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Belgian Endothelial Surgical Transplant of the Cornea (BEST cornea) protocol: clinical and patient-reported outcomes of Ultra-Thin Descemet Stripping Automated Endothelial Keratoplasty (UT-DSAEK) versus Descemet Membrane Endothelial Keratoplasty (DMEK) – a multicentric, randomised, parallel group pragmatic trial in corneal endothelial decompensation

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ABSTRACT

Objectives Corneal blindness is the third most frequent cause of blindness globally. Damage to the corneal endothelium is a leading indication for corneal transplantation, which is typically performed by lamellar endothelial keratoplasty. There are two conventional surgical techniques: Ultra-Thin Descemet Stripping Automated Endothelial Keratoplasty (UT-DSAEK) and Descemet Membrane Endothelial Keratoplasty (DMEK). The purpose of this study is to compare both techniques.

Methods and analysis The trial compares UT-DSAEK and DMEK in terms of clinical and patient reported outcomes using a pragmatic, parallel, multicentric, randomised controlled trial with 1:1 allocation with a sample size of 220 participants across 11 surgical centres. The primary outcome is the change in best-corrected visual acuity at 12 months. Secondary outcomes include corrected and uncorrected vision, refraction, proportion of high vision, quality of life (EQ-5D-5L and VFQ25), endothelial cell counts and corneal thickness at 3, 6 and 12 months follow-up appointments. Adverse events will also be compared 12 months postoperatively.

Ethics and dissemination The protocol was reviewed by ethical committees of 11 participating centres with the sponsor centre issuing the final definitive approval. The results will be disseminated at clinical conferences, by patient partner groups and open access in peer-reviewed journals.

Governance of the trial Both, trial management group and trial steering committee, are installed with representatives of all stakeholders involved including surgeons, corneal bankers, patients and external experts.

Trial registration number NCT05436665.

INTRODUCTION

Corneal transplantation is the oldest, and most frequent, form of grafting in the world. It is indicated when the cornea becomes too opaque or painful to function. When grafting is not available, the disease can progress resulting in painful blindness. Over the past 20 years, the main area of innovation in corneal transplantation has been partial thickness 'lamellar' grafting where only a thin layer of donor tissue is needed to treat endothelial disease.[1 2] Diseases of the corneal endothelium account for approximately 60% of corneal transplantations in Europe

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The Belgian Endothelial Surgical Transplant Cornea study is a pragmatic clinical trial using standardised, data-driven surgical protocols with robust data collection, monitoring and safety reporting built by a consortium of corneal surgeons, patient participants, external experts and corneal banks
- ⇒ The aim of this study is to compare Descemet Membrane Endothelial Keratoplasty with Ultra-Thin Descemet Stripping Automated Endothelial Keratoplasty using wide inclusion criteria, over a large surgical consortium to determine which is the most appropriate surgical approach.
- ⇒ The two types of cornea grafts are prepared using standardised techniques, respectively, in two corneal banks each subspecialised, to reduce preparation variability.
- ⇒ Due to the surgical nature of the intervention, the treating surgeons cannot be blinded to the treatment allocation but a dedicated independent assessor blind to the intervention will perform the visual tests in each centre.

and the USA.[3 4] The majority of cases, however, can be attributed to two diseases: namely, Fuchs endothelial corneal dystrophy (FECD) and bullous keratopathy (BK) currently account for approximately 80% and 20% of endothelium transplantations, respectively.[4]

Lamellar transplantation of the corneal endothelium is known as endothelial keratoplasty (EK) and is minimally invasive, safer and has a faster visual recovery than the traditional penetrating keratoplasty.[5] Two types of surgery have emerged in the past decade as the treatments of choice, Ultra-Thin Descemet Stripping Automated Endothelial Keratoplasty (UT-DSAEK) and Descemet Membrane Endothelial Keratoplasty (DMEK). In the older approach, DSAEK, the donor endothelium is transplanted with a layer of supportive donor stroma, whereas in DMEK only the single layer of endothelium, supported by its basement membrane (the Descemet membrane), is transplanted.[6] Studies comparing DSAEK and DMEK suggest that DMEK is superior to traditional DSAEK in terms of visual outcomes,[6–10] though the DSAEK technique has improved since by the development of UT preparation methods resulting in UT-DSAEK which provides better results than the standard.[11 12]

Which technique is the best remains hotly debated and there is a paucity of data on the basis of which to make a judgement; the most recent Cochrane review in this area concluded that more randomised controlled trails (RCTs) were needed.[13] Proponents of DMEK report better outcomes and faster recovery with lower rejection rates, while supporters of UT-DSAEK claim similar outcomes but with lower levels of reintervention (rebubble).[14 15] Three RCTs have been reported to date,[16–18] two indicating that DMEK provides superior clinical outcomes with the third finding no significant difference. All three were small studies that almost exclusively included FECD patients, with fewer than 30 patients per arm. Moreover, in these studies, patient reported quality of life outcome measures did not indicate any significant difference between the treatments.[19]

From previous research an improvement of best-corrected visual acuity (BCVA) of 0.2 logarithm of the minimum angle of resolution (logMAR) calculated from a smaller RCT resulted in an Incremental cost-effectiveness ratio (ICER) of €2253 per patient in the base case over a time horizon of 12 months.[20] In another study by the same group, DSAEK showed that the ICER calculated per patient with clinical improvement together with quality of life assessment (measured by Visual Function Questionnaire 25 (VFQ25)) resulted in an ICER of €9057. This study indicated that UT-DSAEK was overall more cost-effective as it incurred fewer rebubbling procedures and other reinterventions.[21] To date, ICER data have not been reported for DMEK/DSAEK using the EuroQol-5D-5L (EQ-5D-5L). This will be possible on the conclusion of this trial. We aim to evaluate this trial similarly, with the addition of a wider range of corneal pathologies and the inclusion of the EQ-5D-5L. These analyses will be performed in collaboration with the funders (KCE) to determine the cost-effectiveness arguments for DMEK and DSAEK from the point of view of the healthcare payer (RIZIV/INAMI).

The aim of this study is to compare DMEK with UT-DSAEK using wide inclusion criteria, over a large surgical consortium to determine which is the most appropriate surgical approach. Additional benefits would also include modernising the corneal banks, reducing the number of corneal donations lost by surgeon preparation, reducing numbers of cancelled surgeries due to graft damage, improving the cell quality of a corneal graft (and thereby its longevity), improving operating room efficiency and possibly reducing the rates of graft rejection. Centralising graft preparation in the bank would also allow corneal banks to generate more granular data about Belgian corneal transplantations. One final benefit would be in the training of surgeons to adopt the most appropriate technique, one which will reduce duplication of learning curves and improve the quality and safety of corneal surgery in Belgium and internationally.

METHODS AND ANALYSIS

Objective

This clinical study is designed as a multicentric, randomised, parallel group, pragmatic trial to compare the clinical and patient-reported outcomes of UT-DSAEK with DMEK in corneal endothelial decompensation. The 11 participating surgical centres are located across Belgium with the sponsor co-ordination centre located at Antwerp University Hospital. The primary objective is to report the change in BCVA, compared with baseline, at 12 months after UT-DSAEK and DMEK. The secondary outcomes consist of examining the changes in BCVA at 3 and 6 months, uncorrected visual acuity (UCVA), refractive outcomes, proportion of high vision (patients achieving 0.2 LogMAR or better), quality of life using the EQ-5D-5L and VFQ 25 instruments, endothelial cell

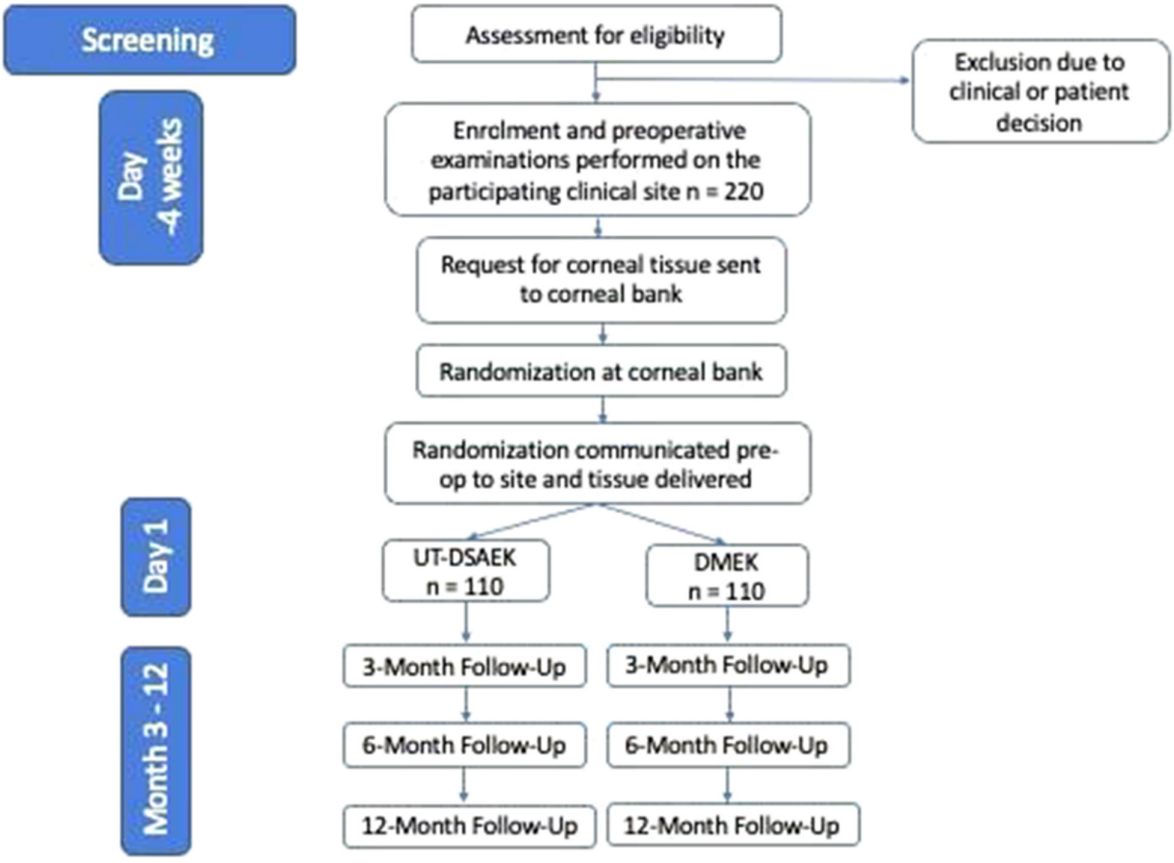

Figure 1 Flow chart overview of the best cornea study. DMEK, descemet membrane endothelial keratoplasty; UT-DSAEK, ultra-thin descemet stripping automated endothelial keratoplasty.

counts (ECCs), central corneal thickness and rate of complications between UT-DSAEK and DMEK.

Trial design

The trial is designed as a pragmatic, parallel, RCT with 1:1 allocation between the UT-DSAEK and DMEK groups. Once a patient is assessed for eligibility, provides informed consent, and is enrolled, data will be recorded in the primary source documents and the coded data will be recorded in the study software Research Electronic Data Capture (REDCap). REDCap is a secure, web-based software platform designed to support data capture for research studies.[22] A flow chart of the trial design is provided in figure 1. The protocol was prepared by a collaborative consortium that included surgeons, corneal bank personnel, patients, patient advocacy groups, the funder and international experts.

Recruitment

Patients will be recruited by the participating centres from patients awaiting surgery on the existing surgical waiting lists or new referrals (figure 2). There is a backlog of patients eligible for inclusion in the study awaiting corneal grafts (estimated to be over 400 patients awaiting treatment on the waiting lists of the consortium's surgeons). The trial considers the waiting lists for patients as there can be no expectation of expedited treatment due to trial participation and recruiting only new patients would delay the trial, complicate logistics and deprive the waiting patients of the chance of participation.

Existing waiting list pathway

Patients waiting who are deemed eligible by their treating physicians may be contacted by telephone. If they wish to participate, then they must have a preoperative evaluation within 3 months of the day of surgery. If the preoperative evaluation is longer than 3 months before the day of planned surgery, another appointment is required.

New referral pathway

Once the patient has been formally diagnosed with an endothelial pathology and has decided to proceed with EK, they will be given the option to discuss the trial further. If the patient wishes to take part in the trial, then they will be consented, and the additional trial baseline questionnaires will be performed.

Screening failures (ie, patients who do not meet eligibility criteria at time of screening) may be eligible for rescreening after a period of 6 weeks, for example, when cataract surgery still has to be performed.

Inclusion criteria

The aim is to adopt a pragmatic approach to include as many causes of endothelial disease as possible. The criteria are as follows:

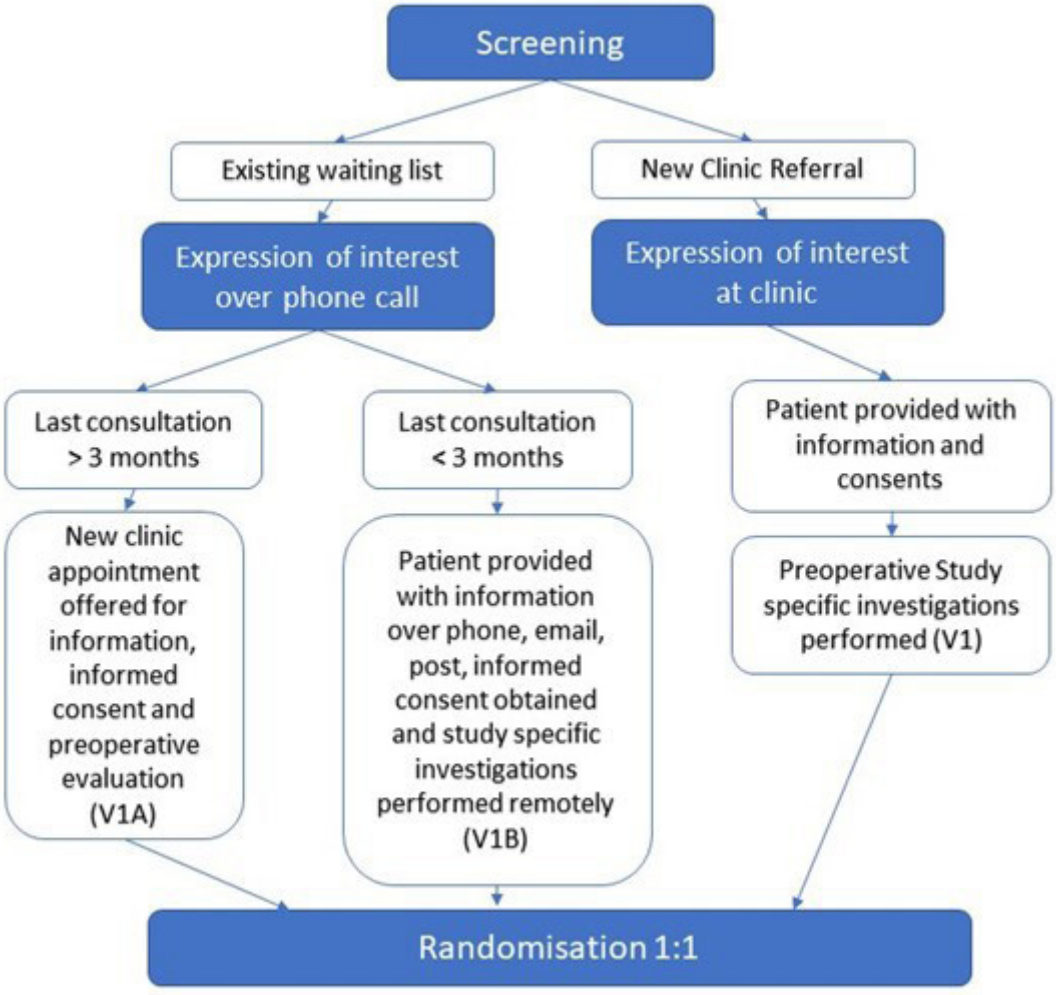

Figure 2 Overview of the screening and recruitment pathways.

Disease-related criteria which require at least one of the following to be present: (1) FECD, (2), BK and (3) other causes of endothelial dysfunction. In addition to one of these diagnoses, the following inclusion criteria are mandatory: (4) All patients must be pseudophakic for at least 6 weeks (post cataract surgery); (5) Prior iridotomy must have been performed at the time of inclusion; (6) Age over 18 years with the capacity to read and to understand the study information and to give informed consent, as well as complete study quality of life questionnaires and (7) The willingness and capacity to attend the 3, 6 and 12 months follow-up appointments.

Exclusion criteria

Exclusion criteria focus on keratoplasties that are technically different from the standard UT-DSAEK/DMEK (ie, sutured grafts) or those combined with a surgery that is highly likely to influence the outcome (ie, combined with tube-based glaucoma surgery). The criteria are as follows: (1) Inability to provide informed consent or are unable to attend the proposed follow-up; (2) Complex surgery combined with multiple pathologies (ie, advanced glaucoma tube surgery); (3) Other contraindications to lamellar corneas surgery; (4) Patients who are currently pregnant or breastfeeding and (5) Inclusion of the fellow eye in the study previously.

Randomisation and blinding

Once the inclusion data are entered by a member of the study personnel into the trial software, randomisation with minimisation (Qminim) will take place with an equal 1:1 allocation to UT-DSAEK or DMEK using the following stratification factors: (1) surgical indication (ie, FECD and non-FECD); (2) surgical site, (3) preoperative visual acuity (patients with 0.6 LogMAR BCVA or lower (ie, better vision) and patients with LogMAR BCVA higher than 0.6 LogMAR (ie, worse vision).

The trial participants will be blinded to the intervention until the end of the trial, unless deemed medically necessary. The surgeons will not be blinded but all outcome assessments that can be influenced (BCVA, UCVA, refraction, surveys) will be measured by assessors blinded to the intervention. The treating surgeon is explicitly not permitted to perform these postoperative examinations. All electronic patient records refer to the intervention in the generic term—either EK, lamellar keratoplasty or similar so that patients cannot be inadvertently unblinded. The intervention will still be recorded in the

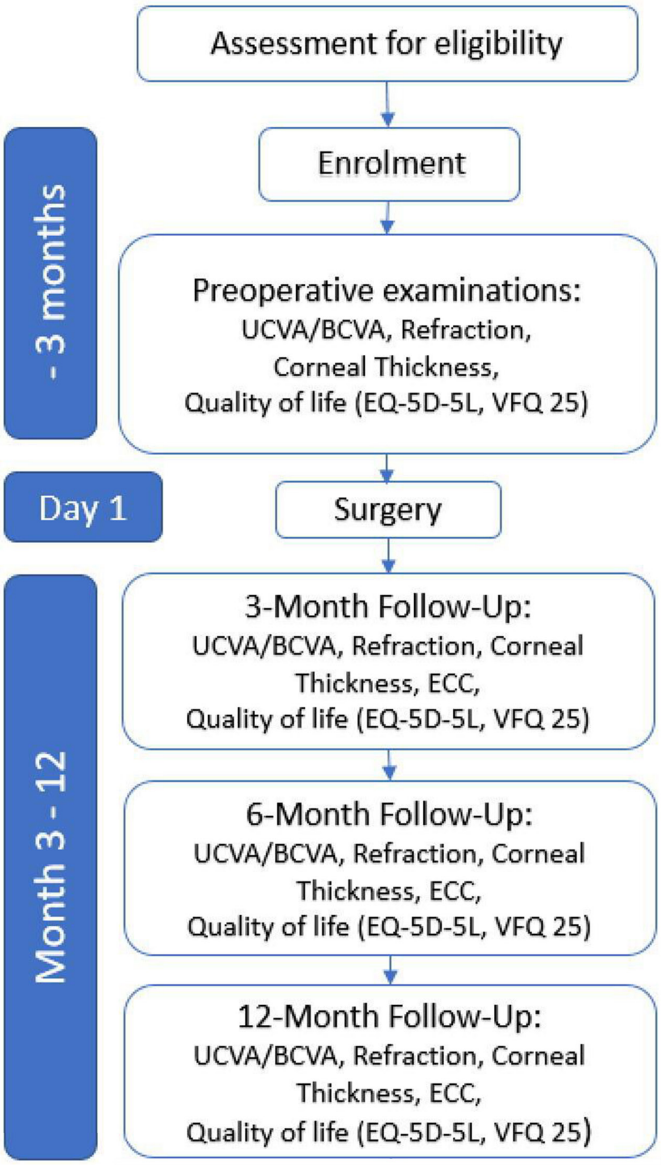

Figure 3 Patient participation pathway. BCVA, best-corrected visual acuity; ECC, endothelial cell count; UCVA, uncorrected visual acuity; EQ-5D-5L, EuroQol-5D-5L; VFQ25, Visual Function Questionnaire 25

patients operating report, but this may not be accessed by the blinded assessors.

Interventions

An overview of the patient pathway is provided in figure 3 and the study calendar is provided in table 1.

Preoperative examinations

UCVA and BCVA will be recorded using standard, in clinic, visual acuity assessment methods. The results will be expressed and analysed in LogMAR. Refraction will be measured in standard format, where the spherical and cylindrical corrections are given, together with the axis of the cylinder. Central corneal thickness will be measured by standard pachymetric methods and expressed in micrometre as obtained by any of the following technologies: Scheimpflug pachymetry or anterior segment optical coherence tomography (AS OCT). The quality of life questionnaires used are the EQ-5D-5L and the VFQ25 instruments which will be administered on a tablet device or paper and are linked to the study electronic case report forms (eCRFs).

Cornea bank preparations

All corneas for the study will be prepared by accredited corneal banks and will meet the quality control parameters for corneal transplantation defined by the Belgian regulatory authority (FAMPH/FAGG). All UT-DSAEK grafts are prepared in advance, in a laminar flow chamber, by the cornea bank technicians of the University Hospital of Liege. Briefly, a donor cornea is placed on an artificial chamber and measured using a portable downward scanning OCT device (Optovue, Visionix, Normandy, France). An automated keratome system coupled to a pressure regulator (Moria Surgical, Ile-de-France) is used to cut the cornea to a thickness equal or less than 110 µm as determined by anterior segment OCT. If the cut is above this thickness, a second cut is performed to achieve the required thickness. The cornea is then transferred to culture medium for transport. Similarly, all DMEK grafts are prepared in advance, in a laminar flow chamber, by the corneal technicians of the University Hospital of Antwerp. The donor cornea is placed endothelium up on a corneal support. The standardised 'no-touch' technique is used to loosen the trabecular meshwork, to gently peel the endothelium.[23] Once the endothelium is peeled, the graft is transferred to a contact lens and trephine to the desired diameter. The roll is then transferred to organ culture medium for transport.

Surgical interventions

Either surgery may be performed under local or general anaesthesia based on the appropriateness and preferences of patient and surgeon. Small technical differences might occur between the surgeons regarding specific brands of instruments and the surgeon's own preferences. These differences will, however, be recorded during the data entry on the day of surgery into the eCRF. We standardise using an air tamponade because gas is, according to a data registry from the Netherlands, associated with poorer outcomes.[24]

Ultra-Thin Descemet Stripping Automated Endothelial Keratoplasty

The main incision (3.5–4.75 mm) is created at the corneal limbus or via a cornea-scleral tunnel with 2–3 smaller (approx. 1 mm) paracentesis incisions. An ophthalmic viscosurgical device (OVD), air bubble or a continuous infusion of water or air can be used to maintain the stability of the anterior chamber, according to the surgeon's preference. The corneal endothelium is scored using a scoring instrument and the central diseased corneal endothelium is removed. After Descemet stripping, the OVD or air needs to be removed, and the eye is

Table 1 Study Calendar showing the trial procedures

Belgian endothelial surgical transplant of the cornea study calendar							
All study patients (UT-DSAEK and DMEK) follow the same calendar							
Study visits	**V1**	**V1A**	**V1B**	**V2**	**V3**	**V4**	**V5**
Visit type timing of visit	Screening/inclusion Up to 3 months prior to day of surgery			Day 0	Postoperative 3 months Month 3	Postoperative 6 months Month 6	Postoperative 12 months Month 12
Eligibility screening	x	x	x				
Discussion of surgery	**x**	**x**	**x**				
Informed consent	x	x	x				
Randomisation	x*	x*	x*				
Baseline characteristics	x	x	x				
Surgery				**x**			
Surgeon questionnaire				x			
UCVA	**x**	x	**x**		**x**	**x**	**x**
BCVA	**x**	x	**x**		**x**	**x**	**x**
Subjective refraction	**x**	x	**x**		**x**	**x**	**x**
Central corneal thickness	**x**	x	**x**		**x**	**x**	**x**
EQ-5D-5L questionnaire	x	x	x		x	x	x
VFQ 25 questionnaire	x	x	x		x	x	x
Endothelial cell count					**x**	**x**	**x**
Adverse events					Continuous reporting		

x in bold refers to standard of care and is not considered as specifically associated with the study.
V2 is highlighted in blue as this is day 0, the day of the surgery.
*Randomisation to the DSAEK/DMEK group is performed after the patient is included and then relayed to the corneal bank.
BCVA, best-corrected visual acuity; DMEK, descemet membrane endothelial keratoplasty; UCVA, uncorrected visual acuity; UT-DSAEK, ultra-thin descemet stripping automated endothelial keratoplasty.

ready for the new corneal graft. The precut corneal tissue delivered by the bank is then gently rinsed and may be stained with 0.06% trypan blue if required. The tissue is loaded into a glide or injector and pulled into the anterior chamber using a smooth-tipped microforceps (eg, Busin forceps). Once the graft enters the eye, it is lifted to the posterior cornea by an air. The graft is further centred using external instrument stroking movements and held in place by air in the anterior chamber for a period of a minimum of 10 min. The air pressure is then slightly reduced, and the case is completed by suturing any incisions required.

Descemet Membrane Endothelial Keratoplasty

The main incision (2.8–3 mm) is created superior or temporally at the corneal limbus and is accompanied by 2–3 smaller (approx. 1 mm) paracentesis incisions. An OVD, air bubble or a continuous infusion of water or air can be used to maintain the stability of the anterior chamber, according to the surgeon's preference. The corneal endothelium is scored using a scoring instrument and the central diseased corneal endothelium is removed. After Descemet stripping, the OVD or air needs to be removed; then the eye is ready for the new corneal graft. The DMEK roll is poured into a basin and rinsed. The graft is then stained with 0.06% trypan blue per surgeon's own protocol to aid in graft visualisation. The graft is then loaded into an injector and introduced into the anterior chamber. The orientation of the graft is confirmed by S stamp preparation or by either the Moutsouris sign or OCT augmented Moutsouris sign. The graft is unrolled using external manoeuvres and once unrolled, it is lifted to the back of the cornea by an air. The eye is then pressurised with a full air fill for a period of a minimum of 10 min. The pressure is then reduced, and the case is completed by suturing any incisions if required.

Postoperative follow-up

Basic surgical descriptive baseline data (eg, date of interventions) plus any adverse events (AEs) will be recorded into the eCRF. A questionnaire regarding possible sources of surgical difficulty and AEs will be recorded as well (online supplemental appendix). Deviations from the descriptions provided will be recorded in the eCRF as protocol deviations.[25]

The patient is required to strictly lie supine for a period of 2 hours. After this strict period, it is further recommended that the patient remain supine for a period of 48 hours with reasonable short breaks to eat or take restroom breaks. This supine period can take place at home. The immediate follow-up appointments for clinical examinations are, as per standard of care, at the discretion of the surgical site's treating physician. The postoperative medication protocol is as shown in the table 2. In the event of

Table 2 BEST Cornea proposed postoperative eye-drop protocol

BEST cornea postoperative eye-drop protocol							
All study patients (UT-DSAEK and DMEK) follow the same calendar							
Medication	**Recommended dosing scheme**						**Duration**
Combination of 2 medications together or apart (Dexamethasone 0.1%+ antibiotic, eg, chloramphenicol or tobramycin) non-steroidal anti-inflammatory drug	08:00	12:00	16:00	18:00	20:00	22:00	Postoperative weeks 1–4
	08:00	12:00	16:00		20:00		Postoperative weeks 1–4
Topical dexamethasone 0.1%	08:00	12:00	16:00	18:00	20:00		Postoperative month 2
Topical dexamethasone 0.1%	08:00		16:00	18:00	20:00		Postoperative month 3
Topical dexamethasone 0.1%	08:00		16:00		20:00		Postoperative month 4
Topical dexamethasone 0.1%	08:00				20:00		Postoperative month 5
Topical dexamethasone 0.1%	08:00						Postoperative month 6
After 6-month of treatment convert to topical fluorometholone 0.1% (FML)							
Fluorometholone 0.1%	08:00		16:00		20:00		Postoperative month 7–8
Fluorometholone 0.1%	08:00				20:00		Postoperative weeks 9–10
Fluorometholone 0.1%	08:00						Postoperative weeks 11–12
After 12 months, long-term therapy with fluorometholone 0.1% (FML) once a day is recommended but is the decision of patient/physician							

The 6 month and 12 month post-operative period are highlighted in blue as important landmarks in the post-operative medication protocol.
BEST, belgian endothelial surgical transplant; DMEK, descemet membrane endothelial keratoplasty; UT-DSAEK, ultra-thin descemet stripping automated endothelial keratoplasty.

a drop intolerance or allergy to the medication defined in the study protocol, substitutions can be made. However, such substitutions should be justified and reported to the study team. At 3, 6 and 12 months UCVA/BCVA, refraction, central corneal thickness, quality of life questionnaires and ECCs will be repeated.

Primary outcome

This study's primary outcome is the change in BCVA, represented in LogMAR units, compared with baseline at 12 months after UT-DSAEK and DMEK.

Secondary outcomes

Vision-related secondary outcomes consist of change in BCVA at 3 and 6 months. In addition, UCVA, refraction and proportion of patients to achieve 0.2 LogMAR visual acuity or less (ie, better vision) at 3, 6 and 12 months between UT-DSAEK and DMEK will be examined. Quality of life-related secondary outcomes consist of change in quality of life will be determined by the EQ-5D-5L questionnaire instrument, change in vision-related quality of life will be determined by the VFQ 25 item questionnaire instrument at 3, 6 and 12 months between UT-DSAEK and DMEK.

Measurements of the cornea consist of ECC, change in central corneal thickness from baseline (pachymetry) between UT-DSAEK and DMEK at 3, 6 and 12 months. Finally, the remaining secondary outcomes consist of an analysis of complications and AEs including primary graft failure between UT-DSAEK and DMEK.

Safety and AEs

While both EK techniques are considerably safer than traditional corneal transplantation (penetrating keratoplasty) techniques, there remains some risks associated with the intervention. The safety data from 34 DSAEK peer-reviewed published articles of sufficient quality were reviewed and reported by the American Academy of Ophthalmology in 2009.[26] DMEK underwent similar review and reporting of safety and outcomes in 2018.[27] The expected AEs associated with the techniques are similar in both DSAEK and DMEK and are as follows:

- Graft dislocation 8%–20% (AE).
- Primary graft failure 1%–2% (AE).
- Iatrogenic glaucoma 3%–10% (AE).
- Cystoid macular oedema 2%–13% (AE).
- Endothelial rejection 0%–3% (AE).
- Infectious endophthalmitis <0.5% (serious AE, SAE).
- Suprachoroidal haemorrhage <0.1% (SAE).

While both techniques are in routine clinical use, it is possible that SAEs (may occur related to the intervention that have not yet been described. For all safety findings, the trial specific AE eCRF will be used and these will be evaluated for duration and intensity, according to the National Cancer Institute Common Terminology Criteria for Adverse Events V.5.0.

Patient and public involvement

The largest non-profit advocacy group for the blind in Belgium, the Brailleliga/Ligue Braille (www.braille.be) and Licht en Liefde have participated in the creation

of this protocol, particularly regarding patient usability in the survey interface, the burden of the trial protocol and the integration of refraction into routine assessments. They have both also nominated a member to contribute to the trial further by participating in the trial steering committee (TSC). They are also very active in the ophthalmological societies and general public with regular publications of brochures and magazines. They will be able to help disseminate the results of the study to both the sighted and the visually impaired population.

In addition to the assistance of the patient groups, we have received the feedback of patients who have already undergone corneal transplantation for endothelial disease. These patients assisted us in designing the protocol and testing it with respect to how difficult and cumbersome excessive trial visits can be for the visually impaired. Two of the advising patients have volunteered to participate in the TSC for further input into the trial, one to represent the French language patients and one to represent the Dutch language patients, the two main languages spoken in Belgium.

Sample size

The primary outcome is the change in BCVA at 12 months, compared with baseline measured in basic decimal Snellen and recorded in LogMAR units. Dunker *et al* reported an improvement of 0.16 logMAR with UT-DSAEK and 0.29 in DMEK, with a variability of 0.20.[28] Given that we are using a pragmatic approach of including all endothelial decompensations, we expect to have a more heterogeneous population and testing centres, we anticipate a larger variability and, therefore, we assume a SD of 0.25. According to Rosser *et al*, a difference of 0.1 logMAR or 1 line is considered clinically relevant.[29] Therefore, we have powered the study around the difference of 0.1 LogMAR. Sample size calculation in PASS 11 for an independent t-test, revealed that we need to include at least 105 participants per group in order to have 80% power to detect a difference of 0.1 with an SD of 0.25 (effect size 0.4) at a two-sided significance level of 0.05. Anticipating a conservative dropout rate of 5%, 110 patients per arm, or 220 patients in total, will be included. As no drop-outs were reported in the previous trials, we expect less than 5% drop-out.[16 28]

Statistical analysis

Baseline measurements include: demographic characteristics (age, gender, a history of diabetes), clinical baseline characteristics (surgical indication, vision at baseline: BCVA, UCVA, refraction), corneal thickness, ECC, quality of life at baseline (vision-related QoL (VFQ 25) and EQ-5D-5L), donor characteristics (age, gender, previous history of diabetes). Continuous variables will be summarised by mean and SD when normally distributed. For variables where the normality assumption is not appropriate, median and quartiles will be reported. Categorical variables will be presented with number and percentages.

A consort flow diagram will be produced to get an overview of the number of patients available at each stage: enrolment, randomisation, discontinuation and follow-up.

Primary outcome analysis

In first instance, BCVA at 12 months will be compared between the DMEK and UT-DSAEK using a linear regression model with treatment as a predictor and correction for baseline BCVA. The analysis will be based on the intention-to-treat population. All randomised patients will be included in the analysis, regardless of subsequent surgery or graft failure.

Secondary outcome analysis

Sensitivity analysis for primary endpoint: an analysis in terms of change from baseline, might be influenced by the fact that there is more room for improvement in patients with a worse vision, so we will include a comparison of BCVA at 12 months, while ignoring the baseline BCVA.

Additionally, a sensitivity analysis will be performed, carrying forward the last BCVA observation before reintervention for patients with primary failure. Change from baseline BCVA, UCVA, refraction, corneal thickness and ECC will be reported for 3, 6 and 12 months in both intervention arms. A linear mixed model using all BCVA observations at 3, 6 and 12 months with subject as random effect and time, group and interaction over time as fixed effects will improve the precision on the estimated treatment effect and give more insight in the evolution of BCVA after surgery. Time will be considered categorical, allowing for a different pace in improvement between different time points. This model will be expanded by including the centre as a random effect and possible confounders (surgical indication, age, gender, diabetes) will be added to the model as fixed effects. This model will be evaluated with and without baseline BCVA as a covariate. Post hoc comparisons will be performed, to further gain insight into the evolution of the BCVA after both interventions, thereby correcting for multiple comparisons using step-down Bonferroni-Holm correction.

Similarly, a linear mixed effects model will be built for UCVA, refraction, corneal thickness and ECC, incorporating the measurements at 3, 6 and 12 months.

The proportion of patients that reach a certain level of visual acuity will be reported per intervention arm. Logistic regression with BCVA greater than 0.2 LogMAR as outcome and intervention as predictor with and without correction for BCVA at baseline will be applied. ORs and 95% CI will be reported.

Quality of life: vision-related quality of life, EQ-5D-5L, will be compared at 12 months by independent t-test. The evolution of these outcomes over time will be studied in a linear mixed effects model, thereby correcting for the baseline measurement.

The number of patients with any complication will be recorded per treatment, rates and 95% CI will be reported.

Comparisons between both arms will be done using χ^2 test or Fisher's exact if numbers are low. Relative risk and 95% CIs will be reported. Additionally, logistic regression models will be fitted, to correct for confounders such as age, gender and surgical indication. Primary failure rates will be reported per intervention arm.

ETHICS AND DISSEMINATION

The protocol and trial will be conducted in compliance with the Belgian law of 7 May 2004, regarding experiments on the human person and any relevant amendments. The protocol conforms to both the principles of Good Clinical Practice as laid down by the Commission Directive 2005/28/EC and Declaration of Helsinki and was reviewed by the ethical boards of the 11 participating sites. Final central ethical approval was obtained by the coordinating ethics board of the Antwerp University Hospital (BUN B3002022000021) and the trial has been registered on ClinicalTrials.gov (NCT 05436665). Any changes in the protocol will be reviewed by the ethical boards and communicated to the participants.

Trial findings will be disseminated in a one-page summary to all potential beneficiaries of the research including patients, carers and relatives, as well as doctors, advisory bodies and healthcare commissioners. This will take the form of papers in high impact, open access peer-reviewed medical journals as well as presentations at national and international medical conferences.

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