Information and Consent form for Corneal Collagen Cross-Linking

What is corneal collagen cross-linking?

Although current treatments for keratoconus, such as contact lenses and corneal ring implants, can improve vision, they do not treat the underlying cause, corneal weakness. As such they do not prevent the keratoconus from progressing. Corneal collagen cross-linking aims to address this problem.

The cornea is made up of many overlapping long strands, termed lamellae, of multiple collagen molecules. These act like multiple criss-crossing support ropes across the cornea. Collagen is a normal and important part of the structure of many tissues in the body, especially skin. Corneal collagen cross-linking (CXL) uses chemicals to form connections, or cross-links, between adjoining strands of collagen. This is currently performed using riboflavin (vitamin B2) and ultraviolet light (UVA). Natural occurring collagen cross-linking has been observed in many different tissues within the body including the cornea, teeth and bones.

In extensive experimental studies in animal and human eyes researchers have demonstrated a significant increase in corneal rigidity or stiffness after collagen cross-linking using the riboflavin/UVA cross-linking treatment. The hope is this stiffening of the cornea can prevent the keratoconus from getting worse, and possibly even lead to some improvement with flattening down of the cone.

CXL has been used in parts of Europe and the USA since the late 1990's to treat patients with keratoconus. A clinical trial was commenced in 2007 at the Melbourne University Department of Ophthalmology based at the Royal Victorian Eye and Ear Hospital Melbourne, Australia. The aim of the study is to assess both the safety and benefit of CXL for people with progressive keratoconus; that is keratoconus that is still getting worse. The type of study being performed is what is referred to as a randomized, controlled trial. This means that half the people with keratoconus that participate in the trial are randomly assigned to be treated with CXL and the other half receives no treatment. These 2 groups of people are then followed

over several years to see if the group that had the treatment had any complications, and very importantly whether their keratoconus progressed at a different rate from the group of people who didn't have the treatment. This type of trial is one of the most powerful ways of assessing the effectiveness of a new treatment.

The results of this trial to date have shown the CXL treatment to be both safe and effective in halting progression of keratoconus. In fact it has found that the group of people with keratoconus who were treated with CXL actually had an improvement in the cornea, with it becoming less steep and out of shape. Very importantly this resulted in an improvement in their vision. This effect was variable being quite marked in some people who were treated and only marginal in others. Interestingly the effect of the treatment seems to lead to continued improvement over a long time, perhaps even years. This study is still underway and has only been following patients for a little over a year and a half so the long-term effectiveness of the treatment is still under investigation. It is not known if patients will require a second treatment at any stage although it is possible that only one treatment ever will be required.

The main national regulator for medical treatments in the USA, the Food and Drug Agency (FDA), has announced that they will sponsor a similar trial to assess the safety and effectiveness of CXL for both people with progressive keratoconus and people with progressive corneal thinning and distortion following LASIK, termed "iatrogenic keratoectasia". These studies are due to commence in 2009 and will run at several hospitals across the USA.

It is important to understand that collagen cross-linking treatment is not a cure for keratoconus in that significant corneal distortion is expected to remain even after the treatment. Rather, it aims to slow or even halt the progression of the condition. After the treatment, it is expected that it will continue to be necessary for individual people to wear spectacles or contact lenses (although a change in the prescription, probably to a lower powered script, may be required). As such it is felt likely that the treatment will prevent further deterioration in vision and the need for corneal transplantation.

The active ingredient of the eye drops used for the cross-linking treatment is riboflavin (vitamin B2). Riboflavin is a vitamin that can be found in many foods and is a common ingredient in a number of multi-vitamin preparations in Australia. The pure pharmaceutical grade solution form of riboflavin that is required for this trial is currently not available in Australia or registered with the Therapeutic Goods Administration (TGA). It is imported from Switzerland where it is registered for this use.

There are several other ways of chemically cross-linking the collagen strands within the cornea, some of these have already been used experimentally on human corneas from eye banks. As yet none are available for treating people with keratoconus however it is quite possible that over time different cross-linking treatments other than UVA and riboflavin will be used.

Who is suitable to have corneal collagen cross-linking (*Inclusion Criteria*)?

1. People with progressive keratoconus or post laser keratoectasia

All patients must sign the attached written informed consent and be available for follow-up examinations as required

Who cannot be treated with corneal collagen cross-linking *(Exclusion Criteria)*?

1. If the cornea is too thin (usually thickness less than 400 μm at the thinnest point), your surgeon will advise you on this.
2. If there is an active ocular disease other than keratoectasia.
3. People with Herpes Simplex Keratitis, a corneal infection caused by the cold sore virus herpes simplex.
4. Women who are pregnant.
5. People who have active uncontrolled eye allergies or an autoimmune disease such as rheumatoid arthritis.
6. People with central corneal scars that significantly affect their vision.

Normally only 1 eye is treated at a time, the worst eye first. You will usually be at the centre where you have the procedure performed for around 2 hours. Prior to the cross-linking being performed you will be asked to lie down on a firm operating bed. Usually you will not need to change out of your normal clothes. Several drops of anaesthetic are put in your eye throughout the procedure, you do not have any injections, the anaesthetic drops numb the eye so you won't have any pain during the procedure.

The central skin (termed the epithelium) on the cornea, is removed and drops of riboflavin are instilled every 3 minutes for 15 minutes to totally saturate the cornea with the riboflavin. This is then checked and the UVA light, a moderate strength blue light, is shone on the eye for a total of 30 minutes. More riboflavin drops are placed on the eye every 3 minutes. You will need to lie still during this stage. If you like you can usually bring an MP3 music player such as an iPod to listen to, to help you to relax and lie still.

At the end of the procedure several drops of antibiotic and anti-inflammatory medicine are instilled and a soft contact lens is usually put on the eye. This contact lens is used to decrease post-operative pain and is usually removed by your surgeon several days after the procedure.

What is normal after the procedure?

The eye is typically sore, even painful, after the procedure. This pain or discomfort improves a lot in a few days when the epithelium is healed. The degree of pain and discomfort during this period is quite variable many people experiencing just mild discomfort, although some people can experience significant pain. The degree of pain that you experience after the procedure does not have any influence on how effective the treatment is, it is only related to the removal of the surface epithelium from the cornea. You will be advised on pain management before you leave the centre where the procedure is performed.

During these first 2 to 3 days it is common for the eye to be watery, blurry, red and the eyelids to be slightly swollen. The vision is usually blurry for up to 2 weeks. If you use a contact lens normally for your

keratoconus you can usually recommence usage after a few weeks. You will have several antibiotic and anti-inflammatory (steroid) drops to use on the eye for the first several weeks following the procedure. These are typically only 4 times a day.

You usually have follow-up appointments to see your surgeon several days, 1 month, 3 months, 6 months, 1 year and each year after the procedure to monitor and assess the effectiveness of the procedure. You will have repeat eye maps done at most of these visits.

For the first year or 2 after the procedure a change in the focus of the eye requiring a change in glasses or contact lens prescription is common. Several changes may be required in the first years after the procedure.

What are the possible complications of the procedure?

- Allergy to medications leading to a red swollen eye. This usually does not cause any long-term problems.
- Postoperative corneal haze (generally temporary and not enough to affect vision)
- Fluctuating and/or decreased vision (generally reported to improve after the first 3-4 months)
- Discomfort wearing contact lenses in the treated eye for up to 8 weeks
- UV damage to the internal structures of the eye (not yet seen in the Melbourne trials but reported overseas, if severe could lead to corneal swelling requiring a corneal transplant)
- An increase in eye pressure due to post-treatment drops, this usually resolves spontaneously with discontinuation of the drops.
- An infection of the cornea is very unlikely but could occur in the first several days to a week after the surgery. This can usually be successfully treated but could lead to scarring of the cornea and permanently lead to blurred vision.

  It is not possible to state every possible complication that may occur following any treatment and this list may be incomplete. Unknown or unforeseen side effects may also occur. You should ask your surgeon if you have any particular concerns.

Although new and as yet not fully assessed corneal collagen cross-linking (CXL) is a very exciting development in the treatment of keratoconus. It holds the promise of effectively stopping further deterioration in the corneal shape and as such of vision. Many questions remain, but with the further development of the treatment, and results from the clinical trials now under way, it is likely that CXL will become an extremely useful addition to our range of treatments for keratoconus. Ultimately it is hoped it will reduce the number of people requiring a corneal graft for advance keratoconus.

IN GIVING MY PERMISSION FOR CORNEAL CROSS-LINKING SURGERY WITH RIBOFLAVIN AND UVA LIGHT, I DECLARE THAT I HAVE UNDERSTOOD THE ABOVE INFORMATION:

I understand there is a very remote chance of partial or complete loss of vision in the eye that has had CL surgery primarily from infection or damage to internal structures within the eye.

I understand this is an elective procedure and that cross-linking surgery is not reversible.

FOR WOMEN ONLY: I declare that I am not pregnant or breast feeding.

I have read, or have had read to me in my first language, and I understand and accept the above information.

I acknowledge that I have been given time to consider the information and to seek other advice.

I have had the opportunity to ask questions and I am satisfied with the answers I have received.

I have been offered a copy of this Information and Consent Form to keep.

I understand that Protocol and Ethics Committee of the Melbourne Excimer Laser Group (MELG) may have access to my medical records to monitor the results. However, my identity will not be disclosed to them or anyone else. I understand that MELG has agreed not to reveal my identity or personal details if research information is published or presented in any public form.

Patients Name (printed) ……

Signature …… Date…….

Name of Witness to Patients Signature (printed)……..

Signature …… Date…….