BMJ Open Ophthalmology

Descemet Endothelial Thickness Comparison Trial 1 (DETECT 1): outcome masked, placebo-controlled trial comparing two types of corneal transplant surgeries and effect of rho kinase inhibitors on endothelial cell loss protocol

Winston Chamberlain,[1] Charles C Lin,[2] Jennifer Y Li,[3] William Gensheimer,[4] Jameson Clover ,[5] Bennie H Jeng,[6] Nicole Varnado,[2] Sarah Abdelrahman,[7] Benjamin F Arnold,[7] Thomas M Lietman,[7] Jennifer Rose-Nussbaumer [2,7]

To cite: Chamberlain W, Lin CC, Li JY, *et al*. Descemet Endothelial Thickness Comparison Trial 1 (DETECT 1): outcome masked, placebo-controlled trial comparing two types of corneal transplant surgeries and effect of rho kinase inhibitors on endothelial cell loss protocol. *BMJ Open Ophthalmology* 2024;**9**:e001454. doi:10.1136/bmjophth-2023-001454

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjophth-2023-001454).

Received 13 August 2023
Accepted 31 December 2023

For numbered affiliations see end of article.

Correspondence to
Dr Jennifer Rose-Nussbaumer; rosej@stanford.edu

ABSTRACT

Background It remains uncertain which endothelial keratoplasty (EK) technique yields the best outcomes while maintaining safety, particularly in eyes with coexisting ocular conditions. Moreover, the impact of endothelial cell loss (ECL) on long-term graft survival requires further investigation. Adjuvant ripasudil, a rho kinase inhibitor, may address the challenge of ECL in corneal transplantation. This paper presents the protocol for the Descemet Endothelial Thickness Comparison Trial 1 (DETECT 1), a multicentre, outcome-masked, randomised, placebo-controlled, four-arm clinical trial.

Methods A total of 160 eligible patients with endothelial dysfunction will be enrolled from five participating sites in the USA. The patients will be randomly assigned in a 2×2 factorial design to one of the following treatment groups: group 1—ultrathin Descemet stripping endothelial keratoplasty (UT-DSAEK) plus topical ripasudil 0.4%; group 2—UT-DSAEK plus topical placebo; group 3—Descemet membrane endothelial keratoplasty (DMEK) plus topical ripasudil 0.4% and group 4—DMEK plus topical placebo. Primary outcomes include the best spectacle-corrected visual acuity at 12 months and ECL at 12 months. Secondary outcomes include visual acuity at different time points, vision-related quality of life, endothelial cell morphology and cost-effectiveness.

Results The study outcomes will be analysed using mixed effects linear regression models, taking into account the treatment arms and relevant covariates. Adverse events, including rebubble procedures, graft failure and graft rejection, will be documented and analysed using appropriate statistical methods.

Conclusion DETECT I aims to provide evidence on the comparative effectiveness of UT-DSAEK and DMEK, as well as the potential benefits of adjuvant topical ripasudil in reducing ECL. The results of this trial will contribute to optimising corneal transplantation techniques and improving long-term graft survival, while also exploring the cost-effectiveness of these interventions. Dissemination of findings through peer-reviewed publications and national/international meetings will facilitate knowledge translation and guide clinical practice in the field of corneal transplantation.

Ethics and dissemination A data and safety monitoring committee (DSMC) has been empaneled by the NEI.All study protocols will be subject to review and approval by WCG IRB as the single IRB of record.This study will comply with the National Institute of Health (NIH) Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although Descemet membrane endothelial keratoplasty (DMEK) may have better visual outcomes, it may have higher complication rates. Adjunctive ripasudil may address the biggest challenge facing corneal transplant surgeons today, protection against endothelial cell loss perioperatively and long-term maintenance of endothelial cell health.

WHAT THIS STUDY ADDS

⇒ Here, we describe an National Institute of Health funded, multicentre, outcome-masked clinical trial in 2×2 factorial design randomising patients to (1) DMEK versus ultrathin Descemet stripping endothelial keratoplasty and (2) adjuvant topical ripasudil 0.4% vs placebo.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This should clarify differences in outcomes between these surgeries in moderate to severe Fuchs patients and those with endothelial dysfunction in the setting of more complex eye disease as well as the role of ripasudil among such patients.

Registration and Results Information Submission rule. Data from the trial will be made available on reasonable request.

BACKGROUND

The field of corneal transplantation is evolving rapidly with few rigorous studies to guide the implementation of novel surgical techniques and medical therapies.[1 2] According to the Eye Bank Association of America, selective endothelial transplantation accounted for approximately 65% of all corneal transplants performed in the USA in 2022.[3 4] Posterior lamellar keratoplasty, which replaces only the posterior cornea including the diseased endothelium and Descemet membrane (DM), has led to faster recovery, fewer complications and better visual acuity outcomes compared with traditional penetrating keratoplasty (PKP).[5]

It is currently unknown which endothelial keratoplasty (EK) technique results in the best outcomes while maintaining an optimal safety profile, particularly in eyes with comorbid ocular conditions such as glaucoma. Descemet membrane endothelial keratoplasty (DMEK), which replaces only DM and endothelium, has the potential to improve visual acuity compared with Descemet stripping endothelial keratoplasty (DSAEK), but is more technically challenging.[6] Descemet Endothelial Thickness Comparison Trial-Therapeutic Exploratory Study (DETECT-TES) was an outcome-masked, two-surgeon TES that randomised patients with primary endothelial disease to Ultrathin (UT)-DSAEK (donor grafts 70–90 µm thick) versus DMEK and found that DMEK had 1.4 lines better visual acuity at 12 months (95% CI 2.2 to 0.1; p<0.001).[7] However, two other similar small studies were unable to detect a difference between DMEK and either UT-DSAEK or Nanothin-DSAEK (donor grafts less than or equal to 50 µm thick).[8–10]

Additionally, DMEK may have higher complication rates, such as primary graft failure.[11 12] DETECT-TES noted more rapid decline in central endothelial cell densities (ECDs) over time compared with UT-DSAEK although this was not statistically significant (12 months: UT-DSAEK, 2070±292 cells/mm^2; DMEK, 1855 ± 448 cells/mm^2 (p=0.051)). The long-term implications of endothelial cell loss (ECL) on graft survival are important, especially if visual acuity in the UT-DSAEK group is similar and warrants further investigation.

Although corneal transplantation has improved over time, it still carries a risk of vision threatening complications such as endophthalmitis, graft rejection and endothelial failure, making medical therapy an attractive alternative. The topically administered rho kinase (ROCK) inhibitor, ripasudil, has been shown to protect against apoptosis and promote endothelial cell proliferation in vitro and in a human ex vivo mode.[13–15] One randomised controlled trial (RCT) has demonstrated improved recovery of corneal clarity in Fuchs endothelial corneal dystrophy after Descemet stripping only with adjuvant topical ripasudil.[16 17] A small series of pseudophakic/aphakic corneal oedema patients achieved complete corneal clearing after cultured donor endothelial cells supplemented with ripasudil were injected into the anterior chamber.[18] Therefore, adjuvant ripasudil may address the biggest challenge facing corneal transplant surgeons today, protection against ECL perioperatively and long-term maintenance of endothelial cell health. Here, we propose a multicentre, outcome-masked clinical trial in a 2×2 factorial design, randomising patients with ECL from a variety of causes including pseudophakic bullous keratopathy, glaucoma surgery and moderate to severe Fuchs endothelial dystrophy to (1) DMEK versus UT-DSAEK and (2) adjuvant topical ripasudil 0.4% vs placebo.

METHODS

Study design

The DETECT 1 is a multicentre outcome-masked, randomised, placebo-controlled, four-arm clinical trial (figure 1, full protocol available as online supplemental file 1). The purpose of this study is to determine differences in visual outcomes between two types of corneal transplant surgeries, UT-DSAEK and DMEK, and to determine the effect of rho-kinase inhibitors on ECL. Patients (N=160) presenting to Oregon Health & Science University (OHSU), Stanford University, University of Pennsylvania, University of California Davis (UCD) or to Dartmouth-Hitchcock Medical Center with isolated endothelial dysfunction who are good candidates for both types of EK performed in this study will be eligible for inclusion.

Those who consent to participate will be randomised to one of four treatment groups in a 2×2 factorial design:

- Group 1: UT-DSAEK plus topical ripasudil 0.4%.
- Group 2: UT-DSAEK plus topical placebo.
- Group 3: DMEK plus topical ripasudil 0.4%.
- Group 4: DMEK plus topical placebo.

Objective and hypothesis

The objectives of this study are (1) to determine whether DMEK or UT-DSAEK has superior postoperative best spectacle-corrected visual acuity (BSCVA) at 12 months and (2) to determine the benefit of adjuvant rho kinases inhibitors ECL in patients who received UT-DSAEK and DMEK. We anticipate that DMEK will have improved visual acuity compared with UT-DSAEK at all time points. We hypothesise that ECL will be higher after DMEK than UT-DSAEK.

Study oversight

A data and safety monitoring committee (DSMC) has been empaneled by the NEI. This committee consists of five individuals and includes (a) cornea specialists, (b) an independent biostatistician, (c) a bioethicist and (d) representation from participating sites. The committee will meet in person at least once per year and will convene biannual teleconferences for progress reports. Ad hoc meetings as needed may also be convened. All study protocols will be subject to review and approval by

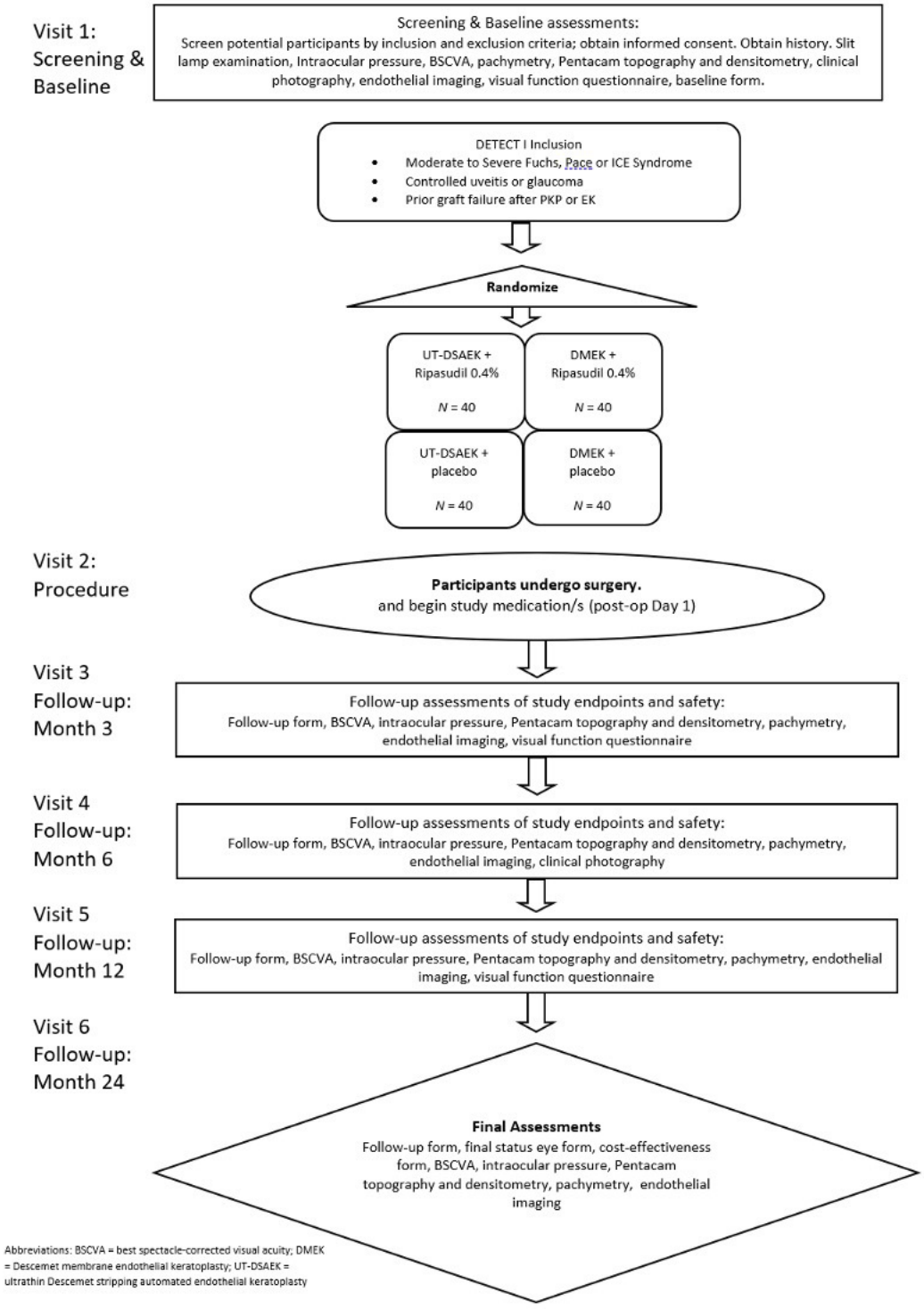

Figure 1 Schema of the Descemet Endothelial Thickness Comparison Trial. DETECT 1, Descemet Endothelial Thickness Comparison Trial 1; EK, endothelial keratoplasty; ICE, iridocorneal endothelial syndrome; PKP, penetrating keratoplasty.

WG IRB as the single IRB of record. Study investigators will conduct site visits at least biannually. The principal investigators notify the DSMC, study sites and institutional review boards of any changes to study protocols or any deviations from the trial protocols. Interim reports for the DSMC will be prepared by the data coordinating centre at the F.I. Proctor Foundation (Proctor) at UCSF. These reports will include (a) recruitment overall and by study site, (b) compliance and (c) retention. The reports will also list study outcomes, and all adverse outcomes, including medication side effects, primary graft failure, graft rejection and mortality. The DSMC will determine the database closure dates for each report in advance; archival copies of the (a) main database and (b) study analysis files as they exist at the time of each report will be maintained. All reports will be sent using secure

email to the members of the DSMC 2 weeks prior to each meeting.

Setting

Participants will be enrolled at five sites in the USA: OHSU, Stanford University, University of Pennsylvania (Penn), UCD and at Dartmouth-Hitchcock Medical Center. Participating surgeons were very experienced in both DMEK and DSAEK procedures and performing these procedures on a regular basis. Surgeries could also be performed by Cornea Fellows who were being directly supervised by the attending physician. VisionGift in Portland Oregon will supply all of the tissue for OHSU, Stanford, Penn and Dartmouth. Sierra Donor Services will supply tissue for UCD.

Eligibility

Inclusion criteria for this study include (1) being a good candidate for either surgery, (2) having dysfunctional endothelium from Fuchs endothelial corneal dystrophy with guttata extending beyond 4.5 mm of the corneal or severe oedema without visualisation of guttata, or pseudophakic corneal oedema, iridocorneal endothelial syndrome, or other primary endothelial dysfunction, or a dysfunctional endothelium from prior graft failure after PKP or EK, (3) having controlled or no uveitis, (4) having medically and/or surgically controlled glaucoma and (5) being age eighteen years or older.

Patients will be excluded if they have any of the following (1) aphakia, (2) have anterior chamber intraocular lens (IOL) or scleral-fixated IOL in study eye prior to or anticipated during EK, (3) have peripheral anterior synechiae involving more than 3 clock hours, (4) have preoperative central subepithelial or stromal scarring that is visually significant, (5) have visually significant optic nerve or macular severe pathology, (6) have hypotony (intraocular pressure<10 mm Hg) or (7) have hypotony (intraocular pressure <10 mm Hg) or (8) the fellow eye visual acuity is worse than 20/200. The investigator will confirm their ability to understand the study and willingness to participate.

Randomisation

Once an eye is enrolled in the study, the study site coordinator will assign the study participant's eye an ID (alpha-numeric code). Each study eye is randomly assigned to the treatment group by the eye bank 1–3 weeks prior to surgery. Block randomisation will be performed using a computer program (Statistical package R; V.3.6; R Foundation for Statistical Computing, Vienna, Austria) by the data coordinating centre. Prior to surgery, the eye bank will assign the study participant corneal tissue, which will be randomised using the Microsoft Excel RANDBETWEEN formula. Once the corneal tissue has been assigned, the eye bank will look at the treatment assignment regarding surgical treatment and prepare the tissue accordingly. Once the study eye has been assigned a study participant ID and randomised to a treatment group, they will be included in the intention-to-treat analysis.

Intervention

Study participants will undergo surgery that will take approximately 1–2 hours. For patients undergoing UT-DSAEK, tissue grafts will be cut to the right thickness using a microkeratome prepared at the eye bank per standard eye bank protocol (about 60–90 µm thick) and will be punched in the operating room to a diameter of 7.0–7.5 by the surgeon. A 4 mm corneal incision will be used, with either the Endoserter or sheets glide as the means of inserting the graft. For DMEK, endothelial grafts will be prepeeled at the eye bank, prepunched to 7.0–7.5 mm and preloaded at the eye bank. The endothelium will be stained with trypan blue. The recipient DM will be stripped to 7.0–7.5 mm. A 2.4 mm corneal incision will be used, and the graft will be inserted with a modified Jones tube injector, micro-Jones tube injector, LEITR glass cannula, micro-Stephens glass cannula or Geuder cannula. The tap technique will be used to position the graft.

All patients will be randomised to receive either topical Ripasudil 0.4% or topical placebo. Patients randomised to receive topical ripasudil will begin medication on postoperative day 1. They will take this medication four times per day for 3 months. For participants randomised to placebo, they will receive topical placebo in place of topical ripasudil. The placebo will be sodium chloride 0.9%. Those randomised to placebo will receive the topical placebo on the same medication schedule described for ripasudil.

Masking

All study participants will be masked to their intervention. The refractionist performing the BSCVA will also be masked. Due to the nature of the intervention, the surgeon and technician performing study visit ECD and other imaging will not be masked as to surgery type (but will be masked as to study medication); however, the image graders at the Proctor Reading Centre and CIARC will be masked. All study medications and placebo will be labelled identically to ensure adequate masking of study physicians and patients.

Data collection and management

Data collection is the responsibility of the clinical trial staff of each site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data reported. Table 1 outlines the schedule of enrolment, interventions and assessments.

Clinical data (including adverse events, concomitant medications and expected adverse reactions data) and clinical laboratory data will be entered into Research Electronic Data Capture (REDCap), a 21 CFR Part 11-compliant data capture system provided by the data coordinating centre at the University of California, San

Table 1 Enrolment procedures for the Descemet Endothelial Thickness Comparison Trial

Procedures	Screening pre-enrolment	Enrolment/ baseline, visit 1 day 0	Procedure, visit 2 day 5 (±14 days)	Follow-up, visit 3 month 3 (±1 month)	Follow-up, visit 4 month 6 (±1 month)	Follow-up, visit 5 month 12 (±2 months)	Final follow-up, visit 6 month 24 (±4 months)
Review inclusion/ exclusion criteria	X						
Informed consent		X					
Demographics		X					
Medical history		X					
Randomisation			X*				
Administer study intervention			X				
Slit lamp examination		X		X	X	X	X
Intraocular pressure		X		X	X	X	X
Pachymetry		X		X	X	X	X
Pentacam topography and densitometry		X		X	X	X	X
Endothelial imaging	X	X		X	X	X	X
Clinical photography†		X			X		
BSCVA/ETDRS/MRx		X		X	X	X	X
Baseline form		X					
Follow-up form				X	X	X	X
Final form							X‡
Visual function questionnaire		X		X		X	
Cost-effectiveness form							X
Interval history				X	X	X	X

*Randomisation performed approximately 1 week prior to surgery.
†Clinical photography also taken on adverse event.
‡If participant does not complete the study, final form will be filled out at time of withdrawal or loss to follow-up.
BSCVA, best spectacle-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; MRx, manifest refraction.

Francisco, USA. These data will be kept confidential. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete or inaccurate.

Primary outcome and statistical analyses

For this factorial design trial, there is a primary outcome for each of the factors. The primary outcome for surgery type will be the 12-month BSCVA measured in logMAR. For patients with irregular astigmatism at enrollment, the primary outcome measurement will be better of BSCVA or Hard contact lens (HCL) over-refraction at 12 months. We will use a mixed effects linear regression model to evaluate BSCVA measured at 12 months with fixed effects for surgical treatment arm (expressed as a binary indicator variable for UT-DSAEK vs DMEK), drug treatment arm (expressed as a binary indicator variable for ripasudil vs placebo), study site (used to stratify surgery treatment) and baseline BSCVA.

The second primary outcome is ECL at 12 months. We will use a mixed effects linear regression model to assess 12-month ECD with fixed effects for adjuvant treatment arm (expressed as a binary indicator variable for adjuvant ripasudil vs placebo), surgery (expressed as a binary variable for UT-DSAEK vs DMEK) and study site (used to stratify surgery treatment). We will perform subgroup analyses evaluating the effect of surgery and ripasudil on BSCVA of those with visually significant comorbidities at baseline versus those without them. We will perform subgroup analyses on the effect of surgery and ripasudil on those with surgical vs medically controlled glaucoma.

Secondary outcomes and statistical analyses

Visual acuity for ripasudil versus placebo, ECL for UT-DSAEK versus DMEK

As secondary endpoints in the factorial analysis, we will estimate the difference in 12-month BSCVA between eyes that receive ripasudil versus placebo, and the difference

in ECL by 12 months between eyes that receive UT-DSAEK versus DMEK.

Visual acuity at other points

We will estimate the effect of treatments on BSCVA at 3, 6 and 24 months following the primary analysis approach but repeated at the additional time points.

We will use best of BSCVA and HCL over-refraction.

Vision-related quality of life

FQ will be compared between groups using the National Eye Institute Vision-Function Questionnaire 25 at 3 and 12 months controlling for 1-day VFQ. This will be conducted using linear regression with baseline and assignment variables.

Endothelial cell morphology

We will use methods similar to the primary analysis for ECL to study the impact of ripasudil on the endothelial cell morphology by comparing the coefficient of variation of cell size and per cent hexagonal cell shape at the 3-month time point while still on ripasudil as well as at 6, 12 and 24 months after cessation of the study drug.

ECD at other points

We will estimate the effect of ripasudil on ECL at 3, 6 and 24 months following the primary analysis approach but repeated at the additional time points.

Pentacam Scheimpflug tomography

A rotating Scheimpflug camera, which provides three dimensional images of the cornea. In addition to topographic maps with keratometric readings of the anterior and posterior cornea, Pentacam reports on the total corneal power, corneal thickness maps, higher order aberrations and densitometry. Statistical analysis will be the same as the primary analysis, linear mixed effects regression using treatment assignment and baseline values as covariates, using the same template as we did for BSCVA.

Cost-effectiveness analysis

A supplementary analysis will use individual-level cost outcomes as well as individual-level health outcomes. We propose to report standard cost-effectiveness acceptability curves based on bootstrap resampling at the individual level from both control and intervention subjects (for a statistical, clinical-trial based, cost-effectiveness analysis from a healthcare system perspective). The outcome variable will be cost per line of vision gained.

Adverse events

All adverse events, including the number of rebubble procedures, secondary endothelial procedures, graft failure and graft rejection will be tabulated and reported. We will use the Corneal Preservation Time Study classification for graft failure and graft rejection. Statistical comparisons will be conducted using Fisher's exact test, but with the caution that failure to find evidence of a difference cannot be used to infer a lack of risk difference for rare outcomes such as primary graft failure since the study is not powered to examine these.

Interim analysis

Interim reports for the DSMC will be prepared by the data coordinating centre. These reports will include (a) recruitment overall, and by study site, (b) compliance and (c) retention. The reports will also list study outcomes, and all adverse outcomes, including medication side effects, primary graft failure, graft rejection and mortality. The DSMC will determine the database closure dates for each report in advance; archival copies of the (a) main database and (b) study analysis files as they exist at the time of each report will be maintained. All reports will be sent using secure email to the members of the DSMC 2 weeks prior to each meeting.

Sample size

We will power the study for each comparison. Given BSCVA and ECL are different, non-correlated outcomes (R=0.08 in the DETECT pilot study) with different randomisation, each will have its own alpha of 0.05. We informed the sample size calculation using measurements from the DETECT pilot study.[1] We sized the trial to have sufficient power to detect small, clinically meaningful effects for both primary outcomes (BSCVA, ECL).

For visual acuity, we estimated that the SD of BSCVA at 12 months was 0.163 and correlation between baseline and 12-month BSCVA was 0.428, leading to an adjusted SD of ⟦SD⟧∧*=SD√(1 r∧2) = 0.147.[2] Since we anticipate slightly higher variability in BSCVA in more complex eyes enrolled in DETECT I, we conservatively assumed SD equal to 0.2. Using a standard sample size equation for a t-test of two independent means, we estimate that 80 eyes per group will provide 90% power to detect a difference of 0.11 logMAR (approximately 1.1 Snellen lines) with a two-tailed alpha of 5% and allowing for 10% loss to follow-up. With 80% power and the same assumptions, the minimum detectable difference is 0.09 logMAR.

For ECL, we estimated the SD of ECL in the DETECT pilot as 0.134. Using a standard sample size for a t-test of two independent means, we estimate that 80 eyes per group will provide 90% power to detect a 7% difference in ECL with a two-tailed alpha of 5% and allowing for 10% loss to follow-up. If we assume a larger outcome SD for more complex eyes (SD=0.18), we will have >90% power to detect a 10% difference in ECL.

Dissemination plan

This study will comply with the National Institute of Health (NIH) Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial is registered at ClinicalTrials.gov, and the results from this trial will be submitted and published on ClinicalTrials.gov. In addition, every attempt will be made to publish results

in peer-reviewed journals and to present these data at national and international meetings. Consistent with the collaborative nature of the proposed research, the principal investigator anticipates sharing all data generated by the study with collaborators. Analytical data sets that will be developed through the project will comply with the NIH Data Sharing Policy. The analytical data sets from this project will include patient-level data generated from the study visits. Data from the trial will be made available on reasonable request.

DISCUSSION

DETECT I, the multicentre RCT described in this paper, aims to address several important knowledge gaps in the field of corneal transplantation. The trial will provide valuable insights into the comparative effectiveness of UT-DSAEK and DMEK in patients with ocular comorbidities such as glaucoma in terms of visual outcomes, ECL and other secondary outcomes. Additionally, it will investigate the potential benefits of adjuvant topical ripasudil in reducing ECL and improving graft survival. The findings from DETECT I will help optimise surgical techniques and refine treatment strategies, ultimately leading to improved outcomes for patients undergoing corneal transplantation.

The number of DMEK procedures performed each year in the US has increased dramatically in recent years. According to the Eye Bank Association of America, DMEK accounted for less than 15% of endothelial keratoplasties in the US in 2015, whereas DSAEK accounted for approximately 50% of all corneal transplants. In 2017, the number of DMEK surgeries increased to 26% of all endothelial keratoplasties and in 2018 DMEK surgeries increased by another 41%.[19] The increase is likely due to a combination of factors including the results of DETECT-TES and other studies, as well as improvements in eye bank prepared tissue (prestripped, prepunched, preloaded), and standardisation of surgical techniques.[12 20] The DETECT-TES evaluated DMEK and UT-DSAEK in eyes with isolated endothelial disease and demonstrated superior visual acuity outcomes for DMEK compared with UT-DSAEK up to 2 years after transplant. However, it is important to note that the study had some limitations, including its generalisability to most corneal specialists and the lack of power to detect differences in secondary outcomes such as rebubble rate, primary graft failure and changes in ECDs.

One of the key concerns in corneal transplantation is ECL, as it can lead to graft failure, imposing a significant burden on patients and society. Previous studies, including the Cornea Donor Study, have highlighted the substantial ECL observed in PKP and DSAEK. The aetiology of ECL is multifactorial, involving surgical trauma and immune-mediated mechanisms. Understanding the patterns and consequences of ECL in different transplantation techniques is essential to protect the donor pool and improve long-term graft survival.

In this context, the potential role of adjuvant rho kinase inhibitors, such as ripasudil, in corneal transplantation is intriguing. Ripasudil has been shown to promote endothelial cell proliferation, inhibit apoptosis and protect against endothelial cell damage in preclinical models and small clinical trials. The selective inhibition of ROCK signalling by ripasudil may offer a promising approach to mitigate ECL and enhance long-term graft survival. However, further research is needed to evaluate the efficacy and safety of ripasudil in corneal transplantation.

While the DETECT I trial aims to address important knowledge gaps in corneal transplantation, it also has certain limitations that should be acknowledged. The trial's inclusion criteria and specific study population may limit the applicability of the results to a broader population of corneal transplantation recipients. DETECT I trial will not assess outcomes, such as graft survival and complications beyond 2 years. Corneal transplantation outcomes can evolve over time, and longer follow-up periods would provide a more comprehensive understanding of the comparative effectiveness and safety of the interventions. The success of corneal transplantation procedures is highly dependent on the surgical expertise of the operating surgeons. The DETECT 1 trial will involve multiple surgeons from different centres, each with varying levels of experience and skill. Variations in surgical technique and proficiency could introduce variability in outcomes that may not solely reflect the differences between the interventions being compared.

In conclusion, the DETECT I trial is poised to contribute significantly to the knowledge base of corneal transplantation by evaluating the comparative effectiveness of UT-DSAEK and DMEK, as well as investigating the potential role of adjuvant topical ripasudil in reducing ECL. The outcomes of this trial, along with other ongoing studies and advancements in the field, will shape the future of corneal transplantation, enhancing visual outcomes and long-term graft survival while minimising complications.

Trial status

This protocol is version February 2023. Recruitment began in September 2023 and is expected to last until approximately September 2026.

Author affiliations
[1]Oregon Health & Science University, Portland, Oregon, USA
[2]Ophthalmology, Stanford University, Stanford, California, USA
[3]Department of Ophthalmology & Vision Science, University of California Davis, Davis, California, USA
[4]Department of Ophthalmology, Geisel School of Medicine, Dartmouth, Massachusetts, USA
[5]Eye Bank, VisionGift, Portland, Oregon, USA
[6]Department of Ophthalmology, Scheie Eye Institute, Philadelphia, Pennsylvania, USA
[7]F.I. Proctor Foundation at the University of California San Francisco, San Francisco, California, USA

Acknowledgements NIH grant funding and the DSMC committee members—Jimmy Le, Don Everett, Emily Gower, Michael Zegans, Donna Kim, Ella Temprosa, Tony Aldave.

Contributors CCL, WC, BHJ, BFA, TML and JR-N were involved in study design. CCL, WC, BHJ, BFA, JYL, WG, NV, SA and JR-N were involved in study implementation. All authors reviewed and edited the paper.

Funding Below are the details of the funders and grand/award number: US Department of Health and Human Services—UG1 EY028518. National Institute of Health—UG1 EY030417. National Eye Institute—UG1 EY05924477. Research to Prevent Blindness—Internal Stanford University.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by WG IRB Review Solutions. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iDs
Jameson Clover http://orcid.org/0000-0001-9682-4941
Jennifer Rose-Nussbaumer http://orcid.org/0000-0002-4905-2528

REFERENCES

1 America EBAo. Eye banking statistical report 2015; 2016.
2 Gain P, Jullienne R, He Z, *et al*. Global survey of corneal transplantation and eye banking. *JAMA Ophthalmol* 2016;134:167–73.
3 Price FW, Price MO. Evolution of endothelial Keratoplasty. *Cornea* 2013;32 Suppl 1:S28–32.
4 Park CY, Lee JK, Gore PK, *et al*. Keratoplasty in the United States: A 10-year review from 2005 through 2014. *Ophthalmology* 2015;122:2432–42.
5 America EBAo. 2014 eye banking statistical report; 2015.
6 Dickman MM, Kruit PJ, Remeijer L, *et al*. A randomized multicenter clinical trial of Ultrathin Descemet stripping automated endothelial Keratoplasty (DSAEK) versus DSAEK. *Ophthalmology* 2016;123:2276–84.
7 Chamberlain WD, Lin CC, Austin A, *et al*. Descemet endothelial thickness comparison trial: A randomized trial comparing Ultrathin DSAEK to DMEK. *Ophthalmology* 2018.
8 Kurji KH, Cheung AY, Eslani M, *et al*. Comparison of visual acuity outcomes between Nanothin Descemet stripping automated endothelial Keratoplasty and Descemet membrane endothelial Keratoplasty. *Cornea* 2018;37:1226–31.
9 Dickman MM, Suryan D, Robert W, *et al*. Preliminary results of a multicenter randomized clinical trial comparing Descemet membrane endothelial Keratoplasty (DMEK) with Ultrathin Descemet stripping automated endothelial Keratoplasty (UT-DSAEK). ARVO abstract 1576. *Invest Ophthalmol Vis Sci* 2018.
10 Guerra FP, Anshu A, Price MO, *et al*. Descemet's membrane endothelial Keratoplasty: prospective study of 1-year visual outcomes, graft survival, and endothelial cell loss. *Ophthalmology* 2011;118:2368–73.
11 Hamzaoglu EC, Straiko MD, Mayko ZM, *et al*. The first 100 eyes of standardized Descemet stripping automated endothelial Keratoplasty versus standardized Descemet membrane endothelial Keratoplasty. *Ophthalmology* 2015;122:2193–9.
12 Okumura N, Koizumi N, Kay EP, *et al*. The ROCK inhibitor eye drop accelerates corneal Endothelium wound healing. *Invest Ophthalmol Vis Sci* 2013;54:2493.
13 Okumura N, Koizumi N, Ueno M, *et al*. ROCK inhibitor converts corneal endothelial cells into a phenotype capable of regenerating in vivo endothelial tissue. *Am J Pathol* 2012;181:268–77.
14 Okumura N, Ueno M, Koizumi N, *et al*. Enhancement on Primate corneal endothelial cell survival in vitro by a ROCK inhibitor. *Invest Ophthalmol Vis Sci* 2009;50:3680.
15 Koizumi N, Okumura N, Ueno M, *et al*. Rho-associated kinase inhibitor eye drop treatment as a possible medical treatment for Fuchs corneal dystrophy. *Cornea* 2013;32:1167–70.
16 Macsai MS, Shiloach M. Use of topical Rho kinase inhibitors in the treatment of Fuchs dystrophy after Descemet stripping only. *Cornea* 2019;38:529–34.
17 Kinoshita S, Koizumi N, Ueno M, *et al*. Injection of cultured cells with a ROCK inhibitor for Bullous keratopathy. *N Engl J Med* 2018;378:995–1003.
18 Ang M, Wilkins MR, Mehta JS, *et al*. Descemet membrane endothelial Keratoplasty. *Br J Ophthalmol* 2016;100:15–21.
19 Chen ES, Terry MA, Shamie N, *et al*. Descemet-stripping automated endothelial Keratoplasty: six-month results in a prospective study of 100 eyes. *Cornea* 2008;27:514–20.
20 Ham L, Dapena I, van Luijk C, *et al*. Descemet membrane endothelial Keratoplasty (DMEK) for Fuchs endothelial dystrophy: review of the first 50 consecutive cases. *Eye (Lond)* 2009;23:1990–8.