The SMIGS-study

(Swedish MicroInvasive Glaucoma Surgery Study)

A Prospective Randomized (Multiarm) Study Comparing Cataract Surgery as Stand Alone and Cataract Surgery Combined with Kahook Dual Blade Glide Goniotomy or iStent Inject W Trabecular Micro-Bypass Stent in Open-Angle Glaucoma.

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Statistical Analysis Plan and Study Protocol

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Abbreviations

AC = anterior chamber; **BCVA** = best corrected visual acuity; **BSS** = balanced salt solution; **dB** =decibels; **GAT** = Goldman applanation tonometry; **IOP** = intraocular pressure; **I/A** = irrigation/aspiration; **IQR** = inter-quartile range; **KDB** = Kahook Dual Blade; **LogMAR** = logarithm of the minimum angle of resolution; **MD** = mean deviation; **MIGS** = microinvasive glaucoma surgery; **PEXG** = pseudoexfoliation glaucoma; **POAG** = primary open-angle glaucoma; **SC** = Schlemm's canal; **SD** = standard deviation; **TCP** = transscleral photocoagulation; **TM** = trabecular meshwork.

1. Introduction

1.1 Background and rationale

Kahook Dual Blade Glide (New World Medical Inc, CA, USA) and iStent Inject W (Glaukos Corp, CA, USA) are two microinvasive Schlemm's canal (SC) surgeries that can be performed in combination with cataract extraction. Although KDB and iStent are in clinical use around the world, there is a need for prospective randomized trials, showing it´s efficacy over time. A three-arm trial with Kahook Dual Blade Glide (KDB), iStent Inject W (iStent) and cataract extraction as stand-alone has not been conducted before.

If KDB and/or iStent in combination with cataract extraction result in better intraocular pressure (IOP)-control over time compared to cataract extraction alone, this can have important implications for the increasing glaucoma population. If glaucoma patients that receive KDB or iStent in addition to cataract surgery get a lower IOP compared to patients that receive cataract surgery as stand-alone, they may get less visual field progression over time and/or need less medications compared to patients that do not receive this treatment.

1.2 Objectives

The objective of this project is to test - in a single-center multi-arm randomized clinical trial (RCT), if KDB and/or iStent in combination with cataract extraction, result in better IOP-control over time, compared to cataract extraction as stand-alone. iStent is a more widespread and studied procedure compared to KDB, although retrospective studies have found a trend toward better efficacy of KDB compared to iStent.[1] [2] The rational for using a multi-arm design is to investigate whether KDB and iStent are equally effective, and to see if they differ in terms of adverse events. Since cataract surgery as stand-alone can have an IOP-lowering effect,[3] there is a rational for using this group as one of the treatment arms as well.

We hypothesize that participants receiving KDB or iStent in combination with cataract surgery will have a larger IOP-reduction and/or less need for IOP-lowering medications postoperatively, compared to participants receiving cataract surgery as stand-alone. Over time there may even be less need for further surgery for participants receiving KDB and/or iStent. We further hypothesize that IOP will not be significantly different between eyes receiving KDB and iStent, but there may be differences in number of reduced medications postoperatively.

The study will be conducted according to the Declaration of Helsinki and the principles of good clinical practice.

2. Clinical Procedures

2.1 Visual acuity with Snellen

Visual acuity is measured before pupil dilation, tonometry, gonioscopy or any other technique that may affect vision.

Snellen visual acuity is measured using any standard visual acuity chart. Standardized refraction is performed prior to Snellen visual acuity testing. The fellow eye is properly occluded, and the participant is not allowed to lean forward or backward, so that a constant testing distance is maintained. After proper instruction and refraction, progressively smaller lines are presented to the participant until two or more errors in a line are made. When the participant is unable to read a letter, the examinator encourages the participant to guess. If two letters on a line are missed, a second chance is provided by asking the participant to read the line backwards. The Snellen visual acuity is recorded as the smallest line in which the participant misses one or fewer optotypes. If the participant´s visual acuity is so poor that the 20/400 line cannot be read, finger counting is tested. Visual acuity will be tested within two (preferable one) months before surgery, and thereafter at each visit up until five years after surgery.

2.2 Testing for finger counting

After proper instruction and refraction, the examiner´s hand is viewed at a distance of two feet (approximately 60 cm) from the participant´s eye. The fellow eye is occluded. If the number of fingers presented cannot be identified, hand motion is tested.

2.3 Testing for hand motions

In testing for hand motion, the examiner´s hand is viewed with all fingers extended and separated at a distance of two feet (approximately 60 centimeters) from the participant´s eye. The fellow eye is occluded. If hand motions cannot be identified, light perception is tested.

2.4 Testing for light perception

Light perception is tested using the same complete occlusion of the fellow eye with no other bright lights visible from the participant´s position. The participant is asked to report “on” when he or she sees the light, and “off” when it disappears.

2.5 Subjective refraction

An approximate beginning refraction may be determined by automated or subjective refraction from a prior visit.

2.6 Slit lamp biomicroscopy

Slit lamp biomicroscopy may be performed with any commercially available instrument, and it is used in a standard fashion starting anteriorly and working posteriorly.

2.7 Goldmann applanation tonometry

The calibration of the Goldmann applanation tonometry (GAT) is checked as described by the manufacturer. One drop with premixed fluorescein and anesthetic is instilled in the eye and the participant´s head is properly positioned in the chin rest and against the forehead rest without leaning forward or straining. The participant is asked to look straight ahead and is instructed not to hold his or her breath. The investigator looks through the slit lamp and gently brings the tip of the prism in contact with the center of the cornea. The investigator adjusts the measuring drum until the inner borders of the two mires just touch each other. When the "two-person method" is used, the investigator is performing the measurement as described above, and an assistant are recording the IOP measurement. Pre-operatively at least two IOP-recordings will be performed within two months, and at least one of those with the two-person method. The two-person method is used at postoperative controls up to two years after surgery. Participants will be followed annually for up to five years after surgery with applanation tonometry and visual field testing. These controls will be performed by an examinator not involved in the trial.

2.8 Gonioscopy

Gonioscopy is performed with the participant sitting at the slit lamp using a gonioscopy lens to examine the anterior chamber for grading of depth. Gonioscopy will be performed preoperatively in all participants, and at six, 12 and 24 months for participants receiving KDB or iStent. Postoperative gonioscopy is performed to evaluate placement of stents in the iStent-group, and presence of scarring or synechia in the KDB-group.

2.9 Perimetry

Perimetry is performed before surgery (within three months) and after six,12 and 24 months. Thereafter yearly examinations up until five years after surgery. Perimetry is performed before tonometry and gonioscopy. Standardized refraction is performed to determine the participant´s distance refraction and visual acuity prior to visual field testing. Standard automatic perimetry with Humphrey® Field Analyzer (SITA faster) is used, and the technician is monitoring the participant during testing.

2.10 Pachymetry

Pachymetry is performed within six months prior to surgery.

2.11 Quality-of-life assessment

Participants will be asked to perform a quality-of-life assessment preoperatively and after six months, using the National Eye Institute Visual Function Questionnaire (25 items) (NEI-VFQ25).

3. Surgical Procedures

3.1 Cataract extraction

Cataract extraction is performed in a standardized fashion. Prior to surgery, topical cyclopentolate (Cyclopentolat ®) 1% and tetracaine (Tetrakain ®) 1% is instilled in the eye. In the beginning of surgery an intracameral mixture of phenylephrine (0.2 mg/ml), lidocaine (3.1 mg/ml) and tropicamide (10 mg/ml) (Mydrane ®) is given. Intracameral cefuroxime (Aprokam ®) 1 mg and ampicilline (Doktacillin ®) 0.1 mg is given at the end of surgery, which is standardized routine at the clinic.

3.2 Kahook Dual Blade Glide

In this study, goniotomy with KDB is done after cataract surgery has been successfully performed. The anterior chamber is filled with additional cohesive viscoelastic, and the operating microscope is tilted about 35°, while the head of the participant is turned 35° from the surgeon to ensure an optimal view into the chamber angle.

The previously made temporal cataract incision is used. After the goniotomy with KDB, all viscoelastic is removed with the I/A instrument and the eyed is filled with balanced salt solution (BSS). Intracameral cefuroxime 1 mg and ampicilline 0.1 mg is given at the end of surgery.

KDB is designed to excise a strip of the trabecular meshwork and inner wall of SC, while minimizing damage to adjacent structures. The KDB has a distal tip that pierces the trabecular meshwork (TM), enters SC, and as it is advanced along the trajectory of the canal, elevates the TM up toward two parallel blades that excise a strip of TM, leaving a clear path for aqueous humor to drain into SC and the distal collector channels. This excisional technique removes between three to five clock hours of TM.

In 2020, the FDA approved a second-generation KDB instrument (KDB Glide, New World Medical), that has incorporated features intended to enhance both its performance and its ease of use. The KDB Glide has incorporated beveled edges and rounded corners to the footplate, reducing its width for enhanced fit within SC to facilitate smooth passage while excising the TM. This second-generation instrument maintains the same ramp technology and distance between the parallel blades (230 microns) as the original instrument.

3.3 iStent Inject W

The iStent is inserted after cataract surgery has been successfully performed. The anterior chamber is filled with additional cohesive viscoelastic, and the operating microscope is tilted about 35°, while the head of the participant is turned 35° from the surgeon to ensure an optimal view into the chamber angle.

The previously made temporal cataract incision is used. After the two stents have been placed in the TM, all viscoelastic is removed with the I/A instrument and the eyed is filled with BSS. Cefuroxime 1 mg and ampicilline 0.1 mg is given intracameral at the end of surgery.

The iStent Inject W is a second generation iStent that comes packed in a two-stent, preloaded, autoinject mechanism. It is made of surgical-grade, heparin-coated, non-ferromagnetic titanium. With a length of only 360 μm and a diameter of 230 μm, a single iStent inject stent is currently the smallest medical implant approved for use in the human body. The iStent inject stents are delivered in an injector system which injects the stents automatically into SC through a stainless-steel insertion tube. The injector is released by the surgeon by pressing a button. Two stents are implanted nasally into the TM and SC with a distance of 30 to 60°.

4. Postoperative Care

After planned surgery, topical nepafenac (Nevanac ®) 3 mg/ml is given one time daily and topical dexamethasone (Isopto-Maxidex ®) 1 mg/ml three times daily for three weeks.

After surgery, glaucoma medications will generally be continued during the first three postoperative weeks. After that, medications will be discontinued if the glaucoma disease is stable and target IOP for the individual is lower than needed. Often, IOP-levels ≤ 21 mmHg is accepted in medically treated intraocular hypertension, ≤ 18 mmHg in mild glaucoma, ≤ 15 mmHg in moderate glaucoma and ≤ 12 mmHg in advanced glaucoma. The Hodapp-Parrish-Anderson criteria will be used to determine glaucoma grade. If visual field progression is seen or IOP becomes unacceptable elevated, medications will be added. To guarantee the safety of participants, further glaucoma surgery or laser is allowed if needed during the follow-up of the study.

Target IOP-levels are affected by factors such as age and rate of progression on visual field examinations, and the treatment strategy will therefore be individualized to ensure the safety of participants. Since participants with all stages of glaucoma will be included in this study, for safety reasons, washout of medications is not planned.

5. Policy Matters

5.1 Participant consent

This RCT requires that written consent is obtained from each participant enrolled in the study. The participant is requested to sign the consent form after participant education is completed, and written information about the study is provided to all participants. The signed consent form is kept with the study records at the clinical center and a copy is given to the participant.

6. Clinical Center Procedures

6.1 Qualifying Assessment

Every eligible participant will be offered enrollment in the study

6.2 Assignment of Participant Identification Number

Any participant who is confirmed to meet the eligibility criteria and is enrolled in the study is assigned a participant identification number.

6.3 Schedule of visits

All study personnel must be familiar with the schedule of visits to ensure that required data is collected and that future visits are scheduled within the appropriate time windows. The need for continued follow-up visits will be stressed to the participant during the informed consent process and throughout the study.

Table 1. Number of Days After Surgery

Follow-Up Visit	Ideal time	Acceptable time
1 Day	1 day	1-3 days
6 Week	42 days	25-60 days
3 Month	90 days	61-120 days
6 Month	182 days	121-270 days
1 Year	365 days	271-455 days
2 Year	730 days	638-912 days
3 Year	1095 days	913-1277 days
4 Year	1460 days	1278-1642 days
5 Year	1825 days	1643-2007 days

Table 2. Schedule of visits

	Pre-operative	1 Day	6 Weeks	3 Months	6 Months	1 Year	2 Years	3 Years	4 Years	5 Years
Snellen VA	X	X	X	X	X	X	X	X	X	X
Slit lamp Biomicroscopy	X	X	X	X	X	X	X			
Tonometry	X	X	X	X	X	X	X	X	X	X
Gonioscopy	X				X	X	X			
Automated perimetry	X				X	X	X	X	X	X
Pachymetry	X			X						
Questionaire	X				X					
Informed consent	X									

7. Study Methods

7.1 Trial design

This single-center multi-arm RCT is conducted at the eye-clinic at the Östersund hospital, Östersund, Sweden. Subjects likely to be eligible for the trial will be identified at their regular consultation for glaucoma and provided with a participant information leaflet. The principal investigator is responsible for deciding whether a patient is eligible for inclusion in the study. Eligible patients, who agree to take part, will sign a consent form before being randomized.

The study is a multi-group RCT with three arms. Subjects will be randomized in a 1:1:1 ratio to either:

- Phacoemulsification (phaco)
- Phacoemulsification in combination with KDB (Phaco-KDB)
- Phacoemulsification in combination with iStent (Phaco-iStent)

Clinical visits are performed preoperatively (preferrable within one month before surgery, acceptable within two months). Thereafter postoperative controls will be at day

1, week 6, month 3, month 6, month 12 and month 24. After participants have been controlled for two years, data will be collected annually from their regular glaucoma controls for three years. Recorded measures will include IOP, visual field examinations and need for further interventions (with medications, laser, or surgery).

7.2 Randomization

Randomization takes place at the time of surgery, before the participant is taken into the operating room. The randomization schedule is constructed using a computer pseudo-random number generator and is randomized in blocks to ensure that there is equal number of participants in each treatment group early in the trial. Block sizes are varied in a random manner between three, six and nine. The randomization is performed by an independent clinical research unit not involved in the project. Sequential envelope system is used to reveal the assignment from the prespecified randomization sequence. Participants are given a study identification number based on their assigned treatment group. All preoperative data will be collected before the randomization. Masking is not applied in this study since the procedures of goniotomy and stent implantation cannot easily be performed with sham-procedures.

7.3 Sample size calculation

The primary outcome measure for the power calculation is the difference between cataract surgery as standalone and cataract surgery combined with either KDB or iStent. It`s currently not known if KDB and iStent are equally effective in terms of IOP-lowering effect since prospective studies comparing KDB and the second generation iStent are sparse. However, we hypothesize that KDB and iStent may be equally effective in terms of IOP-lowering effect. Cataract extraction in combination with KDB or iStent is estimated to have an IOP-lowering effect of 5.5 (7.8) (mean (standard deviation)) mmHg after one year.[2] For cataract extraction, the IOP-reduction is estimated to 1.5 (3) mmHg.[4] For a power above 80%, 37 eyes per group will be needed. A drop-out rate of around 10% is expected. Therefore, enrollment in the study will be offered to a total of 120 participants (40 in each treatment group).

7.4 Framework

Superiority hypothesis testing will be performed between phaco-KDB and phaco, between phaco-iStent and phaco, and between phaco-KDB and phaco-iStent.

7.5 Statistical interim analyses and stopping guidelines

No interim analyses will be performed. Stopping/discontinuation rules for early termination of the trial are not defined since no main difference in safety outcome is

expected. Both iStent and KDB are FDA-approved devices, and no major safety issues has been observed in previous studies.[1 5 6]

7.6 Timing of final analyses

Outcomes will be analyzed according to the timetable displayed under “Schedule of visits”. The analyses of the main trial data for publication purposes will begin once the final randomized subject has reached the 12-month follow-up.

7.7 Timing of outcome assessments

Timing of outcome measures are displayed under “Schedule of visits”.

8. Statistical principles

8.1 Confidence intervals and P values

Confidence intervals of 95% will be reported and P values < 0.05 considered statistically significant.

8.2 Adherence and protocol deviations

Adherence to the protocol is defined as the number of participants receiving the planned surgery and completes the final follow-up time points at 12 and 24 months. If a participant misses an intermediate control, he or she will still be included in the study. The proportion of participants missing each outcome will be summarized in each arm at each time point. Protocol deviations that will be summarized include failure to implant both stents, and failure to perform goniotomy with KDB. A capsular rupture will be recorded as a protocol deviation if vitreous is prolapsed into the anterior chamber and/or an intraocular lens cannot be placed in the capsular bag or sulcus. Other adverse events related to surgery such as choroidal effusion, choroidal hemorrhage or aqueous misdirection will also be recorded, as well as use of mechanical pupil dilation, use of capsular tension rings, iris hooks, capsule retractors or capsular staining with trypan blue.

Time delay between controls will be recorded if they are outside acceptable time limits (se timetable in study protocol). Further glaucoma surgery or cyclodestructive laser will also be recorded as protocol deviations. Selective laser trabeculoplasty (SLT) and neodymium-doped yttrium aluminium garnet (nd:YAG) laser will be allowed, but SLT will be considered as additional glaucoma therapy if done postoperatively.

8.3 Analysis populations

Intention to treat populations (ITT) will be analyzed. Complete cases will be participants that receive the planned surgery according to randomization and does not need further glaucoma surgery or cyclodestructive laser during follow-up.

9. Trial Population

9.1 Screening data

Subjects that fulfill the eligibility criteria but are not included in the study will be reported and the reason for not participating given. Only one eye per participant will be included, and if both eyes are eligible, the first operated eye will be included. The participant can choose which eye he or she wishes to have surgery on first if both eyes are eligible (in most cases, this will be the eye with the most pronounced cataract).

9.2 Eligibility

Inclusion Criteria

One eye per participant

Over 18 years of age

Clinically significant cataract

Glaucoma or intraocular hypertension treated with one to four medications and no need for additional glaucoma surgery at the time of study enrollment

Open chamber angle with Schaffer grading three to four in at least two quadrants

Exclusion Criteria

Previous glaucoma surgery, including cyclodestructive procedures

SLT within 90 days prior to planned surgery

Exudative age-related macular degeneration, proliferative diabetic retinopathy, clinically significant corneal dystrophy, other eye disease that affect intraocular pressure or visual field

Unable to participate and make written consent due to another medical condition

9.3 Recruitment

See the Consort flow diagram in the end of this document.

9.4 Withdrawal/follow-up

Withdrawal from the study will be done if the participant for some reason wishes to be excluded. Withdrawal from intervention is not likely since the randomization will be performed at the day of surgery. Loss of follow-up data will be recorded, and the reasons and details presented.

9.5 Baseline participant characteristics

List of baseline characteristics:

Age

Ethnicity

Gender

Visual acuity (measured with Snellen and converted to logMAR)

Pachymetry (central corneal thickness)

Goldmann applanation tonometry (a mean of two preoperative measurements)

Presence of pseudoexfoliations

Glaucoma grade (ocular hypertension, mild, moderate, or severe glaucoma according to ICD-10)

Diagnosis (intraocular hypertension, primary open angle glaucoma, pseudoexfoliation glaucoma, pigmentary glaucoma or normal-tension glaucoma)

Number of glaucoma medications (number of substances used)

10. Analysis

10.1 Data Management and security

A master log is kept for enrolled participants. An appointment schedule is made for each participant. All data will be kept confidential and only involved researchers will have access to it. All data will be de-identified before publication.

10.2 Outcome definitions

Primary outcome

Number of participants in each group with ≥ 20% IOP-reduction and/or reduction of ≥ 1 medication after 12 and 24 months. This goal must be achieved without added medical therapy, SLT, cyclodestructive laser or further glaucoma surgery.

Change in number of IOP-lowering medications compared to baseline.

Secondary outcomes

Number of participants with IOP-levels ≤ 12 mmHg, ≤ 15 mmHg, ≤ 18 mmHg and ≤ 21mmHg after 12 and 24 months.

Number of participants that need further surgery or cyclodestructive laser during follow-up.

Number of participants that need additional medical therapy or SLT during follow-up.

Subgroup analyses are planned for presence of pseudoexfoliations, age, glaucoma grading (according to MD ≤ − 6 and MD > − 6 dB), preoperative IOP-levels and number of preoperative medications.

Surveys

Participants will be asked to perform a quality-of-life assessment before surgery and after six months. NEI-VFQ25 will be used for this purpose.

10.3 Analysis methods

Subject demographics and baseline characteristics will be descriptively summarized with means and standard deviation (SD) for continuous, symmetric variables, and medians and inter-quartile range (IQR) for continuous, skewed variables, and frequencies and percentages for categorical variables.

Independent-samples *t*-test (for parametric data) or Mann-Whitney U test (for non-parametric data) will be used to detect and compare differences between groups. One-way ANOVA (for parametric data) or Kruskal-Wallis test (for non-parametric data) will be used when comparing the three treatment arms. Chi-square test or Fisher´s exact test will be used to analyze categoric data. For paired variables, dependent samples t-test (for parametric data) or Wilcoxon matched pairs signed ranks test (for non-parametric data) will be used.

Linear or logistic regression models will be fit to the data to adjust for any baseline characteristics which are found to differ between treatment arms. In addition, generalized linear mixed models will be fit to the repeated measures obtained at postoperative visits.

All outcomes will be presented using descriptive statistics; normally distributed data by the mean and SD and skewed distributions by the median and IQR. Binary and categorical variables will be presented using counts and percentages.

Kaplan-Meier analysis will be performed for comparing failure rates between groups during follow up.

IOP-measurements, changes in visual field mean deviation and number of IOP-lowering medications will be compared between the three groups at postoperative visits. P-values < 0.05 will be considered statistically significant. Snellen visual acuity will be converted to logarithm of the mean angle of resolution (LogMAR) and compared between groups. For subjects requiring additional surgery, no further data regarding visual acuity or IOP will be included in the analysis after the procedure. For pre-operative IOP-measurements, the mean of at least two measurements within one to two months will be used. At least one of these measurements will be performed with the two-person method. All postoperative IOP-measurements up to 24 months will be with the two-person method.

NEI-VFQ25 scores will be analyzed using generalized linear models adjusting for baseline NEI-VFQ25 score and other prognostic variables, like the amount of vision loss, number of glaucoma medications and visual status of the fellow eye.

10.4 Missing data

In the event of non-response after each follow-up, the subjects will receive two telephone calls and then two written reminders. Even with the reminders, some loss to follow-up is expected over 24 months. The proportion of participants missing each outcome will be summarized in each arm and at each time point.

10.5 Harms

To assess the safety of study participants, intermediate controls at any time-point will be allowed if needed. Planned extra controls will not be considered as adverse events and intermediate controls between the yearly study-appointments after the first postoperative year will generally be necessary to ensure participant safety.

Postoperative complications that will be registered are hyphema over one mm, IOP-spike ≥ 10 units from baseline, cyclodialysis cleft, postoperative inflammation with prolonged need for treatment after the first three postoperative weeks, and corneal oedema. Capsular opacifications or retinal complications such as macular oedema will also be reported, as well as loss of $\geq$ two lines on Snellen chart at 12 and 24 months. If a rare event such as an endophthalmitis or prolonged hypotony (IOP ≤ 6 mm Hg with shallow anterior

chamber, choroidal effusion or hypotonus maculopathy) occur, this will be registered. If other adverse events occur, they will be reported as well.

After goniotomy with KDB or trabecular implantation with iStent stents, postoperative bleeding from SC can occur. If a hyphema develops, it usually resolves within a week. If an anterior chamber bleeding does not resolve spontaneously or IOP is elevated due to a blood clot, anterior chamber washout will be allowed. If necessary, aqueous release through the existing paracentesis will also be allowed if IOP is elevated in the early postoperative period. This will not be considered as further glaucoma surgery.

All complications that may occur, such as prolonged inflammation, hyphema, IOP-spike or macular oedema will be treated according to standard routine at the clinic.

If a participant needs further glaucoma surgery (microinvasive surgery, filtering surgery or cyclodestructive laser), this will be allowed but future examinations such as IOP and visual field results will not be included for analyses. If a participant develops a medical condition that will interfere with the IOP or visual field such as a retinal vascular event or stroke with hemianopsia, affected examinations after the event will not be included.

Safety will be assessed by monitoring complication rates after surgery. Other measures, such as visual field changes, will also be performed. All adverse events related to the procedures will be reported at each clinic visit.

Safety analyses will be primarily assessed by adverse events, best corrected visual acuity (BCVA) and evaluation with slit-lamp biomicroscopy. Loss of $\geq$ two lines on Snellen chart will be reported.

10.6 Statistical software

SPSS Statistics version 28 (SPSS Inc, Chicago,IL, USA) will be used for statistical analyses.

11. References

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12. CONSORT Flow chart

Se below.

CONSORT Flow Diagram