



# BMJ Open Active-fluidics versus gravity-fluidics system in phacoemulsification for age-related cataract (AGSPC): study protocol for a prospective, randomised, 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 patients' subjective perceptions of cataract surgery with the active-fluidics system and gravity-fluidics system.

**Methods and analysis** This trial will recruit 110 patients with age-related cataract 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 1 day, 1 week, 1 month and 3 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, corneal endothelium parameters, retinal thickness, macular superficial vessel density, pain scores, scores of the Cataract surgery Patient-Reported Outcome Measures 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 (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 number** Chinese Clinical Trial Registry (ChiCTR2100044409).

## 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 years worldwide were cataract.<sup>1–3</sup> It could lead to vision loss, glare, diplopia, secondary glaucoma and even uveitis due to cortical liquefaction.

## Strengths and limitations of this study

- This study is a prospective, randomised, 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 minimise 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.

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.<sup>4–6</sup> 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.<sup>4,7</sup>

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.<sup>8–11</sup> 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.<sup>8 12 13</sup> 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.<sup>8 14</sup> However, high pressure could easily damage intraocular tissues such as the cornea, iris and optic nerve, and induce pain or discomfort to the patient.<sup>13</sup> To address this paradox, the active-fluidics system is created, which monitors intraocular pressure (IOP) 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 IOP.<sup>13 15</sup> This feature will conduce to maintain a stable anterior chamber, and improve surgical safety theoretically.

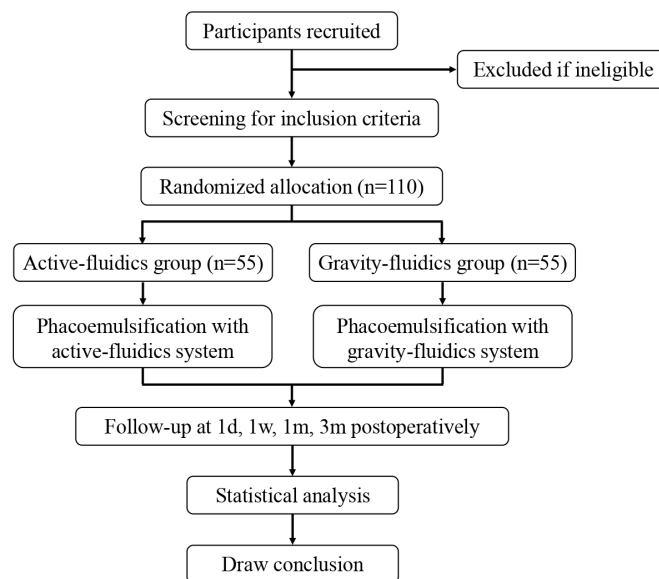
Several studies have reported the successful application of the active-fluidics system in cataract surgery and compared it with the gravity-fluidics system. In a study simulating the anterior chamber by an acrylic chamber, Nicoli *et al*<sup>16</sup> reported that both the active-fluidics and gravity-fluidics system were effective in maintaining the target 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*,<sup>12</sup> 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.<sup>17–19</sup> Some studies have reported that the active-fluidics system conserved CDE, but the results were different, with a variation of 19%–40%.<sup>15 20–22</sup> It might be related to the surgical techniques, incorporating the severity of the patients' condition.<sup>21 23</sup> However, Malik *et al*<sup>18</sup> 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, a randomised controlled trial 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 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



**Figure 1** Flow chart of the trial design.

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 1:1. The main objective of this trial is to assess whether there are differences in efficacy, visual outcomes, safety and patients' 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 People's Liberation Army (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) patients with age-related cataract, whose nuclear colour and nuclear opalescence are scored as 2.0–4.9 according to the Lens Opacities Classification System III;<sup>24</sup> (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 the following: (1) unable to undergo the cataract surgery with good cooperation; (2) the correlation between 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 consult ophthalmologists in the Chinese PLA General Hospital and decide 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 number 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 with the active-fluidics and gravity-fluidics system.<sup>22</sup> In its results, CDE of active-fluidics group and gravity-fluidics group is  $4.82 \pm 2.16$  vs  $6.28 \pm 2.92$ . Based on their data, a sample size of 100 will be adequate to achieve  $\alpha=0.05$ ,  $\text{power}=0.8$  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](http://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 recruitment sequence, 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. 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 case 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 process 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-PROM 5) should be completed at the same time.

The procedures of phacoemulsification consist of: 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 mm Hg, then the aspiration flow rate and vacuum level will be set at 45 cc/min and 450 mm Hg, 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 mm Hg, too. An experienced ophthalmologist (ZL) 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 the following: (1) broad-spectrum antibiotic 0.5% levofloxacin eye drops (Cravit; Santen Pharmaceutical, Osaka, Japan), four times per day from 3 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 anaesthesia; (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), four times per day, for 7 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) four times per day for 7 days, then reduce to two times per day for the next 7 days from the first day after the surgery; (7) 1% pranopfen eye drops (Pranopulin; Senju Pharmaceutical, Hyogo-ken,

Japan), four times per day for 7 days, then two times per day for the next 7 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 postoperative follow-up reveals a damage in the cornea, drugs to promote corneal repair could be supplemented.

### Outcomes

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

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

All participants will be followed up at 1 day, 1 week, 1 month and 3 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 14:00 and 16:00. 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,

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

**Figure 2** Timeline and data collection schedule for the AGSPC Study. 1d, one day; 1w, one week; 1m, one month; 3m, three months; AGSPC, active-fluidics versus gravity-fluidics system in phacoemulsification for age-related cataract; BCVA, best corrected visual acuity; Cat-PROM 5, Cataract surgery Patient-Reported Outcome Measures Questionnaire; CCT, central corneal thickness; CDE, cumulative dissipated energy; CRT, central retinal thickness; CV, coefficient of variation; ECD, endothelial cell density; EFU, estimated fluid usage; FAZ, foveal avascular zone; HEX, hexagonal cells; IOP, intraocular pressure; NC, nuclear colour; NO, nuclear opalescence; RNFL, retinal nerve fibre layer; TAT, total aspiration time.

Japan). (5) OCT and OCTA. The retinal thickness and superficial blood flow density of macula 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 V.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

procedures will be recorded finally. (6) Questionnaires and scales. A brief self-report questionnaire—Cat-PROM 5—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.<sup>26 27</sup> 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 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 randomisation 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 training 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 data sets 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 3 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 receive 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 about the grouping to ensure a correct intervention.

### Statistical methods

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

groups at the same follow-up time point 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 X<sup>2</sup> test or Fisher's exact test for all categorical variables. IBM SPSS Statistics V.26.0 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.

### Non-adherence 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 data set 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, 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 member of the 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 PLA General Hospital (approval no. S2021-068-01). Informed consent will be obtained from each participant (see online supplemental material 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.<sup>2 28</sup> Actually, researches on cataract surgery have not ceased in the past decades in the pursuit of better results.<sup>29-31</sup> 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.<sup>15 21 32</sup> Most of the researches on it are laboratory studies, or focusing on intraoperative parameters; there are few studies on the results and injuries of the surgery.<sup>12 16 18 33</sup> 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 postoperative vision.<sup>34</sup> Reducing the intraoperative damage is essential to the corneal endothelium as it is non-regenerative.<sup>34 35</sup> 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.<sup>11 18</sup> Observation of retinal thickness, particularly macular thickness, by OCT can help to figure out whether lesions such as macular oedema presents after cataract surgery and to develop targeted treatment early.<sup>36 37</sup> Assessment of changes in RNFL thickness is also an important indicator to evaluate the effect of intraoperative perfusion pressure on the optic nerve.<sup>38 39</sup>

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.<sup>40</sup> 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.<sup>41–43</sup> 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 oedema. Our study will devote to analysing 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 pain or discomfort and to promote intraoperative cooperation.<sup>13 22</sup> However, this theoretical advantage has not been proven 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 randomised 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 experienced 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 minimise bias significantly. Optional IOL design and its characteristics are presented in the online supplemental material 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 generalised 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 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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**Contributors** ZL is the principal investigator and led the organisation of the whole study. ZY contributed a lot to the trial design and supervision. YL drafted the first manuscript and HL reviewed it. WC, YG and TM made efforts in the conduction of the trial. All authors read and approved the final version of this protocol for publication.

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