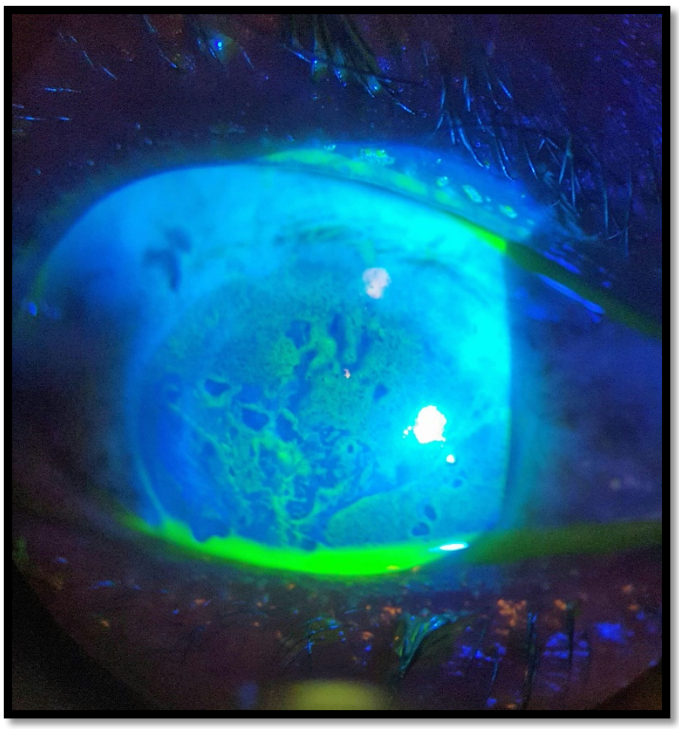
MMed(Ophthalmology) study proposal

Epithelial debridement: Is it an effective intervention to decrease ocular discomfort in patients suffering from bullous keratopathy?



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Study location: Groote Schuur hospital eye clinic, Western Cape, South Africa.

Contents

1. Introduction

Bullous keratopathy occurs when the cornea loses the ability to maintain a relatively dehydrated state.[1] Subsequently, the cornea swells with fluid and blisters form on the surface of the eye. This results in significant pain and loss of vision. It is the main indication for corneal transplantation worldwide.[2]

Unfortunately, in resource-poor settings such as ours corneal transplants are not readily available. For those patients who are able to access corneal transplant services, waiting lists are long.[34]

The debilitating discomfort associated with the condition needs to be addressed while patients are awaiting transplant.[5] Medical treatment may be of use in early disease.[6] Advanced disease often requires surgical intervention. Numerous palliative surgical treatment methods have been described, but none of them is ideal. They are often ineffective, destructive, expensive or unavailable in resource-poor settings.

Epithelial debridement is a simple side room procedure which has been used safely and effectively in the treatment of recurrent corneal erosion[7] and as part of corneal crosslinking in the treatment of keratoconus.[8] There is a well-defined gap in literature regarding the management of BK using epithelial debridement. The main aim of this research study will be to evaluate the safety and efficacy of epithelial debridement in the reduction of ocular discomfort from bullous keratopathy.

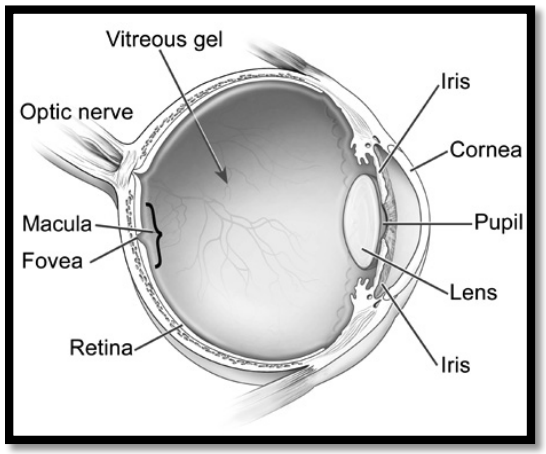


Figure 1: Anatomy of the eye

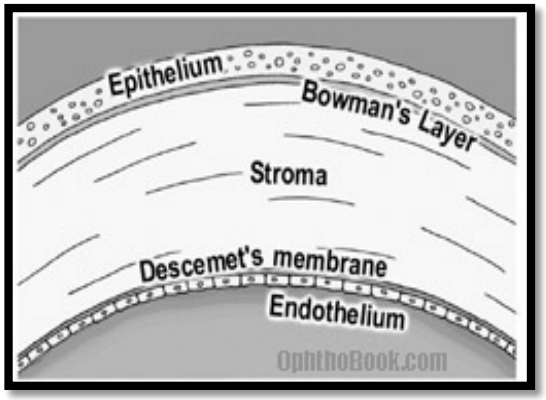


Figure 1: Layers of the cornea

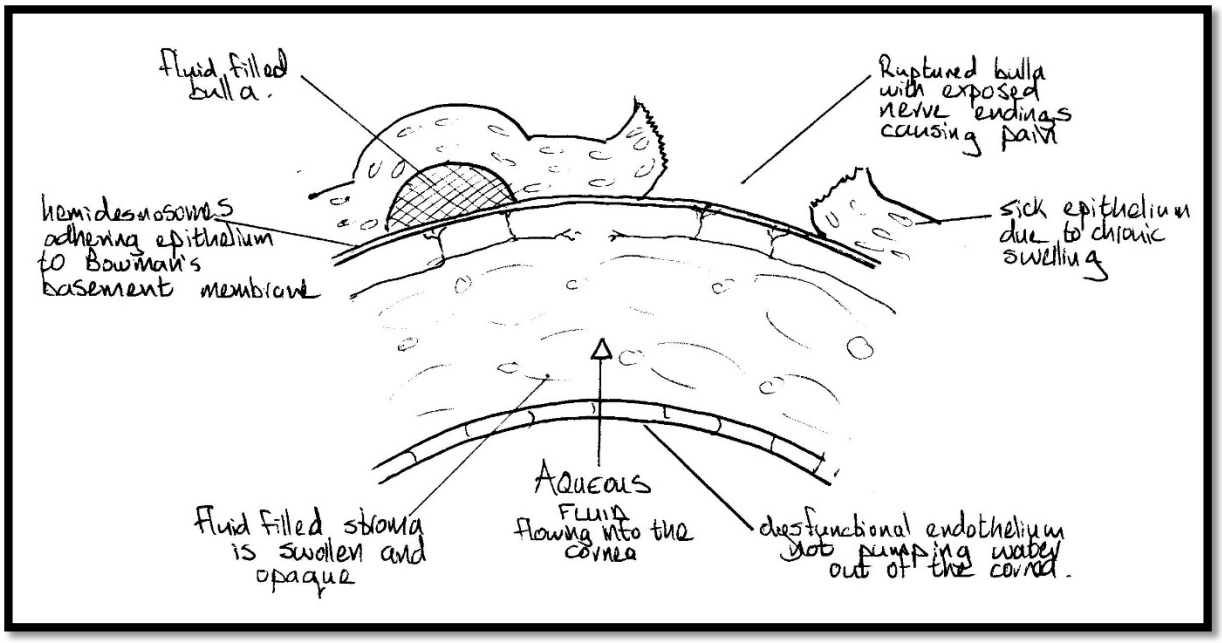


Figure 2: Bullous keratopathy

2. Hypothesis

- Epithelial debridement (ED) alone may be a safe and effective treatment for patients with painful bullous keratopathy.

3. Purpose of this study

3.1 Primary aims

- To evaluate the safety and efficacy of ED in the management of discomfort in patients suffering from symptomatic bullous keratopathy.
- To evaluate the effect of ED on visual acuity, number of corneal bullae and central corneal thickness.

3.2 Secondary aims

- To compare the findings of this study with those of previous studies done on other available surgical options.

4. Background information

4.1 Bullous keratopathy

- Bullous keratopathy (BK) is a visually disabling and painful condition caused by corneal endothelial pump function failure.[1] The main causes are:
    - Pseudophakic BK (following cataract surgery)
    - Fuch's endothelial dystrophy (where the corneal endothelium is intrinsically predisposed to failure)
    - Corneal graft failure (following corneal transplant)

- The ensuing corneal swelling results in sub-epithelial fluid collection with the formation of blisters (bullae). These bullae cause ocular irritation and often rupture, resulting in pain due to the exposure of the underlying nerve endings.[2] Chronic BK results in sub-epithelial fibrosis.[9] BK is the most common indication for keratoplasty as well as for re-grafting.[2]

4.2 Demographics

- The Groote Schuur eye clinic patient population consists of various ages, races, religions and social classes from around the Western Cape.
- BK is the indication for corneal transplant in about 20-25% of the patients currently on the waiting list at Groote Schuur.

4.3 Treatment options

- The definitive treatment of BK is a corneal transplant to replace the damaged endothelium. Patients in resource-poor settings often do not have transplant services readily available to them and if these services are available, patients may wait many months before receiving their transplant.[34] Topical hypertonic saline and "bandage" silicone contact lenses may be useful to relieve symptoms in early disease.[610] There are also various palliative surgical treatments that have been described to relieve pain.
- Common treatment options include:
    1) Corneal crosslinking (CXL) (Epithelial debridement followed by stromal collagen crosslinking with UVA light and Riboflavin)[4511]
    2) Phototherapeutic keratectomy (PTK) (Debridement of the epithelium and anterior stroma using a laser)[1213]
    3) Manual or laser anterior stromal puncture (ASP) (Creating punctures in the anterior cornea using a needle or laser)[14 13]
    4) Amniotic membrane transplant (AMT) (An amniotic membrane flap is sutured over the corneal surface)[151617]
- Less common treatment options include:
    1) Corneal surface thermal or laser cautery (Burning of the corneal surface)
    2) Posterior corneal cryopexy (Freezing of the posterior cornea)[14]
    3) Intrastromal silicone oil/hydrogel lens insertion[18]
    4) Autologous perichondrium transplantation[19]
    5) Cultured endothelial cell injection)[3]
    6) Annular keratotomy (Cutting through the peripheral cornea to transect the corneal nerves)
    7) Gunderson flap (GF) (The conjunctival membrane is sutured over the corneal surface)
- All the commonly used treatment modalities aim to reduce the presence of bullae by one of the following mechanisms:
    1) Allowing fresh epithelium to cover the corneal surface (CXL, PTK)
    2) Increasing adhesion between existing epithelium and underlying basement membrane (Bowman's membrane) (ASP)
    3) Covering the bullae with a protective membrane (AMT, GF)

4) Limiting transmission of intraocular fluid to the sub-epithelial space (CXL)

- None of the treatment modalities mentioned have been proven to be ideal. PTK requires an expensive excimer laser. ASP, AMT and conjunctival flap require extensive surgery which may worsen visual acuity and compromise future transplant outcomes. A minimally invasive procedure capable of providing pain relief would represent a major benefit to these patients.[5]
- CXL following ED has been gaining favour as a measure to reduce the presence of bullae. Unfortunately the crosslinking stage of the procedure is resource and labour intensive, may cause permanent anterior stromal haze and has the potential for UV-A damage to occur in the already compromised endothelium.[20]

TABLE 1. Summary of the Results of Clinical Studies on Collagen Crosslinking in Corneal Edema

Study	N	Indication	Type of Study	FU (mos)	Results		
					CCT (µm)	BCVA	Symptomatic Relief
Krueger et al[13]	1	PBK	Prospective	6	Decreased from 675 to 550 at 1 mo	NA	NA
Ehlers and Hjortdal[14]	11	FED (4), PBK (2), failed graft (3), glaucoma (1), traumatic (1)	Prospective	3	Decreased in 10 out of 11 cases	Improved in 3 out of 11 cases	NA
Wollensak et al[9]	3	PBK (1), failed graft (1), FED (1)	Prospective	8	Decreased by 93 ± 14.44 µm after 8 mos	Visual acuity improved	Reduction in pain and discomfort
Gadelha et al[15]	12	PBK	Prospective	2	No significant change	No improvement of vision	Pain relief on visual analog scale from 8.58 ± 1.51 to 4.25 ± 2.99 ($P < 0.001$)
Ghanem et al[11]	14	PBK	Prospective	6	Decreased from 747 to 623 at 1 mo ($P < 0.001$), which increased to 710 at 6 mos ($P = 0.006$)	NA	No significant pain relief after 6 mos of follow-up on the numeric scale
Cordeiro Barbosa et al[16]	25	Cataract surgery (17), graft failure (5), FED (3)	Prospective	3	Decreased from 712.06 ± 99.7 µm to 657.56 ± 114.8 µm	NA	44% Patients remained asymptomatic
This study	50	PBK	Prospective	6	Decreased from 728 ± 78.4 µm to 694.9 ± 77.9 µm at 1 mo ($P = 0.0001$). At 6 mos 695.3 ± 101.0 µm ($P = 0.01$)	Improved from 2.0 ± 0.5 to 1.8 ± 0.5 at 1 mo ($P = 0.001$). At 6 mos it was 1.9 ± 0.5 ($P = 0.99$).	The mean pain score decreased from 8.1 ± 0.6 on visual analog scale to 2.1 ± 0.7 on day 7, progressively increased to 4.8 ± 1.2 at 1 mo and then remained stable

BCVA, best corrected visual acuity; FED, Fuch endothelial dystrophy; FU, follow-up; N, number of cases; NA, not analyzed.

Figure 3: Table 1 from Sharma et al reference 1

4.4 Epithelial debridement

- Recurrent corneal erosions (RCE) is a condition characterised by recurrent episodes of acute ocular pain. This occurs when the epithelium loses its adherence to the basement membrane and comes loose in patches. ED alone, done either manually or using alcohol delamination,[21] has been used safely and effectively in the management of RCE.[7] ED produces fresh epithelium which improves adherence to the underlying basement membrane.[22]

5. Evidence that ED may be an effective treatment option for patients with BK

- The standard Dresden protocol for CXL consists of epithelial debridement followed by stromal crosslinking using Riboflavin and UV-A. The latest and largest CXL study consisting of 50 eyes showed that there was a significant early reduction in corneal bullae and ocular discomfort lasting 3 to 6 months. Sharma comments "…epithelial debridement may itself be causing a temporary effect on corneal thickness and other study variables such as pain score and BCVA.[1] Although CXL has been proven to increase the tensile strength of the cornea[23], this does not fully explain why the epithelium would resist fluid collecting between it and the corneal stroma.
- RCE and BK consist of similar pathology. ED has been shown to be effective in preventing the recurrence of erosions in RCE. I postulate that ED will have a greater effect in BK than in RCE. The leading cause of RCE is basement membrane dystrophy (Abnormally developed basement membrane).[24] After epithelial debridement for RCE the dystrophic basement membrane is still present which predisposes to the recurrence of bullae. In BK, the basement membrane is not dystrophic. The new layer of epithelium should be able to adhere firmly to it, preventing the recurrence of bullae, temporarily at least.
- Anecdotal evidence exists suggests that ED is a useful treatment option to alleviate pain in BK patients with large bullae. This is according to Dr M. Attenborough who is a local prominent, fellowship trained, corneal specialist.

6. Methodology

6.1 Study design

- Prospective non-comparative interventional case series

6.2 Location

- The study will take place at Groote Schuur hospital eye clinic, Western Cape, South Africa.

6.3 Recruitment process

- Consecutive patients presenting to the eye clinic with a diagnosis of bullous keratopathy to be referred to Dr McClunan.
- Examination and recruitment to take place in an eye clinic examination room.
- Patients presenting between 1 March and 30 September 2016 to be recruited.
- Aim for a sample size of at least 20 patients.

6.4 Inclusion and exclusion criteria

6.4.1 Inclusion criteria

- Patients suffering from painful BK
    - Where discomfort is significant enough for the patient to request the ED intervention
    - In patients with bilateral disease ED will be performed on the eye causing the most discomfort.

6.4.2 Exclusion criteria

- Patients who do not meet the criteria for informed consent
- Vulnerable patients such as children, prisoners, pregnant women, intellectually impaired persons, or economically or educationally disadvantaged persons
- Patients with active eye infections: Blepharitis, conjunctivitis, keratitis
- Patients with ocular conditions which will significantly decrease epithelial healing: entropion or ectropion (eyelids turned in or out), corneal pannus[25] (fibrovascular membrane over the cornea), cicatricial (scarring) conjunctivitis, severe dry eye or uncontrolled significantly raised intra-ocular pressure

6.5 Standard of care research procedures

- Visual acuity
- Slit lamp examination with fluorescein staining and intra ocular pressure measurement
- A-scan ultrasound measurement of central corneal thickness

6.6 Additional research procedures

- Pain score
- Anterior segment photography, with both white light and cobalt blue light after fluorescein staining, using a slit lamp-cell phone adapter
- Epithelial debridement following informed consent

6.7 Timing of ED

- ED to be performed on the day of enrolment or at the patient's earliest convenience.

6.8 Data Collection

- To be collected on pro-forma data sheets (Addendum B). Photographs will be taken of each completed data sheet.
- Data to be collected on the date of enrolment and at 1 week, 1 month, 2 months, 3 months and 6 months.
    - The 1 week follow up visit will be used to remove the bandage contact lens inserted post ED and to monitor for signs of infection.

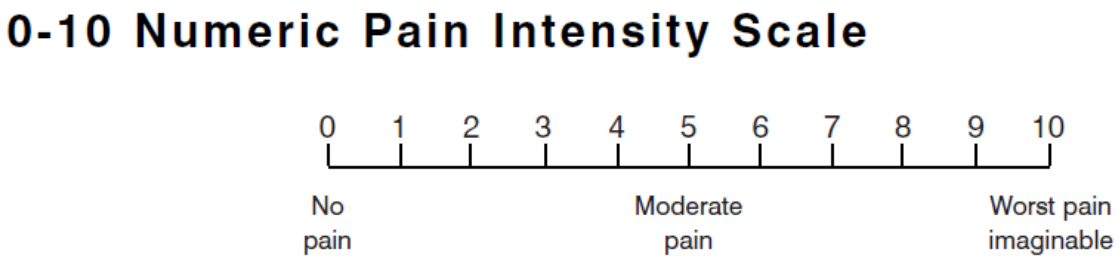
6.9 Parameters used to measure outcome

6.9.1 Pain score

- The 11 item numeric pain rating score (NRS) will be used[26]
    - The NRS for pain is a unidimensional measure of pain intensity in adults
    - Although various iterations exist, the most commonly used is the 11-item NRS
    - A respondent selects a whole number (0–10 integers) that best reflects the intensity of their pain
    - 0 representing one pain extreme (e.g., "no pain") and 10 numeric scale representing the other pain extreme (eg. "pain as bad as you can imagine" and "worst pain imaginable")

- Respondents are asked to report average pain intensity
- The NRS can be administered verbally
- Respondent burden: The pain NRS takes about 1 minute to complete.
- Administrative burden: The pain NRS is easy to administer and score.
- Translations/adaptations. Minimal language translation difficulties support the use of the NRS across cultures and languages.

- For the purpose of this study the NRS will be modified to be an average ocular discomfort rating over the preceeding 48hours. This will include pain as well as other forms of ocular discomfort such as scratching, burning, tearing, foreign body sensation and light sensitivity.



6.9.2 Number of Bullae

- Number of bullae at each follow up will be decided to be less/same/more than before ED by Dr T. Pollock and Prof N. Dutoit by comparing anterior segment photos. They will be blinded as to which photo is from before and after ED.

6.9.3 Visual acuity

- Snellen chart visual acuity with and without pinhole at distance will be recorded.
- A pinhole compensates for any refractive errors present, but may worsen vision in the presence of macular pathology.
- The better of the two documented visions will be used for the purpose of this study.
- The Snellen chart is the most commonly used method for assessing visual acuity.

6.9.4 Central corneal thickness

- A-scan ultrasound pachymetry will be used
- A-scan is the generally accepted method for measuring central corneal thickness and is equivalent to ocular coherence tomography.[4]

6.10 Quality of data

- Only nurses or technicians with ophthalmic training will perform visual acuity testing and central corneal thickness measurement.
- Nurses may be used as interpreters where necessary.
- All other procedures and data collection will be performed by Dr McClunan who has sufficient qualifications and experience.

6.11 Adverse events

- In the case of any adverse events, they will be reported to the Human Research Ethics Committee (HREC).

7. Projected timeline

	2/16	3/16	4/16	5/16	6/16	7/16	8/16	9/16	10/16	11/16	12/16	1/17	2/17	3/17	4/17	5/17
Protocol submission	x															
Ethical clearance		x														
Recruiting + Intervention			x	x	x	x	x	x								
Data collection			x	x	x	x	x	x	x	x	x	x	X	x		
Data analysis													x	X		
Write up														x	x	
Feedback																x
Publication																x

8. Data and statistical analysis

- The expected standard deviation of the mean difference is estimated to be 2.0.
- A change in pain score of 2.0 or more was decided to be statistically significant.
- A sample size of at least 10 patients will then be necessary to demonstrate a significant change in mean pain score with 95% confidence.
- The paired t-test will be used to compare pre and post procedure pain scores at each follow-up visit to determine if there was a significant change in pain score.

9. ED procedure

9.1.1 Examination room - Recruitment

- Inclusion and exclusion criteria assessed
- Informed consent obtained
- Required data captured
- Estimated duration of recruitment process: 20 minutes

9.1.2 Minor procedures room - ED

- Adopted from the Dresden protocol as described by Ramon et al[5]

1) Procedure to be performed explained to the patient

2) 1 drop of 5% Povidone iodine antibacterial solution instilled
3) 1 drop of benoxinate topical anaesthetic solution instilled every minute for 5 minutes. This will achieve corneal anaesthesia and loosen the adhesion of the epithelium from the underlying basement membrane**.
4) Patient cleaned and draped
5) Doctor performing procedure to wear sterile gloves and face mask
6) Eye speculum inserted to hold the eyelids open
7) Conjunctival sac flushed with 5% Povidone iodine
8) Procedure performed using the ophthalmic microscope available in the room
9) 10mm circular trephine centred on the cornea and used to mark the ring of epithelium to be debrided
10) Epithelium debrided using an ophthalmic spoon
11) Weck sel sponge used to clean debris from exposed basement membrane
12) Conjunctival sac flushed with 5% Povidone again
13) Bandage contact lens inserted to promote healing[2728]
14) Speculum and drapes removed
15) Patient given follow-up date in 1 week
16) Patient reminded of RSVP warning signs of infection
17) Prescription for paracetamol 1 gram qid and topical antibiotic ofloxacin drops qid until epithelial closure has occurred. (Thereafter topical steroid / antibiotic combination drop (SpersadexCo) qid will be given for a 2 week period)
18) Estimated duration of procedure: 10 minutes

10. Risks and benefits

10.1 Risks

10.1.1 Physical risk

- Infective keratitis (IK) is the most severe physical risk. The eye will be at increased risk for IK until the new epithelium has grown over completely (+- 1 week). Even so there are only 3 isolated case reports of IK following CXL.[1] Risk will be minimised by following a strict sterile technique, providing prophylactic topical antibiotic drops post-procedure, delaying steroid drop instillation until after the epithelium has grown closed and by advising patients on proper eye hygiene. Patients will be made aware of the RSVP warning signs of infection (redness, sensitivity to light, vision deteriorating, worsening pain). The patient will be instructed to go to Groote Schuur casualty to seek help urgently if any of these occur. In the case of IK the patient would require to be admitted to hospital for intensive topical antibiotic treatment. If the infection is unresponsive to antibiotic therapy or if it were to result in corneal scarring or perforation then the treatment option would be a corneal repair or transplant. IK is a severe and dreaded complication but with the proper preventative measures in place it should be rare. IK will be considered as a severe adverse event.

- A less severe risk (Will be defined as pain score above baseline value for 2 consecutive follow-up visits). Patients can expect to experience increased pain for the first few days while the epithelium is growing closed. They will be counselled regarding this. Simple systemic analgesia (Paracetamol) will be prescribed and a bandage contact lens will be inserted until the new epithelium has healed. Persistent worsened pain will be considered an adverse event.
- Decreased vision is an unlikely risk. Vision is more likely to improve with the growth of a new regular epithelium. Persistent decreased vision of more than two Snellen chart lines will be considered an adverse event.

10.1.2. Social risk

- Possible burden to family members if required to assist with transport and post procedure treatment instillation

10.1.3. Psychological risk

- Uncertainty / anxiety about what to expect from an experimental intervention

10.2 Benefits

9.2.1 Benefits to the patients

- Temporary reduction in pain and discomfort is expected to last between 3 and 6 months.
- Possible temporary improvement in vision
- ED may delay / obviate the need for further medical / surgical treatment.

10.2.2. Benefits to society

- Participants who suffer less debilitating pain may become less reliant on family members for support.
- Future patients may have a safe, simple, cheap and effective option available for managing pain associated with BK.
- It will help patients avoid extensive, destructive and costly procedures.
- Ophthalmologists in resource-poor settings may have a new treatment option available to help them manage this debilitating disease.
- Eye health services may be less burdened if BK patients can be offered a quick treatment option to manage their pain.
- Advancement of medical knowledge in the field of ophthalmology and addressing a gap in the existing literature.

10.3. Alternative treatment options

- None of the other surgical treatment options are currently being used to treat BK at Groote Schuur hospital. This is either due to a lack of resources or because the outcomes have been shown to be unfavourable.
- Patients who prefer not to be enrolled in the study will be offered medical treatment and may be placed on the waiting list for a transplant if they meet the criteria. Alternatively, they can be

referred to a private ophthalmologist for management. The cost of a corneal transplant in the private sector is roughly R50 000.

11. Informed consent process

- Informed written consent for enrolling in the study will be taken by Dr McClunan on the day the patient is recruited.
- Consent will be taken in a closed consultation room with only the patient, patient's family, nurse and doctor present.
- Where decision-making capacity is questionable, patients will be excluded from the study and referred for psychometric evaluation if necessary.
- The patient will be given a consent form explaining their condition and the proposed study (Addendum A).
- The consent form will be translated into English, Afrikaans and Xhosa consisting of simple language presented in a patient friendly manner.
- Consent forms comply with the legal and ethical requirements stipulated in the HREC standard operating procedures.
- Information contained in the consent form will be discussed with the patient and family members, either by the doctor directly, or via an ophthalmic trained nurse acting as interpreter.
- Time will be allocated for participants to ask questions throughout the process. Non-directive and open-ended questions will be used to promote information seeking
- The patient's understanding of the information provided will be tested using the "teach back" method throughout the informed consent process.
- The patient will be offered the option to take time to think about the information provided and to discuss it with family members, religious figures and community leaders.

12. Privacy and confidentiality

- Consultation will be performed in closed consultation rooms with only the doctor, nurse, patient and family members requested by the patient present.
- Personal and medical data collected will only be handled by Dr McClunan. Data sheets will be kept in a secure locker in ward D4's doctor's tearoom of Groote Schuur hospitals eye clinic. Photos of patient's eyes and of data sheets will be kept on a password protected cell phone and backed up to a password protected laptop. Data will be kept for a period of 5 years, after which it will be destroyed or deleted.

13. Adverse events

- Adverse events (AE) will be explained to the patient orally and reported to the HREC in writing using form FHS008 within 7 calendar days.
- Unexpected or severe adverse events which may impact the conduct of the study will be explained to the patient orally and reported to the HREC in writing using form FHS008 within 3 calendar days.

- Early termination will be implemented if advised by the HREC. All patients involved in the study will be informed of the decision to terminate. They will be reassured that ongoing care will nonetheless still be available to them.
- Patients will be advised to claim from the University of Cape Town no fault insurance policy covering injuries incurred during research where applicable.

14. The end of the study

- Patients will be offered further medical and / or surgical treatment as required.
- Patients will be given the option to receive feedback regarding the results of the study when they become available.
- All aspects of the study will be compiled in an MMed dissertation and handed to the UCT post graduate office as well as the HREC.
- Results will be presented to the Groote Schuur department of ophthalmology.
- All effort will be made to publish the findings of the study in either a local or international academic journal.
- The Groote Schuur department of ophthalmology will decide whether to implement ED as a management option for BK patients based on the study findings.

15. Declaration

- This protocol complies with the following regulatory documents:
  - The Declaration of Helsinki (2008)
  - The Department of Health: Ethics in Health Research: Principles Structures and Processes, 2004
  - Guidelines for Good Clinical Practice (GCP) in the Conduct of Clinical Trials in Human Participants in South Africa. Second Edition, 2006

16. Conclusion

Bullous keratopathy is a painful, visually disabling disease. Corneal transplant is the definitive treatment of choice. Unfortunately this is not always possible. Many surgical methods have been attempted to alleviate pain in these patients, each with attendant risks. There are recognised risks associated with epithelial debridement. This study aims to show that the benefits of this simple side room procedure outweigh these risks.

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Approval of Protocol for submission to the UCT Human Research Ethics Committee

X

Supervisor

X

Supervisor

X

Head of department

X

Eye clinic nursing manager

X

Groote Schuur medical manager

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Surgical research committee