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Glaucoma Drainage Device and Endothelial Cell Loss Compare (DECLARE): Study Protocol for a Randomized Controlled Glaucoma Surgical Trial

Ying Han

ying.han@ucsf.edu

University of California, San Francisco

Jennifer Rose-Nussbaumer

Stanford University

Steven Gedde

University of Miami

Iqbal Ike Ahmed

Prism Eye Institute

Yen C Hsia

Diablo Eye Associates

Sandra Sieminski

University at Buffalo, State University of New York

Pradeep Ramulu

Johns Hopkins Hospital

Teresa Chen

Massachusetts Eye and Ear Infirmary

Rodolfo Bonnati

University of North Carolina at Chapel Hill

Jenny Lu

University of California, San Francisco

Erin Prachar

University of Pennsylvania

Thuy Doan

University of California, San Francisco

Gui-shuang Ying

University of Pennsylvania

Study protocol

Keywords: glaucoma, glaucoma drainage device, anterior chamber, ciliary sulcus, tube location, intraocular pressure, endothelial cell loss, metagenomic RNA sequencing

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Authors: Ying Han,[1,2,3*] Jennifer Rose-Nussbaumer,[4*] Steven J Gedde,[5] Iqbal Ike Ahmed,[6] Yen C. Hsia,[7] Sandra Sieminski,[8] Pradeep Ramulu,[9] Teresa Chen,[10] Rodolfo Bonatti,[11] Jenny Lu,[1] Erin Prachar,[12] Thuy Doan,[1,2] Gui-shuang Ying[12], DECLARE Study Group

1. Department of Ophthalmology, University of California, San Francisco, San Francisco, California, USA
2. The Francis I. Proctor Foundation for Research in Ophthalmology, San Francisco, California, USA
3. Ophthalmology Section, Surgical Service, San Francisco Veterans Affairs Medical Center, San Francisco, California, USA
4. Department of Ophthalmology, Stanford University School of Medicine, Stanford, California, USA.
5. Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida, USA
6. Prism Eye Institute, Oakville, Ontario, Canada
7. Diablo Eye Associates, Walnut Creek, California, USA
8. Ross Eye Institute, University at Buffalo, Buffalo, New York, USA
9. Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
10. Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, Massachusetts, USA
11. University of North Carolina, Chapel Hill, North Carolina, USA
12. Center for Preventative Ophthalmology and Biostatistics, Department of Ophthalmology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

***** Ying Han and Jennifer Rose-Nussbaumer are co-first author for this manuscript

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Corresponding author Information:

Ying Han, MD, PhD

Department of Ophthalmology

University of California, San Francisco

490 Illinois St., San Francisco, CA 94158

San Francisco, CA, United States 94158

Ying.Han@UCSF.edu

Title {1a}

Glaucoma Drainage Device and Endothelial Cell Loss Compare (DECLARE): Study Protocol for a Randomized Controlled Glaucoma Surgical Trial

Names of protocol contributors {3a}

Ying Han, MD, PhD, University of California, San Francisco
Jennifer Rose-Nussbaumer, MD, Byers Eye Institute at Stanford
Steven J Gedde, MD, Bascom Palmer Eye Institute
Iqbal Ike Ahmed, MD, FRCSC, Prism Eye Institute
Yen C. Hsia, MD, Diablo Eye Associate
Sandra Sieminski, MD, State University of New York, Buffalo
Pradeep Ramulu, MD, PhD, Wilmer Eye Institute
Teresa Chen, MD, Massachusetts Eye and Ear
Rodolfo Bonatti, MD, University of North Carolina, Chapel Hill
Jenny Lu, BA, University of California, San Francisco
Erin Prachar, BS, University of Pennsylvania
Thuy Doan MD, PhD, University of California, San Francisco
Gui-shuang Ying, PhD, University of Pennsylvania
DECLARE Study Group

Abstract

- **Background**: Glaucoma drainage device (GDD) surgery is increasingly used to manage medically uncontrolled glaucoma, a leading cause of irreversible blindness worldwide. A major long-term complication of GDD implantation is progressive corneal endothelial cell loss (ECL), which can lead to corneal decompensation and require complex management. One proposed mechanism for ECL is direct mechanical damage from the silicone tube when placed in the anterior chamber (AC), the most common location. To mitigate this risk, an alternative technique places the tube in the ciliary sulcus (CS), increasing the distance from the cornea and using the iris as a protective barrier. However, high-quality comparative evidence is lacking. A randomized controlled trial (RCT) is needed to determine the optimal tube location to minimize ECL while maintaining effective intraocular pressure (IOP) control.
- **Methods**: The DECLARE Study is an NIH-sponsored multicenter, participant- and outcome-masked randomized controlled trial conducted at eight clinical sites in the United States and Canada, with a target sample size of 226 eyes from 226 participants. Eligible participants are patients who are surgical candidates for GDD implantation and meet all inclusion/exclusion criteria. Participants are 1:1 randomized to tube placement in either the anterior chamber (AC) or ciliary sulcus (CS), stratified by clinical center and type of surgery (GDD alone vs. GDD combined with phacoemulsification). Only the first eligible eye requiring GDD is included in the study. All participants receive standard GDD surgery

and complete five postoperative follow-up visits over 24 months.

- **Discussion**: The primary objectives of the DECLARE Study are to compare central corneal ECL and IOP at 12 months between CS and AC tube placement. Secondary objectives include characterization of the anterior chamber microenvironment using metagenomic RNA sequencing. By integrating structural, clinical, and molecular outcomes, this study aims to provide comprehensive evidence to guide optimal GDD tube placement in glaucoma patients. Trial participants form a well-characterized cohort that will continue to be followed beyond the study period, providing a unique opportunity to evaluate long-term outcomes and complications after GDD implantation.
- **Trial registration**: ClinicalTrials.gov ID NCT05924477. Registered June 8, 2023, https://clinicaltrials.gov/study/NCT05924477

Keywords

glaucoma, glaucoma drainage device, anterior chamber, ciliary sulcus, tube location, intraocular pressure, endothelial cell loss, metagenomic RNA sequencing

Structured summary {1b}

Item	Description
Primary Registry and Trial Identifying Number {4}	NCT05924477, https://clinicaltrials.gov/study/NCT05924477 07/11/2023
Secondary Identifying Numbers	853474
Source(s) of Monetary or Material Support	National Institutes of Health, National Eye Institute Cooperative Agreement UG1 EY033703
Primary Sponsor and contact information {3b}	University of California, San Francisco
Role of sponsor and funder {3c}	Representatives of the National Eye Institute provide scientific oversight of the study and participated in study governance activities as per National Institutes of Health principles for cooperative agreement awards. Otherwise noted, none of the funders were involved in study design, data collection, data analysis, data interpretation, writing of this manuscript, or the decision to submit for publication.
Contact for Public Queries	declaretrial.org
Contact for Scientific Queries	Dr. Ying Han, ying.han@ucsf.edu
Public Title	DECLARE
Scientific title	Glaucoma Drainage Device and Endothelial Cell Loss Compare
Countries of Recruitment	United States and Canada
Health Condition(s) or Problem(s) Studied	Medically uncontrolled glaucoma, endothelial cell loss post-Glaucoma Drainage Device (GDD) procedure
Intervention(s)	GDD implantation in the anterior chamber or the ciliary sulcus
Key Inclusion and Exclusion Criteria	• Preexisting corneal condition that would affect the corneal endothelium or ungradable baseline endothelial cell density

	images or previous corneal transplant • Presence or history of Cypass Micro-Stent • Previous GDD, Xen Gel Stent, or Preserflo MicroShunt removed less than 6 months before surgery • Presence of GDD implantation, Xen Gel Stent, or Preserflo MicroShunt • Previous trabeculectomy or/and minimally invasive glaucoma surgery within 6 months • Anterior chamber intraocular lens • Presence of nanophthalmos, uncontrolled uveitis, silicone oil, Sturge-Weber syndrome or other conditions associated with elevated episcleral venous pressure • Unwilling or unable to give consent, unwilling to accept randomization, or unable to return for scheduled protocol visits • No light perception vision in the study eye or fellow eye visual acuity < 20/200 • Need for glaucoma surgery combined with other ocular procedures (i.e. corneal transplant, or retinal surgery) or anticipated need for additional ocular surgery
Study Type	multicenter, participant- and outcome-masked, parallel-group randomized controlled trial; 1:1 allocation ratio
Date of First Enrollment (planned)	7/11/23
Sample Size	226
Primary outcome(s)	(1) corneal endothelial cell loss (ECL) at 12 months (2) intraocular pressure (IOP) at 12 months (mmHg).
Key Secondary outcome(s)	(1) Endothelial cell density at baseline, 3, 6, 12, and 24 months (2) IOP at baseline and postoperative months 1, 3, 6, and 24 (3) Endothelial cell morphology (coefficient of variation and percentage of hexagonal cells) (4) Best-corrected visual acuity (logMAR) (5) Number of glaucoma medications (6) Tube position parameters measured by Anterior Segment Optical Coherence Tomography (AS-OCT) (7) RNA-seq analysis at baseline and postoperative month 12
Ethics Review	UCSF Institutional Review Board 21-33490
Individual Trial Participant Data sharing statement	De-identified participant-level data and statistical code may be shared with qualified researchers upon request, participant to institutional policies, data use agreements, and applicable regulations. Results will also be reported in public trial registries in accordance with regulatory requirements.

Protocol version {2}

Version 5 (dated March 30, 2026)

Introduction

Background and rationale {9a}

Glaucoma drainage device (GDD) surgery is increasingly used to manage medically uncontrolled glaucoma, a leading cause of irreversible blindness worldwide. Although historically reserved for refractory cases, indications for GDD implantation have expanded due to its effectiveness in lowering intraocular pressure (IOP).[1-4] However, a major long-term complication is progressive corneal endothelial cell loss (ECL), which can lead to corneal decompensation and necessitate complex management.[5-8] One proposed mechanism for ECL after GDD implantation is direct mechanical trauma from the silicone tube when placed in the anterior chamber (AC), the most common location for tube placement.[9-11] To mitigate this risk, surgical techniques have evolved to position the tube in the ciliary sulcus (CS), increasing the distance from the cornea while the iris acts as a protective barrier. Despite these theoretical advantages, as of 2025, AC placement remains the predominant approach among glaucoma surgeons due to limited high-quality evidence demonstrating superior corneal or surgical outcomes with sulcus placement.[12, 13]

Existing studies evaluating ECL after GDD implantation are limited. Comparisons between CS and AC tube placement are based on a small number of retrospective, non-randomized studies, which suggest a slower rate of ECL with sulcus placement.[14,15] However, these studies are subject to selection bias and lack standardized assessment of tube position. Tube location relative to the cornea may be an important determinant of ECL, as AC tubes positioned farther from the cornea may confer similar risk to sulcus placement, whereas malpositioned sulcus tubes could increase corneal risk.

In addition, surgical outcomes associated with sulcus tube placement remain incompletely understood. Prior studies report inconsistent findings regarding IOP control between sulcus and AC placement.[15-17] Furthermore, sulcus tubes may lead to chronic iris–tube contact, potentially resulting in complications such as inflammation, pigment dispersion, hemorrhage, cystoid macular edema, or tube occlusion.[9,11,18,19] The impact of these factors on long-term surgical outcomes has not been systematically evaluated.

To address these critical knowledge gaps, a well-designed randomized controlled trial is needed to directly compare ciliary sulcus and anterior chamber tube placement. The DECLARE Study aims to evaluate the effect of tube location on corneal endothelial cell loss, intraocular pressure control, and the anterior chamber microenvironment. By integrating structural, clinical, and molecular outcomes in a multicenter setting, this trial seeks to provide high-quality evidence to guide optimal surgical technique and improve long-term outcomes for patients undergoing GDD implantation.

Explanation for the choice of comparator {9b}

The comparator groups are AC and CS tube placement during GDD implantation. AC placement is the current standard of care with established efficacy but is associated with ECL. CS tube placement may

reduce ECL by increasing the distance between the tube and cornea; however, supporting evidence is limited and largely retrospective.[14,15] A randomized clinical trial is therefore needed to determine whether sulcus placement provides superior corneal protection while maintaining comparable surgical outcomes.

Objectives {10}

The objectives of this study are to compare central corneal ECL, IOP , and AC microenvironment changes assessed using metagenomic RNA deep sequencing after GDD implantation with tube placement in the CS versus the AC.

Methods: Patient and public involvement, and trial design

Patient and public involvement {11}

The study was developed by clinical investigators based on identified gaps in evidence and patient care needs in glaucoma management. Participants are involved through informed consent and standard follow-up procedures. Study results will be disseminated through scientific publications, conference presentations, and clinical trial registry. Patients and the public were not directly involved in the design, conduct, or reporting of this trial. Future efforts will include broader communication of findings to patients and the public to enhance understanding and impact of the study results.

Trial design {12}

The DECLARE Study is a National Institutes of Health-supported, multicenter, participant- and outcome-masked, parallel-group randomized controlled trial conducted across 8 clinical sites in the United States and Canada. Participants are randomized in a 1:1 allocation ratio to one of two intervention arms: GDD implantation with tube placement in the AC or in the CS. Randomization is performed at the individual participant level and stratified by clinical site and type of surgery (GDD alone vs. GDD combined with phacoemulsification) using permuted block randomization with variable block sizes (2 or 4) to ensure balance between treatment arms within each site.

The trial adopts a mixed analytical framework. A superiority framework is used for the primary outcome of ECL and for AC microenvironment changes assessed by metagenomic RNA deep sequencing, with the objective of determining whether CS tube placement reduces ECL and alters molecular profiles compared to AC placement. In parallel, an equivalence framework is used for IOP control, with a pre-specified equivalence margin of ±2 mmHg to evaluate whether the two tube locations achieve comparable IOP outcomes.

Masking is implemented to the extent feasible in a surgical trial. Study participants and outcome assessors, including personnel measuring endothelial cell density (ECD), IOP, and performing molecular analyses, are masked to treatment allocation. Due to the nature of the surgical intervention, operating surgeons and certain imaging technicians (e.g., those acquiring anterior segment OCT images) are not masked. To minimize bias, outcome measurements are taken by trained, masked evaluators, and imaging analyses are

performed at centralized reading centers independent of the clinical sites.

Methods: Participants, interventions and outcomes

Trial setting {13}

The DECLARE trial is conducted at academic centers and a private practice across the United States and Canada. Eligible participants are recruited from the following 8 sites: University of California, San Francisco; Bascom Palmer Eye Institute; Prism Eye Institute; Massachusetts Eye and Ear Institute; University at Buffalo/State University of New York; Wilmer Eye Institute; University of North Carolina at Chapel Hill; and Diablo Eye Associates in California. University of California, San Francisco serves as the Clinical Coordinating Center, overseeing study implementation, coordination across sites, and overall trial management. The Center for Preventative Ophthalmology and Biostatistics at University of Pennsylvania serves as the Data Coordinating Center, responsible for managing data collection, database systems, randomization, data quality monitoring, and statistical analyses. Image graders at the Center for Ophthalmic Research and Novel Image Analysis (CORNIA) at Stanford conducts masked grading of specular microscopy. The Ralph & Sophie Heintz Laboratory processes and analyzes biological specimens.

At each site, eligible participants are screened by the primary surgeon and the site study coordinator. Potential participants are identified and approached during routine outpatient clinical visits as part of standard care. All patients considered for enrollment require GDD surgery regardless of participation in the study.

Characteristics of the people who are needed for the trial

Characteristic	The people we would expect to see included
Age	Patients age 18 years and over
Sex	Not selected for
Gender	Not selected for
Race, ethnicity and ancestry	Not selected for
Socioeconomic status	Not selected for
Geographic location	Residents in the United States and Canada
Other characteristics relevant to the trial	Participants who meet all inclusion and no exclusion criteria

Eligibility criteria for participants {14a}

Eligible participants are adults (≥18 years) with medically uncontrolled glaucoma requiring GDD implantation, with or without concurrent phacoemulsification, and who are suitable candidates for both AC and CS tube

placement. Key exclusion criteria include preexisting corneal conditions affecting the endothelium, prior corneal transplantation, ungradable baseline ECD images, or recent or existing glaucoma drainage or minimally invasive glaucoma devices or surgeries within 6 months. Additional exclusions include aphakia, anterior chamber intraocular lenses, phakic lens status without plan for concurrent lens extraction, ocular or systemic conditions associated with elevated episcleral venous pressure, inability or unwillingness to provide consent or comply with study visits, severely limited vision (no light perception in the study eye or fellow eye visual acuity <20/200), and the need for concurrent or anticipated additional ocular surgeries.

Eligibility criteria for sites and those delivering interventions {14b}

Participating study centers are high-volume academic institutions or private practice. They are all specialized ophthalmology practices with expertise in glaucoma surgery and the infrastructure to support clinical trials, including recruitment, standardized imaging, and longitudinal follow-up. Centers must be able to adhere to protocol requirements for data collection, imaging, and regulatory compliance. Surgeons are required to be experienced glaucoma specialists with prior experience in GDD implantation, including at least 30 GDD procedures and a minimum of 10 cases each of AC and CS tube placement. All surgeons must complete protocol-specific training, including review of standardized techniques and operative video assessment. Study personnel, including coordinators and technicians, must also undergo training and certification prior to study initiation.

Who will take informed consent? {32a}

Written informed consent is obtained by the ophthalmologist and/or study coordinator after explaining the nature of the study, including the randomization of the surgical intervention, as well as the potential risks and benefits of participation. Participants are informed that participation is voluntary and that they may withdraw from the study at any time without penalty.

Additional consent provisions for collection and use of participant data and biological specimens {32b}

Patients are informed that biological sample specimen collection (i.e., aqueous fluid samples) is a non-standard of care procedure done for research purposes only. Participants are informed that samples are stored in a de-identified manner. In rare cases, patients may enroll in the study without consenting to sample collection. The de-identified data are used for statistical analysis.

Intervention and comparator

Intervention and comparator description {15a}

Participants undergo GDD implantation and are randomized to tube placement in either the AC or CS. Surgery is performed under local or general anesthesia, with the device (Ahmed Valve Model FP7, Baerveldt, or Ahmed ClearPath) implanted in the superotemporal quadrant or an alternative site. The plate is

secured to the sclera 8–10 mm posterior to the limbus. In the AC group, the tube is inserted 2–4 mm posterior to the limbus into the anterior chamber with a trajectory directed parallel to the iris plane. In the CS group, the pupil is dilated and the tube inserted into the CS behind the iris. In both groups, the tube is covered with a patch graft and the conjunctiva is closed per standard practice. Tube position is confirmed intraoperatively using direct contact and postoperatively using anterior segment optical coherence tomography.

Postoperative care is standardized, including topical antibiotics for approximately one week and corticosteroids tapered over several months, with additional medications as clinically indicated. Follow-up visits occur at baseline, surgery, and postoperative months 1, 3, 6, 12, and 24.

Criteria for discontinuing or modifying allocated intervention/comparator {15b}

Allocated interventions may be modified or discontinued at the discretion of the treating surgeon based on clinical indications. These include intraoperative inability to safely place the tube in the randomized location, significant intraoperative or postoperative complications (e.g., hypotony, tube malposition, tube occlusion, or other adverse events), or the need for additional surgical intervention to control IOP. Participants may also withdraw from the study at any time upon request. All deviations from the assigned intervention, including crossover or reoperation, are documented. Participants will continue to be followed according to the study protocol whenever possible, consistent with the intention-to-treat principle.

Strategies to improve adherence to intervention/comparator {15c}

Adherence is promoted through standardized training and certification of surgeons and study personnel, with predefined surgical techniques supported by instructional materials and video training. Protocol adherence is ensured by intraoperative confirmation of tube placement and postoperative AS-OCT verification. Ongoing monitoring includes regular communication with the Clinical Coordinating Center, site visits, and review of operative records and imaging data. Protocol deviations are documented and addressed to maintain consistency across sites.

Concomitant care permitted or prohibited during the trial {15d}

Permitted concomitant care includes the use of topical antibiotics, corticosteroids, cycloplegics, and anti-glaucoma medications as clinically indicated. Additional procedures or interventions necessary for patient safety or management of complications (e.g., reoperation for uncontrolled IOP) are allowed at the discretion of the treating surgeon.

Prohibited interventions include concurrent ocular surgeries at the time of GDD implantation other than planned phacoemulsification, as well as enrollment of participants requiring anticipated additional ocular procedures (i.e. corneal transplant, or retinal surgery) that may confound study outcomes. All concomitant treatments and interventions are recorded throughout the study period.

Ancillary and post-trial care {34}

Participants receive standard clinical care throughout the trial, including management of any complications arising from GDD implantation at the discretion of the treating surgeon. As the study procedures align with routine clinical practice, no additional ancillary care beyond standard care is provided. Participants do not incur additional costs related to study participation, and clinical care is billed to insurance as appropriate. There are no specific provisions for financial compensation for harm; however, any adverse events are managed according to standard clinical practice and institutional policies.

Outcomes {16}

Primary outcomes

The primary outcomes are (1) central endothelial cell loss (ECL) at 12 months, measured as change in central endothelial cell density (ECD) from baseline (cells/mm²), and (2) intraocular pressure (IOP) at 12 months (mmHg). ECL is analyzed as mean change from baseline ECD, and IOP as mean value at 12 months, with comparisons between tube placement groups. ECL is a clinically relevant measure of corneal health and risk of decompensation, while IOP control is the primary goal of glaucoma surgery.

Secondary outcomes

Secondary outcomes include longitudinal ECD at baseline, 3, 6, 12, and 24 months; IOP at baseline and postoperative months 1, 3, 6, and 24; endothelial cell morphology (coefficient of variation and percentage of hexagonal cells); best-corrected visual acuity (logMAR); number of glaucoma medications; and tube position parameters (such as tube-corneal distance, tube length and angle of the tube relative to the cornea) measured by AS-OCT. These outcomes are analyzed using mean values or change from baseline over time. Additional secondary outcomes include postoperative complications and adverse events, analyzed as proportions. These measures provide complementary assessment of structural, functional, and safety outcomes after GDD implantation.

Exploratory outcomes

Exploratory outcomes include anterior chamber microenvironment changes assessed by metagenomic RNA sequencing at baseline and 12 months, analyzed as differential gene expression profiles and pathway enrichment. These outcomes aim to provide mechanistic insight into biological responses associated with tube location.

Harms {17}

Harms are defined as adverse events (AEs) and serious adverse events (SAEs) occurring during the study period. AEs are assessed systematically at scheduled study visits through participant inquiry and clinical examination, as well as through spontaneous self-reporting. Events are classified as expected or unexpected and evaluated for severity and relatedness to the intervention. Standardized terminology (e.g., MedDRA) is used for coding. All AEs are documented and followed until resolution or stabilization, with reporting focused on clinically significant and treatment-related harms. SAEs are reported promptly according to regulatory

requirements and reviewed by the Data and Safety Monitoring Committee (DSMC).

Site	Severity	Adverse Event
Ocular	Serious	Endophthalmitis
		Serious ocular event considered to be related to the study intervention resulting in hospitalization, systemic treatment, or loss of function
	Nonserious	Complications outlined in the *Complications List* not resulting in hospitalization or loss of light perception
		Any other ocular event considered to be related to the study intervention NOT resulting in hospitalization, systemic treatment, or loss of function
Systemic	Serious	Myocardial infarction
		Stroke
		Other systemic event thought to be related to study intervention resulting in hospitalization or loss of function
		Death
	Nonserious	Other systemic event thought to be related to study intervention not requiring hospitalization or systemic treatment, and not resulting in loss of function

Participant timeline {18}

Procedures	Screening, Pre-Enrollment (+/- 0 days)	Enrollment/Baseline, Visit 1 Pre-operative (+/- 0 days)	Procedure, Visit 2 (+/- 0 days)	Follow-Up, Visit 3 Month 1 (+/- 7 days)	Follow-Up, Visit 4 Month 3 (+/- 1 month)	Follow-Up, Visit 5 Month 6 (+/- 1 month)	Follow-Up, Visit 6 Month 12 (+/- 2 month)	Final Follow-up, Visit 7 Month 24 (+/- 2 months)
Informed consent	X							
Demographics	X	X						
Medical history	X	X						
Randomization			X*					
Administer study intervention (GDD implantation)			X					
BCVA/EDTRS/MRx	X	X		X	X	X	X	X
Intraocular pressure	X	X		X	X	X	X	X
Pachymetry	X	X		X	X	X	X	X

Gonioscopic exam		X					X	X
Motility exam		X$					X$	X$
Slit lamp examination	X	X		X	X	X	X	X
Fundus examination	X	X		X	X	X	X	X
Specular microscopy		X			X	X	X	X
Humphery perimetry		X					X	X
AS-OCT				X		X	X	X
Aqueous humor sample			X				X	
Baseline form		X						
Follow-up form				X	X	X	X	X
Final form								X@
Interval History				X	X	X	X	X

*Randomization performed when patient's data are initially entered into Research Electronic Data Capture system (REDCap)
$Motility exam performed when participant has diplopia
@If participant does not complete the study, final form will be filled out at time of withdrawal or loss-to-follow-up
BCVA = best corrected visual acuity, GDD = Glaucoma Drainage Device, EDTRS = Early Treatment Diabetic Retinopathy Study, MRx = manifest refraction; RNA-seq = metagenomic RNA deep sequencing, AS-OCT = anterior segment optical coherence tomography

Sample size {19}

A total of 226 participants (226 eyes) will be enrolled, with 1:1 randomization to AC versus CS tube placement. The sample size was determined based on the primary outcome of corneal endothelial cell loss (ECL) at 12 months. Assuming a standard deviation of 380 cells/mm² in ECD change from baseline at 12 months [15,20], a two-sided significance level of 0.05, and 15% loss to follow-up, a sample size of 226 provides 90% power to detect a clinically meaningful difference of 180 cells/mm² in ECL between groups.

This sample size also provides adequate power for the co-primary outcome of intraocular pressure (IOP), with approximately 93% power to demonstrate equivalence within a predefined margin of ±2 mmHg, assuming a standard deviation of 4 mmHg. For the exploratory RNA sequencing analysis, a subset of approximately 80 participants per group will provide at least 90% power to detect a two-fold change in gene expression at a false discovery rate of 0.01.[21]

These assumptions are based on prior studies and clinical relevance of differences in ECL and IOP following GDD implantation.[5, 22]

Recruitment {20}

Adequate participant enrollment is achieved through a multicenter design involving high-volume academic and private practice sites with established expertise in glaucoma surgery. Participating centers collectively perform a large number of GDD procedures annually, providing a sufficient pool of eligible patients. Potential participants are identified during routine clinical care by treating surgeons and study coordinators. Enrollment progress is monitored regularly by the Clinical Coordinating Center and Data Coordinating Center with feedback provided to sites to optimize recruitment. If enrollment targets are not met, additional high-volume sites may be considered.

Assignment of interventions: randomisation

Sequence generation: who will generate the sequence {21a}

The allocation sequence will be generated by the Data Coordinating Center using a computer-generated randomization scheme.

Sequence generation: type of randomisation {21b}

Participants are randomized in a 1:1 ratio to AC or ciliary sulcus tube placement. Randomization is stratified by clinical center and type of surgery (GDD alone vs. GDD combined with phacoemulsification) to ensure balance across groups. Permuted block randomization with variable block sizes (e.g., 2 and 4) is used to maintain allocation balance while reducing predictability. Details of the blocking scheme are maintained in a secure document by the Data Coordinating Center and are not accessible to investigators or study personnel involved in participant enrollment or intervention assignment.

Allocation concealment mechanism {22}

The allocation sequence is implemented centrally using a secure web-based system (REDCap) managed by the Data Coordinating Center. After participant enrollment and entry of baseline information, the site study coordinator initiates randomization through the system on the day of surgery. The assigned intervention is revealed only after randomization is completed, and the treating surgeon is then notified of the allocation. Allocation concealment is maintained by restricting access to the randomization sequence, which is stored securely by the Data Coordinating Center and not accessible to investigators or study personnel involved in participant enrollment.

Implementation {23}

The allocation sequence is generated by the Data Coordinating Center. Participants are screened and enrolled by the site principal investigator and study coordinator at each clinical center. Randomization is performed by the site study coordinator using the secure REDCap system, which assigns participants to interventions according to the pre-specified allocation sequence. The treating surgeon is informed of the assigned intervention after randomization.

Assignment of interventions: blinding

Who will be blinded {24a}

Trial participants and outcome assessors are masked to treatment allocation. Outcome assessors include personnel performing endothelial cell measurements, IOP assessments, and metagenomic RNA sequencing analyses. Due to the nature of the surgical intervention, treating surgeons and certain imaging technicians (e.g., those acquiring AS-OCT images) cannot be masked. To minimize bias, outcome measurements are conducted by trained, masked personnel, and imaging analyses are performed at centralized reading centers independent of the clinical sites.

How will be blinding be achieved {24b}

Participants and outcome assessors are masked to treatment allocation. Masking of participants is achieved by not disclosing the tube location, as both interventions involve standard GDD surgery with similar perioperative and postoperative care. All participants are assigned a unique study identification number, and all associated data, including specular microscopy images and aqueous humor samples, are deidentified and labeled using this study ID. ECD graders at CORNIA are masked to treatment assignment during endothelial cell analysis. Similarly, investigators at the Proctor Foundation are masked to treatment allocation when conducting analyses of aqueous humor samples.

Procedure for unblinding if needed {24c}

Unmasking is not routine and occurs only if required for clinical management or participant safety. In such cases, allocation is disclosed to the treating investigator as needed, and the reason for unmasking is documented, while maintaining masking of outcome assessors and data analysts whenever possible.

Data collection and management

Plans for assessment and collection of outcomes {25a}

Baseline, outcome measures, and follow-up data are collected at scheduled study visits using standardized procedures across all sites. Clinical assessments include best-corrected visual acuity (ETDRS protocol), IOP (Goldmann applanation tonometry), slit-lamp and fundus examinations, and gonioscopy. Imaging assessments include specular microscopy for ECD and morphology and AS-OCT for tube position. Aqueous humor samples (100 microliters) are collected for metagenomic RNA sequencing using standardized protocols.

Primary outcome ECD is graded manually by the CORNIA at Stanford. Specular microscopy images are obtained in triplicate for each study eye at central corneal location using standardized acquisition protocols. Images are graded at a centralized reading center by trained and certified graders masked to treatment allocation. All graders undergo structured training using standardized image sets and must achieve predefined inter-rater agreement (Cohen’s kappa >0.7) against expert reference grading prior to certification,

with annual re-certification to maintain consistency. ECD is assessed using the Konan Center Method. Two independent masked graders evaluate each image, and averaged values across the three images are calculated. If the difference between graders exceeds 5% of the mean value from two graders, a senior grader adjudicates to determine the final value. Image quality is assessed using standardized criteria, and re-imaging may be requested if images are not gradable. Ongoing quality assurance includes periodic re-grading of randomly selected images to assess intra- and inter-grader reliability and a random sample of same 15 image sets are regraded periodically to monitor grading drift. All grading data are stored in the REDCap database for analysis.

To promote data quality, all study personnel undergo training and certification in study procedures prior to trial initiation, with periodic re-certification as needed. Standardized protocols are used for all measurements, including duplicate or repeated measurements when applicable (e.g., IOP), and centralized reading centers perform masked grading of imaging outcomes. Data are entered into REDCap with built-in validation checks, and ongoing monitoring includes data queries, site visits, and quality assurance procedures.

All study instruments and procedures used (e.g., ETDRS visual acuity testing, Goldmann tonometry, specular microscopy) are widely validated and routinely used in ophthalmic clinical trials. Data collection forms and detailed procedures are specified in the study Manual of Operations and Procedures.

Plans to promote participant retention and complete follow-up {25b}

Participant retention is promoted through routine clinical follow-up, visit reminders, and coordination by site study coordinators, with ongoing monitoring by the Clinical Coordinating Center and Data Coordinating Center. Participants who discontinue or deviate from the assigned intervention are encouraged to continue follow-up, and key outcome data (e.g., ECD, IOP, visual acuity, and safety outcomes) is collected whenever possible and analyzed according to the intention-to-treat principle.

Data management {26}

Study coordinators are trained and certified for data collection and data entry into RedCap. Data are entered into REDCap with built-in validation checks, including range and consistency checks, to ensure data accuracy and completeness. Study coordinators verify data against source documents prior to entry. The DCC regularly performs checking of data to detect any data problems and sends data queries to the clinical sites for resolution. The DCC also performs a random sample of entered data at the clinical site against original data collection forms after data editing has been completed. All data are de-identified and stored on secure, password-protected servers with restricted access. Regular data monitoring, audits, and backups are performed to ensure data integrity and security. Detailed data management procedures are described in the study Manual of Operations and Procedures.

Confidentiality {33}

Personal information is collected as part of routine clinical care and study procedures and is handled in accordance with applicable privacy regulations. Participants are assigned unique study identifiers, and identifiable information is stored separately from study data. Only authorized study personnel have access to identifiable data, which is maintained on secure, password-protected systems. Data shared with coordinating

centers and collaborators is de-identified. All study records are stored securely during the trial and retained after study completion in accordance with institutional and regulatory requirements to ensure confidentiality.

Statistical methods

Statistical methods for primary and secondary outcomes {27a}

Primary analyses follow the intention-to-treat principle. For ECL at 12 months, comparisons between groups are performed using ANCOVA, adjusting for baseline ECD and stratification factors. For IOP at 12 months, ANCOVA is also used, with baseline IOP and stratification factors included as covariates. Equivalence testing for IOP is conducted using a predefined margin of ±2 mmHg based on the confidence interval of the between-group difference.

Secondary outcomes measured longitudinally (e.g., ECD, IOP, BCVA, and medication use) are analyzed using linear mixed-effects models to account for repeated measures over time. Categorical outcomes, including complications and adverse events, are compared using chi-square or Fisher's exact tests. Multivariable regression analyses may be performed to evaluate predictors of outcomes. All analyses use a two-sided significance level with adjustment for multiple comparisons where appropriate.

For the metagenomic RNA deep sequencing (RNA-seq) analysis, transcript abundance in the aqueous humor is compared between two tube location groups. Bioinformatics analysis is performed to identify functional pathways. All bioinformatics analyses are performed at the Ralph & Sophie Heintz Laboratory at Francis I. Proctor Foundation at UCSF.

Additional details on the statistical analyses can be found in the study Manual of Operations and Procedures.

Who will be included in each analysis {27b}

All analyses follow the intention-to-treat principle. All randomized participants areI ncluded in the primary analyses. RNA-seq analyses include participants with adequate aqueous humor samples from each tube location group. Sensitivity or multivariable analyses use subsets with complete covariate data.

How missing data will be handled in the analysis {27c}

The primary analysis population follows the intention-to-treat principle, including all randomized participants analyzed according to their assigned intervention regardless of protocol adherence. Secondary analyses may include per-protocol analyses excluding participants with major protocol deviations.
Missing data are minimized through active follow-up; however, if present, appropriate methods are applied. Primary analyses use available data, and sensitivity analyses are conducted using multiple imputation and, if necessary, inverse probability weighting to assess the impact of missing data.

Methods for additional analyses (e.g., subgroup analyses) {27d}

Additional analyses include prespecified subgroup and adjusted analyses. Subgroup analyses evaluate the

effect of treatment across clinically relevant factors, including type of GDD (e.g., AGV PF7 vs BGI vs Ahmed ClearPath), glaucoma diagnosis, and surgery type (GDD alone vs combined with phacoemulsification), by incorporating interaction terms in regression models. Adjusted analyses include baseline covariates (e.g., baseline ECD, IOP, age) and stratification factors (clinical center and surgery type) to improve precision of treatment effect estimates.

Sensitivity analyses are conducted to assess the robustness of findings, including per-protocol analyses, alternative model specifications, and approaches to handling missing data (e.g., multiple imputation or inverse probability weighting). Where appropriate, predictor analyses may be performed using multivariable regression methods to identify factors associated with outcomes.

Interim analyses {28b}

Interim analyses are conducted by the Data Coordinating Center and reviewed by the independent DSMC at predefined time points, when approximately 25% and 50% of participants have completed the 12-month primary outcome assessment. Interim analyses evaluate safety and efficacy using group sequential methods with a Lan-DeMets alpha-spending approach.[23] Stopping guidelines consider evidence of benefit, harm, or futility based on predefined statistical thresholds and clinical judgment.

Access to interim results is restricted to the DSMC and designated statisticians to preserve trial integrity. The DSMC reviews interim data and makes recommendations regarding continuation, modification, or termination of the trial. The final decision to terminate or modify the trial is made by the Executive Committee in consultation with the DSMC.

Protocol and statistical analysis plan {5}

The full study protocol and Statistical Analysis Plan can be made available upon reasonable request and may be published as part of the trial report.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {3d}

The trial is coordinated by a Clinical Coordinating Center, which oversees overall study management, including protocol implementation, training and certification, regulatory compliance, and coordination across sites. A Data Coordinating Center manages data collection, database systems, randomization, data quality monitoring, and statistical analyses.

Central resource centers support standardized outcome assessment, including the CORNIA as the imaging reading center for masked grading of specular microscopy, and the Ralph and Sophie Heintz Laboratory at the Francis I. Proctor Foundation, University of California, San Francisco, for processing and analysis of biological specimens.

An Executive Committee (trial steering committee) provides scientific and operational oversight, including monitoring study progress and protocol adherence. The committee meets regularly (e.g., weekly during initiation and biweekly thereafter). Day-to-day trial activities are supported by site investigators and study coordinators, with ongoing communication to ensure consistent trial conduct.

Monthly Principal Investigator meetings provide updates on study progress and site performance. Separate monthly meetings among Study Coordinators address logistics, troubleshoot issues, and review study updates.

Composition of the data monitoring committee, its role and reporting structure {28a}

An independent DSMC was established and convened by the National Eye Institute. The DSMC includes experts in glaucoma and cornea, biostatistics, and other relevant members with no direct involvement in the conduct of the trial. The DSMC is independent of the study investigators and sponsor and has no competing interests.

The DSMC monitors participant safety, trial conduct, and interim efficacy data, and makes recommendations regarding continuation, modification, or termination of the trial. The DSMC reviews data at regular intervals (e.g., semi-annually via in-person meetings or teleconferences) and receives reports prepared by the Data Coordinating Center.

The DSMC reports its recommendations to the Executive Committee. Further details regarding DSMC roles and procedures are described in the study protocol and DSMC charter.

Frequency and plans for auditing trial conduct {29}

Trial conduct is monitored through regular oversight by the Clinical Coordinating Center, including periodic site visits, review of study records, and assessment of protocol adherence and data quality. In addition, data audits and quality checks are performed by the Data Coordinating Center. Auditing activities are conducted independently of site investigators, and findings are reported to the study leadership to ensure compliance with the protocol and regulatory requirements.

Protocol amendments {31}

Any important protocol modifications are reviewed and approved by the DSMC and Executive Committee and relevant regulatory bodies prior to implementation. Changes are communicated to investigators, institutional review boards/ethics committees, and other relevant parties, and updated in trial registries as required. Participants are informed of modifications that may affect their participation, and protocol updates are reflected in study documents and future publications.

Dissemination policy {8}

Trial results will be disseminated to participants, healthcare professionals, and the scientific community through peer-reviewed publications, conference presentations, and updates to clinical trial registries (e.g., ClinicalTrials.gov). Results may also be shared with participants upon request. Publications and presentations will be reviewed and approved by the Executive Committee in accordance with study publication policies. There are no undue publication restrictions, and reporting will follow established guidelines (e.g., CONSORT).

Discussion

This NIH-funded multicenter randomized controlled trial compares AC versus CS tube placement in GDD surgery. The study addresses an important gap in evidence regarding optimal tube location. By evaluating corneal endothelial outcomes, IOP, and AC microenvironment changes, the results may inform surgical decision-making and improve outcomes for patients with glaucoma.

The clinical significance of this trial is substantial. Progressive ECL after GDD implantation is a major cause of corneal decompensation, which can lead to vision loss and the need for corneal transplantation. Identifying a surgical approach that reduces ECL while maintaining effective IOP control would directly improve long-term patient outcomes. If CS tube placement demonstrates superior corneal protection without compromising IOP, these findings could influence routine surgical practice, particularly in patients at higher risk for corneal disease. Given the increasing use of GDD surgery and prior evidence that many glaucoma specialists would change practice based on high-quality randomized data, DECLARE has strong potential to be practice-changing.

A key strength of this trial is its comprehensive and multimodal approach. In addition to standard clinical outcomes, DECLARE integrates high-resolution AS-OCT to quantify tube position and its relationship to the cornea and iris over time. This allows evaluation of how tube location and positioning contribute to ECL. Furthermore, the incorporation of metagenomic RNA sequencing represents a novel and innovative aspect of the study. This approach enables unbiased, transcriptome-wide profiling of aqueous humor to characterize molecular changes in the AC microenvironment after GDD implantation. Such data may reveal subclinical inflammatory or biological pathways associated with tube location, particularly in the context of potential chronic iris–tube interaction. Together, these structural, clinical, and molecular data provide a unique opportunity to better understand both outcomes and mechanisms.

Several limitations should be considered. First, due to the nature of surgical interventions, masking of surgeons and certain imaging personnel is not feasible, although outcome assessors and data analysts are masked to minimize bias. Second, the use of multiple GDD types may introduce heterogeneity; however, this reflects real-world practice and enhances generalizability. Third, a 24-month follow-up period may be insufficient to fully capture long-term ECL and late complications, although extended follow-up is planned and participants will form a well-characterized longitudinal cohort.

Despite these limitations, the study is designed to maximize generalizability. The inclusion of both

pseudophakic and combined phacoemulsification cases, a range of glaucoma diagnoses, and multiple commonly used GDD devices reflects routine clinical practice across diverse settings. This broad applicability increases the likelihood that findings will be relevant to both academic and community ophthalmology.

Overall, this NIH-funded DECLARE study is positioned to have meaningful clinical and scientific impact. The results may inform surgical technique, guide training of glaucoma surgeons, and guide device selection and tube placement strategies. In addition, the findings could contribute to the development of clinical guidelines and stimulate future research on long-term outcomes and molecular mechanisms after GDD implantation. By addressing a common yet understudied surgical question with rigorous methodology, this trial has the potential to advance both the science and practice of glaucoma care.

Trial status

The trial started enrollment in July 2023 and is expected to finish enrollment by September 2026. The current protocol is version 5.

Abbreviations

AC	ANTERIOR CHAMBER
AE	Adverse Event
AGV	Ahmed Glaucoma Valve
AS-OCT	Anterior Segment Optical Coherence Tomography
BGI	Baerveldt Glaucoma Implant
BCVA	Best Correct Visual Acuity
CCC	Clinical Coordinating Center
CS	Ciliary Sulcus
DCC	Data Coordinating Center
DECLARE	Glaucoma Drainage Device and Endothelial Cell Loss Compare Trial
DSMC	Data Safety and Monitoring Committee
ECD	Endothelial Cell Density
ECL	Endothelial Cell Loss
GDD	Glaucoma Drainage Device
IOP	Intraocular Pressure
IRB	Institutional Review Board
MDS	Metagenomic RNA Deep Sequencing
MOP	Manual of Operations and Procedures
NEI	National Eye Institute
NIH	National Institutes of Health
NSAE	Non-Serious Adverse Event
PI	Principal Investigator
POM	Postoperative Month
RCT	Randomized Clinical Trial
REDCAP	Research Electronic Data Capture System
SAE	Serious Adverse Event
SD	Standard Deviation
UCSF	University of California, San Francisco
UPENN	University of Pennsylvania

Declarations

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Clinical Coordinating Center (UCSF): Ying Han, Ethan Liang, Jenny Lu, Patrick Takla, Ashika Kuchhangi, Mariko Costantini, Sean Yonamine, Aishwarya Vadivel, Lily Wang, Xinyi Xu, Yuan Zhao, Can Zhao, Huiying Zhang, Yang Zhang, Nicole Mercho, Eric Ricker, Jennifer Currier, Tiffany Chen.

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Data Coordinating Center, University of Pennsylvania: Gui-Shuang Ying, Erin Prachar, Kathy McWilliams, Yinxi Yu, James Dattilo, Kehinde Oguntunde

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All individuals listed have contributed to the conduct of the study and have provided permission to be acknowledged.

Authors' contributions {3a}

YH and JRN are co-first authors. YH is the Chief Investigator and corresponding author; she conceived the study, led the proposal and protocol development, and oversaw overall study design and implementation. JRN and GSY co-led the study design and contributed substantially to protocol development. GSY is the lead trial statistician; he designed the statistical analysis plan.

SJG, IIA, YCH, SS, PR, TC, and RB contributed to study design, clinical protocol development, and implementation across participating sites. TD contributed to the design of molecular analyses and RNA sequencing components. JL and EP contributed to protocol development, study coordination, and operational planning.

All authors contributed to drafting and revising the manuscript, read and approved the final version, and agree to be accountable for all aspects of the work.

Authorship for future trial publications will be determined according to standard ICMJE guidelines and study group publication policies.

No artificial intelligence technologies were used in the design or conduct of the trial; their use in manuscript preparation is limited to language editing support.

Sources of funding and other support {7a}

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Availability of data and materials {6}

De-identified participant-level data and statistical code may be shared with qualified researchers upon request, subject to institutional policies, data use agreements, and applicable regulations. Results will also be reported in public trial registries in accordance with regulatory requirements.

Ethics approval and consent to participate {30}

UCSF Institutional Review Board 21-33490. Written, informed consent to participate will be obtained from all participants.

Consent for publication

Not applicable.

Competing interests {7b}

Ike Ahmed has served as a consultant for manufacturers of glaucoma drainage devices (New World Medical and Johnson & Johnson). This relationship has been disclosed and managed in accordance with institutional policies. All other authors report no conflicts of interest.

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