drops (Tobradex®;

Alcon, Fort Worth, Texas, USA) qid for seven days, then reduce to twice a day (bid) for the next seven days from the first day after the surgery; (7) 1% Pranoprofen Eye Drops (Pranopulin®; Senju Pharmaceutical, hyogo-ken, Japan), qid, for seven days, then bid, for the next seven days from the first day after the surgery.

If complications, such as a rupture of the posterior capsule or a fall of nucleus into the vitreous cavity, occur during the surgery, or if the zonules are too weak to undergo phacoemulsification, an alternative surgical approach will be applied instead. When the post-operative follow-up reveals a damage in the cornea, drugs to promote corneal repair could be supplemented.

Outcomes

The primary outcomes of this study include: (1) the CDE, which will be presented at the parameters panel of Centurion®; (2) the postoperative BVCA, measured at each follow-up.

The secondary outcomes include the following items: (1) estimated fluid usage (EFU), U/S time and total aspiration time (TAT), which will also be obtained from the panel; (2) IOP by non-contact ocular tonometer; (3) the central corneal thickness (CCT), endothelial cell density (ECD), percentage of hexagonal cells (HEX) and coefficient of variation (CV) counted by non-contact specular microscope; (4) central retinal thickness (CRT) and retinal nerve fiber layer (RNFL) thickness measured by optical coherence tomography (OCT); (5) macular superficial vessel density and the area of the foveal avascular zone (FAZ) measured by optical coherence tomography angiography (OCTA); (6) pain scores during the surgery valued by Wong-Baker Faces Pain Rating Scale[25]; (7) scores of the Cat-PROM 5 questionnaire[26]; (8) the operation-related complication rates.

All participants will be followed up at one day, one week, one month and three months after the operation. The corresponding dates for each item are listed in Figure 2.

Data collection

The following items will be measured and assessed after the operation: (1) BCVA, which is supposed to be the first examination item at each follow-up. An objective refraction will be measured by the autorefractor (KR-800, Topcon, Japan) in the first place, then a manifest refraction with standard illumination will be conducted. The Standard Logarithmic Visual Acuity Chart (Chinese Standards GB 11533-2011) will be applied to evaluate visual acuity in a distance of 5 m without pupil dilation, and all the results will be recorded in decimal. (2) Non-contact tonometry, which is supposed to be carried out between 2 to 4 pm. A Full Auto Tonometer (TX-20P, Canon, Japan) will be used to measure the IOP. The measurement will be repeated three times and the average value will be recorded as the final result. (3) Slit-lamp biomicroscopy, a device to detect whether the inflammation or any complication exists. All the uncomfortable complaints and adverse events will be fully documented. (4) Corneal specular microscopy. The focus will be put on the centre of the cornea and the participant will be requested to blink several times before taking the picture. Forty adjacent corneal endothelial cells will be counted and analysed in the corneal specular microscope (SP·3000P, Topcon, Japan). (5) OCT and OCTA. The retinal thickness and superficial

blood flow density of macular will be measured by a same device (CIRRUS HD-OCT 5000, Carl Zeiss, Germany) in modes of macular cube 512×128, optic disc cube 200×200 and angiography 6×6 mm respectively. The data of vessel density will be analysed by the software (Carl Zeiss Meditec Review Software 10.0.0.14618) automatically. All the scanning will be conducted in the afternoon in a dark room, centring on the macular fovea or optic disc, and the signal strength is required to be greater than or equal to six. The average values of three valid scanning will be recorded finally. (6) Questionnaires and scales. A brief self-report questionnaire: Cat-PROM5 is selected to assess the effect of cataract and cataract surgery on a patient's vision and life. Its reliability and effectiveness have been tested before[26, 27]. The Wong-Baker Faces Pain Rating Scale will be used to evaluate the level of pain during the phacoemulsification. There are six levels of pain with different corresponding expressions from smile to sorrow to tears. Patients will be asked to make a choice according to their feelings immediately after the operation.

All the examiners will be trained before the start of the trial and stick to a standardised procedure. Each single of the examinations will be performed by the same doctor throughout the whole trial.

Data management

The personal information of participants is as confidential as their trial data and medical history. Each participant will be coded with an identity and only the investigator responsible for randomization will be able to decode it at the end of the trial. Data managers will be unaware of the allocation throughout the whole process. All of the raw data will be sealed as soon as the recording is completed, and the electronic files will be kept in a separate computer with a password. There will be separate trainings for technicians involved in data management. Two individual researchers will input the data separately to the analysis software, any discrepancies will be verified by a third manager. The data collected during these processes will be limited to define clinical characteristics and the datasets will be available from the corresponding author after the trial concludes.

Strategies to promote adherence

This trial will recruit residents living in the local area or nearby cities. They will be aware prior to the enrolment that the study contains four times of follow-up in three months. All researchers will be available to offer assistance and answer questions as needed.

The protocol of this study will be made available to all investigators involved. As the intervention is a one-off event, compliance will be focusing on ensuring patients receiving the correct treatment group. The person responsible for randomization will check the patient's identification code before the operation, and then the first assistant surgeon (YG) will be informed with the grouping to ensure a correct intervention.

Statistical methods

Continuous variables that conform to a normal distribution will be recorded as mean ± standard deviation (SD), and those that do not conform to a normal distribution will be recorded as median with interquartile range (IQR). Categorical variables will be presented as whole numbers and percentages. The data will be analysed by the

statistical team (HYL et al.) independently. To assess the balance between the two groups, baseline characteristics will be compared firstly. Then, results from both groups at the same follow-up timepoint will be compared to verify whether differences exist. The group t-test will be used for continuous variables that conform to a normal distribution with a uniform variance, while the t' test will be applied when the variance is not uniform. The Mann Whitney U-test will be used for continuous variables that do not conform to a normal distribution, and the Chi-square test or Fisher's exact test for all categorical variables. IBM SPSS Statistics 26.0 (SPSS Inc., Chicago, IL, USA) will be selected as the statistical analysis software, and all tests will be two-sided, with $P < 0.05$ as the threshold. This study will not involve the interim analysis.

Nonadherence and missing data processing

The missing data may bias the results, so we will further strengthen our communication with participants to promote their retention. With multiple efforts, we anticipate that the amount of missing data will be small. When there are missing values, we will perform the multiple imputation and sensitivity analysis. If the results of the sensitivity analysis showed that the assumption of missing at random mechanism is valid, the filled dataset will be adopted. Otherwise, the mixed-effect pattern-mixture model will be used.

Oversight and monitoring

The steering committee (SC) will be established accountable for the whole study, and it will obtain the authority to direct the conduction, specify the rules and modify the protocol. It will be composed of the principal investigator (PI), researchers, data analysts and a monitoring group. The monitoring group will be appointed and qualified by the SC and be responsible for monitoring investigators' compliance with protocols as well as the protection of participants' interests.

Patient and public involvement

No patient or public was involved in either the design, or conduct, or reporting, or dissemination plans of this research.

Ethics and dissemination

This study was approved by the Ethics Committee of Chinese People's Liberation Army (PLA) General Hospital with approval No. S2021-068-01. Informed consent will be obtained from each participant (see online Supplementary materials A for details). All the results will be published in peer-reviewed journals and used for scholarly communication or technical guidance.

Discussion

The vision loss caused by cataract is a huge burden on society and families, fortunately, it is curable [2, 28]. Actually, researches on cataract surgery have not ceased in the past decades in the pursuit of better results [29-31]. Therefore, studies are in emergent need to verify whether updates in the surgical systems do lead to better outcomes. The active-fluidics system has been put into use for many years, but it is not yet widespread [15, 21, 32]. Most of the researches on it are laboratory studies, or focusing on intra-operative parameters, there are few studies on the results and injuries of the surgery [12, 16, 18, 33]. In order to fully evaluate changes caused by the active-fluidics system in phacoemulsification, more items need to be taken into account. To our knowledge,

this is the first comprehensive study aiming at comparison of clinical outcomes between the active-fluidics system and gravity-fluidics system with a sample size like this volume.

Achieving good visual acuity is the ultimate goal of cataract surgery, and the degree of damage brought by phacoemulsification to the cornea is an important factor influencing post-operative vision[34]. Reducing the intraoperative damage is essential to the corneal endothelium as it is non-regenerative [34, 35]. The advantages of the active-fluidics system in reducing CDE have been reported, and it remains to be further explored whether it will lead to a reduction in corneal endothelial damage[11, 18]. Observation of retinal thickness, particularly macular thickness, by OCT can help to figure out whether lesions such as macular edema presents after cataract surgery and to develop targeted treatment early[36, 37]. Assessment of changes in retinal nerve fiber layer thickness is also an important indicator to evaluate the effect of intraoperative perfusion pressure on the optic nerve[38, 39].

The interest in retinal blood flow has begun in the past few years. Thanks to the advent of OCTA, which helps to visualise and analyse the retinal vasculature in a non-invasive way and allows quantitative calculation of vessel density with the aid of specific software[40]. Changes in the microcirculation of the retina may be an early stage of some diseases but relevant mechanism has not been studied in sufficient detail[41-43]. It is not yet clear whether there is a correlation between perfusion pressure, CDE and vessel density, between changes in blood flow and changes in retinal thickness or macular edema. Our study will devote to analyse the clinical significance of changes in vessel density after cataract surgery and whether there is a difference in the effect of surgery on blood flow under the two systems.

The assessment and analysis of the patient's subjective perception is another feature and strength of our study. When using an active-fluidics system, the target IOP could be set at an appropriate level to avoid causing pains or discomfort and to promote intraoperative cooperation[13, 22]. However, this theoretical advantage has not been proved in previous studies. A subjective pain scale will be selected and scored by each patient, and the results obtained from both systems will be compared and analysed in order to draw reliable conclusions.

This article describes a rigorously designed randomized controlled clinical trial in order to compare the active-fluidics versus gravity-fluidics system for performing cataract surgery. In order to avoid the confounding factor caused by surgical techniques, the most experiences surgeon is selected to complete all the trial surgeries. This surgeon is capable of performing cataract surgery with high quality and dealing with all kinds of adverse events. The same operator, phacoemulsifier and phaco tip used in both groups will increase credibility and minimize bias significantly. Optional IOL design and their characteristics are presented in the Supplementary materials B. They are all aspherical hydrophobic acrylic IOLs but with different A constant. The surgeon will select an appropriate IOL for each patient that best meets the target refraction based on their biometry measurement. The structural changes in the eyes after cataract surgery will be fully studied and the evidence-based data will also provide a basis and reference for future work and treatment.

There are several limitations in this study. It is a single centre study on Chinese subjects and some data will be collected from only one experienced surgeon. It may result in our findings to be unrepresentative and the surgical experience of using the active-fluidics system may not be well generalized to others. Nevertheless, any positive or negative results are still of significant guidance, especially for some medical centres of our calibre. Another limitation concerns the follow-up period, it is not sufficient to observe long-term outcomes, and it is what we will be working towards in the future.

Trial status

Recruitment for this trial started in March 2021, and is planned to be completed in March 2022. The process might be interrupted or extended due to the COVID-19 pandemic.

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Author Contributions

ZHL is the principal investigator and lead the organization of the whole study. ZY contributed a lot in the trial design and supervision. YL drafted the first manuscript and HYL reviewed it. WQC, YG and TJM paid efforts in the conduction of the trial. All authors read and approved the final version of this protocol for publication.

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Competing interests

The authors declare that they have no competing interests.

Provenance and peer review

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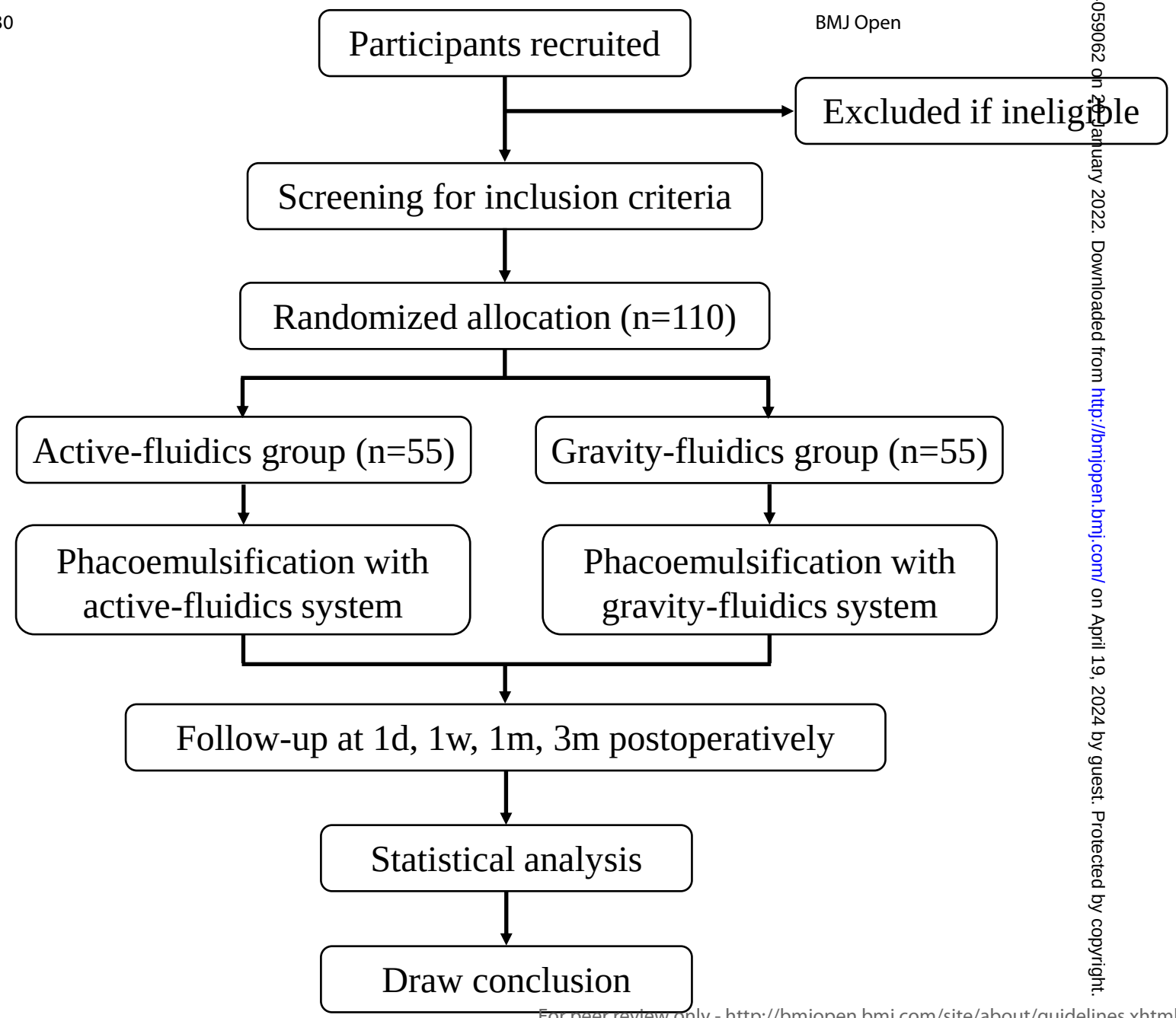
Figure 1. Flow chart of the trial design.

Figure 2. Timeline and data collection schedule for the AGSPC study.



	Baseline	Operation	Follow-up			
			1d	1w	1m	3m
Pick-up information:						
Demographics	×					
NC	×					
NO	×					
Biometry measurement	×					
Medical history	×					
Informed consent	×					
Allocation		×				
Outcomes:						
Adverse events		◆———	———	———	———	———◆
Efficacy						
CDE		×				
EFU		×				
U/S time		×				
TAT		×				
Effects						
BCVA	×		×	×	×	×
Subjective perceptions						
Pain scores		×				
Cat-PROM 5	×				×	
Safety						
Slit lamp biomicroscopy	×					
IOP	×		×	×	×	×
CCT	×		×	×	×	×
ECD	×		×	×	×	×
CV	×		×	×	×	×
HEX	×		×	×	×	×
CRT			×	×	×	×
RNFL thickness			×	×	×	×
Macular superficial vessel density			×	×	×	×
FAZ			×	×	×	×

NC, nuclear colour; NO, nuclear opalescence; CDE, cumulative dissipated energy; EFU, estimated fluid usage; TAT, total aspiration time; BCVA, best corrected visual acuity; Cat-PROM 5, cataract surgery patient-reported outcome measures questionnaire; IOP, intraocular pressure; CCT, central corneal thickness; ECD, endothelial cell density; CV, coefficient of variation; HEX, percentage of hexagonal cells; CRT, central retinal thickness; RNFL, retinal nerve fiber layer; FAZ, foveal avascular zone;1d, one day; 1w, one week; 1m, one month; 3m, three months.

Supplementary materials

A. Patient consent form

知情同意书

尊敬的受试者：

我们在此邀请您参加一项中国人民解放军总医院眼科医学部开展的“主动液流控制系统与重力液流控制系统行白内障超声乳化手术效果”的临床研究。本知情同意书提供给您一些信息以帮助您决定是否参加此项研究。请您用一定的时间仔细阅读下面的内容，如有不清楚的问题或术语，可以与有关医生进行讨论。您参加本项研究是完全自愿的。本研究已经得到解放军总医院医学伦理委员会的审查和批准。

研究背景：

白内障是世界首位不可逆性致盲性眼病，手术是治愈白内障的唯一方式。白内障手术是眼科常见的手术之一，其中超声乳化手术是首选的手术方法。超声乳化术的出现给白内障手术带来了革命性的变化，并能够显著改善患者的术后视力。手术安全性和手术效率是白内障手术考虑的主要因素，它们受到多种因素的影响，包括外科医生的经验，使用的手术技术、手术设备以及患者个体差异等。近年来,为了提高白内障手术的效率并改善患者的预后，超声乳化手术系统、超乳手柄尖端和套筒等方面的研究不断取得新的进展。目前在临床使用的白内障超声乳化手术灌注液流系统包括重力液流控制系统和主动液流控制系统。但目前关于不同液流系统对白内障手术的围术期结果与预后结局影响的研究仍然较少。

研究目的：

比较在主动液流控制系统与重力液流控制系统下行白内障超声乳化联合人工晶状体植入术的围术期结果与预后结局。

研究内容：

1）研究概况

本研究拟招募年龄相关性白内障患者，随机将待手术眼分入主动灌注组与重力灌注组进行常规白内障手术，术后进行随访记录。

“随机分组”表示您会被随机地分配到一个治疗组中。您有 1/2 的机会接受在主动液流控制系统下进行的白内障手术，1/2 的机会接受在重力液流控制系统下进行的白内障手术。

“双盲”表示您和您的研究医生均不知道您接受的是哪种手术系统。在研究期间，您和您的研究医生也不会被告知您接受了哪种治疗。这样可以保证参与本试验性研究的每一个人都能够公平公正地应答主观感受，并评价手术的安全性和有效性。但在紧急情况下，您和您的医生都有权知晓相关信息。

本研究不存在“安慰剂对照”。在整个研究过程中，我们将通过一系列检查来评价您对手术的反应和您的健康状况。

2）研究程序

本研究将持续 3 个月共 4 次随访，分别为术后 1 天、1 周、1 个月和 3 个月。在此期间，您需要来医院做一些检查、按日程进行回访、填写问卷，并告诉我们您的任何变化。检查包括：裂隙灯、视力、眼压、角膜内皮镜、OCTA、视觉质量。

该研究可能会带来的影响：

这些回随访和检查需要您合理安排就诊时间，涉及的检查都是无创的。如果您关于研究中检查和步骤有疑问，可以随时向研究医生咨询。

研究的风险和不良反应：

研究过程中您可能会出现不良反应。我们会监测研究中所有患者的不良反应。如果您在随访期间出现任何不良反应，请及时给您的研究医生打电话咨询。

已知风险：

目前，白内障超声乳化手术是治疗白内障最常用的方法。但由于医学科学的特殊性及个体差异，任何手术方法均存在风险。具体如下：在手术过程中可能出现：(1)各种感染（细菌、真菌、病毒等）；(2)麻醉及手术意外导致球后出血、视力下降甚至丧失；(3)眼心反射，严重心律失常；(4)爆发性出血，动脉硬化、高龄、患有高度近视、小眼球等基础眼病的患者风险大大升高；(5)因高龄玻璃体液化明显，患者配合度差，高度近视、网脱术后眼等等各种基础眼病，使玻璃体腔失去支撑所致的后囊膜破裂及玻璃体脱出，需行前部玻璃体切割，或晶状体核坠入玻璃体腔需行后段玻璃体切除，人工晶体需要悬吊植入甚至一期不能植入，需 1-3 个月后根据眼部恢复情况行二期人工晶体悬吊植入；(6)硅油眼硅油溢出，需行玻璃体切割，补充硅油；(7)术前存在角膜病变、高龄角膜结构疏松、白内障程度过重、青光眼、小眼球、小角膜、浅前房等等原因导致角膜内皮损伤，需行进一步治疗或角膜移植手术；(8)其他难以预料的、危及患者生命或致残的意外情况。

在手术后可能出现：(1)因术前存在眼底病或其他眼病，术后视力提高有限；(2)因术后早期活动、受伤、剧烈咳嗽、低头等原因所致人工晶体位置偏移、脱位需二次行手术处理；(3)术前存在角膜病变、高龄患者角膜内皮细胞数过少、白内障程度过重等原因导致角膜内皮无法承受手术损伤而出现进行性角膜失代偿，需行进一步治疗或角膜移植手术；(4)术后早期粘弹剂代谢障碍出现高眼压需行前房穿刺放液；(5)因青光眼等基础眼病或其他原因导致术后眼压高需进一步药物治疗或手术治疗；(6)术前屈光不正患者，尤其是高度近视患者，人工晶体度数测量存在误差，致术后屈光不正，需配镜矫正，甚至行二次人工晶体置换；(7)正视眼患者术后老花需佩戴老花镜，近视患者术后仍保留近视需佩戴眼镜及调整近视度数；(8)术前干眼患者术后干眼加重，老年患者术后睑板腺功能障碍导致眼磨、眼干、眼痛、眼胀、畏光、流泪等需药物治疗；(9)黄斑水肿，尤其是术前糖尿病、高血压或患有基础眼病患者发生风险大大提高，需进一步治疗；(10)因手术必须散瞳，而高龄、青光眼等眼部基础病导致虹膜张力差，术后出现不可逆性瞳孔散大无法恢复；(11)术后晶体囊膜混浊，出现后发性白内障，需激光治疗；(12)玻璃体混浊术后突显；(13)其他可能出现的情况。

未知风险： 可能存在一些目前无法预知的风险及不良反应。

手术的风险：见上。

其他风险：无。

研究获益：

如果您同意参加本研究，您将获得直接的医疗受益，并享受部分项目免费检查的权益。我们希望本研究得到的信息能够对与您病情相同的病人有指导意义，或有助于确定哪种治疗方法可以更安全有效地治疗与您患有相似病情的其他患者。本研究获得的相关研究信息与结果将会适时告知您。

生物标本和医疗信息的处理和利用：

本研究将不会采集额外的生物标本。所有患者的医疗信息将进行保密存储，仅研究成员及伦理委员会成员可见。

您的权利和义务：

您有充分的时间考虑和随时提问的权利，且是否要参加本研究的最终决定权在您。如果您决定不参加本研究，也不会影响您应该得到的其他医学治疗；如果您决定参加，请您如实的告诉研究医生有关自身病史和身体状况的真实情况，告诉研究医生自己是否曾参与

其他研究，或目前正参与其他研究，并请您在这份书面知情同意书上签字。签字后，您仍然可以在研究的任何阶段退出本研究。如果在研究期间发现任何新的、重要的，并且可能会影响您继续参加这一研究意愿的信息，您的研究医生或其他研究小组成员会立即通知您。您也可以随时了解和咨询研究情况。

如果您没有遵守研究计划，或者研究医生认为您继续参加本研究不符合您的最大利益，研究医生可以让您退出研究；如果您出现了手术后严重的并发症，或研究期间有关于研究手术系统的新的安全性的信息出现，研究医生或申办者可能会在未征得您同意的情况下终止您参与本项研究。

如果您因为某些原因从研究中退出，您可能被询问有关您进行手术的情况。如果研究医生认为需要，您也可能被要求进行计划外的体格检查和实验室检查，研究医生将会和您讨论退出研究后的医疗事宜。

参加研究的相关费用：

随访时接受的裂隙灯、眼压、角膜内皮镜、OCTA、视觉质量检查是免费的，门诊的医师诊疗费、验光费用需要您自己承担。

报酬或补偿：

本研究无报酬或补偿。

研究所致损害的处理措施：

上述两种手术系统已有广泛的临床应用资料。 如果您的健康确因参加这项研究而发生与研究相关的损害，请立即通知研究医生，研究医生将负责对您采取适当的治疗措施。

即使您已经签署这份知情同意书，您仍然保留您所有的合法权利。如您的权益受到侵犯，您可以联系解放军总医院医学伦理委员会，电话： 010-6xxxxxx6。

保密性：

如果您决定参加本项研究，您在研究中的个人资料均会保密。负责研究的医生及其他研究人员将使用您的医疗信息进行研究。您的档案仅供研究人员查阅。研究中会用编号来标识您的研究信息,您的身份不会被识别。任何有关本项研究结果的公开报告均不会披露您的个人身份。我们将遵循有关法律和规定，确保您个人医疗资料的隐私得到充分保护。

自愿参加：

参加本研究是完全自愿的， 您可以拒绝参加研究，或者研究过程中的任何时候选择退出研究，不需任何理由。该决定不会影响您未来的治疗。

如果您决定退出本研究，请提前通知您的研究医生。为了保障您的安全，您可能被要求进行相关检查，这对保护您的健康是有利的。

研究中如何获得帮助：

您可随时了解与本研究有关的信息资料和研究进展，如果您有与本研究有关的问题，请与中国人民解放军总医院眼科医学部的罗 x 医生联系，电话：19xxxxxxx01,地址：北京市海淀区复兴路 28 号。

本人已知晓研究相关收益及风险，同意参加此项研究

患　　者：_____　　**日期：**_____

研究相关收益及风险已与患者本人交代清楚

研究人员：_____　　**日期：**_____

B. Supplementary Table 1. Types of IOLs and their characteristics

IOL Model	Manufacturers	A constant	Characteristics
HOYA 250	HOYA corp., Japan	118.8	preloaded
ZCB00	Johnson & Johnson Vision, US	119.3	one-piece
CT Lucia 601PY	Carl Zeiss Meditec AG, Germany	119.2	heparin coated
AR40e	Johnson & Johnson Vision, US	118.4	three-piece
AcrySof IQ	Alcon Laboratories Inc., US	118.7	UV and blue light filtered
AcrySof IQ TORIC	Alcon Laboratories Inc., US	N/A	astigmatism corrected

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	9
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	1,9

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3

Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3-4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4-5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4-5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4-5

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-7
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7

Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7-8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7-8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7-8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7-8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7-8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7-8
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	8
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	4,7-8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	5,7
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	7-8

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	7-8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	4,7-8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary materials A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	4