**PROTOCOL**

Interventional cohort study

**Cost Effectiveness of Standalone Stents as Second-Stage Surgery Study: SUCCESSES**

Version 3

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**1. SUMMARY**

***PARTICIPATION CENTRES***

This will be a single centre study: recruitment, intervention and follow up will be conducted at the eye clinics and operating theatres of Capital & Coast District Health Board (CCDHB).

***STUDY OBJECTIVE***

To understand, in patients with both mild-moderate glaucoma and cataract, whether it would be more cost-effective to perform:

1. a trabecular bypass stent (iStent) combined with cataract surgery in every case, or
2. cataract surgery alone, followed by iStent as a second-stage procedure in those for whom it is still indicated.

***DESIGN***

This will be a prospective, interventional study of patients with visually significant cataract and mild to moderate open angle glaucoma or treated ocular hypertension, who have either: a) side effects of topical glaucoma medications or b) inadequate intraocular pressure (IOP) control despite topical glaucoma medications.

All participants will undergo cataract surgery as the first stage (standard of care). Participants who continue to have either criterion of a) side effects or b) inadequate IOP control between 3 months and 3 years after cataract surgery will have iStent implantation as the second stage.

The main outcome is the proportion of patients who proceed to second stage iStent implantation at 12 months. We will also consider this proportion at 6 months and out to 3 years as a survival curve. Secondary outcomes include IOP control, glaucoma-related quality of life, and thus cost-utility analysis.

***PARTICIPANTS***

Participants will be recruited through the Eye Clinic, Wellington Regional Hospital and Kenepuru Community Hospital, CCDHB.

***Inclusion criteria:***

* Visually significant cataract requiring surgery with visual acuity (VA) 6/9 or worse. **Important issues about equity of access to cataract surgery are addressed below.**
* Diagnosis of OHT or mild to moderate open angle glaucoma (including primary open angle, pigment dispersion, pseudoexfoliation), taking at least one topical glaucoma medication (eye drops)
* Target IOP ⋝ 15 mmHg
* Either a) IOP over target; OR b) at least one recognisable side effect of drops
* Willing and able to give informed consent
* Age >18yrs

***Exclusion criteria***:

* Low tension, angle closure, neovascular, uveitic, traumatic or other secondary glaucoma
* Prior incisional glaucoma surgery or cyclodestructive procedure
* Selective laser trabeculoplasty (SLT) performed within 60 days of recruitment
* Inability to safely perform iStent implantation, such as corneal opacity impeding gonioscopy view of nasal angle
* Inability to attend follow up

***DATA COLLECTION***

Participants will attend their usual clinical visits for pre-operative assessment and post-operative follow up. Key data points will include:

Collected once

* Demographics (age, gender, ethnicity)
* Diagnoses (glaucoma subtype, comorbidities)
* Baseline severity, based on mean deviation (MD) of 24-2 visual field test
* Previous ocular treatment such as SLT, allergies or adverse reactions

Collected every 4-6 months

* Routine glaucoma assessments (repeated scans and visual field tests) as appropriate to document progression, severity, and update target IOP if needed

Collected at every visit

* Visual acuity (VA): unaided and best corrected
* Masked intraocular pressure (IOP, using Goldmann applanation tonometry)
* Current topical medications and side effects of treatment
* Glaucoma utility index (GUI) questionnaire

We will also collect costing data from theatre, procurement and department managers.

***ANALYSIS AND SAMPLE SIZE***

We will use a de-identified database of results to analyse the need for iStent implantation after cataract surgery in this group of patients, the success of iStents as a second stage procedure, and the costs saved or extra costs incurred by the as-needed approach to iStent use (as compared to the theoretical situation where all of our participants had primary iStent implantation with cataract surgery). In addition, we will be able to compare the cost-effectiveness of primary and secondary use of iStents.

The primary outcome of the study is thus the proportion of patients who require second-stage iStent implantation, which drives the cost calculation. The utility, or benefit, side of the equation is measured with the glaucoma utility index (GUI, a short questionnaire) and other secondary outcomes such as visual acuity, number of glaucoma drops, and the need for more glaucoma surgery.

A sample size calculation (see below) estimates that at least 50 but preferably closer to 100 participants would be required.

***STUDY PERIOD***

Recruitment will span from September 2021 to September 2024. All data will be collected between September 2021 and December 2027.

We will report on 6 month, 1 and 3 year outcomes (measured from the time of first-stage cataract surgery). Provisional results from 1, 2 and 3 years after study initiation will be reviewed with the department and made available to the ethics committee.

**2. INTRODUCTION, HYPOTHESIS AND OBJECTIVES**

**2.1 Background**

Glaucoma is a progressive optic neuropathy that, if left untreated, results in permanent vision loss. Affecting more than 80 million people, it is the leading cause of irreversible blindness worldwide (1). Current treatment options aim to reduce intraocular pressure (IOP), the condition’s only known modifiable risk factor. First line treatment options include topical medications and selective laser trabeculoplasty. Traditional surgery for glaucoma (trabeculectomy and tube implantation) are generally reserved for advanced cases, given their risk of significant complication and failure rate (2).

Over the past decade, a range of devices and techniques for minimally invasive glaucoma surgery has emerged, aiming to lower IOP with less risk than traditional glaucoma surgery, which would suit management of mild and moderate cases when first line treatments are insufficient or unsatisfactory (e.g. eye drop side effects).

The iStent (Glaukos Corporation, Laguna Hills, CA, USA) is one such minimally invasive glaucoma surgery device. It is an ab-interno (i.e. inserted from inside the eye) trabecular bypass stent (i.e. crosses the trabecular meshwork, the point of maximum resistance in most glaucoma). The iStent is made of non-ferromagnetic, heparin-coated, surgical grade titanium. When inserted correctly it creates direct passage for aqueous to drain from the anterior chamber into Schlemm’s canal. The iStent has developed from a single device to the iStent inject (two stents in one injector), to the iStent inject W with wider flanges to assist insertion.

The iStent has usually been inserted in combination with cataract surgery (phacoemulsification), but more recently the outcomes of iStent insertion as a standalone procedure have been reported (3).

A Cochrane review published in 2019 (3) graded the evidence for iStent use as “very low quality”, due to substantial statistical heterogeneity, potential risk of bias, imprecision, inconsistency and potential publication bias. Notably, all of the seven randomised controlled trials included in the review received financial support from Glaukos (4-10).

Clinical trials comparing phacoemulsification/iStent to phacoemulsification did not show large differences in IOP outcomes because IOP is known to fall after cataract surgery alone(7,11). In one trial the IOP was 1.6mmHg lower (4), in another trial 2.7mmHg lower, in the iStent group at 12 or 15 months (9). These trials have used an alternative outcome measure, the number of IOP-lowering topical medication (drops), and found between 0.2 and 0.9 fewer drops taken in the iStent/phacoemulsification groups at 12-15 months (4,7,9), but with low numbers of drops in all participants. These differences in medication use did not persist on longer follow up (12, 13). The inclusion criteria (indications for use) are variable between studies.

Several studies have investigated istent use as a standalone procedure, including 4 randomized trials (5,6,8,14) and 7 prospective, uncontrolled, single arm studies (15-21). A recent metaanalysis of existing data, calculated a mean IOP reduction of 31.1% and 30.9% from baseline at 6-12 and 36-60 months, respectively; as well as a mean reduction of 1.0 medication at 6-18 months (22).

Whilst almost all studies demonstrate a tendency toward lower IOP and reduction in medication burden, there is substantial heterogeneity among published studies. (P<0.05; I2 =96%) (22). Study populations vary greatly, ranging from treatment naive eyes to uncontrolled, advanced glaucoma (otherwise indicated for traditional glaucoma surgery). Additionally, discrepancies in study design, in respect to the use of medication wash out, reinstating of medication following stent insertion and outcomes measured, also impact the interpretation of results. These variations amongst studies are reflected in the highly heterogenous range of results, with effect on IOP ranging from -1.0 (14) to -10.9 (8).

Glaukos’ provision of funding and/or editorial assistance for 10 out of 11 of the aforementioned studies, places these at considerable risk of publication and sponsorship bias.

Crucially, there is no significant literature addressing the cost-effectiveness of iStent use. This is of utmost importance when the cost of an iStent is high and the indication of glaucoma is common. The current study addresses this need for health-economic and unbiased research into the appropriate use of the iStent in publicly funded glaucoma care.

**2.2 Study objectives**

To understand

1. In patients with both mild-moderate glaucoma and cataract, would it be more cost-effective to use iStent combined with cataract surgery, or delayed for use in those for whom it is still indicated after cataract surgery?;
2. Using the glaucoma utility index as an outcome measure, would standalone iStent use be considered cost-effective in pseudophakic eyes?
3. To assess the effectiveness of standalone iStent implantation in pseudophakic eyes (using other outcomes such as IOP, medication use)

**3. STUDY DESIGN, PARTICIPANTS AND RECRUITMENT**

**3.1 Study design**

This study is based on the concept of staging iStents. In patients with both cataracts and glaucoma, who would meet criteria for iStent with cataract surgery, we would perform only cataract surgery (which is standard of care) and delay the insertion of an iStent (which is still an emerging technology, not offered in all public hospital departments). Then, three months after surgery, if the same indications for iStent are still met, a second-stage standalone iStent insertion would be performed. The fundamental idea is that if iStent insertion is not usually required after cataract surgery, then two-stage insertion would save money on stents, but if iStent insertion is required after most cataract operations in glaucoma patients, then two-stage insertion would cost more money in additional theatre visits.

Thus the inclusion criteria are indications for cataract surgery with iStent insertion. There is an asymmetry in the use of iStents with cataract surgery or as standalone procedures. iStents are commonly added to cataract surgery in glaucoma patients for the possible benefit of reducing medication use. However this would seem insufficient indication for a standalone iStent, and therefore standalone stents are deemed indicated when IOP is not on target (higher than deemed safe, despite medications). This asymmetry is an issue for this study, so we have created inclusion criteria and indications for second stage iStent that are more symmetrical.

The final key issue here is access to cataract surgery. The clinical prioritisation and access criteria (CPAC) system is used to generate a priority score for cataract surgery, incorporating quality of life questions, best corrected visual acuity (BCVA) in each eye and some aspects of prognosis and cataract morphology. In Capital & Coast District Health Board at the time of writing the CPAC score required for cataract surgery is 60. Patients in the glaucoma clinic have increased access to cataract surgery, partly because there is no barrier of referral or delay. Glaucoma patients can get immediate prioritisation if their doctor indicates ‘risk of angle closure’ (90 points) or ‘cataract preventing safe management of glaucoma’ (80 points), and then there are some patients who have an insufficient priority score who the doctor deems cataract surgery is required for another reason, such as the expectation of IOP lowering or as preparation for other glaucoma surgery (clinical over-ride). Here, we wish to ensure that cataract surgical access is equitable and not influenced by the study. The other criterion “Either a) IOP over target; OR b) eye drop side effects” represents the type of reasoning made by doctors in recommending cataract surgery earlier for some glaucoma patients.

**3.2 Participants**

Participants will be glaucoma patients, attending hospital eye clinics for their glaucoma care, and developing a need for cataract surgery. Sometimes new patients referred to the hospital will have both glaucoma and visually significant cataracts at presentation: they may also be suitable for recruitment. Both eyes of each participant will be considered eligible for the study, if all criteria are met in both eyes

***Inclusion criteria:***

* Visually significant cataract requiring surgery with visual acuity (BCVA) 6/9 or worse.
* Diagnosis of OHT or mild to moderate open angle glaucoma (including primary open angle, pigment dispersion, pseudoexfoliation), taking at least one topical glaucoma medication (drops)
* Target IOP ⋝ 15 mmHg
* Either a) IOP over target; OR b) at least one recognisable side effect of drops
* Willing and able to give informed consent
* Age >18yrs

***Exclusion criteria***:

* Low tension, angle closure, neovascular, uveitic, traumatic or other secondary glaucoma
* Prior incisional glaucoma surgery or cyclodestructive procedure
* Selective laser trabeculoplasty (SLT) performed within 30 days of recruitment
* Corneal opacity impeding gonioscopy view of nasal angle
* Inability to attend follow up

**4. DATA COLLECTION PROCESSES**

Each participant will attend the eye clinics at Wellington Regional Hospital and Kenepuru Community Hospital of Capital & Coast District Health Board for their usual glaucoma care. Those patients who meet inclusion and exclusion criteria will be invited to participate. Informed consent will be obtained, and if possible participants wish to reconsider their decision, they can discuss consent at any point before cataract surgery to join or exit the study.

A database of participants will be collected, linking identifying information to their study number. An anonymous database of study data will be created using only the study number, and collecting non-identifiable information. Both databases will be secured in a password protected laptop with a back-up in the cloud.

Study visits will not deviate from normal clinical care of glaucoma patients at the time of cataract surgery.

Baseline data to be extracted from the clinical record include:

* Demographics (age, gender, ethnicity)
* Diagnoses (glaucoma subtype, comorbidities, glaucoma severity)
* Previous ocular treatment such as SLT, allergies or adverse reactions

At baseline, data on the severity of glaucoma will be collected from the most recent automated visual field (VF) test, also establishing glaucoma progression and target IOP.

Target IOP will be standardised (as is usual in our clinical practice) based on the MD of VF:

1. if there is no glaucoma (ocular hypertension requiring treatment), target IOP = 21 mmHg,
2. if glaucoma is mild (MD > -6 dB), target IOP = 18 mmHg
3. if glaucoma is moderate (-6 dB > MD > -12 dB), target IOP = 15 mmHg
4. if glaucoma is advanced (MD < -12 dB), target IOP = 12 mmHg

all of these categories and targets are modified by the clinician as appropriate, such as when progression is known to occur despite achieving target IOP .

A preoperative visual acuity (VA, both unaided and best corrected), IOP, list of topical medications, and glaucoma utility index (GUI) questionnaire will be obtained. The GUI includes two questions on side effects of treatment, and if “some difficulty” or more is indicated on those questions, or another side effect is described by the patient, the participant will be said to have side effects. Only the GUI will deviate in any way from the standard clinical record. All IOP measurements in the study will be collected with Goldmann tonometry in a repeated (twice, a third time if >2 mmHg difference) and masked manner, standard in glaucoma clinical trials.

At postoperative visits on day 1, month 1, month 3, any additional visits and longer term follow up visits as clinically indicated, the same core data will be collected each time:

* Visual acuity (VA): unaided and best corrected
* Intraocular pressure (IOP, using Goldmann applanation tonometry)
* Clinical examination findings particularly complications and intraocular inflammation
* Current topical medications
* GUI questionnaire, including the same two questions on side effects of treatment

These data are sufficient to determine at any stage after cataract surgery whether the participant meets criteria for second-stage iStent insertion (section 5). The same data are collected at each visit after iStent insertion, with follow up at day 1, month 1, month 3 after iStent insertion plus any clinically indicated additional visits and longer term follow up.

Every 4-6 months patients will return for standard glaucoma care, which will include Spectralis optical coherence tomography (OCT) scans of the retinal nerve fibre layer and automated 24-2 VF tests as indicated to detect progression of the glaucoma.

**5. TREATMENT**

All participants will undergo standard phacoemulsification cataract surgery which is the standard of care. Notwithstanding the risk of complications, an intraocular lens will be placed in the lens capsule. Participants will use the normal postoperative eye drops recommended by their surgeon, usually including a steroid such as G. prednisolone acetate 1% 4x/day for a month. Their usual glaucoma drops usually continue unaltered after cataract surgery.

Patients are examined on the first postoperative day, including measurement of intraocular pressure, and if pressure is significantly higher than target, the doctor may choose to increase treatment in the short term, usually with the goal of returning to the pre-operative level of treatment before one month. Any other modifications to treatment such as use of antibiotics, non-steroidal anti-inflammatories or lubricants, more treatment for surgical complications or comorbidities such as diabetic retinopathy, will all be permitted.

At the one month postoperative visit, examination is usually to check for residual inflammation, which can require longer treatment with steroids and/or non-steroidal anti-inflammatories and more follow up appointments. The IOP is also checked and treatment modified if necessary.

From 3 months the participants would be eligible for iStent insertion, if the following criteria are met:

* Eye remains suitable for iStent with no worse than moderate glaucoma
* Target IOP remains ⋝ 15 mmHg
* Either a) IOP over target despite drops; OR b) recognised side effects of drops

Patients who meet these criteria will be offered implantation of two iStent Inject-W devices under local anaesthesia, via a clear corneal temporal incision. This procedure, often assisted by the iStent representative, requires a surgical gonioprism and tilting microscope. Viscoelastic will be injected into the anterior chamber, two iStent devices implanted into the trabecular meshwork under direct visualisation, and viscoelastic is washed out using a cataract surgery irrigation and aspiration device. Postoperative steroid drops (G prednisolone acetate 1%) are given at a similar dose and duration to cataract surgery.

Further follow up and glaucoma treatment is entirely at the discretion of the treating doctors, but with the addition of collecting GUI questionnaires at subsequent visits.

**6.0 STUDY METHODOLOGY, INSTRUMENTS AND PROCEDURES**

**6.1 Recruitment**

As described above, patients with glaucoma/ocular hypertension attending eye clinics in Capital & Coast District Health Board and requiring cataract surgery will be considered for eligibility. Those meeting inclusion/exclusion criteria will be invited to participate, have the core issues of the study explained to them, given the patient information sheet and consent form at the same visit that they go on the waiting list for cataract surgery. After ample time for reflection, and if needed discussion with family/whānau and/or other healthcare providers as desired, informed consent will be obtained: most likely at the pre-operative visit in which they give consent as they would for routine cataract surgery .

Participation does not affect any pre-operative care, so recruitment does not need to interfere with their surgical pathway. The only additional information collected that is not standard in typical care is the GUI questionnaires.

The recruitment period will extend from September 2021 to September 2024.

**6.2 Equipment**

The clinical assessments are all standard in the hospital clinics and all are required for safe glaucoma care. Only the GUI questionnaires are additional data collected for the study. The questionnaires will be laminated and distributed around clinic, and the scores recorded in the clinical record, so that there is no additional data source outside the clinical record. The questionnaires consist of 15 and six questions respectively and take around 5 minutes to administer. Some questionnaire data may require phone calls to collect if they are missed in the clinic.

The surgical equipment is all standard in hospital theatres. Cataract surgery may be performed with a variety of phacoemulsification devices, and a range of minor modifications to technique, but these variations are all acceptable in this study.

The iStent inject-W is the current iStent device and has been licenced for use in New Zealand and approved within the district health board. It is supplied as two stents arranged on one implantation device which can deliver up to four ‘pushes’ of the device into the target tissue of the eye. To visualise the trabecular meshwork, into which the iStent is injected, a gonioprism is required, usually supplied as a single use plastic lens with the iStent.

**6.3 Data analysis**

The study data will all be obtained from the clinical record in the hospital (source material).

A database of participants will be collected, linking identifying information to their study number. An anonymous database of study data will be created using only the study number, and collecting non-identifiable information. Both databases will be secured in a password protected laptop with a back-up in the cloud and weekly off-line copies on a secure external drive.

The anonymous study database will consist of baseline demographics, diagnoses, and previous ocular treatment, visual field (VF) and target IOP, and for each visit the VA, IOP, examination notes, current treatment, and GUI scores.

Statistical analysis is discussed below.

**7.0. ADVERSE EVENTS**

All adverse events during the study will be recorded, and participants will have all appropriate medical care. Complications of cataract surgery will be recorded but this risk is not modified by participation in the study. Patients who experience severe complications such as posterior capsule tear, vitreous loss or aphakia may no longer be suitable for iStent implantation in the postoperative period, and so patients who are deemed no longer to meet the criterion of suitability for iStent implantation will be withdrawn from the study. Complications of iStent implantation, also rare and usually trivial, will be recorded and managed appropriately.

All clinically significant unexpected adverse events considered to relate to participation in the study will result in withdrawal from the study and reporting to Medsafe/CARM.

**8.0 ETHICAL ASPECTS**

**8.1. Ethical committees**

Evaluation and approval by the Health and Disability Ethics committees prior to the start of the study.

**8.2. Informed consent**

Written consent will be obtained from all study participants before any study testing or treatment begins.

**8.3. Privacy and Confidentiality**

Clinical care will be provided by study investigators Dr Nicole Lim, Dr Jesse Gale, Prof Tony Wells and other staff (doctors, optometrists and nurses) in the glaucoma clinics and operating theatres. Some cataract surgery may be provided by other surgeons.

All care will be recorded in the clinical record, including GUI questionnaires, with the same privacy protections of clinical care in CCDHB.

Data will be extracted by Dr Nicole Lim, Dr Jesse Gale, and designates. One database linking study numbers to the national health index (NHI) number will be maintained on a laptop with password protection. The study data database will be anonymous with non-identifiable information such as age and ethnicity and glaucoma data, but no potentially identifiable information.

**8.4 Risks and benefits**

There is potential benefit for patients participating in the study to receive closer than usual monitoring of their IOP and glaucoma status, as well as being offered an iStent as surgical intervention with greater access than the current standard of care.

There is potential benefit for the CCDHB, as we expect that conducting this study will reduce the number of iStents used and allow more economic considerations of access to iStent devices.

Both cataract and iStent surgery have favourable, low risk, safety profiles. Cataract surgery has well documented risks of up to 5% complications and around 1:1000 permanent severe loss of vision in the affected eye. These risks are accepted by cataract surgery patients as there is a much greater chance of tangible immediate improvement in vision. iStent implantation has smaller risks, probably in the order of 1:200 risk of significant bleeding or inflammation causing longer lasting effects. iStent occlusion, malposition, or falling out have been reported more commonly (up to 18%, resulting in a loss of benefit and sometimes requiring a return to theatre to reposition them (Wellick; Samuelson). The risk of serious adverse events is very small (never reported) and thus easier to justify when the potential benefit of the iStent is small.

Cataract surgery is standard of care for our participants with visually significant cataract warranting surgery. Clearly the informed consent discussion between patients and surgeons is not regulated by this study, and the decision whether to have surgery is not affected by the decision whether to participate.

**8.5. Good Clinical Practice (GCP)**

Appropriate New Zealand regulations related to good practice for medical research activities will be followed. The study investigators are GCP trained.

**8.6 Data storage and destruction**

Data storage and destruction will comply with ethics and regulatory standards in New Zealand. The laptop with the study database (de-identified) will be password protected. All paper documentation will be part of the clinical record, maintained in the clinical record systems of CCDHB. Extracted anonymous data will be kept for a minimum of 10 years from date of study completion. The extracted anonymous database may be shared with international researchers to maintain transparency and allow alternative analyses and meta-analysis.

**9. ANALYSIS**

**9.1. Data Analysis**

The first analysis is the survival curve representing the proportion of patients who remain free of side effects and at their target IOP after cataract surgery alone. Those who do not meet both criteria will have second-stage stent implantation. This proportion receiving stents will grow over time, and the comparison group is the concept that 100% of the participants would be considered eligible for stent implantation before their cataract. We are analysing whether the costs of the stent at the time of cataract surgery are outweighed by the costs of theatre for second stage implantation in some patients.

The null hypothesis is that the total cost of stents implanted as a primary procedure with cataract surgery in these participants would be the same as the cost of delaying the stent implantation for only those who still meet indications at 3 months (no difference). The alternative hypothesis is that the cost of second-stage implantation is different to the cost of implanting stents as a primary procedure with cataract surgery (greater or less, a two-tailed analysis). This outcome is modelled from the cost per cataract operation, the cost of cataract surgery with stent implantation, and the cost of standalone stent implantation.

The primary outcome of the study is thus the proportion of patients who require second-stage stent implantation, which drives the cost calculation.

The utility, or benefit, side of the equation is measured with the glaucoma utility index (GUI, a short questionnaire) and other secondary outcomes such as visual acuity, number of glaucoma drops, side effects (GUI questions 5 and 6) and the need for more glaucoma surgery.

A secondary analysis will be pre-operative factors that predict the need for, or benefit from, iStent implantation.

**9.2 Sample size**

A sample size calculation was performed regarding the accuracy of the estimate of proportion requiring stent. As our point of cost neutrality is estimated to be 50% of participants, we wished to estimate this proportion with confidence intervals of +/- 10%, requiring 97 participants. If 50 participants are enrolled, the confidence interval increases to +/- 14%.

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