London South Bank University
EST 1892

A randomised control trial of corneal vs. scleral rigid gas permeable contact lenses for ectatic corneal disorders

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Thesis Abstract

Introduction. Keratoconus and related corneal ectatic disorders are conditions characterised by a misshapen cornea. Keratoconus is typically managed with corneal rigid gas permeable contact lenses (CRGPcl) and when these are unsuccessful patients may be fitted with the much larger scleral rigid gas permeable contact lenses (SRGPcl). It has been hypothesised that due to their superior performance, SRGPcl might be considered as the first option for management of keratoconus and the present research investigates this hypothesis.

Purpose. To assess the visual performance, vision related quality of life (Qol) and subjective perception of vision (SPV) and the subjective perception of comfort (SPC) in two contact lens types: CRGPcl and SRGPcl, in successful CRGPcl wearers with keratoconus (and related ectatic corneal disorders).

Methods. Thirty-four successful CRGPcl wearers, with keratoconus or related disorders, participated in a crossover randomised control trial (RCT). This research was approved by the National Research Ethics Service (NRES) of London-Camden and King's Cross as well as the research ethics committees of London South Bank University (LSBU) and the Institute of Optometry. Participants were randomised into two groups, group 1 (sequence AB) were fitted with new CRGPcl and after a washout period, in which habitual CRGPcl were worn, were fitted with and crossed-over to SRGPcl. Group 2 were first fitted with SRGPcl and after a washout period were fitted with and crossed-over to new CRGPcl (sequence BA). Data for experimental outcome measures were collected three times: first on recruitment in habitual CRGPcl, and once after each period in experimental CRGPcl and SRGPcl. The outcome measures were: The *Early Treatment Diabetic Retinopathy* (ETDRS) *log of minimum angle of resolution* (logMAR) *best corrected visual acuity* (BCVA); the *VectorVision 1000E contrast sensitivity function* (CSF), expressed in both numeric and log contrast sensitivity (logCS); the *National Eye Institute Visual Function Questioannaire-25* (NEI-VFQ) to assess the *visual* Qol; and the reported SPV and SPC, recorded on a Likert-like scale from 1–10. The final measure was at the end of the second period, each participant selected the preferred lens type, out of the two experimental lenses, for future habitual use.

Results. Thirty participants completed the trial, 13 in group 1 and 17 in group 2. Randomisation demographics revealed no significant differences between the two

randomised groups except in corneal pachymetry (thickness): group 1[*Mean 423.2 (±45.1)*], group 2 [*Mean 462.8 (±44.7)*] (*p= 0.002*).

The SPC in the experimental lenses and the SPC in the experimental CRGPcl in participants who selected CRGPcl as the habitual lens for future use, were the only measures, which exhibited significant differences. The SPC was not-normally distributed in SRGPcl, [*Median=9.0, IQR=2.0, Mean=8.85, (±1.10)*] and normally distributed in CRGPcl [*Mean=7.78, (±1.45), Median=8.0, IQR=2.0*]. The intra-subject period differences in SPC between group 1 (*Median=1.0*) and group 2 (*Median=-1.0*), revealed significantly higher scores in SRGPcl (*p=0.002*), rejecting H_0. The preferred habitual lens choice outcome was: 14 participants (47%) chose SRGPcl and 16 (52%) chose CRGPcl. Higher SPC scores in the experimental CRGPcl, were found in participants who chose CRGPcl, (*p=0.006*) and (*p=0.009*) by independent samples *t-test* and *Mann-Whitney U* test respectively, rejecting H_0. The only significant carryover effect was found in the logCS scores (*p=0.019*), no other outcome was found to have significant carryover or period effects.

No other outcome was found to have significant differences between the two lens types, supporting H_0, with respect to: the ETDRS logMAR BCVA, the CSF numeric and logCS, the specific logCS at 6 cycles per degree (CPD), the 12 domains of the NEI-VFQ, the specific ocular pain domain of the NEI-VFQ and the SPV.

Conclusion. The research population exhibited significantly better comfort in SRGPcl compared with CRGPcl, as measured by the Levit Subjective Comfort Scale (LSCS). Furthermore, participants who chose to remain in CRGPcl had significantly higher LSCS scores in CRGPcl than those who chose SRGPcl. Successful CRGPcl wearers whose LSCS in CRGPcl is < 7 are likely to achieve better comfort / tolerance with SRGPcl. No significant differences were found in this research population between the two experimental lens types, in the visual outcomes of logMAR, logCS and SPV and no significant difference was found in the visual Qol outcomes in the 12 domains of the NIE-VFQ. This research indicates that on average, successful CRGPcl wearers find SRGPcl more comfortable and there should be no visual and visual Qol advantage or disadvantage in refitting successful keratoconic CRGPcl wearers with SRGPcl and vice versa.

Research purpose statement

The purpose of this research was to determine whether significant differences in a number of outcome measures could be established, when comparing the performance of CRGPcl versus the performance of SRGPcl in participants with keratoconus, who are successfully managed with habitual CRGPcl wear. It was hoped that the findings of this research may help to formulate the scope of application of SRGPcl in the management of keratoconus and other ectatic corneal disorders.

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I would like to thank my supervisors Prof Bruce Evans and Dr Martin Benwell, for their support and invaluable advice throughout the research and writing of this thesis. It has been a privilege and a pleasure to work with them.

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Contents

List of Abbreviations

AAD	Age at diagnosis
BCVA	Best corrected visual acuity
CLEK	Collaborative longitudinal evaluation of keratoconus
CMH	Central Middlesex Hospital
COR	Coefficient of repeatability
CPD	Cycles per degree
CRGPcl	Corneal rigid gas permeable contact lenses
CS	Contrast sensitivity
CSF	Contrast sensitivity function
CXL	Collagen cross-linking
DED	Dry eye disease
DFCL	Definite Apical Clearance
DLK	Deep lamellar keratoplasty
DS	Dioptres
ETDRS	Early treatment diabetic retinopathy survey
HOA	High Order Aberration
INTACS	Intrastromal corneal ring segments
NEI-VFQ	National eye institute-visual function questionnaire-25
NRES	National research ethics services
PMD	Pellucid marginal degeneration

LogCS	Logarithm of contrast sensitivity
LogMAR	Logarithm of the minimum angle of resolution
LSBU	London South Bank University
LSCS	Levit subjective comfort score
LSVS	Levit subjective vision score
MAR	Minimum angle of resolution
NaFl	Sodium fluorescein
OCT	Optical coherence tomography
PMD	Pellucid Marginal Degeneration
Qol	Quality of life
RCT	Randomised controlled trial
RGP	Rigid gas permeable
REC	Research ethics committee
ROS	Randomised OS
RGPcl	Rigid gas permeable contact lenses
SRGPcl	Scleral rigid gas permeable contact lenses
SRI	Surface regularity index
SPC	Subjective perception of comfort
SPV	Subjective perception of vision
VA	Visual acuity

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Chapter 1: Introduction

Background overview

The purpose of this chapter is to provide an overview for non-eye care professionals, of the structure of the anterior part of the eye and its optical properties. The cornea is the ocular (eye) tissue affected by corneal ectatic disorders such as keratoconus, the structure and function of the cornea will therefore be emphasised. This chapter also includes a summary of the main methods of assessing visual function and visual quality of life (Qol), both of which are highly relevant to the thesis.

The structure and function of the human cornea and sclera

Introduction

The cornea and the sclera consist of dense connective tissue and form the outer shell of the eyeball (Figure 1.1). The cornea forms the transparent ocular 'window', which refracts* the light entering the eye [**refraction is the change in the direction and speed of a light when light passes from one medium such as air to another, such as a lens or an eye*]. The corneal physical curvature and optical regularity* determine its optical properties, which vary between individuals, due to normal variation and / or disease [**optical regularity is a measure of the amount of physical and optical distortions present in the cornea*]. The transition from the clear cornea to the opaque sclera, the *limbus*, contains a reservoir of corneal stem cells (Nishida and Saika, 2011).

The sclera is an opaque protective outer layer of the eye. Interwoven *collagen fibres* provide the mechanical strength of the cornea and sclera, protecting the inner eye from physical injury and maintaining ocular contour (Figure 1.1) (Birk and Trelstad, 1984). The regular corneal collagen fibres facilitate corneal transparency, the lack of transparency of the sclera is due to the non-uniformity in the arrangement of its collagen fibres (Watson and Young, 2004).

The cornea, covered by a thin layer of *tear film* is exposed to the environment, whereas the sclera is covered with the semi-transparent mucous membrane the *conjunctiva* and has no direct exposure to the environment. The conjunctiva is critical to maintaining the integrity of the eye, it protects the soft tissues of the eyelid and orbit and is the main site for the production of the *mucous* components of the *tear film* (Figure 1.2). Abnormalities of the conjunctiva may lead to restriction of ocular movement (loss of elasticity), deficiency of the tear film (deficient production of tear components), and decreased resistance to infection (deficient production of immune components), which also adversely affect the cornea (Nelson and Cameron, 2011).

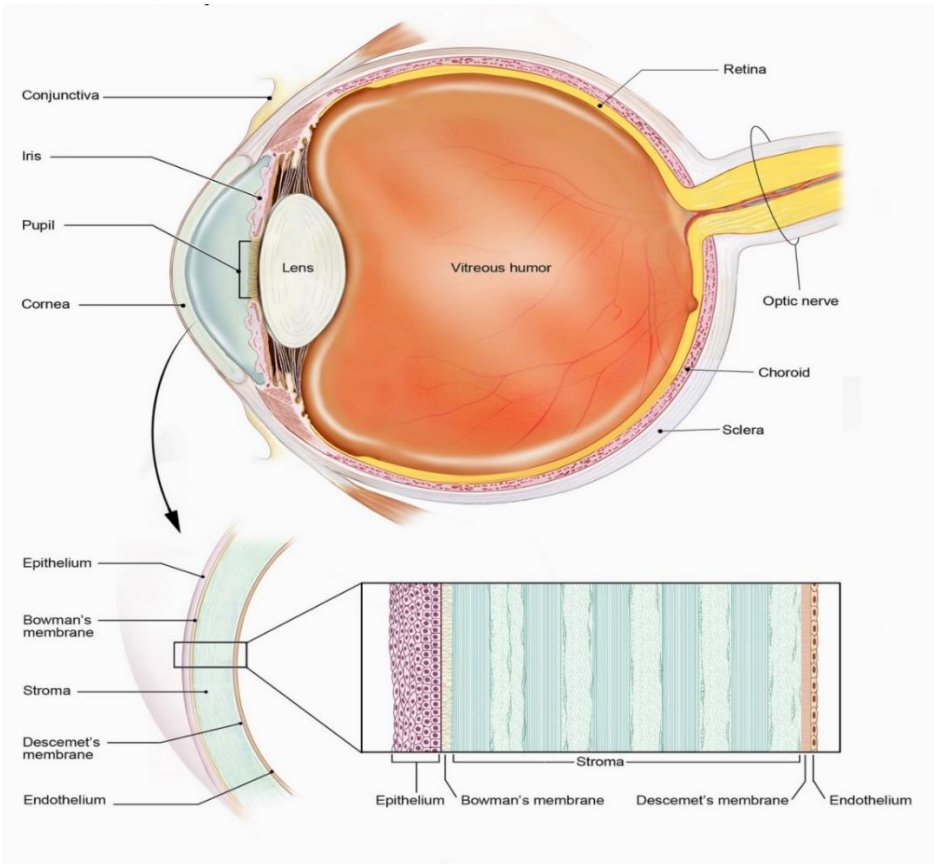


Figure 1.1 *Major Ocular Structures + multilayer structure of the cornea https://www.flickr.com (licence type: all creative commons).*

The cornea is approximately 500µm (0.5mm) thick and has a multilayer structure comprised of precisely arranged component layers (Figures 1.2), which interact with each other to maintain corneal function, transparency and structural integrity.

These layers are (Nishida and Saika, 2011):

1. Six layers of *epithelial* cells, to which the tear film complex is attached.

2. The *Basement membrane* to which the epithelial cells are anchored.

3. Thin collagen layer of the anterior stroma: *Bowman's layer.*

4. A thick central collagen fibrous structure called the *substantia propria or stroma*

5. Discovered in 2013, a tough, well-defined, acellular lining of 10µm-15µm between the corneal stroma and Descemet's membrane: *Dua's layer* (Dua *et al.*, 2013).

6. A thin homogeneous elastic lamina called *Descemet's membrane*

7. A single, non-regenerating layer of *endothelial cells* forming part of the lining membrane of the anterior chamber of the eye (Nishida and Saika, 2011).

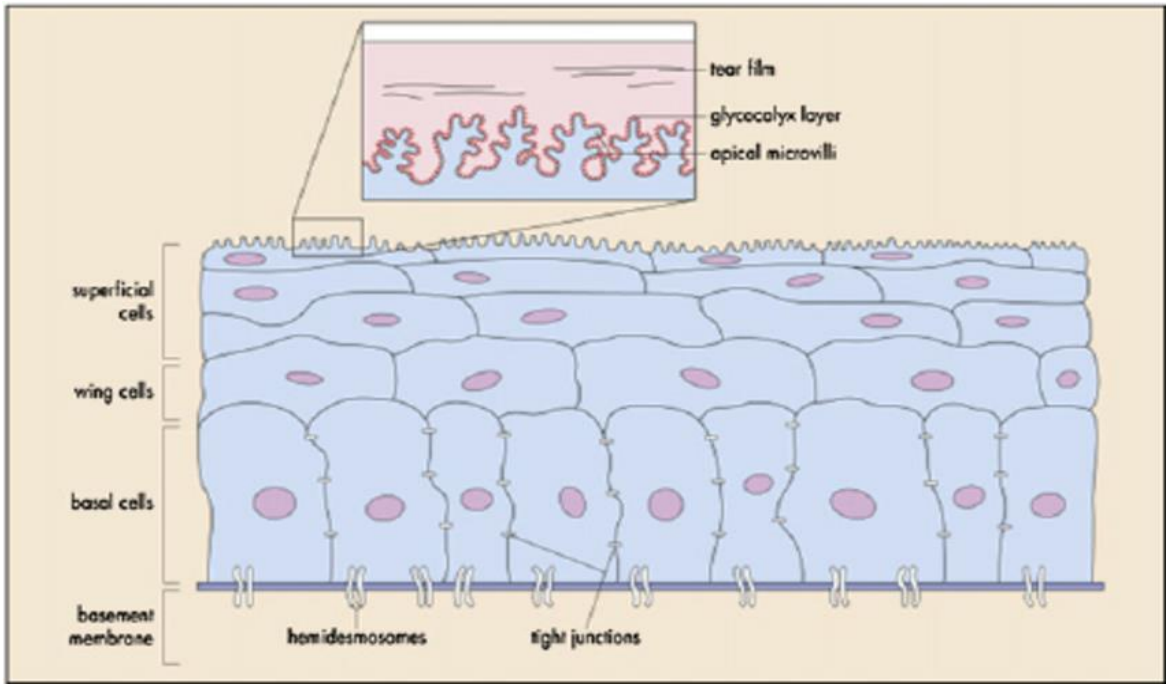


Figure 1.2. *The anterior Cornea: tear film, epithelium and epithelial basement membrane (https://www.researchgate.net).*

Tear film

The tear film is a complex composite structure which is a mixture of components from multiple sources (Nishida and Saika, 2011), it consists of three layers: a superficial *lipid layer* approximately 0.1µm thick, an *aqueous layer* 7µm thick comprising 98% of the tear volume and a *mucinous layer* 0.02µm–0.05µm (Holly and Lemp, 1977). Normal tear volume and production rates are about 6µL and 1.2µL / minute respectively, with a turnover rate of about 16% per minute (Mishima *et al.*, 1966). The base of the tear film is in contact with the outer surface membrane of the corneal and conjunctival epithelial cells, which incorporates elaborate folds and filaments, which increase the corneal surface area of contact, aiding adherence with the tear film (Lemp and Beuerman, 2011).

The tear film protects the cornea from dehydration, it acts as a lubricant, a source of nutrients and a source of regulatory factors required for corneal epithelial cell maintenance and repair. Optimal physiology and immunology are maintained by biologically important ions and molecules, including electrolytes, glucose, immunoglobulins, lactoferrin, lysozyme, albumin, and oxygen as well as a wide range of active substances such as histamine, prostaglandins, growth factors, and cytokines (Nishida and Saika, 2011).

Apart from lubrication, protection from disease and provision of nutrition to the cornea, the tear film is critical for the maintenance of the optical properties of the eye. The pre-corneal tear film stability between blinks allows clear vision; this limited stability is compromised in dry eye disease (DED), leading to optical image degradation between blinks (Goto *et al.*, 2006).

Corneal epithelium

The corneal epithelium thickness is approximately 50µm. It forms an effective mechanical barrier and together with the cellular and chemical components of the conjunctiva and tear film, protects against potential pathological agents and microorganisms. The epithelial cells on the base layer of the cornea constantly divide to produce new cells. The superficial epithelial cells

differentiate and gradually emerge at the corneal surface. The differentiation process requires 7-14 days to complete, after which the superficial cells are desquamated (shed) (Hanna *et al.*, 1961). Ultraviolet radiation, hypoxia [*deprivation of oxygen*] and mechanical stress induce apoptosis (cell death) and desquamation of corneal epithelial cells (Estil *et al.*, 2000; Ma and Bazan, 2001; Esco *et al.*, 2001).

Corneal stroma

The smooth surface of the cornea is essential for visual clarity. The regular arrangement of collagen fibres in the corneal stroma accounts for corneal transparency (Freegard, 1997). The size of and the distance between the collagen fibres in the corneal stroma are relatively homogeneous and are less than half of the wavelength of visible light (400–700nm). This anatomic arrangement generates a *cancelling interference* of scattered light rays allowing light to pass through the cornea (Maurice, 1984). If the diameter of or the distance between collagen fibres becomes heterogeneous, as in fibrosis (scarring), injury or oedema, incident rays are scattered randomly and the cornea loses its transparency (Nishida and Saika, 2011).

Corneal endothelium

The corneal endothelium contributes to the maintenance of corneal stromal transparency by the regulation of corneal hydration (Nishida and Saika, 2011). The healthy cornea is maintained at a relatively dehydrated state by the endothelial ion-pump, which maintains corneal transparency (Schmedt *et al.*, 2012). Impaired endothelial function due to disease process or physiological endothelial insult may allow water to accumulate in the cornea causing corneal oedema and impair its transparency (Schmedt *et al.*, 2012).

Innervation

Tissue sensory innervation is required for pain sensation as well as for tissue repair. Most of the sensory nerves in the cornea are derived from the ciliary nerves of the ophthalmic branch of the trigeminal nerve (cranial nerve V). The density of nerve endings in the cornea is about 300-400 times greater than that in the skin (Muller *et al.*, 2003). It is one of the most innervated and therefore most sensitive tissues in the body.

Damage or loss of the corneal epithelium results in severe ocular pain due to exposure of the nerve endings. Two of the 5^{th} nerve branches, short and long posterior ciliary nerves, penetrate the sclera and provide fine sensory branches to the scleral stroma. Scleral innervation and sensitivity are significantly reduced compared to the cornea due to reduced tissue innervation.

Wound healing

Smooth corneal epithelium, transparent stroma, and a functioning endothelium are all essential for clear vision. Wound healing in the human body is generally initiated by the exit of blood constituents as a result of disruption of blood vessels. The mechanism of wound healing in the cornea is different since the cornea is avascular. The surface epithelial cells renew continuously to maintain the normal layered structure of the corneal epithelium. The existence of corneal epithelial stem cells at the limbus (Cotsarelis *et al.*, 1989) and their importance for corneal epithelial homeostasis has been established (Secker and Daniels, 2008). Corneal injury which results in an epithelial defect is normally repaired by a rapid epithelial cell migration, proliferation, and differentiation, resulting in restoration of the stratified structure of the epithelium (Ljubimov and Saghizadeh, 2015). These processes are controlled and regulated by complex immune, neural, chemical and biological mechanisms and interactions (Ljubimov and Saghizadeh, 2015).

Vasculature

The normal cornea does not contain blood vessels (Nishida and Saika, 2011). However, factors derived from the vascular arcade at the corneal limbus are important for corneal metabolism and wound healing (Ljubimov and Saghizadeh, 2015). In certain pathological conditions, and due to hypoxia during contact lens wear, new vessels may enter the corneal stroma from the limbus and result in a loss of corneal transparency (Cohen, 2011; Schmedt *et al.*, 2012). In contrast to the cornea the sclera contains rich vasculature.

Metabolism

Corneal epithelial and endothelial cells require a supply of glucose and oxygen to maintain their normal, high metabolic functions (Aguayo *et al.*, 1988). The cornea is supplied with glucose by diffusion from the internal aqueous humour (Nishida and Saika, 2011).

Corneal oxygen supply is by diffusion from the tear fluid, which absorbs oxygen from the atmosphere. Disruption of the direct exposure of the tear film to the atmosphere interferes with oxygen supply to the cornea and may lead to corneal hypoxia and consequent stromal oedema (Schmedt *et al.*, 2012). This may result, for example, from wearing of contact lenses made of materials with reduced gas permeability (Holden *et al.*, 1985; Thoft and Friend, 1975).

Corneal refractive properties

The average adult human cornea measures 11-12mm horizontally and 9-11mm vertically. It is approximately 0.5mm thick at the centre, with gradually increasing thickness toward the periphery, where it is about 0.7mm thick (Mishima, 1968). The central 3mm optical zone of

the normal cornea is almost perfectly spherical with an average, radius of curvature of 7.5mm to 8.0mm. Normal corneal curvature has shortest (steepest) radius of curvature at the centre, which gradually increases (flattens) towards the periphery giving it a prolate elliptical shape (flattening ellipse). The optical properties of the cornea are determined by its transparency, surface regularity, shape, and refractive properties (Maurice, 1984).

The total refractive power of the cornea is determined by the sum of refraction at the anterior and posterior interfaces. The central corneal refractive power averages +43.0 *dioptres* (DS)*, being the sum of the air–tear fluid interface (+44.0DS), tear fluid–cornea interface (+5.0DS) and cornea–aqueous humour interface (−6.0DS), the cornea contributes about 2/3 of the total refractive power of the eye (Nishida and Saika, 2011). [**Dioptre is a unit of refractive power, which is equal to the reciprocal of the focal length (in metres) of a given optical element such as a lens*].

The maintenance of regular corneal shape and transparency are critical for the regular refraction of light and the formation of clear retinal image. The cornea may lose its transparency due to changes in the physical properties as discussed above. Changes in corneal contour caused either by pathological conditions such as scarring, thinning, refractive surgery or keratoconus may significantly disrupt corneal surface regularity and render the corneal surface irregularly astigmatic (Feder and Gan, 2011) (see below for explanation of astigmatism).

The refractive status of the eye

The refractive status of the eye refers to the position of an optical image generated by the refracting elements of the eye of an object positioned at an optical infinity [*optical infinity is often taken to be a distance further than 4meters (0.25 dioptres)*]. Ametropia is a term used to indicate that an imperfect refractive status is present as opposed to a perfect refractive status, emmetropia. In emmetropia the object of regard is imaged perfectly on the retina by the refractive elements of the eye. In emmetropic, hyperopic (long-sighted) and myopic (short-sighted) eyes incident parallel rays of light are brought to focus upon the retina, behind the retina and in-front of the retina respectively. Astigmatism which means “lacking” a “point” is

a form of ametropia in which incident parallel rays of light are not brought into a single focus. Astigmatism may be classified as regular or irregular, with respect to the contributing ocular component, by orientation or with respect to the refractive error. In regular astigmatism the optical meridians having the maximum and minimum refractive powers are orthogonal. In irregular astigmatism the maximum and the minimum refractive power meridians are separated by an angle other than 90°. Irregular astigmatism is a hallmark of diseases such as keratoconus and occurs due to the irregular shape of the cornea (Rosenfeld, 2006).

Corneal power is normally distributed in the population of normal eyes (Steiger, 1913; Stenstrom, 1948), the cornea reaches its adult power at around age 3yrs with only minor changes between aged 3-13yrs (Zadnik *et al.*, 1993). Changes in corneal power contribute only to a portion of all refractive errors and variations in corneal curvature may play a significant role in the development of refractive error in a limited number of individuals (Rosenfeld, 2006).

The refractive power of the crystalline lens (Figure 1.1) is 15-20DS, less than 50% of the corneal power, (Zadnik *et al.*, 1993).

The axial length (eye length from cornea to retina) and anterior chamber depth of the eye reach adult levels around age 15yrs and are considered to have the greatest effect on the refractive status of the eye. The excessive prevalence of emmetropia has led to the proposal of an active emmetropizing process, in which the growth of one or more ocular components compensate for the changes in the dimensions of other components (Rosenfeld, 2006).

Visual acuity (VA)

The assessment of visual function is an essential part of any research involved in the evaluation and comparison of various methods of correcting and managing disorders which cause visual disability such as keratoconus. Visual acuity is the most widely used measure of visual function both in optometric clinical practice and research (see chapter 4). Other important diagnostic measures of visual performance, such as colour perception and contrast sensitivity are used in research but less frequently in clinical practice. Visual acuity measurement is routinely used for the assessment of refractive error, ocular health screening, following the course of eye

disease, evaluating the effectiveness of refractive, medical and surgical treatments, prescribing aids for the visually impaired, and setting vision standards for employment and driving. The British Standards Institution has published standards of visual acuity for the UK (British Standards Institution., BS 4274-1:2003).

Visual acuity expresses the resolution which detects the threshold size of a spot or a line against its background or the smallest angular size of the detail that can be resolved and recognised by the observer. Most clinical tests of visual acuity are based on the visual system's ability to correctly recognise the smallest optotypes [*figures or letters of different sizes used in testing visual acuity*] (Bailey, 2006).

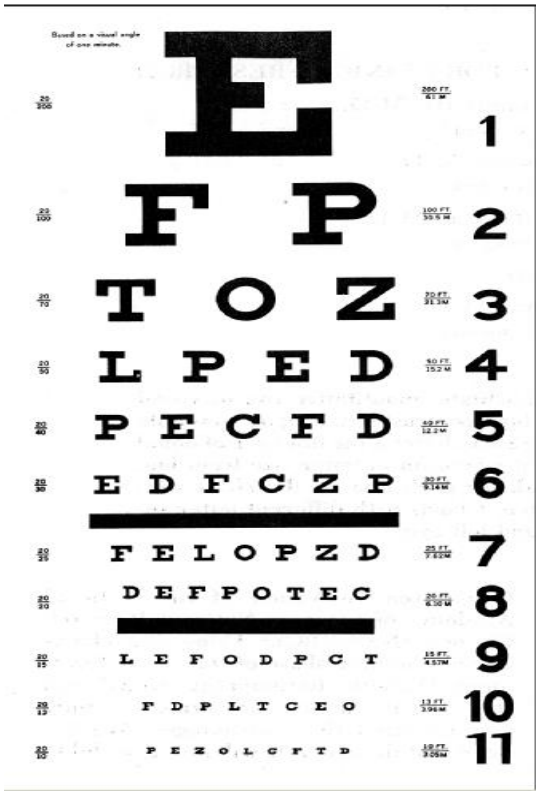
The minimum angle of resolution (MAR) is typically expressed in minutes of arc and specifies the angular size of the critical detail within the just-resolvable optotype. For visual targets comprised of letters the critical detail is taken as 1/5 of the letter height (Figure 1.4b). The MAR of 1 minute of arc (1´) represents visual acuity of 6/6 (metric notation) or 20/20 (imperial notation). For a letter twice, the size of a 6/6 letter: 6/12 (20/40) the MAR is 2´. The MAR in minutes of arc is equal to the reciprocal of the metric or imperial decimal acuity value (Table 1.1) (Bailey, 2006). The logarithm of MAR (logMAR) is a measure of visual acuity represented by the common logarithm of the MAR (Bailey and Lovie, 1976). For example, the logMAR of the MAR of 1´: $Log_{10}1=0.00$. The logMAR of 2´: $\log_{10} = 0.3$. When the visual acuity score is better than 6/6 the logMAR value becomes negative, for example visual acuity of 6/4.8 in which the MAR=0.8´, the logMAR=- 0.1 (Table 1.1).

Until recently visual acuity was quite commonly scored in coarse, whole line steps when a criterion number of letters, e.g., 3 out of 5 letters in a line were identified correctly. Alternatively, the number of incorrectly identified letters would be designated by a negative sign e.g., $6/6^{-2}$, or a positive sign in front of the number of letters identified from the next line of optotypes, e.g., $6/6^{+2}$. Visual acuities are reported in what is known as the Snellen fraction, where the numerator indicates the test distance, and the denominator indicates the relative size of the letter, usually in terms of the distance at which the optotype width to be resolved would subtend a visual angle of 1´. Thus 20/40 or 6/12 indicate that the actual test distance was 20 feet or 6m and that the strokes of the optotypes would subtend 1´ at 40 feet or 12 m, i.e. the size of the optotypes in this line is twice as large as in the 20/20 or the 6/6 line (Bailey, 2006).

Modern visual acuity chart design

Bailey and Lovie (1976) improved the conventional Sloan (Sloan, 1959) visual acuity chart to include 5 letters per line, as opposed to 1-8 per row, with interline size progression of 0.1 log units and following it use in the ETDRS this chart became widely used (Ferris *et al.*, 1982) (Figure 1.4a). The revised ETDRS 2000 series chart, better equates the letter recognition difficulty on all lines, and it is generally agreed that whilst gaining a role in clinical trials, its acceptance in the routine clinical use is limited (Shamir *et al.*, 2016).

Figure 1.4a. *ETDRS LogMAR Optotype chart*



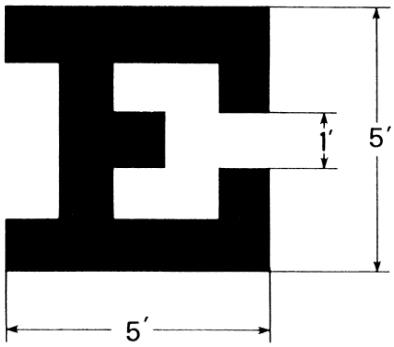


Figure 1.4 b *Snellen optotypes for visual acuity testing copied from https://www.flickr.com.*

Table 1.1. *Visual Acuity Conversion Table*

Feet	Metre	Decimal	LogMAR
20/200	6/60	0.1	1
20/160	6/48	0.125	0.9
20/125	6/38	0.16	0.8
20/100	6/30	0.2	0.7
20/80	6/24	0.25	0.6
20/63	6/19	0.32	0.5
20/50	6/15	0.4	0.4
20/40	6/12	0.5	0.3
20/32	6/9.5	0.63	0.2
20/25	6/7.5	0.8	0.1
20/20	6/6	1	0
20/16	6/4.8	1.25	−0.10
20/12.5	6/3.8	1.6	−0.20
20/10	6/3	2	−0.30

Visual acuity testing procedures

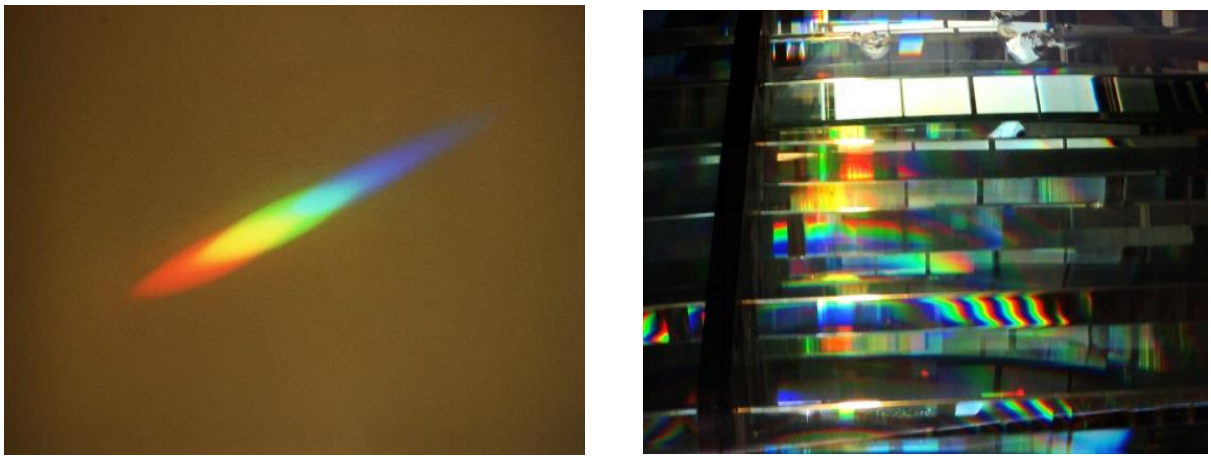
The logarithmic progression of letter sizes in the ETDRS charts facilitates use at a variety of distances by the facility of accurate conversion of scores at different distances (VectorVision, 2013). The standard test distance is 4 meters, with c*hart illumination standards* vary from 100 cd / m^2 in the USA to 300 cd / m^2 in Germany, in normal subjects a plateau in performance is reached at about 200 cd / m^2 (Sheedy *et al.*, 1984).

It has been shown that *criterion-dependent* test procedures, in which patients decide when the letters become indistinguishable, lead to inaccurate and unreliable test results (Higgins *et al.*, 1984). *Forced-choice* procedures, which are criterion-free because the examiner, rather than the patient, determines whether the letter is correctly identified, are preferable (Ricci *et al.*, 1998). It has been shown that letter-by-letter scoring is more reproducible than line-by-line scoring (British Standards Institution., BS 4274-1:2003; Arditi and Cagenello, 1993).

The physiological limits to visual acuity

When the eye is in ideal focus a point object is imaged on the retina as a *diffraction pattern*, which is a small circular patch with faint surrounding rings called the *Airy disc* (Figure 1.5c top image). The limits to visual acuity are imposed by a combination of optical and neural factors (Bailey, 2006). The retinal image quality may be degraded by optical factors such as the various ametropias, which limit the resolution achieved by the visual system. Even with optimal refractive correction of ametropia, there still maybe image degradation as a result of chromatic (colour spectrum) optical aberrations, (as seen when light is refracted through a prism) (Figure 1.5a and b) and monochromatic (black and white) high order optical aberrations (HOA) degrade the retinal image (may be expressed by the point spread function, which is the appearance of a point of light due to a specific HOA distortion) (Figure 1.5c) (Thibos *et al.*, 2006).

Pupil size of the eye will also affect the retinal image quality, if the pupil is too small a diffraction pattern degrades the image formed, if too large increases the HOA, the ideal calculated pupil diameter for 1' resolution is 2.5mm (Bailey, 2006). Neural limitations relate to the anatomy and physiology of the retina and subsequent visual pathways. The calculated neural limit of resolution, is 0.82', which is similar in magnitude to the calculated optimal optical limit of resolution of 1' (Bailey, 2006).



a. **b.**

Figure 1.5 a. *Chromatic Aberrations visual spectrum,* ***b****. Chromatically aberrated reflected light https://www.flickr.com (licence type: all creative commons).*

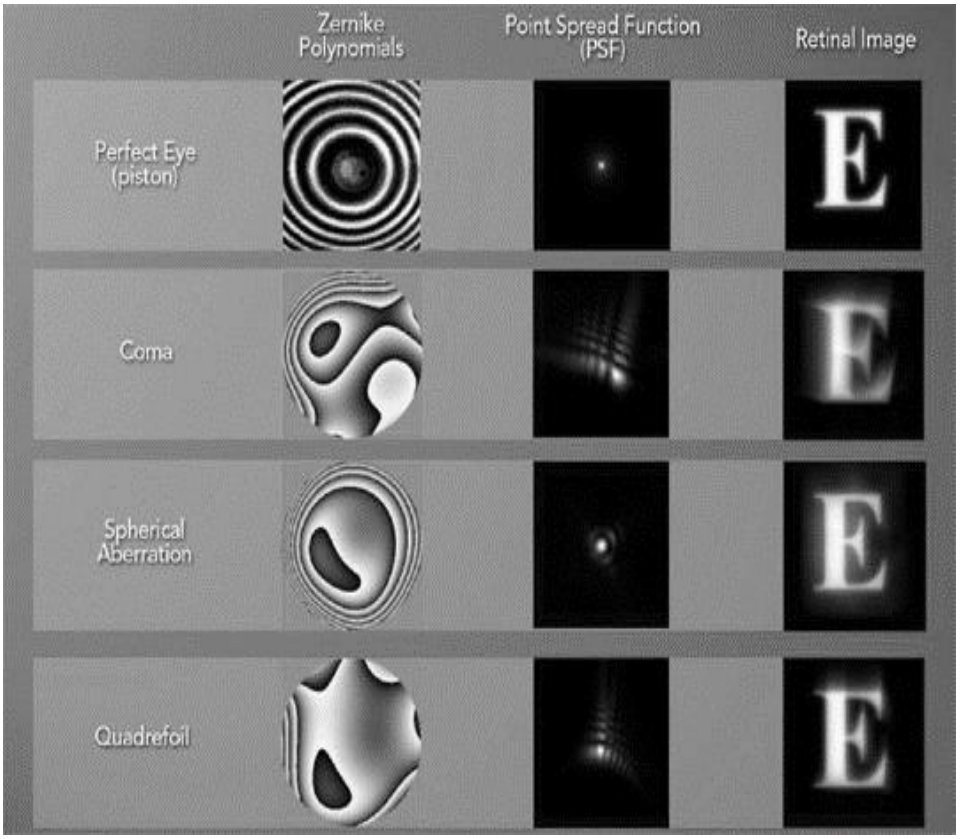


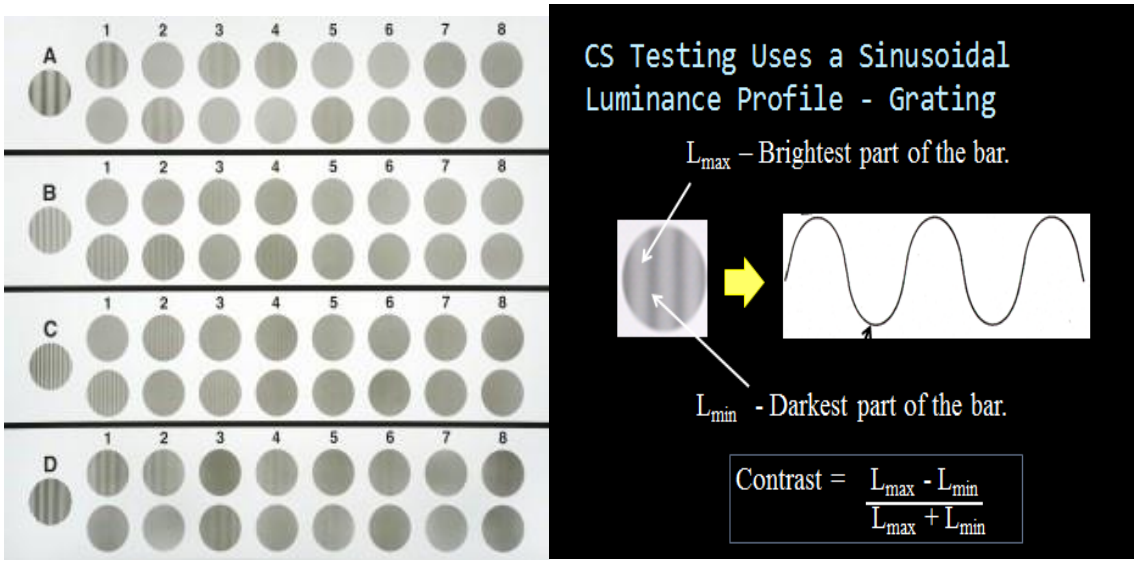
Figure 1.5 c. *High Order Aberrations. Reprinted with permission from Optometric Management (http://www.optometricmanagement.com)*

Contrast sensitivity (CS)

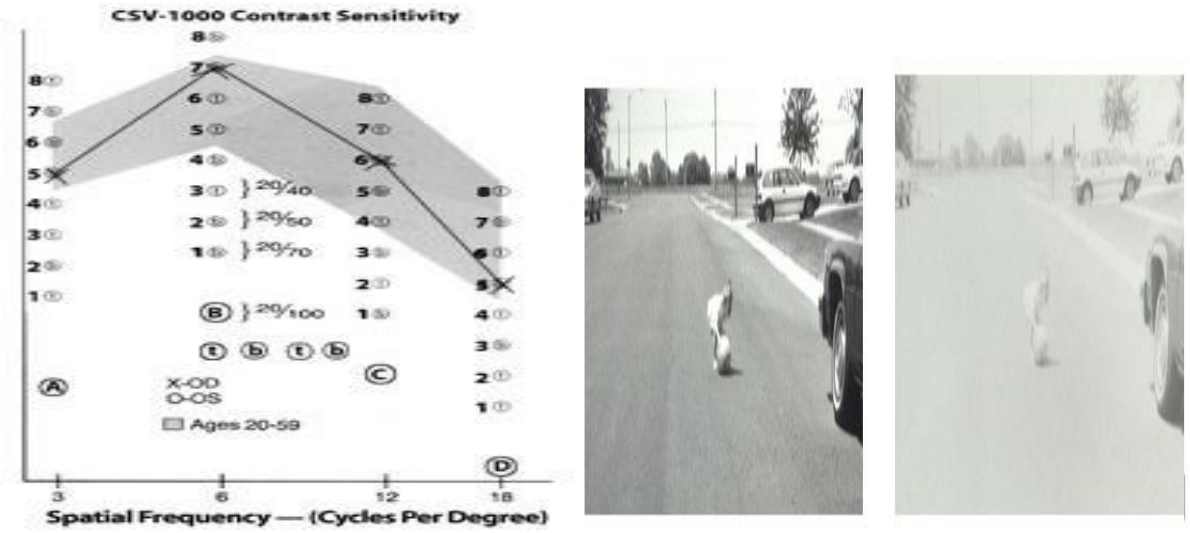
Contrast sensitivity testing was originally developed as a research tool by vision scientists interested in characterizing normal visual function. Visual acuity measures the eye's ability to resolve fine detail at 100% contrast; black optotypes on white background. In the real world, a range of contrasts present visual challenges, for example the challenge of seeing and recognising relatively large low-contrast objects such as faces, or important details in an environment affected by fog or glare (Figure 1.6d). Sine-wave grating stimuli are commonly used as visual targets in contrast sensitivity testing; these are patterns consisting of alternating light and dark bars, which have a sinusoidal luminance profile. The size variation in the sine-wave gratings is generated by varying the spatial frequency of the grating bars by steps

measured by CPD (Sukha and Rubin, 2013). A CSF is derived by measuring the lowest detectable contrast across a range of spatial frequencies. A thorough assessment of contact sensitivity would involve establishing the minimum contrast that can be detected over a range of spatial frequencies (Elliott, 2006), (Figure 1.6a).

Clinical CS testing provides a better understanding of the impact of visual impairment on visual function. Studies have shown that CS loss can lead to mobility problems and difficulty recognizing signs or faces even when adjusted for loss of acuity (Rubin *et al.*, 2001; Rubin *et al.*, 1994). Measuring both VA and CS as outcomes of a clinical trial may provide a more complete picture of the effects of treatment on the quality of vision than either measure alone (Rubin, 2013). CS tests in clinical use which employ sine-wave grating in a chart form include the *Functional Acuity Contrast Test* and the *CSV-1000E*.



a. b.



c. d.

Figure 1.6. **a.** *CSF chart, with sine-wave grating.* ***b.*** *Sinusoidal grating pattern.* ***c.*** *CSF numeric scores curve.* ***d.*** *high and low contrast scene. With permission from VectorVision (http://www.vectorvision.com)*

The CSV-1000 CS test is a grating chart-based test, which has an internal illumination system. The chart presents 3, 6, 12, and 18 CPD spatial frequencies, with each row containing 17 circular patches. CS levels in each row range from 0.70-2.08, 0.91-2.29, 0.61-1.99, and 0.17-1.55 logCS units for 3, 6, 12, and 18 CPD respectively (Table 1.2) (VectorVision, 2013). Contrast levels diminish in a logarithmic fashion. The CSV-1000 test was reported to be clinically reliable for monitoring visual changes in patients with glaucoma treated with beta-blockers (Pomerance and Evans, 1994).

The impact of the reduction in the quality of VA and CS depend on the task the individual is required to perform, which suggests that defining disability using a single threshold for VA or CS loss is arbitrary. Nevertheless, after many decades of acuity testing, a consensus has been reached, which states that a doubling of the MAR (increase of 0.3 logMAR or 15 ETDRS letters) represents significant loss in VA (Rubin *et al.*, 2001). Data from large population-based studies suggest that a doubling of contrast threshold; reducing sensitivity by 0.30 logCS (Table 1.2) has a comparable impact on task performance and Qol (Rubin *et al.*, 2001; West *et al.*, 2002).

Table 1.2 *Contrast Sensitivity Values for the CSV-1000E in Log Units*

Target *No* (reducing contrast)									
Row (CPD)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
A (3.0)	0.7	1	1.17	1.34	1.49	1.63	1.78	1.93	2.08
B (6.0)	0.91	1.21	1.38	1.55	1.7	1.84	1.99	2.14	2.29
C (12.0)	0.61	0.91	1.08	1.25	1.4	1.54	1.69	1.84	1.99
D (18.0)	0.17	0.47	0.64	0.81	0.96	1.1	1.25	1.4	1.55

When the VA scoring is performed letter by letter, Bailey *et al.*, (1991) showed that for normally sighted subjects, a five letter change equivalent to a 0.10 logMAR difference, is sufficient evidence (95% confidence) that a significant change has occurred (Bailey *et al.*, 1991). The same difference of five letters in VA between the right and left eyes is considered clinically significant and requires further investigation to establish the cause for that difference (Brown and Yap, 1995). Most optometrist would recommend a change of glasses if a 0.10 logMAR improvement is achieved compared with the habitual correction.

Summary

Chapter 1 has provided an overview of the structure and function of the eye with emphasis on important topics in this thesis: the cornea, sclera and the assessment of visual function. The next chapter is a review of keratoconus and other ectatic corneal disorders and their management with contact lenses.

Chapter 2: Literature review, keratoconus and its diagnosis and principles of management

Methodology of literature search

For chapters 2 and 3 the initial literature search was made for full articles in English, between Jan 1980 to February 2015 in PubMed employing the following terms: {Contact lenses} AND {keratoconus OR cornea ectasia} NOT {soft contact lenses} NOT {refractive surgery}, which yielded 326 articles. The purpose was to present a narrative review addressing the various aspects of corneal ectatic disorders with emphasis on keratoconus. In addition to these articles, appropriate, referenced textbooks in the fields of ophthalmology and optometry were referred to and where appropriate cited. Articles prior to 1980 that were identified in the reference list of publications found in the search were included if seminal work. In the PubMed search the command NOT excluded research which describes the use of soft contact lenses in keratoconus and research which describes iatrogenic keratoconus secondary to refractive surgery.

In chapter 2 the literature from PubMed and referenced textbooks was used to present a narrative review of current knowledge of corneal ectatic disorders, with emphasis on keratoconus. The review includes definition, prevalence, incidence, demographics and aetiology of keratoconus and aspects of disease classification and diagnosis. Chapter 2 ends with a general outline of management and treatment of keratoconus.

In chapter 3 the literature selection from PubMed and referenced textbooks is focused on contact lens management of keratoconus and related ectatic disorders. The research is selected to represent the current state of knowledge concerning contact lens management of keratoconus, concentrating on CRGPcl and SRGPcl. Research dealing with aspects of fitting methods and complications and morbidity associated with both lens types is critically appraised to highlight unresolved clinical questions and areas which require further research to improve the state of current knowledge and contact lens management of ectatic disorders. This chapter also includes research describing contact lens related outcomes such as visual acuity, contrast sensitivity, visual Qol and other objective and subjective measures important to contact lenses wearers.

Updated searches for newer relevant research were performed regularly and relevant new literature added. The searches were last updated in September 2018.

Definition

Keratoconus; *conical cornea,* is a clinical term used to describe a non-inflammatory ectatic corneal disorder, in which the cornea assumes a conical shape because of an inherent compromise in its structural integrity due to a naturally occurring, traumatic or iatrogenic corneal thinning and protrusion (Feder and Gan, 2011). It involves the central two thirds of the cornea with the apex [*steepest and thinnest part of the cone*] typically positioned inferiorly, infero-temporally, infero-nasally or centrally, although superior thinning has also been described (Weed *et al.*, 2005), with mild to marked impairment of visual function (Feder and Gan, 2011) (Figure 2.1). The sclera in eyes with keratoconus remains normal, with no difference in thickness compared with healthy eyes (Schlatter *et al.*, 2015).

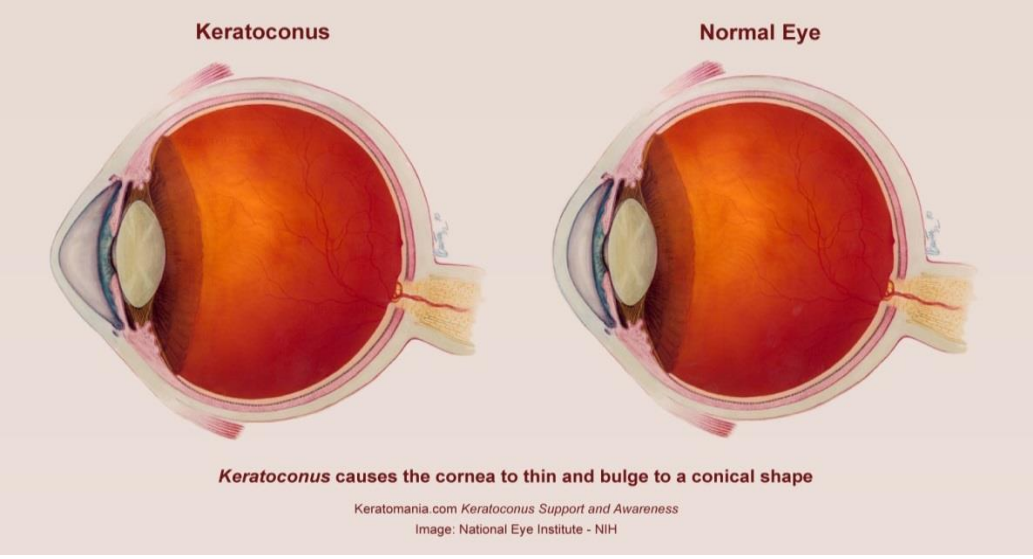
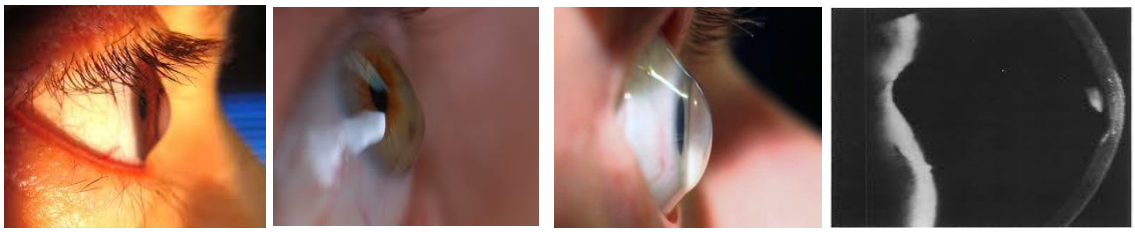


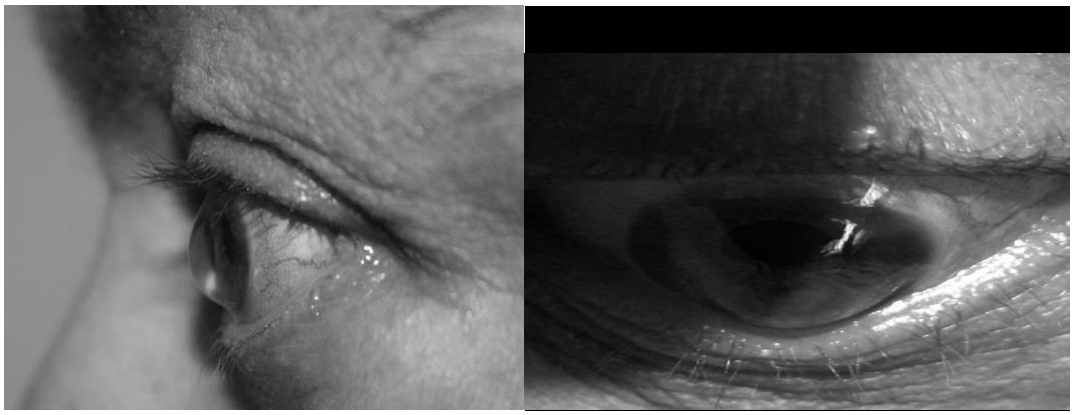
Figure 2.1. *Keratoconus https://www.flickr.com all creative commons license*

Keratoconus is the most common of a group of ectatic corneal disorders causing corneal irregularity, such as pellucid marginal degeneration (PMD), Terrien's corneal marginal degeneration, keratoglobus and posterior keratoconus (Figures 2.2, 2.3, 2.4, Table 2.1). These conditions and corneal irregularity due to trauma or surgery generate a degraded retinal image due to induced HOA and therefore usually require optical management with specialty contact lenses (Feder and Gan, 2011). Eyes with keratoconus were shown to have 5.5 times more HOA than eyes with regular corneae (Pantanelli *et al.*, 2007). In practice HOA in keratoconus result in reduced vision that, in moderate and severe cases, cannot be fully corrected with spectacles (Watts and Colby, 2017).



a. Keratoconus b. PMD c. Keratoglobus d. Posterior KC

Fig 2.2 *Cornea ectatic disorders (https://images.google.co.uk/)*

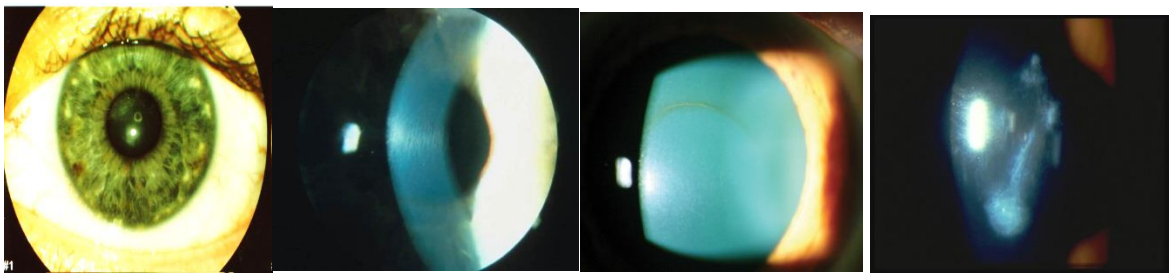


a. b.

Figure 2.3 *a. Keratoconus, side view, b. Keratoconus Munson's sign*

Table 2.1 *Noninflammatory ectatic disorders – clinical presentation and appearance compared and contrasted (Feder and Gan, 2011).*

Condition	Keratoconus (KC)	Pellucid marginal degeneration (PMD)	Keratoglobus	Posterior keratoconus
Features ↓				
Frequency	Most common	Less common	Rare	Least common
Laterality	Usually bilateral	Bilateral	Bilateral	Usually unilateral
Age at onset	Puberty	Age 20 to 40 years	Usually at birth	Birth
Corneal thinning	Inferior paracentral	Inferior band 1-2 mm wide	Greatest in periphery	Paracentral posterior excavation
Corneal protrusion	Thinnest at apex	Superior to band of thinning	Generalized	Usually none
Iron line (Figure 2.4c)	Fleischer ring*	Sometimes	None	Sometimes
Scarring (Figure 2.4a)	Common	Only after hydrops***	Mild	Common
Striae** (Figure 2.4b)	Common	Sometimes	Sometimes	None



a. b. c. d.

Figure 2.4. a. Authors image, corneal scarring **b**. Vogt's striae **c**. Fleischer's ring **d.** Stromal Scarring. (https://images.google.co.uk/)

[**Fleischer's ring is not always found in keratoconus but when it is present it is pathognomonic of the condition and consists of a deposit of ferrous metal in the gutter created by the bulging protrusion of the cornea. It is a partial or complete annular line, commonly starts at the base of the cone. When identified, it provides a landmark for the peripheral edge of the cone. As the ectasia progresses, the ring tends to become more densely pigmented and narrower, and it may completely encircle the cone at its base.*

***Striae occur in the posterior stroma, just anterior to Descemet's membrane. They disappear when intraocular pressure is raised, by exerting digital pressure on the globe. Striae are to be distinguished from the superficial linear scars, which may be seen in keratoconus at the corneal apex; scars do not disappear when pressure is applied.*

****Corneal Hydrops occurs in more advanced ectasiae, when aqueous humour penetrates into ruptures in Descemet's membrane. This causes acute corneal oedema, which may persist for weeks or months, usually diminishing gradually. Eventually, it is replaced by scarring which in some cases may result in flattening of the cone*].

Prevalence, incidence, distribution and disease course

Keratoconus occurs in all races with no clear gender predominance (Ramez *et al.*, 2017). Due in part to varying diagnostic criteria the prevalence of keratoconus may vary significantly in different studies, on average from 50-200 per 100,000 (Feder and Gan, 2011). The prevalence of keratoconus exhibits significant demographic variations from the extremely low prevalence of 0.0003% in Russia to 2.3% in central India (Gorskova and Sevost'ianov, 1998; Jonas *et al.*, 2009). The role of ethnicity in the prevalence of keratoconus is demonstrated in the two survey reports from the United Kingdom; these indicate a 4.4–7.5 times greater prevalence of keratoconus in Asians (Indian, Pakistani and Bangladeshi) compared with Caucasians, suggesting a significant role of ethnicity (Georgiou *et al.*, 2004; Pearson *et al.*, 2000).

Ethnicity was also found to play an important role in the incidence of keratoconus, which exhibits a significant difference between the Asian: 25 per 100000 (1 in 4000) and white 3.3 per 100000 (1 in 30000), per year respectively ($p<0.001$), with Asians presenting at significantly younger age (Georgiou *et al.*, 2004).

Unlike the displaced apex syndrome, where the off axis corneal apex appears like early keratoconus on corneal topography (Belin and Khachikian, 2011), keratoconus is a progressive disorder with an onset typically at puberty and a progression course of 10-20 years (Ramez *et al.*, 2017). The rate of progression is variable and by the time it stops it may range from mild irregular astigmatism to severe protrusion, thinning and scarring, which may require *keratoplasty* (corneal transplant surgery) for restoration of reasonable vision (del Barrio *et al.*, 2017).

Aetiology

Heredity

Heredity seems to play an important role in the aetiology of keratoconus as very high concordance is found in monozygotic twins (Edwards *et al.*, 2001). Keratoconus prevalence of first-degree relatives was found to be 3.34% which is up to 68 times higher than in the general population (Wang *et al.*, 2000). Gordon-Shaag *et al.*, (2013) reported that in an Arab keratoconic population in Jerusalem, children of consanguineous parents had a fourfold risk of keratoconus compared with those of unrelated parents. Woodward (1981) found that keratoconus was maternally age related and was reflected in the social class (professional and intermediate class) of the patients attending the Moorfields contact lens clinic, were born at older maternal age compared with the general population ($p<0.001$) (Woodward, 1981). It is possible that some forms of keratoconus are under direct genetic control, other forms may require environmental stimuli to develop and progress (Gordon-Shaag *et al.*, 2013).

Eye rubbing

Despite the various associations with systemic disorders and ocular disease and the attempt of early theories to link the systemic and ocular disease associated with keratoconus, the aetiology of keratoconus remains unclear. Eye rubbing prevalence among keratoconus patients ranges from 66%-73% (Krachmer *et al.*, 1984) and has been implicated as a causative and contributory factor in the development and progression of keratoconus (McMonnies, 2016; Gordon-Shaag,Millodot,Kaiserman *et al.*, 2015; Gasset *et al.*, 1978; Rahi *et al.*, 1977) by inducing a direct mechanical trauma and by increasing the *protease* tear film inflammatory mediators (Balasubramanian *et al.*, 2013). The mechanical micro-trauma associated with eye rubbing may be the etiologic link between keratoconus and associated systemic and ocular diseases. Itching, ocular irritation, and eye rubbing are common features of vernal keratoconjunctivitis and atopic disease which are significantly more prevalent in keratoconus (Gasset *et al.*, 1978). Vigorous eye rubbing is commonly observed in trisomy 21 (Down's syndrome), which has a higher incidence of keratoconus and may explain the high incidence of associated corneal hydrops. Eye rubbing is also commonly seen in Leber's tapeto-retinal degeneration and retinopathy of prematurity, both of which are associated with keratoconus (Feder and Gan, 2011). Regular repeated counselling against eye rubbing is indicated in patients with keratoconus and other corneal disorders to avoid corneal trauma associated with eye rubbing (McMonnies, 2016).

Biomechanics

The corneal biomechanics in keratoconus are thought to be abnormal; the keratoconic cornea is more fragile and has impaired capabilities to recover from chronic corneal epithelial trauma, which is considered a causative factor in the thinning of the corneal stroma and therefore associated with the pathogenesis and progression of keratoconus (Kim *et al.*, 1999; Wojcik *et al.*, 2014). Corneal thinning may be caused by weak stromal inter-lamellar attachments, which result in free lamellar sliding and the biomechanical instability of this tissue, which may be caused by the significant alterations in the orthogonal arrangement and the reduced number of

the collagen fibrils (Daxer and Fratzl, 1997). The reduced inter-lamellar collagen fibrils strength profile in the inferior compared with central stroma in the normal cornea, may explain the association of keratoconus with eye rubbing, which applies pressure gradient from top to bottom (Smolek and Beekhuis, 1997).

Biochemistry

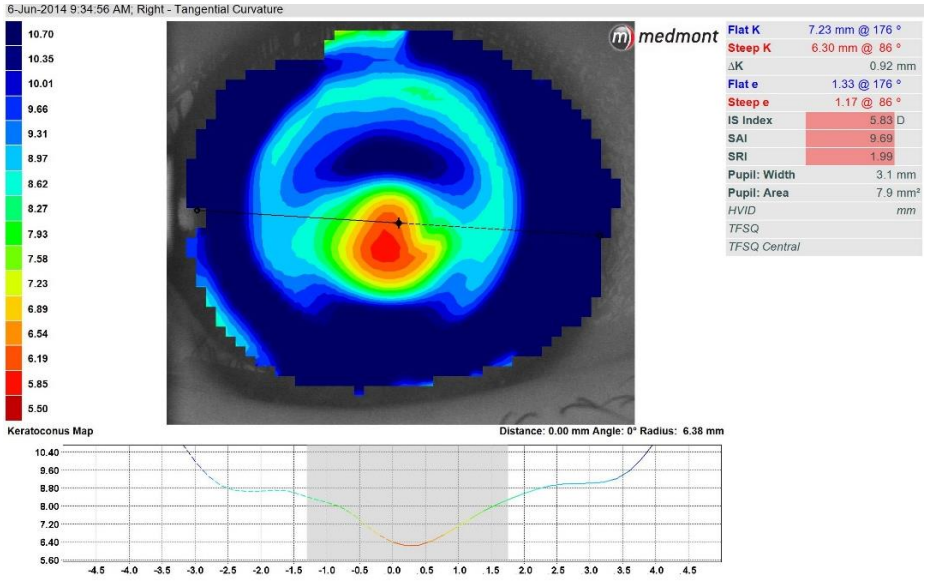
Biochemical studies show that the total amount of corneal protein is decreased in keratoconus (Critchfield *et al.*, 1988). The micro trauma caused to the keratoconic corneal epithelium by eye rubbing or interaction with the rigid surface of a contact lenses elevates the secretion levels of matrix metalloproteinase MMP-1 and MMP-13 (Mackiewicz *et al.*, 2006) and inflammatory mediators such as IL-6 and TNF-α (Lema *et al.*, 2009). The release of these factors by the corneal epithelium in response to the mechanical insult of eye rubbing or contact lens wear triggers an undesirable apoptosis of corneal stromal keratocytes and loss of stromal volume and may lead to scarring in individuals with heightened sensitivity to interleukin-1 such as occurs in keratoconus (Wilson *et al.*, 1996). These processes suggest that keratoconus may have inflammatory aetiology.

Pathology

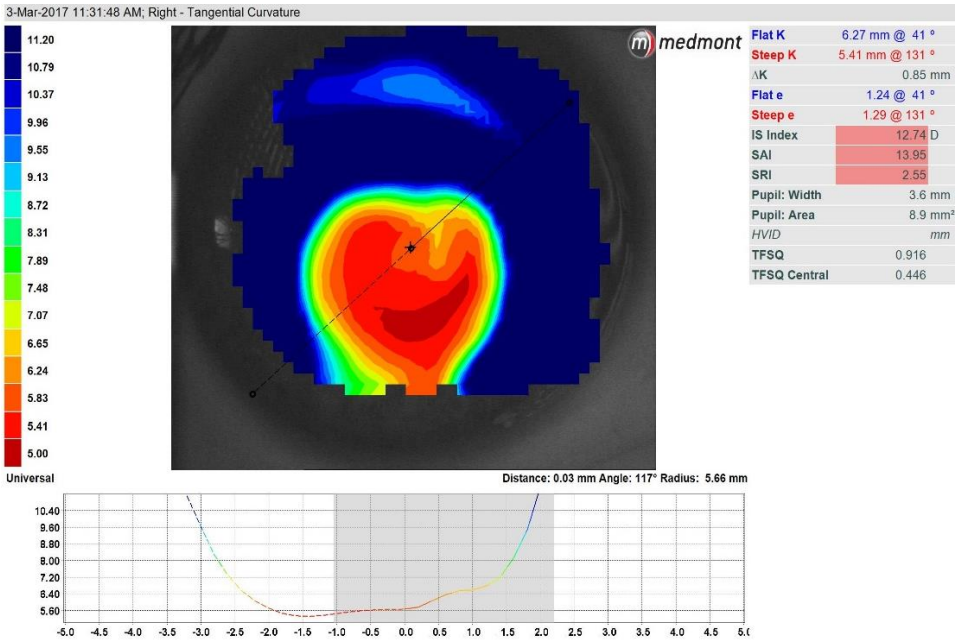
Every layer of the cornea may be involved in the pathologic process of keratoconus. Fragmentation of the Bowman's layer is an early change which leads to the progression of the disease and is specific to keratoconus (Sawaguchi *et al.*, 1998). Z shaped interruptions, which are typical to keratoconus, are formed at the level of Bowman's layer allowing the corneal epithelium to grow backwards into the stroma and the stromal collagen to grow anteriorly into epithelium. The basal epithelium accumulates ferritin (iron) particles which eventually form

the Fleischer ring. The breaks in the Bowman's layer are correlated to the clinically observed spaces within the thin stroma of the cone and are postulated to later fill with scar tissue and create the reticular branching opacities (Shapiro *et al.*, 1986).

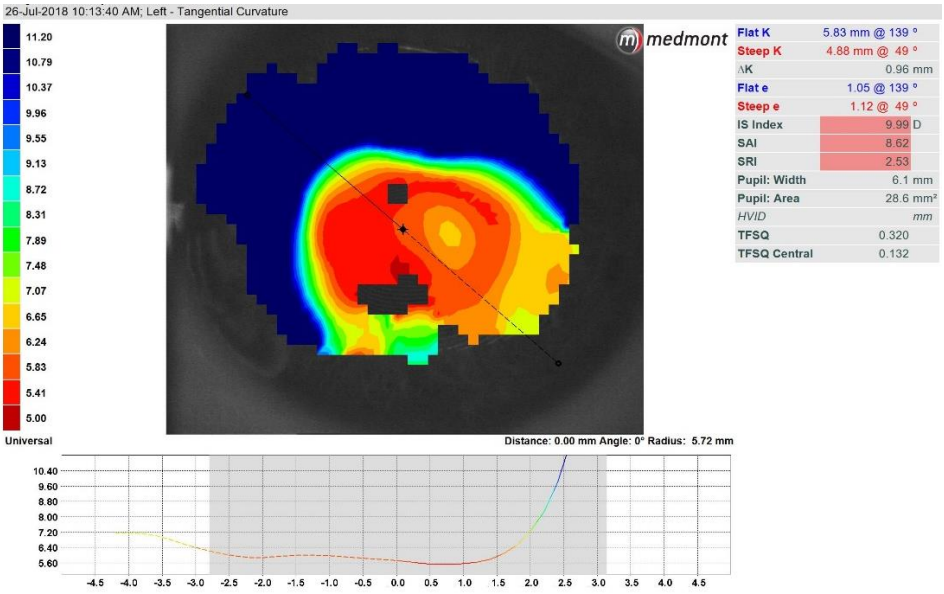
Very early keratoconus may show small islands of corneal steepening, as keratoconus progresses, the conical area increases in size and decentration and may be classified into one of three shapes: nipple, oval (Perry *et al.*, 1980) and globus (Feder and Gan, 2011) (Figure 2.5). Nipple cones typically display a central or infero-nasally decentred apex and are characterized by the presence of a 5mm steepened region surrounded by normal peripheral cornea. Oval cones, which are the most common, are larger than nipple cones. They are characterized by an inferior area of steepening with an infero-temporally displaced apex. In early stages of the disease superior cornea remains relatively normal. As the oval cone progresses, it proceeds in a radial fashion, with ectasia spreading into the temporal cornea, and in later stages it encompasses the superior cornea as well. Often a small island of normal cornea will persist in the superior nasal quadrant. Unlike nipple cones, oval cones show greater destruction of the underlying corneal layers (Perry *et al.*, 1980). Globus cones are the largest in area and rarest of the three types. These cones generally involve at least 75% of the corneal surface (Robertson and Cavanagh, 2011).



A. Nipple cone



B. Oval Cone



C. Globus cone

Figure 2.5. *Corneal Topography of the 3 cone types, red indicates a steeper corneal curvature and blue flatter.*

Diagnosis

Presenting visual symptoms may range from a minor deterioration in vision to symptoms of considerable blur, photophobia [*discomfort in bright light*], glare, monocular diplopia [*double vision*] and ocular irritation (Feder and Gan, 2011).

Age of presentation is typically during teens or twenties (Ramez *et al.*, 2017). CS testing may uncover visual dysfunction before the more standard high contrast VA examination (Zadnik *et al.*, 1987).

Characteristic findings during slit lamp bio-microscopy examinations are prominent corneal nerves and fine parallel striae (Vogt's striae) observed in the posterior stroma, anterior to Descemet's membrane, these striae disappear when gentle pressure is applied on the globe (Sherwin *et al.*, 2017). Iron deposits at the base of the cone known as Fleischer ring, may be observed as incomplete initially, to complete rings at the demarcation of the base of the cone. As the disease progresses corneal thinning may be observed at the cone apex as well as superficial linear scars which result from ruptures in the Bowman's layer. In more advance keratoconus ruptures in Descemet's membrane create deeper opacities at the cone apex. Aqueous imbibition into the stroma through these defects in Descemet's membrane may cause corneal oedema (*hydrops*) also known as acute keratoconus, which may persist for weeks or months, eventually replaced by scar tissue (Feder and Gan, 2011). Intra-stromal cysts or clefts may occur as a result of corneal hydrops, which may lead to stromal neovascularisation (invasion of small blood vessels), which poses a higher risk of future corneal graft rejection (Parker *et al.*, 2015).

Corneal scarring due to keratoconus disease progression occurs in approximately 30% of eyes (Barr *et al.*, 2000; Zadnik *et al.*, 1998). Corneal scarring induces forward and backward scatter and absorption of light, which results in reduction of VA. Corneal scarring may occur as a natural disease progression in keratoconus or may be induced or accelerated by external factors such as CRGPcl flat fitting CRGPcl (Korb *et al.*, 1982).

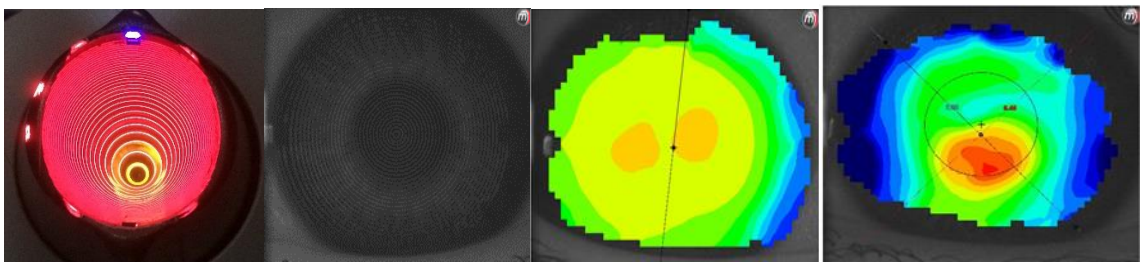
Keratometry and Topography

The keratometer measures corneal curvature of the principal meridians only at a central 3-4mm, by superimposing fine images of projected mires (targets) reflected from the cornea. Inability to superimpose these images suggests irregular corneal astigmatism, a hallmark of keratoconus. There is no keratometric value beyond which the diagnosis of keratoconus is definite. Steepening of the inferior cornea compared to central cornea is typical in keratoconus and may be identified by keratometry (Feder and Gan, 2011).

Corneal topographers were developed to enable accurate measurement of larger corneal surface area, originally introduced by Antonio Placido in 1880, consisted of circular, alternating black and white mire pattern, with a central aperture through which the clinician could view the reflected virtual image (Versaci and Vestri, 2017). Video capture of Placido disk images and the automatic detection of the mires facilitated calculation of corneal shape and power distribution, represented in modern topography with the color-coded contour maps introduced by Maguire and associates (Maguire *et al.*, 1987). The 'warmer' colours represent higher dioptric powers and steeper curvatures, the 'cooler' colours represent the lower dioptric powers and flatter curvatures. Similar color-coded maps can be used to present changes in corneal elevation.

The slit-based tomographers measure both the anterior and posterior corneal surface, which enables the measurement of corneal pachymetry (thickness), which greatly aids in the diagnosis of corneal ectasiae (Versaci and Vestri, 2017). Pachymetry measurements have become essential in the diagnosis of early keratoconus, grading disease severity and shown that the thinnest areas of the corneal stroma are generally infero-temporal to the line of sight (Ambrósio *et al.*, 2017).

The two topographical approaches in general use currently are the Placido disk or reflection-based topographers, and the scanning slit-based tomographers. However, other methods to measure corneal shape have been developed and include scanning slit technology, raster stereography, scanning high-frequency ultrasound, holography, Fourier profilometry, and optical coherence tomography (OCT) (Martinez and Klyce, 2011; Versaci and Vestri, 2017; Cavas-Martínez *et al.*, 2017).



A. **B.** **C.** **D.**

Figure 2.6. ***A*** *Topographer with Placido rings* ***B*** *Rings reflected from cornea* ***C*** *color-coded contour map normal cornea.* ***D*** *color-coded contour map Keratoconus*

Computer-assisted corneal topographers have become an essential standard in the diagnosis of subclinical keratoconus and for tracking the progression of the disease (Wilson and Klyce, 1991a; Duncan *et al.*, 2016a). Various methods for the measurement and display of corneal topography have emerged. The original reflected Placido rings systems have evolved and are used in isolation or in conjunction with slit-scan systems; raster-stereography and scheimpflug photography in the analysis of corneal topography and keratoconus detection (Versaci and Vestri, 2017) (Fig 2.6). Corneae are radially asymmetric, aspheric, and may be irregular (Bogan *et al.*, 1990). This is particularly true for corneae of patients who have corneal ectatic disorders (Martinez and Klyce, 2011).

A number of statistical indices have been created from corneal topography data in order to derive corneal quantitative measurements, classification and screening algorithms, such as the simulated keratometry, which measure the power derived from the four points in the central 3–4mm of the principal meridians and may be used for numerous tasks from diagnostics to contact lens fitting. Irregularity of the corneal topography over the pupil is represented with the Surface Regularity Index (SRI) (Wilson and Klyce, 1991b), which is correlated to potential visual acuity and is a measure of local fluctuations in central corneal power. It represents the regularity of the central corneal surface in front of the pupil; higher values suggest higher irregularity and a consequent reduction in visual acuity (Cavas-Martínez *et al.*, 2017).

Conversion of corneal topography to corneal wave-front may be used for the presentation and evaluation of corneal optics. Fourier transforms and Zernike polynomials are also quantitative descriptors of corneal surface optics and can be used to calculate the optical aberrations of the cornea (Figure 2.7) (Keller and van Saarloos, 1997; Oliveira *et al.*, 2012).

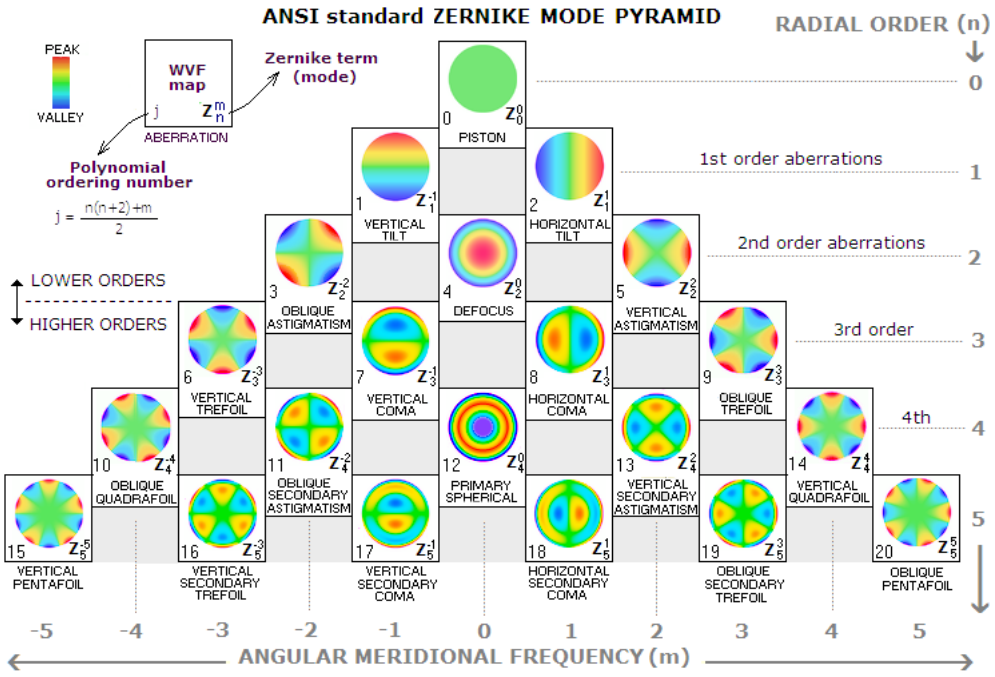


Figure 2.7. *Zernike Polynomials https://images.google.co.uk/*

Other indices were developed to detect specific patterns seen in corneal ectatic conditions, and artificial intelligence techniques were used in the algorithms to recognize topographical appearances of keratoconus and other abnormal corneal conditions (Swartz *et al.*, 2007; Duncan *et al.*, 2016b; Lopes *et al.*, 2016).

Management and treatment of keratoconus

When keratoconus is mild it may be successfully managed with spectacle and soft contact lens correction. If disease progression is detected, treatment to increase corneal rigidity, collagen cross-linking (CXL), may be considered to halt or slow the progression of keratoconus (Wittig-Silva *et al.*, 2008; Giacomin *et al.*, 2016; O'Brart, 2017). CXL is achieved by corneal stromal saturation with riboflavin followed by irradiation with ultraviolet-A light, which induces cross-links at the surface of collagen fibrils, with resultant overall increase in mechanical stiffness, which usually halts the progression keratoconus (Bao *et al.*, 2017).

If spectacles and standard contact lenses fail to provide adequate visual function, specialist contact lenses are required to manage the visual disability caused by the corneal irregularity in keratoconus (Watts and Colby, 2017). Contact lens intolerance may result from epithelial breakdown over a sub-epithelial scar at the apex of the cone. This epithelial abnormality may be debrided by a special laser assisted procedure, phototherapeutic keratectomy and after the cornea has healed, contact lens wear may be resumed (Rapuano, 1997).

Individuals with early to moderate keratoconus, without central scarring who are intolerant to contact lenses, may be candidates for intra-stromal ring segment (INTACS) insertion. This procedure flattens the central cornea when circular plastic implants are inserted into specially created tunnels in the peripheral corneal stroma aiming to reshape the cornea and reduce its irregularity (Alio *et al.*, 2006; Kılıç *et al.*, 2017).

When stable and comfortable contact lens fit cannot be achieved or when contact lenses fail to provide adequate vision, surgical management may be considered. Keratoplasty (corneal transplantation) depend on the individual's needs and the surgeon's preferred technique. Traditionally full thickness corneal replacement, penetrating keratoplasty, which entails removing the entire thickness of the cornea and replacing with donor tissue, has been the surgery of choice (Bao *et al.*, 2017). The partial removal and replacement of stromal tissue; lamellar keratoplasty may be considered for mild to moderate disease. A more recent alternative used is deep anterior lamellar keratoplasty, in which only the anterior corneal layers are removed and replaced with healthy donor tissue, leaving Descemet's membrane and endothelium, with the advantage of preserving these tissues (Feder and Gan, 2011; del Barrio *et al.*, 2017).

Summary

Chapter 2 outlines relevant aspects of corneal ectatic disorders, specifically keratoconus, the most commonly encountered corneal ectasia. The complex, multifactorial aetiology of keratoconus remains only partially understood, with inconclusive evidence regarding environmental and genetic influences. Recent research, which revealed evidence to overexpression of inflammatory mediators undermines the very definition of keratoconus as a non-inflammatory corneal disorder. The consensus regarding keratoconus is that it is a bilateral, progressive disorder, with highly variable prevalence and incidence, due in part to its

complex aetiology, but also the variability in diagnostic criteria. The significantly detrimental effect of keratoconus on the integrity of the retinal image and therefore on vision is universally accepted, and results from irregular astigmatism and high order aberrations and in many cases corneal scarring. The impact of keratoconus is exacerbated by young age at which the disease presents. When keratoconus progresses to levels which are not amenable to standard optical corrections with spectacles and soft contact lenses, the preferred mode of management is RGPcl, which neutralise the corneal irregularity and facilitate restoration of clear vision. Contact lens management of keratoconus will be discussed in the next chapter.

Chapter 3: Literature review: contact lenses in the management of keratoconus.

In this chapter, key literature on the contact lens management of keratoconus and related disorders will be presented. Based on the literature presented, the rationale for the research described in successive chapters will be outlined. The methodology of literature search in this chapter is outlined in the section *Methodology of literature search* section at the beginning of chapter 2 page 30.

Introduction

Contact lenses have evolved since the 1900s when they were made from materials impervious to air such as glass or polymethylmethacrylate, to the modern highly gas permeable soft and rigid materials (Robertson and Cavanagh, 2011). Soft contact lenses became commercially available in 1965 and have improved considerably over the years, in design, manufacture, and material (e.g., improved oxygen permeability).

Contact lenses are routinely used as the primary mode of vision correction and in 2007 were estimated to be used by 125million wearers worldwide (Key, 2007). They offer obvious cosmetic benefits and improvement in Qol (Plowright *et al.*, 2015), compared with glasses (Ehsaei *et al.*, 2011). Superior visual performance over spectacles is achieved by the elimination of the magnification effects, which degrade visual quality in individuals with high myopia / hyperopia, astigmatism or anisometropia [*large difference in refractive error between the eyes*] (Benjamin, 2006; Taylor Kulp *et al.*, 2006). The well-centred optical zone of contact lenses, unlike the fixed optical zone of spectacles, moves with the eyes, providing improved optical alignment with the direction of gaze, thereby improving peripheral and binocular vision. For patients with uncorrected regular and irregular astigmatism, rigid lenses often provide superior to spectacle visual quality through the formation of an aqueous ‘lens’ in the post lens

tear film, which optically neutralizes regular and irregular corneal astigmatism (Robertson and Cavanagh, 2011; Watts and Colby, 2017). Modern contact lens designs can meet almost any individual optical requirement in both healthy and pathological eyes. These optical advantages of contact lenses may be offset in some cases by the contact lens interaction with the tear film, such as occur in ocular surface abnormalities associated with dry eyes and other tear film dysfunctions (Muntz *et al.*, 2015). Other significant limitations of contact lenses are interruption of oxygen (O_2) supply to the cornea, risk of infection and mechanical trauma.

Contact lenses pose a barrier to natural corneal respiration since the cornea, which has no direct blood supply, relies on its contact with the atmosphere for supply of O_2 and removal of carbon dioxide (CO_2). The barrier that contact lenses pose to normal gas exchange between the cornea and the atmosphere was found to cause corneal warpage, vascularization, oedema, and susceptibility to infection (Robertson and Cavanagh, 2011). Contact lens materials have evolved continuously over the past several decades to improve O_2 permeability, to maintain healthy corneal physiology.

Contact lens material permeability to air is defined as Dk, where D is the *diffusion coefficient* of the material and k is the *air solubility constant* (Fatt, 1986). The *O_2 transmissibility* of a specific lens is a measure of O_2 permeability as a function of lens thickness, Dk/t (Fatt, 1986; Nicolson and Vogt, 2001). The higher the DK and the DK/t values the better the transmission of air through the contact lens matrix, leading to healthier the corneal physiology during contact lens wear (Fatt, 1996).

Microbial keratitis is the most serious complication of contact lens use, and contact lenses are a major risk factor for corneal ulcers (Cohen, 2011). Corneal ulcers are usually caused by bacteria such as pseudomonas, other microorganisms such as fungi and amoeba may be involved in microbial keratitis in contact lens wearers.

Mechanical corneal trauma from contact lenses such as corneal abrasion, can cause discomfort, compromise the physical barrier to resident and foreign microorganisms and can produce scarring that impairs visual function. Intensive antibiotic treatment may be required if the abrasion is associated with immune-mediated infiltrates because it may rapidly develop into a microbial keratitis (Cohen, 2011). In keratoconus mechanical trauma is associated with reduced contact lens tolerance, scarring and disease progression due to corneal scarring, which will be discussed in detail below.

Contact lens types

Soft contact lenses

Conventional soft, flexible lenses are composed of a HEMA (*2-hydroxyethylmethacrylate*) core polymer and a hydrophilic monomer which functions to absorb water. To reduce the rate of infection and other complications associated with contact lens wear, materials with better lens-cornea *biocompatibility* and oxygen transmissibility were developed to optimize corneal physiology during contact lens wear (Holden and Mertz, 1984).

Corneal rigid gas permeable contact lenses (CRGPcl)

In the early 1980s, newer Rigid Gas Permeable contact lens (RGPcl) materials and designs emerged replacing the original impermeable polymethylmethacrylate material. Compared with early soft contact lenses, CRGPcl offer significant physiological advantages as well as improved comfort and safety because they do not cover the entire corneal surface, feature high O_2 permeability/transmissibility values and due to their mobility during blinks generate continuous tear exchange. Additional advantages of CRGPcl over soft lenses include increased durability, enhancement of visual acuity, due to neutralization of both regular and irregular corneal astigmatism (Benjamin, 2006) and a decrease in adverse reaction due to resistance to binding of tear film deposits and chemically preserved contact lens care solutions. Despite the advantages of RGP materials, the majority of contact lens wearers use soft lenses owing to greater comfort during adaptation (Morgan and Efron, 2006).

Scleral gas permeable contact lenses (SRGPcl)

SRGPcl vault (bridge over) the cornea and limbus and are physically supported entirely by the conjunctival tissue overlying the sclera (van der Worp, 2015). The lack of widespread use of SRGPcl since their inception in the 1880s is attributable to limitations in corneal imaging systems, problems with contact lens manufacturing technology and products and skills required for fitting, cost and patient perceptions. The use of SRGPcl has recently increased due to availability of large-diameter RGP buttons, from which lenses are lathe cut, improvement in corneal and scleral contour assessment and computer-driven lathes, which are now able to accurately produce large-diameter lenses to precise specifications. The development of complex modern SRGPcl designs and availability of diagnostic fitting sets have recently facilitated a more widespread utilisation of these lenses (van der Worp *et al.*, 2014).

Contact lenses in corneal disease

Common indications for therapeutic contact lenses include their use as a bandage to support and protect the cornea, manage pain, and aid in epithelial healing following abrasions or recurrent corneal erosions. Bandage contact lenses most commonly fitted are the soft highly O_2 permeable, such as silicone hydrogel contact lenses, although large diameter CRGPcl and SRGPcl may occasionally be utilised in the rehabilitation of diseased ocular surface (Christie, 1999).

In eyes with keratoconus the visual distortions lead to significantly lower visual Qol scores compared to individuals with normal corneal health (Tatematsu-Ogawa *et al.*, 2008; Aydin Kurna *et al.*, 2014). Vision in eyes with keratoconus may be markedly improved by RGPcl, by the optical neutralisation of the corneal irregularity by the tear layer formed by the regular rigid contact lens surface (Benjamin, 2006). Due to the similarity in the refractive index of the cornea and the tear film under the RGPcl, 90% of the corneal irregularity is optically neutralised (Figure 3.1) (Szczotka-Flyn *et al.*, 2006).

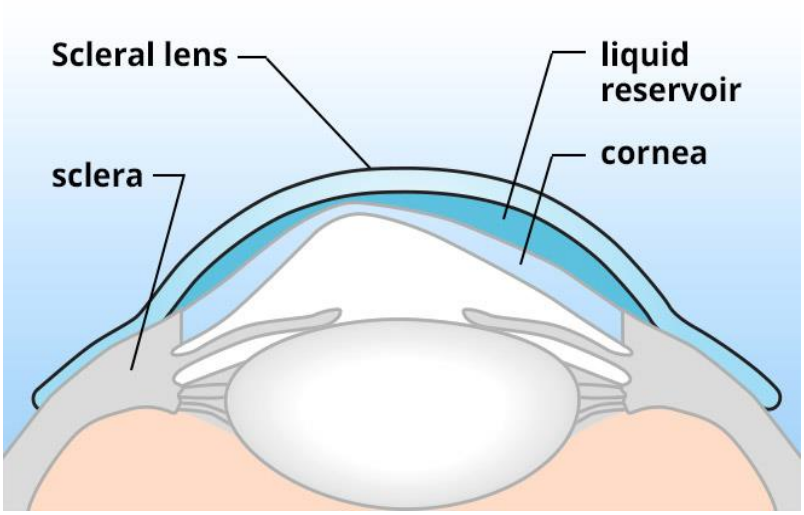


Figure 3.1. *Neutralisation of corneal irregularity by tear film reservoir (https://images.google.co.uk/.)*

According to the *Scleral lens education society*, the classification of RGPcl is determined by the area of contact between the lens and the ocular surface (van der Worp, 2015). If a lens bears on the cornea only, it is called a CRGPcl (Figures 3.2. a, b). A lens which partly rests on the cornea and partly on the sclera is called a corneo-scleral lens. A lens which rests entirely on the sclera is classified as a SRGPcl (Figure 3.3) (van der Worp *et al.*, 2014). Over the years a plethora of contact lens designs has emerged.

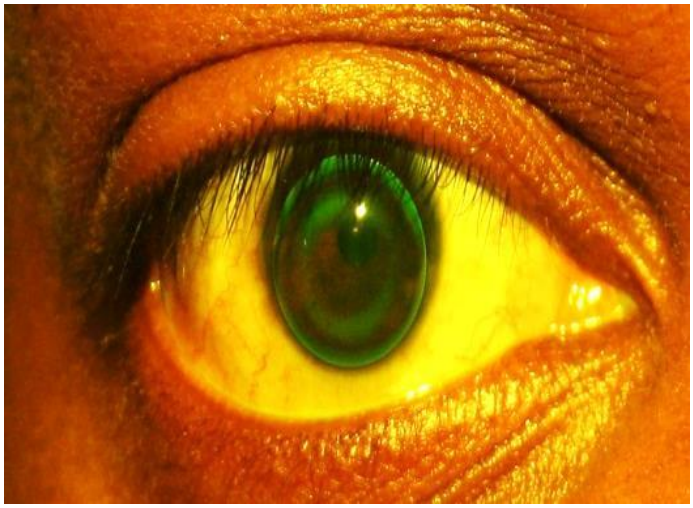


Figure 3.2. *CRGPcl on eyes with keratoconus*

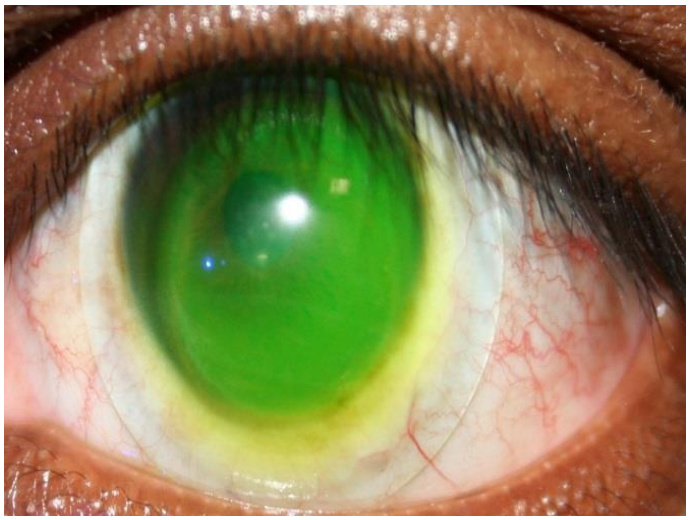


Figure 3.3 *SRGPcl on an eye with keratoconus*

The relatively smaller CRGPcl, which distribute their weight on the cornea, are currently considered the gold standard in the management of the visual disability caused by keratoconus (Robertson and Cavanagh, 2011). Until a few years ago SRGPcl were fitted by a handful of specialized contact lens practitioners around the world and manufactured by few manufacturers (van der Worp *et al.*, 2014). Despite the recent resurgence in the use of SRGPcl, these lenses are used mainly for advanced disease, a problem solver in the more challenging cases, or where other contact lens management options fail. (Schornack, 2015; Visser *et al.*, 2016).

In the initial early stages of keratoconus spectacles and soft contact lenses may be sufficient to manage the ametropia. Corneae often become hypersensitive in the initial stages of the disease due to stretching of the corneal nerve fibres within the steepened corneal area, which may make adaptation to CRGPcl more difficult (Robertson and Cavanagh, 2011).

Although soft contact lenses offer better initial comfort then CRGPcl, because of low modulus of elasticity soft contact lenses as a rule conform to the irregular corneal shape (Holden and Zantos, 1981) and therefore do not effectively neutralise the irregular astigmatism induced by keratoconus. Thicker than standard custom soft contact lenses are manufactured to reduce the cornea draping effect and similar to RGPcl generate a tear reservoir to neutralise the irregular corneal astigmatism. A study by Jinabhai *et al.* (2014) investigated the performance of such lenses in habitual CRGPcl wearers. They found that these soft lenses failed to match the superior visual performance achieved by the habitual CRGPcl (Jinabhai *et al.*, 2014).

Management of keratoconus

Contact lens types for the management of keratoconus are summarised in Table 3.1. CRGPcl are fitted directly onto the corneal surface to correct the corneal optical abnormalities, these lenses are relatively small and cover up to 80% of the corneal surface area, attached to it by *surface tension* forces. There is no standard fitting algorithm for every cornea with keratoconus, it is therefore imperative to employ a variety of lens designs to address individual cases. Although multiple CRGPcl designs are utilised in the management of keratoconus, there is to date a lack of high-quality evidence from controlled prospective clinical trials comparing the performance of different proprietary CRGPcl designs (Downie and Lindsay, 2015).

Topographical assessment of corneal shape and curvature, revealing the shape, type, size and position of the cone, is an essential first step in CRGPcl fitting. Specialist designs of CRGPcl are available, such as the *Rose-K* design (Menicon USA, Clovis, CA), which was found to be successful for centrally positioned cones (Ozkurt *et al.*, 2008). The Rose-K and other CRGPcl for keratoconus are designed with steeper than normal central lens curvature to fit the steep corneal cone, and flatter peripheral lens curvature to align the more normal corneal periphery and distribute the weight of the lens in that area, to avoid excessive mechanical pressure on the cone (Watts and Colby, 2017). These lenses are available in overall diameters of 7.9–10.2mm, with central curves ranging from 4.75mm (steep) to 8.0mm (relatively flat). Variable peripheral curves are designed for attaining the recommended peripheral corneal alignment and the desired *lens edge lift* of 0.8mm in order to facilitate good tear exchange. The newer Rose-K2 lens design incorporates a posterior, central aspheric curve, for further optimisation of lens fit and vision and is advocated not only for centrally positioned nipple cones but also for oval cones (Romero-Jimenez *et al.*, 2013).

The stability of CRGPcl is affected by the lens cornea fitting relationship: eyelid forces (e.g., during blinking) and gravitational forces. These lenses therefore exhibit a level of inherent positional instability on the cornea, which is more pronounced when fitted to eyes with keratoconus. CRGPcl may display *multidirectional movement*, *decentration*, *rotation*, *rocking*, *tilt* and *flexure*, all of which may reduce comfort and cause retinal image degradation by inducing optical aberrations. Zadnik *et al.*, (2000) reported in the *Collaborative Longitudinal*

Evaluation of Keratoconus (*CLEK**) study, that CRGPcl fitted to unscarred keratoconic eyes achieved what is considered normal BCVA in only 34.6% of cases (Zadnik *et al.*, 2000).

*[*The (CLEK) study is an eight-year, multi-centre, natural history study of 1,209 CRGPcl wearing patients with keratoconus who were examined annually for eight years. Its goals were to prospectively characterise changes in vision, corneal curvature, corneal status, and vision related Qol*].

Large diameter RGPcl ranging from 10.4-12.0mm, the *intra-limbal* designs are also used in keratoconus fitting (Ozbek and Cohen, 2006). The resulting larger optic zone (circa 9.4 mm) may improve vision, especially in corneae with decentred cones, due to better lens centration (Watts and Colby, 2017). The drawbacks of these lenses relate to sub-optimal distribution of lens weight over the cone and peripheral cornea and more challenging lens handling.

With advanced cones and significant irregular astigmatism, clinicians may not be able to achieve adequate lens centration and stability with CRGPcl, the semi-scleral and SRGPcl may be fitted. These lenses are designed to rest on the sclera and vault the entire cornea and limbus. The reduced lens movement and minimal lens edge interaction with the eyelids result in comfort similar to soft contact lenses (Visser *et al.*, 2016). SRGPcl are currently available in advanced and varied designs with the aim of achieving better physical fit and optical performance. Fitting of modern SRGPcl is performed through diagnostic lens assessment using trial lenses (van der Worp *et al.*, 2014).

Patients intolerant of CRGPcl may also be fitted with hybrid lenses (Figure 3.4), which have a rigid centre of 8-8.5mm and a soft lens skirt reaching diameters of 14-15mm. In 2008, *SynergEyes* have developed hybrid lenses with skirts made of silicone hydrogel material, with good oxygen transmissibility, which makes these an ideal hybrid lens for keratoconus (Nau, 2008). The commonly encountered problems of corneal hypoxia, oedema and neovascularization with the older hybrid lenses are less likely to occur with the newer materials (improved oxygen permeability) and designs. However, the occasional lens tightening may cause corneal abrasions and allergic reactions such as giant papillary conjunctivitis (Chung *et al.*, 2001).

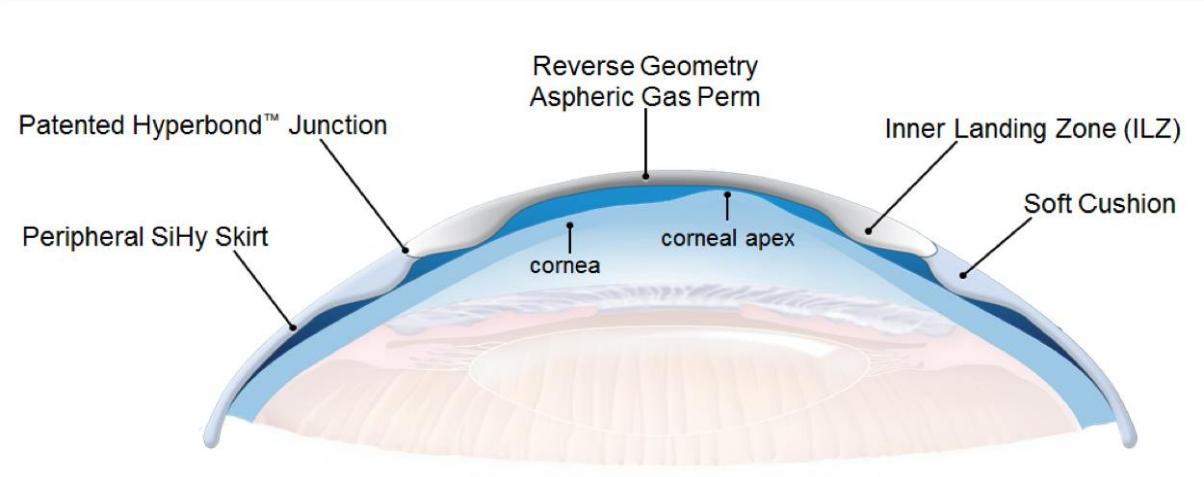


Figure 3.4. *SynergEyes UltraHealth* Hybrid lens for keratoconus *(image kindly supplied by SynergEyes UK)*

Another alternative to CRGPcl are the *piggyback* lens combination (O'Donnell and Maldonado-Codina, 2004). Lens fit is accomplished by first fitting a low plus-power soft contact lens and on top of it a 9.0–9.5mm CRGPcl. Custom soft lens designs are available, such as the *Flexlens* with a *cut-out* or depression to hold the CRGPcl and maintain optimal centration (Watts and Colby, 2017) . My own impression is that the main drawbacks of the piggyback system are the cost of lenses, patient compliance with the complex cleaning regimen of soft and hard lenses and sub-optimal physiological performance due to reduced O_2 transmission through the combination of two lenses.

Table 3.1 *Contact lens options for keratoconus (*Robertson and Cavanagh, 2011 *P.1223)*

Contact lens type	Indication
Conventional hydrogels	Early cones with little astigmatism, lenses will drape the cornea
Silicone hydrogel	Early cones, less lens drape due to higher modulus
Toric hydrogels	Early cones with regular astigmatism
Soft keratoconic designs	Early to moderate cones, increased central lens thickness to mask irregular astigmatism
Corneal RGP standard design	Early to moderate cones, individual lens parameters may be modified to enhance lens fit
Aspheric corneal RGP	Early to moderate cones, lens decentration may cause problems with vision
RGP keratoconus designs	Moderate to advanced cones, may add toric surfaces to enhance vision
Semi-scleral and scleral RGP	Advanced cones, vault the cornea, may use toric designs to enhance lens fit, bi-toric designs to enhance lens fit and vision
Piggy-back and hybrid designs	Moderate to advanced cones, comfort of soft lenses vision of RGP lenses.

CRGPcl in the management of keratoconus

In the following section key literature will be used to describe aspects related to the management of keratoconus with CRGPcl, their fitting approaches and effects on the visual Qol of the lens wearers and corneal pathophysiology.

Quality of life with CRGPcl

Patients with keratoconus require prolonged daily contact lens wearing schedules because their visual wellbeing depends on contact lens correction of their corneal irregularity. The aim of the diagnostic fitting process, which utilises fluorescein* for the assessment of lens fitting patterns, is to achieve the optimal lens cornea fitting relationship. [**sodium fluorescein, NaFl, is a diagnostic dye used routinely in optometric practice for enhancing visualisation of the tear film, cornea and conjunctiva. In RGPcl fitting the NaFl enhanced tear film thickness is evaluated to achieve the desired lens cornea relationship*].

CRGPcl are considered the gold standard in the management of keratoconus. However, their fitting, especially in the more advanced stages of the disease, is not as straight-forward as in normal corneae. Even well-fitting lenses may result in complications such as sub-optimal vision, reduced tolerance and exacerbation of the corneal disease.

Kymes *et al.,* (2004) validated the vision related Qol instrument, the NEI-VFQ for patients with keratoconus. They found that CRGPcl wearers with keratoconus had significantly lower scores in all domains of the NEI-VFQ compared with an age matched reference group from a study of Walline *et al.,* (2000), of healthy CRGPcl wearers (Kymes *et al.*, 2004; Walline *et al.*, 2000). It is therefore suggested that clinicians should carefully evaluate and address the full range of Qol issues that may affect patients with keratoconus (Tatematsu-Ogawa *et al.*, 2008).

Tatematsu-Ogawa *et al.,* (2008) and Kurna *et al*., (2014) also found that vision related Qol was worse in individuals with keratoconus than in healthy individuals when assessed by NEI-VFQ and suggested that the maintenance of good BCVA with contact lens correction may improve vision related Qol (Tatematsu-Ogawa *et al.,* 2008; Aydin Kurna *et al.,* 2014).

Wu *et al*., (2015) reported that CRGPcl do not improve the visual Qol of patients with the more advanced stages of keratoconus. They recommended that other contact lens modalities should be available for those patients to achieve better subjective outcomes (Wu *et al.*, 2015).

Jones-Jordan *et al*., (2013) reported on 961 subjects with keratoconus who completed the NEI VFQ. They found relatively small changes in the NEI-VFQ scores due to the maintenance adequate BCVA in CRGPcl. The authors found that larger ocular asymmetry; decreases in VA and increase in corneal steepness in the better eye were associated with decreasing Qol scores.

They concluded that the vision of the better eye typically has a more significant effect on visual Qol than the difference between the eyes (Jones-Jordan *et al.*, 2013).

Effects of CRGPcl on the keratoconic cornea

Although the scarring of Bowman's layer and the anterior corneal stroma may occur as a natural disease process (Feder and Gan, 2011), the increased susceptibility of the keratoconic corneae to trauma (Wojcik *et al.*, 2014) is thought to be associated with abnormal expression of genes responsible for the biochemical processes in wound healing. Chronic corneal epithelial trauma is therefore thought to be associated with the pathogenesis and progression of keratoconus (Kim *et al.*, 1999; Wojcik *et al.*, 2014). Corneal abrasions and scarring which arise as a result of chronic corneal injury by CRGPcl are therefore a major concern and led to critical reviews and refinements of CRGPcl fitting techniques (Ruben, 1975; McMonnies, 2005; Szczotka-Flyn *et al.*, 2006).

Fitting methods of CRGPcl

There are three philosophies for fitting of CRGPcl in keratoconus (Loft and Wolffsohn, 2016; Szczotka-Flyn *et al.*, 2006; Watts and Colby, 2017).

1. The *apical bearing* fitting method (Figure 3.5a)
2. The apical clearance or *cone vaulting* fitting method (Figure 3.5b)
3. Three-point-touch, or the *divided-support* fitting method (Figure 3.5c)

1. The apical bearing with primary lens support and bearing on the apex of the cornea and minimal peripheral stabilisation.

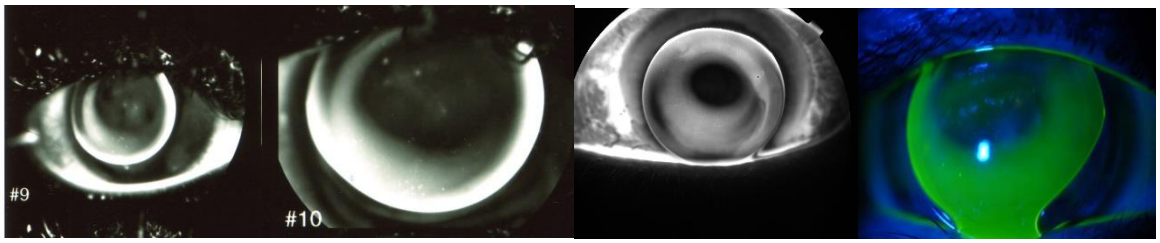


Figure 3.5a. *Examples NaFl patterns in flat central fitting with cone bearing.*

2. Apical clearance or cone vaulting, with lens support and bearing directed away from the apex to the para-central cornea.

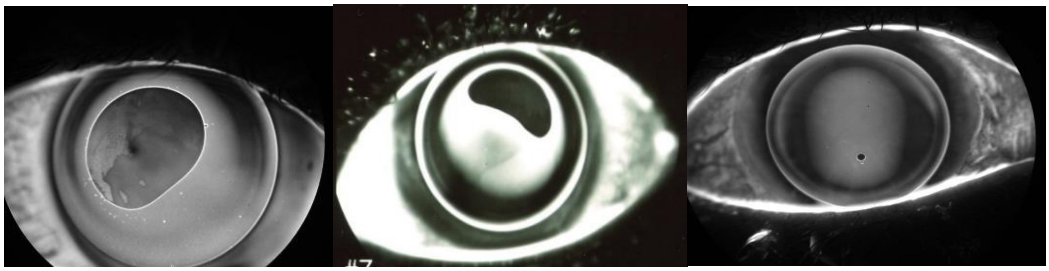


Figure 3.5b. *NaFl patterns in central clearance fitting with excessive (bubbles) to acceptable cone clearance*

3. Three-point-touch, or the *divided-support* method, with emphasis directed towards reducing or "*feathering*" the apical touch to minimise scarring of the fragile apical cone area. This is done by distributing the lens weight and spreading it over a larger area, including the central and peripheral cornea.

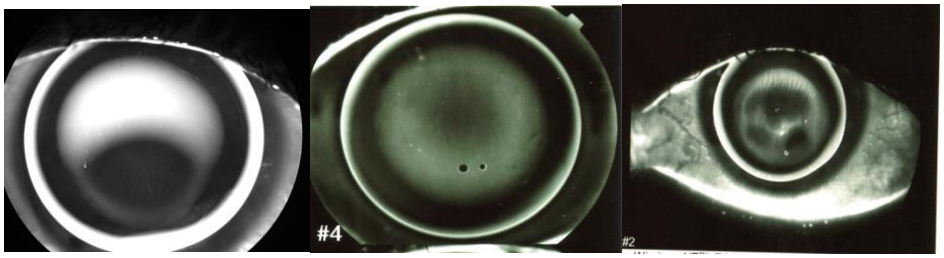
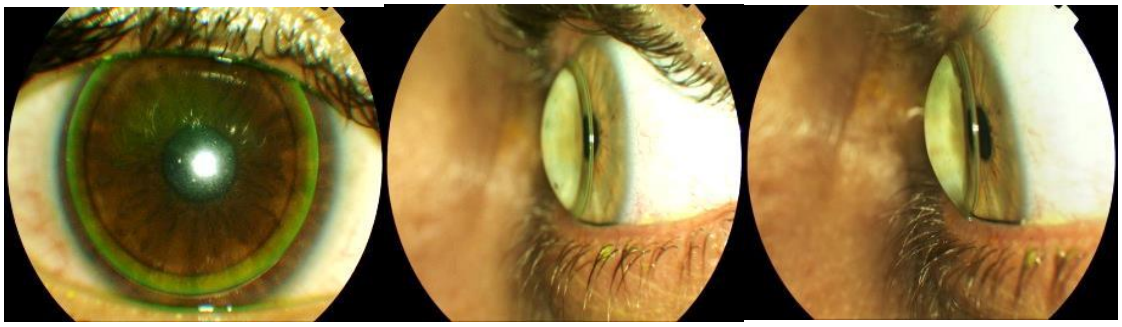


Figure 3.5c. *NaFl patterns in divided support, three-point touch, fitting*

Currently the most widely accepted corneal lens fitting philosophy is the *three point touch* or the divided support method, in which the intention is to distribute the weight of the lens between the cone area and the normal peripheral cornea (Loft and Wolffsohn, 2016; Szczotka-Flyn *et al.*, 2006; Woodward, 1989; Watts and Colby, 2017), thus achieving good physical lens fit and minimal physiological corneal insult (Figure 3.5d).



Optimal centration lens centration side view translation/movement in down gaze

Figure 3.5d. *Optimal physical CRGPcl fit.*

Fitting methods and their relation to corneal pathology progression

Corneal bearing fitting method of CRGPcl

Mechanical interaction between the CRGPcl and cornea is inevitable, irrespective of the method of fitting. If as a result of these interactions the ectatic cornea fails to maintain an intact epithelium, its deficient wound healing mechanisms may contribute to stromal scarring and disease progression.

Korb *et al*., (1982) suggested that the harsh contact between the CRGPcl and the fragile corneal apex in keratoconus is likely to be associated with corneal scarring (Korb *et al.*, 1982). They investigated whether apical corneal insults such as corneal abrasion and scarring may be the consequence of the *apical-bearing* lens fitting method. They recruited 7 patients with keratoconus who had never worn contact lenses and fitted them with CRGPcl. The experimental eye was fitted with a lens bearing on the cone; the control eye was fitted with cone clearance. The authors postulated that this fitting difference between the eyes in the same individual would ensure that the primary variable would be the lens-cornea relationship. The intra-subject variability was minimised by selecting individuals fulfilling nine criteria of disease severity equivalence.

Both lens fitting modalities were fitted to the better and worse eyes in equal numbers. Detailed examinations of the state of the cornea were performed at baseline and during follow up at intervals of 1, 2, 4, 8, and 12 weeks. Further follow-up was performed at 3-month intervals for the first year. After one year the authors found no significant or permanent changes in the corneae of any of the seven eyes fitted by *apical clearance*. In contrast, 4 of the 7 experimental eyes fitted with *apical bearing*, developed superficial opacities (scarring) after 3-12 months. A fifth eye wearing the apical bearing lens developed a moderate corneal fold after 12 months. The experimental, cone-bearing lenses were reported to be more comfortable than the control (apical clearance) in all 5 eyes, which exhibited the adverse findings (the better reported comfort was most likely due to better vision, normally achieved with cone bearing). The acquired corneal opacities in the four eyes remained permanent.

These results led to the conclusion that lenses fitted with *apical bearing* produced corneal scarring, whilst lenses fitted with *apical clearance* did not. Interestingly of the four corneae which developed scarring, two occurred with the more advanced and two with the less advanced level of keratoconus. This finding suggests that the fitting characteristics of CRGPcl may be more important in the development of scarring than differences in the degree of keratoconus.

The authors recommended that attempts to achieve central *apical clearance* or at least a *three-point divided support* fit should be attempted in eyes with keratoconus and *heavy apical bearing* of CRGPcl on the cornea should be avoided.

Despite the small sample size and the selection of participants with early keratoconus, inexperienced in contact lens wear, this study supported the clinical impressions and reports of previous investigators (Bier and Lowther, 1977; Black and in Girard, 1967; Williams, 1960) who have advised against the fitting of CRGPcl by the *apical bearing* method. The authors did not address other important aspects of contact lens wear, such as differences in comfort and quality of vision between the two fitting methods, furthermore the lens designs used for the two methods of fitting were not identical; this introduces an additional variable which may have affected the results.

Zadnik *et al.*, (2005) compared the safety and efficacy of flat and steep fitting CRGPcl in 761 keratoconic participants who completed an 8-year follow up in the CLEK study. At baseline they found that 41% of eyes with CRGPcl had a corneal scar compared with 24% corneal scarring in non-CRGPcl wearers (Zadnik *et al.*, 2005). CRGPcl were fitted with apical bearing and apical clearance to 87% and 13% respectively. They found that 43% of the corneae fitted with apical bearing were scarred compared to 26% of those fitted with apical clearance. When the eyes with unscarred corneae at baseline were evaluated, they found that by year 8, 32% of these eyes developed scarring during wear of apical bearing lenses, compared with 14% scarring of corneae fitted with apical clearance ($p=0.007$).

The authors postulated that despite the significant differences in corneal scarring between the two methods of fitting, only a randomised study would be able to assess the risk of corneal scarring due to a particular fitting method. The CLEK study is a natural history sample; therefore, the correlation of fitting method and corneal scarring is not necessarily causal. As more advanced disease presents higher risk for scarring and CRGPcl tend to fit flatter and bear on the corneal apex in advanced keratoconus, it is impossible to statistically discriminate

between the effects of flat fitting lenses and disease severity on the incidence of corneal scarring. This principle also applies to other CLEK studies such as measurement of VA in (Zadnik and Mutti, 1987), assessment of contact lens comfort (Edrington *et al.*, 2004) and evaluation of ocular pain (Kymes *et al.,* 2008).

The difference between the *divided support* and *apical bearing* fitting methods is often difficult to establish, especially in a progressive disorder such as keratoconus. As the disease progresses, the *divided support* lens fit, with minimal bearing on the apex may alter into heavy bearing even when disease progression is relatively minor, as described by Edrington *et al.,* (1999). The authors re-fitted the 808 patients according to a protocol of fitting from their previous study (Edrington *et al.,* 1996) and analysed the lens-cornea fitting relationship of the habitual lenses worn by these patients. They found prior to refitting the participants, that despite the clinically established association between *cone bearing* and corneal scarring, 88% of eyes had their habitual CRGPcl bearing on the cone apex, and only 12% exhibited corneal clearance (Edrington *et al.*, 1999).

A report by Szczotka *et al.,* (2001) in the CLEK study, evaluated corneal scarring, visual acuity, corneal curvature and Qol in 1209 CRGPcl wearers with keratoconus. They found that 88% wore CRGPcl with apical bearing, 53% had corneal scarring in one or both eyes, and that corneal scarring was associated with corneal staining, contact lens wear, age, the presence of a Fleischer's ring and a steeper cornea. All these parameters except age contributed to, or may have been the result of, CRGPcl bearing on the cornea (Szczotka *et al.*, 2001).

Since almost 90% of keratoconic CRGPcl in the CLEK study exhibited apical bearing (Edrington *et al.*, 1999) and more than 50% had corneal scarring in one or both eyes (Szczotka *et al.*, 2001), these findings appear to support the conclusions of Korb *et al.,* (1982), which attributed a causal relationship between chronic CRGPcl bearing on cornea and corneal scarring. Furthermore, the CLEK study concluded that corneal scarring was associated with decreased measures of high and low-contrast visual acuity, and possibly the reduced visual Qol in keratoconic CRGPcl wearers. Since the nature of CRGPcl fit may be causal or contributory to the complications associated with corneal morbidity, reduced visual performance and visual Qol, it follows that practitioners should take measures to minimise contact lens wear related complications such as corneal scarring when managing corneal ectasiae with CRGPcl.

Apical clearance fitting of CRGPcl

Clinical experience shows that the steep central curvature of CRGPcl required to achieve a vault of the corneal apex, may also cause problems such as: the trapping of air bubbles in the flatter areas adjacent to the corneal apex, which may disrupt vision by corneal deformation (Szczotka-Flyn *et al.,* 2006). The small optic zone and lens diameters used in fitting keratoconus, may lead to discomfort and visual disturbances such as halos, ghosting and glare due to the encroachment of the peripheral (non-optical) part of CRGPcl into the pupil area. The steep lens curves required in this approach may reduce tear exchange and lens mobility resulting in tear stagnation, oedema, corneal insult and lens intolerance. The positively powered tear lens created by the steep central back curve, requires high negative optical powers, which may reduce retinal image quality and increase lens thickness (Szczotka-Flyn *et al.,* 2006). Lens flexure resulting from the steep central fit will induce astigmatism and reduce vision (Sorbara *et al.,* 2000).

Gundel *et al.,* (1996) investigated the feasibility of fitting keratoconic patients with apical clearance, as recommended by Korb *et al.* (1982). To achieve apical clearance, they used the lens design developed and validated by Edrington *et al.,* (1996) (Gundel *et al.,* 1996). Thirty eyes of 17 participants were randomly assigned to a steep lens-fitting protocol*; the lenses dispensed had on average a 0.6mm steeper central radius than their habitual CRGPcl *[*Their fitting protocol stipulated that a 0.2 mm steeper radius than the diagnostic lens which exhibits a definite apical clearance (DFCL) is used*]. The strict criteria for success were based on the measurement of VA, hours of daily lens wear and observable levels of corneal fluorescein staining, erosions, distortion from CRGPcl pressure, corneal oedema and scarring. All these changes were noted at different stages for some subjects, including central corneal scarring in one eye after 12 months. At 12 months the mean visual acuity was 6/7.5 (logMAR 0.10) and the average wearing time was 14 hours a day, both features are indicative of a successful result.

As no control group was implemented in this study, no comparative results with alternative fitting approaches such as divided support or corneal bearing lenses are available. Nevertheless, the conclusion of this study was that fitting keratoconic corneae with apical clearance is a viable method.

An interesting finding in this study is the corneal steepening in 14 eyes (47%), the flat meridian increased by 2.29D, the steep meridian increased by 1.28D, which indicates corneal moulding. This effect was especially obvious in 5 of the 14 eyes that showed a mean increase of 5.9D (0.83mm) in the flattest meridian and 3.92D (0.56mm) mean increase in the steepest. These findings demonstrate a marked increase in the level of keratoconus in those eyes, which is known to be associated with increased risks of scarring (Zadnik and Mutti, 1987), reduced visual acuity (Zadnik *et al.*, 2005) and a reduction in almost all aspects of NEI-VFQ scores (Kymes *et al.*, 2004; Kymes *et al.*, 2008; Aydin Kurna *et al.*, 2014).

McMonnies (2004) reported a case in which a keratoconic patient wore a substantially steeper lens in the right eye and flatter lens in the left eye due to accidental lens switching. The right eye required an alteration in contact lens fitting due to a progression in keratoconus at a higher rate than exhibited previously and more than the progression exhibited by the left eye. The author suggested that: *It is possible that the adventitious apical clearance fitting on the right eye served to promote an increase in ectasia that might not have occurred if the intended apical support fitting had been worn* (McMonnies, 2004). This case report is in agreement with the findings of Gundel *et al.,* (1996) regarding the possible contribution / causation of disease progression by CRGPcl fitted to vault the cone apex.

The corneal shape changes occurring in orthokeratology*, a method in which centrally flat fitting CRGPcl worn overnight, generate tear fluid pressure to alter the shape of the cornea in a controlled manner to achieve a desired optical change (Maseedupally *et al.*, 2013), may be useful in understanding the tendency of even the healthy corneae to adopt the shape and curvature of the CRGPcl. These changes which affect corneal thickness and shape (Gifford *et al.*, 2011) are reversible, the healthy cornea returns to its original shape and thickness, exhibiting no significant difference to controls in the frequency or severity of corneal NaFl staining during wear (Lui *et al.*, 2000), no alteration in the corneal epithelial permeability and no clinically significant changes in corneal biomechanical properties on lens removal (Yeh *et al.*, 2013).

Hartstein and Becker (1970) examined the corneal rigidity in three groups of patients who were successful long-term wearers of CRGPcl. Despite the inability to perform statistical analysis due to the small numbers involved, the authors postulated that higher ocular rigidity is associated with a better maintenance of a normal corneal shape and that at least one type of

keratoconus may be related to the long-term wearing of CRGPcl in eyes with unusually low ocular rigidity (Hartstein and Becker, 1970) .

Hill *et al.,* (1974) found that even healthy corneae are susceptible to deformation by CRGPcl by showing that corneal steepening occurred in 85% with centrally steep lenses over a period of 1 to 6 years. (Hill and Rengstorff, 1974).

In keratoconus the central cornea is abnormally thin, soft and pliable compared with the normal cornea, it exhibits reduced total protein, variable total collagen, and reduced levels of sulphate proteoglycans (Kenney and Brown, 2003). The pathological thinning in keratoconus may develop as a result of altered biomechanical properties (Bao *et al.*, 2017) such as the loss of tensile strength and elasticity (Wojcik *et al.*, 2014) or may be the primary change, which if associated with loss of elasticity and increased plasticity, may reduce the corneal ability to recover from trauma associated with external mechanical insult such as contact lens wear or eye rubbing (Gordon-Shaag *et al.*, 2015). Kenney and Brown (2003) who examined the hypothesis of a cascade of events causing keratoconus and its progression, recommend that patients with keratoconus should minimize their exposure to oxidative stress by wearing ultraviolet protection, minimize the mechanical trauma like eye rubbing, poorly fitting contact lenses and keep eyes comfortable with artificial tears, non-steroidal anti-inflammatory drugs and/or allergy medications (Kenney and Brown, 2003). The recovery from deformation by a healthy cornea such as observed in orthokeratology and poorly fitting CRGPcl may not occur in keratoconus, in which corneal biomechanics are impaired (Wojcik *et al.*, 2014; Kenney and Brown, 2003; Bao *et al.*, 2017). This impaired recovery may predispose the cornea to permanent deformation by the mechanical pressure induced by sub optimally fitting CRGP and lead to progressive pathological changes as demonstrated by Gundel et al., (1996) and noted by McMonnies (2004, 2005).

McMonnies (2005) analysed the possible influence of eyelid tonus, tear fluid pressure and intraocular pressure on the generation and progression of keratoconus during CRGPcl wear. He postulated that the lens bearing on the peripheral cornea and suction forces in the central area generated by lenses fitted with apical clearance are compounded by the rise in intraocular pressure due to eyelid squeeze forces during blinks, which may be pushing and stretching the softer central cornea and cause keratoconus progression by additional forward protrusion. This would occur due to strong sub-atmospheric fluid pressure forces under the lens that draw the lens to the cornea and the cornea to the lens, which flattens the mid peripheral cornea and

facilitates compensatory steepening of the apex. He concluded that the known risk of scarring responses to excessively flat fitting CRGPcl must be balanced against the possible risk of corneal moulding and keratoconus progression responses to CRGPcl fitted with apical clearance. He suggested that fittings by *divided support*, where there is minimal central bearing or clearance may be the most appropriate fitting approach. He stipulated that this is difficult to achieve in practice in view of the high level of accuracy required and the dynamic-progressive nature of keratoconus. The author further suggested that any large increases of intraocular pressure due to activities such as vigorous eye rubbing, strong squeeze blinks, inverted body positions, and strenuous muscular effort, should be recognised as risk factors in patients with, or at risk of keratoconus, glaucoma, or progressive myopia (McMonnies, 2005).

McMonnies summarised the known risks associated with *apical support* fitting method.

1. Chronic corneal epithelial changes, which may not be evident on bio-microscopy.

2. Chronic, visible epithelial trauma caused by friction between CRGPcl and cornea.

3. Acute or chronic epithelial trauma that results in permanent scarring of the corneal apex.

4. Chronic epithelial trauma that may cause corneal stromal thinning.

McMonnies summarised the known risks associated with the *apical clearance* fitting.

1. Corneal moulding may be greater in keratoconus due to reduced tensile strength and elasticity, and/or greater plasticity of the softer and thinner cornea.

2. Reduced oxygen tension caused by the thicker lens and post-lens tear layer, leading to corneal oedema and increased tendency to mould to the steeper lens curvature.

3. Progression of ectasia if moulding to the steeper lens curvature becomes a permanent change.

4. Tighter lenses with sharper transitions may reduce lens movement and cause *imprinting* insult of the corneal epithelium.

5. Apical clearance may facilitate fine bubbles formation, increase light scatter and glare.

6. Cornea moulding to a steeper shape during lens wear may cause a myopic shift and reduction in unaided visual acuity on lens removal.

7. Reduced acuity with contact lenses may result from residual astigmatism (McMonnies, 2004; McMonnies, 2005).

Summary of CRGPcl fitting methods and their effects on keratoconus progression

The available evidence suggests that corneal changes associated with both CRGPcl fitting philosophies have significant negative effects on VA and disease status. The scarring associated with CRGPcl wear (Barr *et al.,* 2000) is likely to be caused by *apical support-cone bearing* lenses, found in the majority (88%) of patients (Edrington *et al.*, 1999). The *cone clearance* fitting philosophy recommended to safeguard against corneal scarring (Gundel *et al.*, 1996; Korb *et al.*, 1982) appears to negatively affect disease progression by inducing permanent corneal steepening (McMonnies, 2004; McMonnies, 2005). The theoretically desirable fitting method of divided support may not be achievable or sustained in many wearers (McMonnies, 2005). CRGPcl may therefore contribute to disease progression and adversely affect vision, corneal health, contact lens tolerance and subsequently all aspects of visual Qol, as demonstrated by Kymes *et al.* (2008), who found that a decline in visual acuity of 10 letters, and a disease progression equivalent to a corneal curvature increase of 3.00D, were associated with significant declines (10 points) in the NEI-VFQ scale scores (Kymes *et al.,* 2008).

Clinical implications of SRGPcl management of keratoconus

CRGPcl provide better high and low contrast BCVA than spectacles and soft lenses in eyes with keratoconus (Griffiths *et al.,* 1998) and are the most widely prescribed optical management in keratoconus (Zadnik *et al.*, 1998; Mandathara *et al.,* 2017). The conclusion from the discussion above is that irrespective of the fitting philosophy, CRGPcl may contribute to or cause pathological changes in keratoconic corneae. It is therefore understandable that

SRGPcl, which vault (bridge over) the cornea attracted considerable interest in the management of keratoconus.

Both SRGPcl and CRGPcl, almost completely neutralise the anterior corneal surface irregularities caused by ectatic corneal disorders. Unlike CRGPcl, which distribute their weight and mass on the cornea, SRGPcl are fitted to bear on the sclera, without contact with any part of the cornea, which precludes mechanical interaction between the cornea and contact lens surface. The cornea is immersed in the tear and saline reservoir vaulted by SRGPcl (van der Worp *et al.*, 2014; Visser *et al.*, 2013; Visser *et al.*, 2007a). The cornea is therefore protected not only from mechanical interaction with the rigid contact lens surface but also from the shearing forces of the eyelids, eye rubbing, exposure to ultraviolet radiation and external debris, all of which are recognised irritants with the potential to exacerbate keratoconus (Wojcik *et al*., 2014; Kenney and Brown, 2003). However, SRGPcl are not prescribed as a first option but only when other lenses did not provide adequate management (van der Worp *et al.*, 2014; Szczotka-Flyn *et al.*, 2006). This view was supported by Rathi *et al*., (2013) who stipulated that contact lenses can improve the vision and delay or obviate the need for keratoplasty and that the lenses of choice are CRGPcl. They recommend that if discomfort with or intolerance to CRGPcl occur, then customized soft toric, piggyback combination or hybrid contact lenses should be fitted. SRGPcl in their opinion are only to be used when all other options fail, or if patients present with associated ocular allergic disease (Rathi *et al.*, 2013). This reluctance to use SRGPcl remains, despite significant improvements in manufacturing techniques, wider availability of improved lens designs, systematisation of the fitting protocols, availability of preformed SRGPcl fitting sets and substantial reductions in costs (van der Worp *et al*., 2014).

Other researchers suggest that long-term management with SRGPcl reduced the indication for corneal transplant surgery in severe keratoconus by more than 50% (Koppen *et al.*, 2017) and was well accepted in patients with advanced ectasia who are intolerant to other contact lenses, or when surgery is not available or considered inappropriate (Maharana *et al.*, 2016).

Visser *et al.* (2007) performed a prospective study to evaluate the indications for modern SRGPcl and their clinical performance (Visser *et al.*, 2007a). In part II: the authors have evaluated patient satisfaction with their SRGPcl (Visser *et al.*, 2007b). All 178 participants (284 eyes) in these studies failed with other contact lens modalities, 143 (50.3%) eyes had keratoconus, 56 (19.7%) eyes had penetrating keratoplasty [*full thickness central corneal graft surgery*], the rest had irregular astigmatism due to various causes such as PMD and ocular

surface disorders such as *keratitis sicca* [*severe dry eye disorder*] and corneal dystrophies, totalling 25 eyes (8.8%). SRGPcl were fitted according to a strict fitting protocol which aimed to achieve the desired clearance of the cornea and the limbus, the peripheral-haptic zone of the lens was fitted precisely to align the sclera and distribute lens weight without causing undue local pressure. When required, custom made toric scleral lenses were used to achieve this. The authors claimed that optimal lens fitting characteristics were achieved with most eyes. Fifty-nine eyes (20.8%) had to be refitted due to adverse clinical findings. Most patients showed no adverse clinical signs during their review appointments, with the exception of bulbar conjunctiva [*the area which bears the weight of the lens*] hyperaemia [*redness due to local blood vessel dilation*], which occurred in 20.8% of eyes. The authors stipulated that a well-balanced scleral bearing area, gentle movement of the lens with digital push up testing, approximately 250μm of corneal clearance and 50μm-100μm of limbal clearance are all essential fitting attributes to avoid contact lens related complications. The authors claimed to achieve visual rehabilitation with SRGPcl for this group of patients by demonstrating significant increases in monocular and binocular visual acuities compared to glasses. This improvement was most apparent in participants with keratoconus and penetrating keratoplasty. No comparison was made between SRGPcl and CRGPcl with respect to visual acuity.

Earlier studies by Kok and Visser (1992), Tan *et al.,* (1995), Pullum and Buckley (1997), Segal *et al.,* (2003), Pullum *et al.,* (2005) and Rosenthal and Croteau (2005), all found similar favourable visual improvements and positive clinical performances of SRGPcl in cases of challenging diseased corneae, in eyes which could not be managed by other contact lens options (Kok and Visser, 1992; Tan *et al.*, 1995; Pullum and Buckley, 1997; Segal *et al.*, 2003; Pullum *et al.*, 2005).

Despite variations in study design, sample sizes, conditions managed, definition of diagnoses, fitting methods, scleral lens types, materials, and so forth their results highlight the usefulness of SRGPcl in clinical practice. As in the earlier studies the conclusions of Visser *et al.,* (2007) were: *"modern scleral lenses can be used successfully for visual rehabilitation and management of a wide range of corneal disorders that have not responded adequately to other treatment modalities"* (Visser *et al.*, 2007a).

In a follow up publication Visser *et al.,* (2007b) examined the satisfaction levels with SRGPcl in the same 178 participants. Fifty per cent were refitted from CRGPcl, 30% wore no lenses at all, and the rest had various other lens types. The participants were asked to state the number

of insertion attempts, lens wearing hours, number of breaks from wearing lenses and the previous correction before they had received SRGPcl. Scores from a Likert scale questionnaire; from 1 (very poor) to 5 (excellent) were obtained for the original lenses as well as for the SRGPcl fitted during the first phase of the study. The questionnaire covered 3 topics: comfort, visual quality and overall satisfaction as well as 7 aspects of contact lens wear: comfort, lens dryness, visual quality, air bubbles during lens wear, tear debris during lens wear, lens cleanliness and lens handling. Significantly higher scores were obtained with SRGPcl. Scores of 3 (out of 5) for comfort were given by 98.9%, for visual quality by 97.9% and overall satisfaction by 98.9% of participants. In comparison scores of 3 or more were given with the former correction by 54.6% for comfort, by 51.8% for visual quality, and by 50.4% for overall satisfaction. Significant increases were found in the scores with SRGPcl for all three topics ($p<0.001$). Higher scores for comfort, visual quality, and overall satisfaction were found in more than 75%, furthermore in the 99 eyes refitted from a spherical SRGPcl to toric design [*for better scleral fit*], significant increases in comfort, visual quality, and overall satisfaction were observed (Visser *et al.*, 2007b). The authors suggested that this was because of better lens weight distribution on the naturally toric peripheral sclera, as found by other studies (Visser *et al.*, 2006; Visser *et al.*, 2013).

High level of subjective satisfaction was confirmed in patients with keratoconus refitted with SRGPcl despite mid-day lens fogging, reported by 50% of them (Bergmanson *et al.*, 2016). A retrospective cohort study by Baran *et al.,* (2012) investigated the success rate of fitting SRGPcl in the management of corneal ectasia (Baran *et al.*, 2012). They reviewed the records of 59 patients with corneal ectasia disorders, the majority of whom (74.6%) wore CRGPcl. SRGPcl were fitted to 89 eyes of 49 patients. Forty-three patients, 78 eyes (88%) with keratoconus completed the validated NEI-VFQ (Mangione *et al.*, 2001; Aydin Kurna *et al.*, 2014) at six months. The authors measured an improvement of 27.6/100 points ($p < 0.001$). In the 10 patients who passed the selection criteria but were not dispensed with SRGPcl, no significant difference in the score was found at six months ($p<0.697$). The authors concluded that a satisfactory fit of SRGPcl in participants with ectasia results in a positive impact on visual acuity and continued successful contact lens wear. The authors further stipulated that SRGPcl treatment is an alternative to penetrating keratoplasty for patients with corneal ectasia who are contact lens intolerant.

A retrospective study by Pecego *et al.,* (2012) reported the results of fitting the *Jupiter* SRGPcl in 107 eyes of 63 participants with a variety of ocular conditions; the majority (63%) had

keratoconus. Eighty-six eyes (80%) were either unhappy with their visual acuity or intolerant to their previous contact lenses. The authors found that the SRGPcl were comfortable in 84% of eyes, but 23% of eyes abandoned wear after 3 months. Patients who abandoned SRGPcl exhibited significantly less subjective comfort and less improvement in BCVA compared to those who remained in SRGPcl. The BCVA was 20/30 (6/9.5) or better in 73% of eyes wearing SRGPcl with a mean improvement of 3.5 (±2.6) Snellen lines (Pecego *et al.*, 2012).

SRGPcl are fitted in alignment with the sclera and thus spread the weight of the lens evenly to avoid excessive local compression of the conjunctiva and sclera. The science and art of design and fitting of modern SRGPcl has benefited from research into the topography of the ocular surface obtained from the micron precise imaging of the cornea, the *corneo-scleral* junction and the sclera by Optical Coherence Tomography (OCT) (Gemoules, 2008; van der Worp *et al.*, 2010; Kojima *et al.*, 2013).

Researchers from the Pacific University suggest that the scleral shape around the limbus is tangential [*a continuous straight-line*] with the peripheral cornea and not a convex surface which continues to flatten as was previously assumed. The sclera was found to be of a *non-rotationally symmetrical* shape around its four quadrants, with the nasal quadrant being the flattest, the temporal quadrant the steepest and the superior is somewhere between the inferior and the temporal quadrants (van der Worp *et al.*, 2010). This rotational asymmetry is more pronounced further from the limbal area; from 15mm-20mm diameter away from the centre of the cornea. These researchers found that at approximately 15mm from the corneal apex, the scleral angles appear on average fairly similar in all four quadrants. Based on these results and past clinical experience with large diameter [*over 18 mm in size*] SRGPcl the authors suggested that rotationally asymmetrical, toric or quadrant specific, large diameter scleral lenses should be used to achieve optimal scleral alignment. Optimal scleral alignment should ensure even weight distribution, gentle lens positioning and balancing, which would result in better lens comfort and tolerance, better lens centration and stability as well as improved scleral and conjunctival health. This positional stability of SRGPcl facilitates the application of more complex optical correction such as *front surface toric* [*correcting the residual ocular astigmatism*] and *wavefront* HOA corrections [*correcting the residual HOA*], both of which often remain uncorrected with RGPcl. Both Sabesan *et al*., (2013) and Marsack *et al.*, (2014) demonstrated that SRGPcl with customised *wavefront* optics are capable of fully or partly correcting the residual HOA in keratoconus. However, despite the improved retinal image

quality generated by these lenses, the improved high contrast visual acuity did not reach normal, age-matched levels (Sabesan *et al.*, 2013).

Visser *et al.,* (2013) published an evaluation of the performance of a SRGPcl design which featured a non-rotationally symmetrical peripheral (haptic) lens area. This design differs from traditional SRGPcl in two ways. The first is the configuration of the peripheral haptic to match the non-rotationally symmetrical sclera at an area beyond 15mm from corneal centre. The second difference is that rather than having the customary curved spherical shape, these haptic lenses feature a *tangential* design. The authors postulated that the adjustable flat and steep meridian of this bi-tangential haptic would improve lens fit by the generation of a more even distribution of lens pressure over the sclera. A total of 213 eyes of 144 participants were fitted, keratoconus (n=121 eyes; 56.8%), ocular surface diseases (n=31eyes; 14.6%), penetrating keratoplasty (n=29 eyes; 13.6%), and other forms of irregular astigmatism (n=28 eyes; 13.1%). The most common lens diameter was 20.0 mm (162 lenses; 76.1%, range: 18.5-21.5 mm). The results revealed that 77% of participants (164 eyes) gave high ratings for comfort. Median BCVA was decimal 0.8 (Snellen 6/7.5, range: 0-1.5, Snellen equivalent 6/600-6/4). Most lenses were observed to have good fitting characteristics, optimal values were seen for lens movement (208 lenses; 97.7%) and lens position (208 lenses; 97.7%). Median central corneal clearance was 200µm. The lenses exhibited good rotational stability with an oblique median lens stabilization axis at 140° (range: 0°-180°) in the right eyes and 60° (range: 0°-180°) in the left eyes. The researchers concluded that the bi-tangential SRGPcl fitting and performance characteristics were beneficial for both the health professional and the patient (Visser *et al.*, 2013).

Picot *et al.,* (2015) conducted an observational retrospective study, evaluating quality of life with the French version of the NEI-VFQ before and after SRGPcl adaptation, of 47 patients (83 eyes, 56 eyes with keratoconus) all of whom failed to adapt to CRGPcl and were refitted with SRGPcl. The mean duration of wearing SRGPcl was 18 (±10) months and the mean daily wearing time was 14 (±3) hours. The average scores on the NEI-VFQ after six months were significantly higher than with CRGPcl, with a global score of 80.2/100 with SRGPcl versus 48.1/100 with CRGPcl ($p<0.0001$). The authors concluded that because SRGPcl showed a significant improvement in quality of life for patients who failed to tolerate CRGPcl they represent a viable alternative prior to consideration of surgery (Picot *et al.,* 2015).

A recent literature review of the complications and fitting challenges associated with SRGPcl (Walker *et al.*, 2016) reveal that serious complications as a result of infection, inflammation and corneal hypoxia are rare with modern materials and designs. To prevent corneal hypoxia, the materials of SRGPcl need to feature high Dk values such as Boston EO (Dk 82), XO (Dk 100) and Menicon Z (Dk 160), as well as having a tear lens thickness of not more than 200µm (Jaynes *et al.*, 2015). They highlight the challenges of obtaining optimal fitting characteristics in view of the natural asymmetry of the sclera, such as lens seal-off, which may cause lens suction and reduced tear exchange. Lens bearing on the corneal limbus should be avoided due to the importance and sensitivity to mechanical lens pressure of this stem cell rich area (Figures 3.6a. and b.).

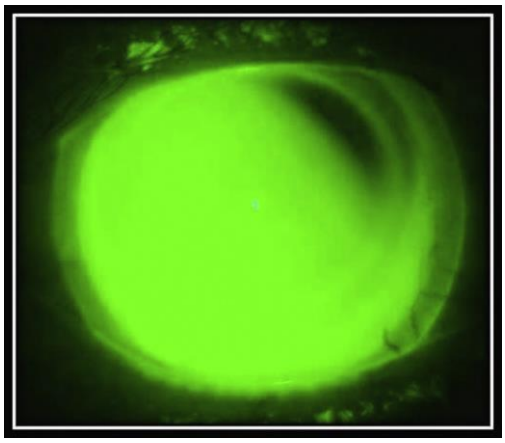


Figure 3.6a. *NaFl fit of SRGPcl with dark area at 1 o'clock indicating heavy lens bearing on the cornea. Copied from Walker et al., (2016) with permission from Maria K. Walker, OD, MS, FAAO, FSLS.*

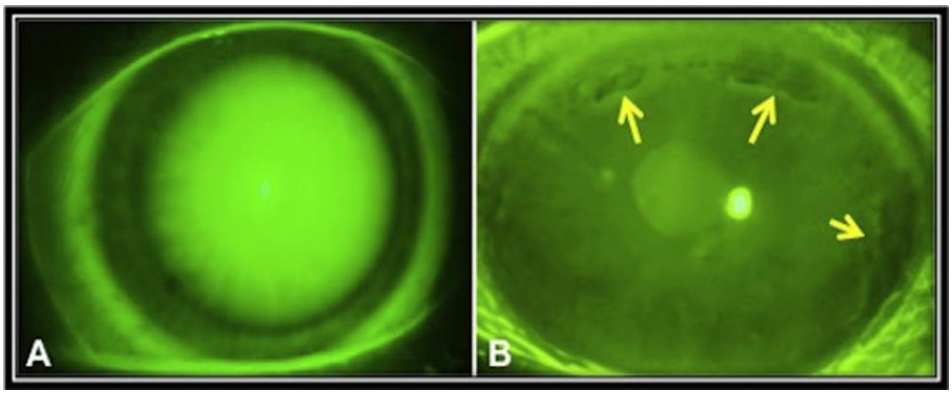


Figure 3.6b *A. Circum-limbal bearing. B. Local epithelial breakdown staining. Copied from Walker et al., (2016) with permission from Maria K. Walker, OD, MS, FAAO, FSLS.*

Other undesirable ocular side effects were highlighted, such as conjunctival prolapse (Figure 3.7), epithelial bogging (Figure 3.8) and mid-day fogging (Figure 3.9) of lenses as limiting factors unique to SRGPcl, which at present have no known, clinically significant long-term consequences (Walker *et al.*, 2016).

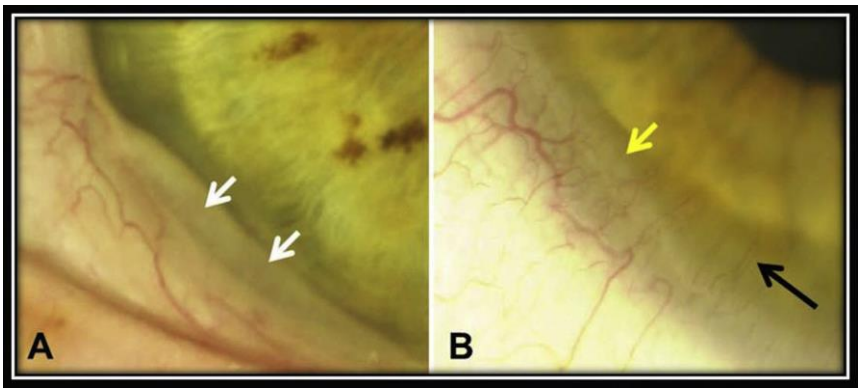


Figure 3.7. *Conjunctival prolapse under the lens edge, white arrows, corneal vascularisation due to chronic hypoxia caused by conjunctival adhesion to the cornea. Copied from Walker et al., (2016) with permission from Maria K. Walker, OD, MS, FAAO, FSLS.*

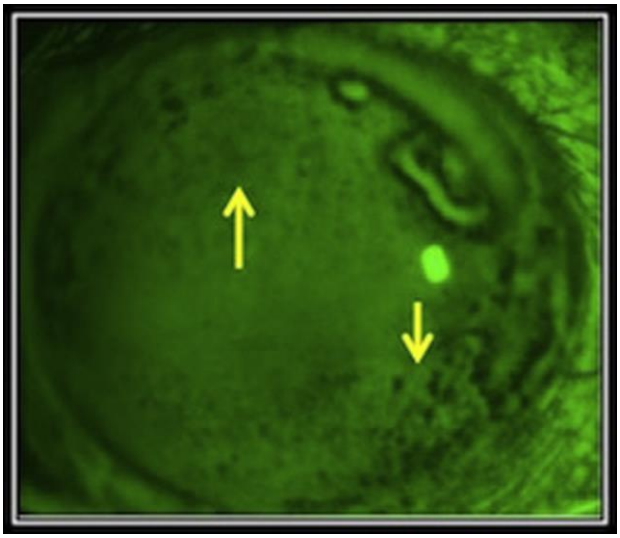


Figure 3.8. *Epithelial bogging. Copied from Walker et al., (2016) with permission from Maria K. Walker, OD, MS, FAAO, FSLS.*

Mid-day lens fogging was reported by 50% of satisfied keratoconic SRGPcl wearers, refitted from CRGPcl (Bergmanson *et al.*, 2016). A study by Carracedo *et al.,* (2016) evaluated the turbidity and thickness of the post lens tear layer and its effect on visual quality in 36 participants with keratoconus. They found a x8 higher number of particles per mm^2 after eight hours of SRGPcl wear compared to 5minutes after lens insertion ($p < 0.05$). A decrease in BCVA ($p < 0.001$) and contrast sensitivity ($p < 0.05$) after eight hours of SRGPcl wear was found, both of these visual outcome measures showed a significant correlation with post-lens tear turbidity: r=0.567 ($p=0.002$) for turbid tear layer area and r=0.469 ($p=0.049$) for the number of particles per mm². Tear layer thickness was considered to positively correlate with tear turbidity, no correlation between turbidity and post-lens tear layer thickness was found ($p > 0.05$) (Carracedo, Serramito-Blanco *et al.*, 2017).

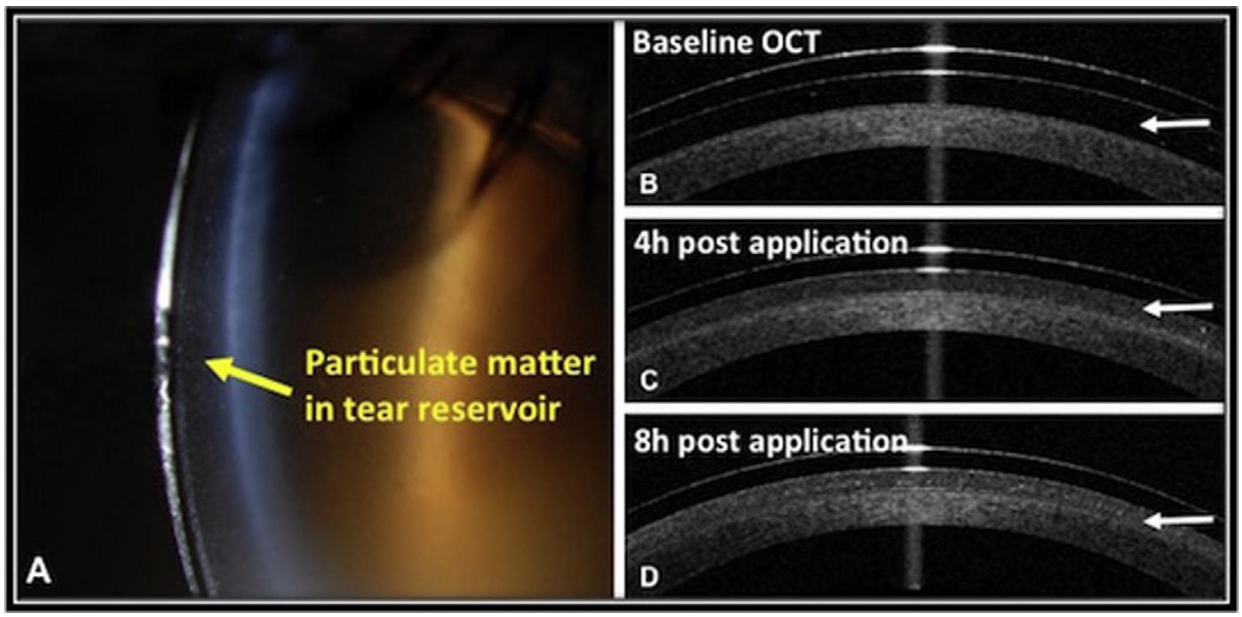


Figure 3.9. *Lens fogging due to accumulation of particular matter behind the lens. The arrows point to the post-lens tear film, which exhibits change in thickness and clarity. Copied from Walker et al., (2016) with permission from Maria K. Walker, OD, MS, FAAO, FSLS.*

In an earlier study exploring the utility of SRGPcl in the management of dry eye symptoms in patient with keratoconus Carracedo *et al.,* (2016) found that despite a significant decrease in signs and symptoms of dry eyes, the MMP9 [*inflammation bio-marker*] increased significantly, most likely due to tear stagnation and the use of saline in lens cavity at insertion (Carracedo *et*

al., 2016). These researchers found in a later study that corneal and limbal temperatures are not affected by SRGPcl wear, which suggests that not enough inflammation occurs during SRGPcl wear to increase temperature, the researchers also found no effect on tear volume or tear break up time after lens removal (Carracedo,Wang *et al.*, 2017).

Nixon *et al.,* (2017) published a case series report which highlighted an unintended contact lens related complication of corneal limbal bullae in all 14 participants fitted with small diameter SRGPcl. [*Corneal epithelial bullae are oval, larger than 40µm in size, gas and / or fluid field lesions manifesting corneal epithelial oedema*]. The authors concluded that due to the unique design of these lenses an unintended mechanical bearing on the corneal limbus, caused the undesirable local mechanical compression, which led to contact lens induced epithelial edema after only 6 hours of lens wear (Nixon *et al.*, 2017).

Weber *et al.,* (2017) used conjunctival impression cytology to evaluate the changes in goblet cell density and the inflammatory mediator HLA-DR [*Human Leukocyte Antigen – antigen D Related*] after 12 months wear of SRGPcl in patients with moderate to severe dry eye disease. They found that the goblet cell density did not differ significantly ($p>0.05$) and the inflammatory mediator was also unchanged except in participants with Sjogren syndrome, in which there was an increase in HLA expression (Weber *et al.*, 2017).

Giasson *et al.,* (2017) measured the in vivo oxygen tension available to the cornea and found that after 5minutes of wear, SRGPcl fitted with a 400µm corneal clearance reduces oxygen tension by 30% compared to a 200µm clearance (Giasson *et al.*, 2017). Reduced oxygen to the cornea may cause undesirable complications such as corneal oedema and vascularisation. Rathi *et al.,* (2017) described corneal vascularisation, which resolved on discontinuation of lens wear (Rathi *et al.*, 2017). Esen and Toker (2016) examined the influence of SRGPcl settling and corneal clearance on clinical performance and hypoxia induced corneal changes. They found that the corneal swelling after 8 hours was 62.8µm (1.3%) (80% occurred during the first 4hrs) and wearers comfort scores were not significantly influenced by corneal clearance. They nevertheless recommended fitting according to the current guidelines of using high DK materials and minimising apical clearance and lens thickness, to facilitate long-term corneal health (Esen and Toker, 2017)

The large size of SRGPcl may be challenging with respect to lens handling, in a retrospective review of 34 patients fitted with SRGPcl, 8 patients (25%) were unable to handle these lenses

(Barnett *et al.*, 2016). Even in successful SRGPcl wearers Suarez *et al.*, (2018) found that 40% of patients had persistent handling difficulties after 1 month of lens wear (Suarez *et al.*, 2018).

Optimal fitting characteristics of SRGPcl are achievable nowadays due to the advent of computerized lathe cutting technology, which enables manufacturing of very smooth lens surfaces and edges with sub-micron precision. Contact lens practitioners are now able to adjust individual lens parameters after assessing the lens fit during trials (Rathi *et al.*, 2015). The fitting characteristics of complete corneal clearance, the maintenance of liquid lens and the physical protection from mechanical and other external irritants make SRGPcl useful in cases of ocular surface pathology (Pullum and Buckley, 1997; Romero-Rangel *et al.*, 2000; Stason *et al.*, 2010), corneal protection and aid in healing in cases of exposure keratitis (Chahal *et al.*, 2017; Zaki, 2017) and as a means in aiding management of oculo-plastic pathology such as exposure keratitis and pain after blepharo-ptosis (droopy eyelids) surgery (Scofield-Kaplan *et al.*, 2017; Chahal *et al.*, 2017). SRGPcl have demonstrated long term safety and efficacy in complex cases such as ocular rehabilitation after penetrating keratoplasty (Severinsky *et al.*, 2014) or long-term maintenance of visual acuity in cases of dry eyes, when the fluid reservoir between the cornea and SRGPcl needs to be increased (Sonsino and Mathe, 2013). In their review of modern scleral lenses Maharana *et al.*, (2016) concluded that SRGPcl are extremely useful in patients with advanced ectasia intolerant to other contact lenses. (Maharana *et al.*, 2016). The majority of participants in the studies above were individuals whose management with CRGPcl failed to deliver adequate tolerance and/or visual performance. These studies conclude that SRGPcl are a viable management option where other correction modalities fail to deliver the required comfortable and safe contact lens wear and / or the desired visual outcome.

The decision regarding the most appropriate contact lenses in individual cases must be based on the degree of corneal irregularity and on secondary factors, such as tear film deficiency and corneal scars. Visser *et al.*, (2016) developed a contact lens selection algorithm, based on peer reviewed literature, which takes these primary and secondary factors into account. They identified sub-optimally fitting lenses in 58% of the participants in their study, who benefitted from a refitting (Visser *et al.*, 2016).

Schornack (2015) published a literature review of 184 publications selected from 899 peer-reviewed scientific publications related to SRGPcl design, fabrication, prescription, and management. The author concluded that current literature provides little insight into the

potential effects of SRGPcl on anterior segment anatomy and physiology. The differences in the physical features as well as the fitting characteristics of the various available SRGPcl, precludes the assumption of consistency of their performance and effect on the anterior eye. The author suggested that before embracing the use of SRGPcl in healthy eyes it would be advisable to fully explore potential metabolic and mechanical challenges to anterior segment structures. Specific aspects which are characteristic to SRGPcl such as fluid reservoir thickness, may present a significant barrier to oxygen transmissibility and may lead to hypoxic complications, furthermore the rate and volume of tear exchange beneath the lens and its effects on the physiology of the anterior segment are not yet known. There are currently no evidence-based guidelines for ideal scleral lens fitting characteristics and use of appropriate care products, or reports regarding incidence of complications and risk factors for complications.

The author concluded that for patients with few other options for disease management,

> ” *we can be reasonably confident that the risks of inaction or surgical intervention outweigh potential risks of scleral lens wear, but the exact placement of scleral lenses within an overall management strategy has yet to be defined”* (Schornack, 2015).

After reviewing the literature my conclusion is that the current clinical approach in the management of keratoconus and other irregular corneal disorders is to fit SRGPcl in two circumstances. First for patients who are intolerant to CRGPcl, second when pathology is either adversely affected by CRGPcl or too advanced to be effectively managed by CRGPcl or other contact lens modalities such as soft, hybrid and piggyback combination lenses, with corneal transplant surgery remaining the only option.

Summary

In the management of keratoconus and related conditions with CRGPcl, researchers highlight the importance of avoiding corneal trauma, chronic irritation, scarring and deformation through moulding, to preserve corneal integrity and protect against contact lens related exacerbation of pathology.

Individuals with keratoconus may not only suffer from sub optimally fitting CRGPcl (Edrington *et al.*, 1999) but also exhibit higher prevalence of atopic disease and therefore greater sensitivity to external irritants such as glare, dust, pollen and contact lens edges and movement (Feder and Gan, 2011). These factors may reduce their tolerance to the small diameter, highly mobile, sub-optimally fitted CRGPcl. The close proximity of CRGPcl to the fragile, bio-mechanically compromised keratoconic cornea has the potential to cause undesirable effects, exacerbating corneal pathology. Due to the progressive nature of keratoconus, the requirement to distribute the weight of the CRGPcl evenly over the fragile cone and the peripheral cornea is difficult to achieve and maintain. The most commonly encountered feature in CRGPcl fitting of a keratoconic cornea is lens bearing on the cone, which is considered by most researchers to lead to corneal scarring, with detrimental consequences on vision, comfort and Qol.

When CRGPcl are fitted with corneal clearance to avoid corneal bearing, the resultant lens cornea interaction may result in compromised comfort, reduced vision and lens tolerance and most worryingly the exacerbation of pathology.

Due to their size and large, 360° area of contact / alignment with the sclera, SRGPcl are minimally mobile and the thin and well-rounded lens edges are tucked-in under the eyelids, which facilitate eyelid gliding over the smooth lens surface without undue irritation during blinking. The complete vault of the entire cornea by the central portion of SRGPcl protects the cornea and surrounding tissue from direct mechanical insult by the lens and external irritants and debris. SRGPcl may therefore not only reduce or eliminate the adverse effects of direct mechanical lens / cornea interactions but also provide a barrier to other external irritants.

SRGPcl may enable through utilisation of more complex optics improve the quality of the retinal image. The additional advantage of modern highly gas permeable contact lens materials

and customisation of SRGPcl with modern computerised manufacturing make the use of these lenses logical in the management of keratoconus and other irregular cornea disorders, not only as the last resort in patients who failed with other contact lenses, but also as suggested by (Bergmanson *et al.*, 2016) as a lens of first choice. Despite these theoretical advantages of SRGPcl there has not been a marked shift from using these lenses as a problem solver to lens of first choice. Possible reasons for this may be greater costs, required fitting expertise, and lack of high-quality evidence-based research.

In agreement with Mandathara *et al.,* (2017), I found no randomised controlled trials evaluating the management of keratoconus with contact lenses, nor other clinical studies which compare the performance of SRGPcl on patients whose management with CRGPcl is satisfactory. A RCT comparing outcome measures of visual performance, vision related Qol and SPC and SPV, may be useful in the consideration of a wider use for modern SRGPcl in specialist contact lens practice, not just as a problem solver but as a management of choice to positively enhance the contact experience and potentially as first choice management option in patients with ectatic disorders.

To address the issues raised above, a research question may be formulated as follows: Is there a significant difference in the visual performance, visual Qol, SPC and SPV between CRGPcl and SRGPcl in successful CRGPcl wearers with keratoconus.

The null hypothesis (H_0) of this RCT is that there will be no difference between CRGPcl and SRGPcl in any of the research outcome measures.

The alternative hypothesis is that a significant difference between CRGPcl and SRGPcl would be found in one or more of the research outcomes.

Chapter 4: Methods

Introduction

In this section the research experimental design, interventions, outcome measures and statistical methods will be described.

The chosen experimental design for this research is RCT with a crossover. The RCT when appropriately designed, conducted, and reported, represents the gold standard quantitative design for evaluating healthcare interventions (Schulz *et al.*, 2010; Burns *et al.*, 2011). The crossover is described in more detail below, compares intra-subject differences between the two groups, thus avoiding problems of comparability with regard to confounding variables such as gender and age, as participants are their own controls (Wellek and Blettner, 2012). RCT with a crossover was therefore considered the most appropriate experimental design to show if a difference existed between the performance of the two experimental lens types. The literature review showed to date no RCT researching contact lens management of keratoconus was performed, this was also confirmed by other researchers (Mandathara *et al.*, 2017).

Crossover design

A crossover design is a repeated measurements design such that each participant receives different treatments during different time periods, by crossing over from one treatment to another during the course of the trial. This is in contrast to a parallel design in which participants are randomized to a treatment and remain on that treatment throughout the trial. In crossover clinical trials the disease/condition should ideally be *chronic* and *stable,* and the *treatments should not result in total cures* but only alleviate the disease / condition. Crossover design therefore works well for chronic conditions, where there is no cure and the treatments attempt to improve Qol.

Crossover design is considered appropriate in this experiment because, the condition investigated: corneal ectasiae generally and keratoconus specifically, are chronic in nature (Gordon-Shaag *et al.*, 2015) and although progressive, tend to stabilise with time and are rarely diagnosed after age 50 (Ramez *et al.*, 2017). The treatment investigated in this research are two different contact lens types, which both optimise VA by masking the irregular astigmatism and reducing the HOA. These lenses are not curative but a mode of management of the optical / visual disability caused by keratoconus (Feder and Gan, 2011; Watts and Colby, 2017). Furthermore, we were interested in comparing two contact lens management alternatives with respect to outcomes measures of visual quality, Qol and SPC and SPV, thus to control for individual confounds, it was desirable to administer both management options to each participant.

In this experiment the 2×2 crossover design was used (Table 4.1), participants who were randomized to the sequence AB received treatment A in the first period and treatment B in the second period, those randomised to sequence BA receive treatment B in the first period and treatment A in the second period (Figure 4.1).

Table 4.1 *Crossover design sequences*

Period / Sequence	**Period 1**	**Period 2**
Sequence AB	CRGPcl	SRGPcl
Sequence BA	SRGPcl	CRGPcl

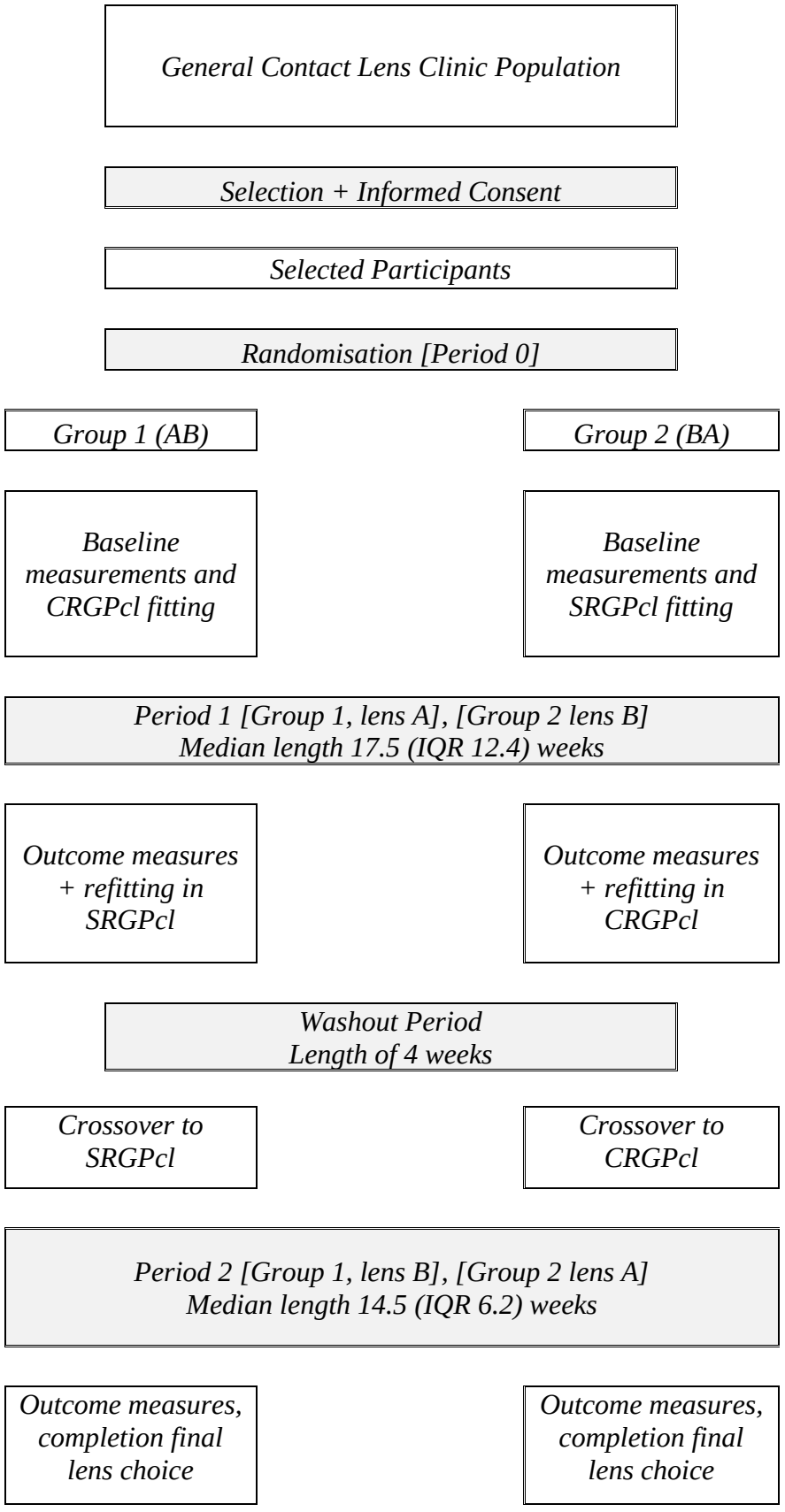


Figure 4.1 *sequence of randomisation and crossover*

The main disadvantage of a crossover design is that *carryover, period and sequence effects* (see below) may be confounded with treatment effects and cannot be estimated separately, which may bias results [*treatment effect is the effect of a treatment at the time of its application*].

A carryover effect is defined as the effect of the treatment from the previous time period on the response at the current time period, i.e., measurements taken during the second period may be a result of the direct effect of the treatment in period 2 and/or the carryover or residual effect of the treatment applied in period 1, yielding statistical bias. The incorporation of appropriate *washout periods* in the experimental design can diminish the impact of carryover effects. The presence of a differential carryover effect must be tested for by an appropriate independent samples test comparing the sums of the treatments between the 2 groups (Wellek and Blettner (2012). If a differential carryover effect is significant, this must be appropriately accounted for in the statistical analysis (Jones and Kenward, 2015).

A washout period is defined as *the time between treatment periods*, the rationale for this is that the previously administered treatment is "washed out" and therefore should not affect the measurements taken during the current period with the exception of permanent effects which alter the participant in some manner. Assuming that no significant permanent alteration of the participant occurs, it is important to identify if a differential carryover effect, (carryover effect due to [A] differs to carryover due to [B]), because if the carryover effects for [A] and [B] are equivalent, this common carryover effect is not confounded with the treatment difference.

A sequence effect can result if participants assigned to one sequence are different from those assigned to the other sequence, but under a randomized design it is reasonable to assume that sequence effects are minimized (Diaz-Uriarte, 2002).

A period is each occasion on which a treatment is applied, a period effect must be accounted for due to changes of the participants during the intervals between the measurements, or through habituation to the measurement itself (Diaz-Uriarte, 2002). To test for the presence of period effects, the crossover differences, which are equivalent to the differences in scores of treatments for all subjects (A-B), are computed and compared by an appropriate independent samples test (Diaz-Uriarte, 2002). The presence of a period effect must be accounted for in the statistical analysis of the results (Table 4.2).

Wellek and Blettner (2012) in agreement with Diaz-Uriarte (2002), stated that crossover trials are not typical matched-pairs designs, however are often analysed inappropriately, as if they were. The main problems with this approach according to Diaz-Uriarte (2002) are

1. Not accounting for period effects, which may affect the results of measurements depending on the period these measurements occurred.

2. Failure to consider carryover effects when comparing treatment effects.

These errors may lead to questionable results, where the lack of significant treatment effects could be the consequence of inflated variances (type II error), and the significant effects reported could be the result of either period or carryover effects (type I error) (Diaz-Uriarte, 2002).

The AB/BA design employed in this research is considered to be balanced [*each treatment precedes every other treatment the same number of times (once)*], which means that if the carryover effects are equal, then carryover effects are not confounded with treatment differences.

The AB/BA design is also uniform within sequences [*each treatment appears the same number of times within each sequence*], which means that sequence effects are not confounded with treatment differences and are uniform within periods [*each treatment appears the same number of times within each period*] minimising the confounding period effect.

Due to the design being balanced, one approach for the statistical analysis of the 2×2 crossover is to conduct a preliminary test for differential carryover effects, if this is found to be not significant, then the data from both periods are analysed in the usual manner. If there is a differential carryover effect, then only the data from the first periods are analysed, where differences between participants in the two groups are compared as in a parallel RCT (Wellek and Blettner, 2012; Armitage and Hills, 1982).

Because this experimental design involves repeated measurements on participants, the statistical modelling must account for between-participant variability [*dispersion in measurements from one participant to another*], and within-participant variability [*dispersion in measurements from one time point to another within a patient*]. The crucial variable for analysis in a crossover design is the within subject difference in outcome between the two study

periods. In order to assess the difference between treatment effects, a statistically valid test for independent samples has to be carried out with the values obtained for this variable.

The statistical analysis of normally-distributed data from a 2×2 crossover trial, under the assumption that the carryover effects are equal is as follows:

The statistical model we assumed for continuous data from the 2×2 crossover trial [(Table 4.2 Jones and Kenward (2015)]:

Table 4.2 *Crossover design sequence by period statistics (Jones and Kenward, 2015)*

Sequence / Period	**Period 1**	**Period 2**
Sequence AB	$\mu_A + \nu + \rho$	$\mu_B + \nu - \rho + \lambda_A$
Sequence BA	$\mu_B - \nu + \rho$	$\mu_A - \nu - \rho + \lambda_B$

μ_A and μ_B represent population means for the direct effects of treatments A and B, respectively, ν represents a sequence effect, ρ represents a period effect, and λ_A and λ_B represent carryover effects of treatments A and B, respectively. For sequence AB, the Period 1 vs. Period 2 difference has expectation $\mu_{AB} = \mu_A - \mu_B + 2\rho - \lambda$. For sequence BA, the Period 1 vs. Period 2 difference has expectation $\mu_{BA} = \mu_B - \mu_A + 2\rho - \lambda$. Therefore, we construct these differences for every participant and compare the two sequences with respect to these differences using an appropriate independent samples test. Thus, we are testing: H_0: $\mu_{AB} - \mu_{BA} = 0$ for each outcome measure (Jones and Kenward, 2015).

Study population recruitment

Participant selection

Most of the participants were recruited from the contact lens clinic in the ophthalmology department at the Central Middlesex Hospital (CMH) in North-West London. The CMH ophthalmology department provides specialist contact lens care to patients with corneal pathologies or other conditions, which require contact lens care beyond the scope of many community optometrists. Patients are usually referred to the department by community optometrists via their general practitioners. Three patients, who completed the study, were recruited from the chief investigator's community practice. One patient approached the investigator by email but did not fulfil the selection criterion of being free of problems with his current CRGP contact lenses and therefore was rejected.

The CMH contact lens clinic offers a single, weekly clinical session, during which up to twelve patients may be examined. Two optometrists provide specialist contact lens management to patients in this clinic; the chief investigator Mr A. Levit and the research coordinator Mr A. Stanton. Both optometrists are contact lens specialists with many years of experience of working in the NHS hospital eye service and private specialist contact lens clinics. Both optometrists achieved the *Good Clinical Practice* certification prior to starting this research (Appendix IIIA).

Inclusion criteria

1. Diagnosis of Keratoconus or related primary and secondary irregular cornea conditions [*see chapter 2*].

2. Participants are successful CRGPcl wearers.

3. Age 18 to 69. These ages were decided upon since contact lens management of keratoconus rarely occurs before the age of 18, and additional eye morbidities which may affect vision are more common after the age of 70.

Exclusion criteria

1. Patients with keratoconus who are satisfied with their unaided vision in both eyes.

2. Patients with keratoconus who have additional eye disease which affects their vision, such as significant cataract, glaucoma etc.

Most participants were fitted with the experimental lenses in both eyes. For four participants only one eye was fitted with both experimental lenses recruited. This is because, although keratoconus is a bilateral disease (Gomes *et al.*, 2015), there may be a significant asymmetry between the two eyes (Zadnik *et al.*, 2002). It is not unusual for patients to require keratoconus management in one eye only, with the other eye having sub-clinical disease or having undergone a corneal graft due to severe disease. It was therefore considered appropriate not to exclude participants with eye asymmetry, who either required no treatment or wore contact lenses which could not be included in this research. Including these patients was considered an appropriate representation of the variety of patients with corneal ectasiae requiring contact lens management.

Participants recruitment

The recruitment process was performed during the regular contact lens clinics. At CMH, the research coordinator, would inform the prospective patients that they were eligible to

participate in the study and would provide them with written information about the study (Appendix IA). In community practice the chief investigator's clinical assistant Mr Daniel Gorjian, would inform the prospective participants that they may be eligible to participate in this research and provide the written information. The recruitment started in January 2016, following ethical approvals in September 2015 and was completed in July 2018.

No direct payments were made to participants. However, all contact lenses were supplied free of charge during the trial period. At the end of the trial participants could keep either of the contact lenses used in the trial, under the usual optometric supervision at the contact lens clinic.

Confirmation of suitability was based on satisfactory performance of CRGPcl. The symptoms and history examination conducted during the standard, routine contact lens check-up established whether the prospective participant was experiencing any significant difficulties during their contact lens wear. Examination of contact lens fit and BCVA were performed subsequently to ensure that the habitual CRGPcl exhibited acceptable physical fit and enabled adequate visual performance (Appendix IIA). The integrity of the corneal surface and the rest of the ocular adnexa were checked to confirm that no significant adverse effects were caused by contact lens wear.

Suitable candidates were given the research participant information document (Appendix IA and IB) to read and if interested were invited to participate in the research after the completion of the formal informed consent procedure (Appendix IC).

Informed consent procedure

After reading the *participant information document* the prospective candidates had an opportunity to ask questions and discuss these with the chief investigator during their regular follow up appointment or other appropriate time during the contact lens clinic. The chief investigator gave the informed consent document (Appendix IB) to the prospective candidates and discussed all aspects of the RCT, prior to signing the consent form within three months from the invitation to participate. All prospective participants had sufficient time to ask questions and to consider and decide whether they wished to participate.

After signing the consent form (Appendix IC), all participants were reminded that they were free to withdraw at any time without any explanation. It was made clear to them in writing and verbally that should they choose not to participate in the research or withdraw from the research prior to its completion their standard of care will not be affected.

Communication of urgent and routine matters

The participants were informed in their consent document that should an issue arise, which would influence their continued participation; it would be conveyed to them by e-mail, telephone or by a written letter depending on the urgency. Participants' details were available to the chief investigator in the participants' hospital records and the digital practice records kept on password protected computer. Routine information was conveyed to the participants during their routine check-ups.

Loss of capacity

Participants were informed during their consent procedure that in the unlikely event of a loss of capacity, the research team would retain research data collected and continue to use it confidentially for the purposes for which consent was sought. This could include further research after the current project has ended as this was made clear in the information for participants.

Access to research results

At the completion of the study a lay summary of the anonymous results would be prepared and published on the Institute of Optometry website. The participant information highlighted this and any participants who did not have web access could contact the researchers for a paper version.

Randomisation

After the completion of the consent process the participants were randomised to group 1 [sequence AB]and group 2 [sequence BA] according to the randomisation order generated by the online research randomiser http://www.randomizer.org/ (Figure 4.1 Appendix V.E). The online randomiser created a list of 30 numbers from 1-30 randomly allocated to the 2 groups. The participants were allocated their treatment arm in the order of their recruitment from participant 1 to participant 30 (Table 4.10). The protocol for replacing participants who were unable or unwilling to complete this study was to recruit additional, appropriate participants to replace the drop outs with treatment allocation by sequential alternation in participants 31-34.

The length of participation in the study for most participants did not exceed 9-12 months during which they attended on 4-6 occasions. Study total length was from May 2015 to June 2018. The extra clinic attendance required by this study (compared with the normal 2 check-ups per year) was necessary because most participants were not familiar with SRGPcl and these lenses needed to be fitted in the same way as to a new patient, which requires both lens collection and lens handling instruction appointments as well as an early review to ensure that no adverse effects occurred with these lenses. These additional check-ups as well as the two appointments for outcome measures data collection were required in this study. All participants were informed about these additional requirements during the informed consent procedure.

Experimental contact lenses

The experimental contact lens was the SRGPcl, *Zenlens*™ and the control contact lens was the CRGPcl *Rose K2*™. Both lens types were fitted to achieve optimal contact lens fit on the ocular surface according to recognised clinical criteria (see chapter 3) and manufacturers fitting instructions. The CRGPcl Rose K2 lenses were fitted with the aim to achieve the most widely recognised best fit of a *divided support / three-point touch* fitting relationship between the lens and the cornea (Loft and Wolffsohn, 2016; Szczotka-Flyn *et al.*, 2006; Woodward, 1989; Watts and Colby, 2017).

The desired lens cornea fitting relationship was achieved with the Rose K2 lenses by utilising a comprehensive fitting set, consisting of 26 lenses, with optical lens radius range 5.10 to 7.60mm (full range 4.30-8.59mm), in a variable lens diameter from 8.50 to 9.20mm (full range 7.90-10.40mm), with variable power to approximate the final lens power (range -2.00 to -23.00DS). Lens adjustments were implemented following the recommended fitting guidelines (Art Optical, 2013). Central fitting of *cone clearance* or *feather cone touch* was achieved by selecting the appropriate central optic zone radius from the fitting set until the desired central fit was achieved. Modification of the central lens radius and or diameter was possible if required, when the fitting set lens central parameters did not achieve an acceptable fit. Peripheral lens fitting was optimised by utilising the *flexible edge lift system*, with 5 levels of symmetrical edge lift variation.

When necessary central and / or peripheral toric lens designs or quadrant specific *asymmetrical corneal technology* were employed in moderate to high corneal asymmetry (Art Optical, 2013). The CRGPcl mean OZR was 7.05mm, Mean lens diameter was 9.11mm, mean lens power was -5.79DS, cylinder -1.92DC and axis 145°. Standard lens design was used in 32 lenses (57%). The 24 (43%) of non-standard lenses used were 6 (11%) toric (central and /or peripheral), 1 (2%) was quadrant specific, the remaining 17 (30%) had adjusted, symmetrical, non-standard peripheral lens curves. The CRGPcl were manufactured and supplied by the CE approved British contact lens manufacturer Menicon David Thomas.

The SRGPcl were initially manufactured by the CE approved Dutch contact lens manufacturer UCO-Lavec-BV and later by the Bausch and Lomb speciality contact lens manufacturing division in Hastings UK. The desired fitting relationship between the eye and the SRGPcl was

achieved by following the published manufacturer fitting guidelines (Alden Optical, 2016) and recognised standards of clinical experts (van der Worp, 2015). The lenses were fitted from 2 comprehensive fitting sets (26 lenses in each set), one with symmetrical peripheral (haptic) design the other with a toric haptic design. The fitting sets contained lenses in 2 diameters, 16mm [n=54 (96%)] and 17mm [n=2 (4%)] and in two designs, prolate (flattening ellipse) (n=56) and oblate (steepening ellipse, nil used in this research), with central SAG (lens height) increments of 300µm, range 4100-5800µm, with a total, customisable SAG range of 3200 - 6700µm in 10µm micron steps. The customisable SAG range facilitated the achievement of the required 200-300µm corneal clearance after lens settling. This was achieved by allowing the best fitting trial lens to settle for a minimum of 60min and then comparing the tear layer thickness, between the cornea and the lens, to the standard lens thickness across the fitting set of 350µm (van der Worp, 2015).

The control of limbal clearance could be achieved separately from central corneal clearance by modifying the lens SAG at the limbal area, without affecting the central clearance by the utilisation of the *smart curve*, a design feature unique to the Zenlens, which enables the fitter to achieve the desired central lens clearance from the cornea, with minimum effect from other lens modifications (Alden Optical, 2016). The mean OZR of the 56 lenses fitted was 7.48mm, mean SAG = 4627.7µm, mean lens power = -3.25DS and -1.61 cylinder with a mean axis of 120°.

The modification of the *Alignment Peripheral Curve System* facilitated appropriate scleral alignment via symmetrical 360° modification or the utilisation of toric haptic curves. The toric *Alignment Peripheral Curve System* fitting set facilitated the fitting of SRGPcl with toric haptic or bi-toric lenses (toric haptic with front toric optics). Standard APS was used in 16 (29%) lenses, in the non-standard APS in the 40 (71%) lenses, 36 (64%) were with a toric haptic portion, 10 (18%) were bi-toric (toric haptic and toric front optics). Other custom features such as front surface toric optics [n=1 (2%) with a standard APS] and pinguecula / pterygium channels called *MicroVaults* [n=6 (11%)] were employed when required to optimise visual acuity and lens sclera fitting relationship respectively.

Appropriate clinical guidelines and best practice were followed for the fitting and use of both types of contact lenses (Appendix ID and IE). The chief investigator who is a hospital eye service contact lens practitioner with over 20 years' experience, personally fitted all the

experimental lenses. During the research, contact lens supply and after-care was carried out to the usual standard adopted at CMH.

Once the fitting had been completed the lenses were checked by the chief investigator at collection and rechecked one to three weeks after collection. All participants were appropriately instructed regarding contact lens wear, care and safety and written information was provided to them (Appendix ID and IE). The final check was performed 8-12 weeks post initial lens collection. During the final check appointment, the visual performance was measured and recorded by the research coordinator Mr Anthony Stanton or Mr Daniel Gorjian in the hospital clinic and by Mr Daniel Gorjian in community practice, during this time both were naive to the type of lenses worn by the participants (Appendix IIB). The visual quality of life questionnaire completed by the participants during that appointment or a few days prior was collected by the chief investigator.

After this check-up the other lens type was fitted by the chief investigator and ordered from the manufacturer. The collection appointment was scheduled to a date in accordance with the mandatory washout period at least one month later. During the washout period, participants wore their original CRGPcl until the scheduled appointment to collect the crossover intervention to start the second period. During the crossover phase, check-ups were performed in an identical manner to the first phase. At the end of the crossover phase the participants were informed that their participation in this research was completed and they asked to choose one of the two experimental lenses as their lens of choice for continued habitual wear.

Research outcome-measures

The primary outcome measures of the RCT is ETDRS logMAR, monocular VA measurement (see below). The secondary outcome measures were the CSF visual performance measured by the CSV 1000E console (VectorVision, 2013), the validated NEI-VFQ (Mangione, 2000; Mangione *et al.*, 2001) and the SPV and SPC developed by the chief investigator, the Levit subjective vision score (LSVS) and the Levit subjective comfort scores (LSCS).

The ETDRS logMAR VA is the most commonly used measure of high contrast visual resolution in research and clinical practice (British Standards Institution., BS 4274-1:2003; Arditi and Cagenello, 1993; Ferris *et al.*, 1982). The ETDRS logMAR and the CSF scores were measured by repeated, forced choice, letter by letter scoring for logMAR (Vanden Bosch and Wall, 1997), and each of the eight pairs of gratings in each of the 4 CPD rows for CSF.

These outcome measures were assessed at the beginning of the study with the participants' habitual CRGPcl for baseline and familiarisation purposes and at the end of the two interventions. Both BCVA and CSF were measured using the commercially available instruments: the CSV 1000E manufactured by Vector Vision (VectorVision, 2013) for the CSF and the chart manufactured by Precision Vision http://www.precision-vision.com/ for the logMAR BCVA at the CMH. The 1000E console was used for both CSV and logMAR BCVA in the three participants recruited in the community practice. Both instruments are used extensively in research and clinical trials worldwide, and are approved and recommended by both the FDA and NEI (VectorVision, 2013). Chart illumination in this research was a standardized uniform retro illumination of 85 cd/m², which is the ideal standard for research (Ricci *et al.*, 1998), generally in clinical practice there is insignificant change in performances above 80 cd/m^2 (Sheedy *et al.*, 1984).

The other secondary outcome measure was the NEI-VFQ validated by Mangione (2000). This is a vision related Qol instrument designed to assess subjective perception of visual function and quality of life. This instrument, which has been used by other researchers investigating keratoconus (Kymes *et al.*, 2008c; Kymes *et al.*, 2004; Tatematsu-Ogawa *et al.*, 2008) was applied to give baseline values at the beginning of the study and repeated the completion of the period of use of each intervention.

Further secondary outcome measures were the SPV and SPC assessed with LSVS and LSCS respectively, which are Likert-like scales from 1-10 (worse- best) grading of the participants' perception of their own vision and comfort in each experimental lens.

The final outcome measure of this research was the participants' choice of one of the two experimental lenses for future habitual wear. This choice was correlated to other outcome measures to establish if there are possible clinical reasons for that choice.

The tertiary outcome measure, which was not expected to differ with the two lens types but was measured as a precaution, was the ocular integrity post contact lens wear. The integrity of

the cornea and the conjunctiva was examined on lens removal and was accurately recorded utilising the validated scales of contact lens induced corneal fluorescein staining scales (Efron, 1996; Efron, 1998; Efron *et al.*, 2001). For the conjunctiva the validated scale of conjunctival hyperaemia was used (Efron, 1997a). These measurements of contact lens wear induced complications are a mandatory part of standard clinical practice and as such their accurate assessment and recording in this research enabled an objective comparison of the effects of the two lens types on the ocular status of the participants.

Data

Visual outcome measures

It was considered that in this clinical trial the measurement of both BCVA and CS, whilst wearing contact lenses may provide a more complete understanding of the effects of treatment on the quality of vision than either measure alone (Rubin, 2013). ETDRS logMAR BCVA and CSF numeric and logCS values were measured at baseline and at the completion of each period. Detailed discussion of these outcome measures is presented in the chapter 1.

Visual acuity (VA)

VA is the most widely used measure of visual function both in optometric clinical practice and in vision research and is routinely used for evaluating the effectiveness of refractive, medical and surgical treatments (British Standards Institution., BS 4274-1:2003). The preferable forced-choice testing, with letter counting scoring procedure were used in this research (Ricci *et al.*, 1998). A difference of 1 line (5 letters or 0.10 logMAR) was considered significant, with 95% confidence that a real change has occurred (Bailey *et al.*, 1991).

Contrast sensitivity

The CSV-1000E provides a full contrast sensitivity curve, which is very useful for the evaluation of ocular disease, particularly cataracts (Shandiz *et al.*, 2011), glaucoma (Gandolfi *et al.*, 2005), optic neuritis in multiple sclerosis (Sisto *et al.*, 2005), diabetes (Sadeghpour *et al.*, 2015), macular degeneration (Richer *et al.*, 2004), visual performance in contact lenses (Porisch, 2007; Wachler *et al.*, 1999) and after refractive surgery (Tuan and Liang, 2006). Two different charts versions were used in this research to provide apparently randomised locations for the grating targets (Ginsburg, 1984; VectorVision, 2013). The forced choice testing procedure was implemented for CSF testing as well.

The NEI-VFQ

The validated NEI-VFQ (Mangione, 2000; Mangione *et al.*, 2001) was used in this research as a subjective measure of the participant's perceptions of their visual wellbeing during the periods of use of both the experimental and control contact lenses. The first time this questionnaire was completed by the participants as a baseline was in the beginning of the study, describing the visual Qol in their habitual CRGPcl. The following two times this questionnaire was completed were at the end of each treatment period.

NEI-VFQ was developed as a survey which measures various aspects of self-reported vision-targeted health status in individuals with chronic eye diseases. The survey measures the influence of visual symptoms and disability on health issues such as emotional well-being and social functioning, as well as task-oriented visual functions. The survey contents were based on issues which were identified during a series of condition-specific focus groups, using patients who had variety of ocular pathologies (Mangione *et al.*, 1998). The NEI-VFQ represents a shortened version of the 51-item version, it consists of 25 questions representing

12 domains, 11 vision-related and a single general health rating question [Table 4.5 Appendix V.F. Mangione (2000)].

The NEI-VFQ generates the following vision-targeted subscales: 1 global vision rating question, 3 questions regarding difficulty with near vision activities, 3 questions regarding difficulty with distance vision activities, 2 questions regarding limitations in social functioning due to vision, 2 questions regarding role limitations due to vision, 3 questions regarding dependency on others due to vision, 4 questions regarding mental health symptoms due to vision, 3 questions regarding driving difficulties, 1 questions regarding limitations with peripheral vision and colour vision, 2 questions regarding ocular pain and 1 general health rating question.

NEI-VFQ data entry, coding and analysis

Detailed description of data entry, data extraction, recoding individual answers, accounting for missing answers and generating average scores are in Appendix IV. A. B and C. Table 4.6 exhibits the items which are averaged to generate VFQ-25 + optional in the NEI-VFQ (Mangione, 2000).

Table 4.6 *Averaging of items to generate (VFQ-25+optional Items) (Mangione, 2000)*

Scale	No of Items	Items to be averaged
General Health	2	1, A1
General Vision	2	2, A2
Ocular Pain	2	4, 19
Near Activities	6	5, 6, 7, A3, A4, A5
Distance Activities	6	8, 9, 14, A6, A7, A8
Vision specific		
Social Functioning	3	11, 13, A9
Mental Health	5	3, 21, 22, 25, A12
Role Difficulties	4	17, 18, A11a, A11b
Dependency	4	20, 23, 24, A13
Driving	3	15c, 16, 16a
Colour Vision	1	12
Peripheral Vision	1	10

Subjective perception of comfort (SPC) and subjective perception of vision (SPV)

The assessment of the SPC and SPV in contact lenses is an integral part of symptoms and history examination in optometric practice. Typically, these variables are assessed in an informal, binary way: "Are your contact lenses comfortable?" and "Is your vision with the contact lenses clear?". For this research, a numerical rating scale was used as described below.

Numerical rating scales and visual analogue scales are considered equally useful tools in the assessment of subjective quality of vision in contact lenses (Gullon and Schock, 1991; Papas and Schultz, 1997) and comfort during contact lens wear (La Hood, 1988). Grading scales are commonly used in clinical research, particularly in relation to the grading of pain. Williamson and Hoggart (2005) reviewed the literature regarding the visual analogue, verbal, and numerical pain rating scales and concluded that, *"all three pain-rating scales were valid, reliable and appropriate for use in clinical practice",* further, they reported that *"the Numerical Rating Scale has good sensitivity and generates data that can be statistically analysed for audit purposes"* (Williamson and Hoggart, 2005).

In this research the subjective measures of comfort and vision with the two experimental lenses were elicited after each period of lens wear and graded on a specially designed Likert-like scales from 1-10, with 1 constituting the worst and 10 the best vision and comfort scores (Appendix IIA and IIB). These grading scales were designed by the chief investigator and are routinely used by the chief investigator in his contact lens practice and have been found to be useful for decision making in contact lens management. These instruments however, were never validated. It was nevertheless considered appropriate to use these instruments alongside the other validated outcomes and apply statistical analyses to establish their significance in this research.

Final lens choice

The final outcome was the participants' lens choice to use as their habitual lens. The plan was to find out whether a correlation could be established between the final lens choice and any statistically significant differences between the primary and secondary outcomes in the two experimental lenses.

Recommendation for validation of significant findings and their implementation in specialist and general optometric practice to aid in the decision-making processes would be made regarding the appropriateness of CRGPcl and SRGPcl and the likelihood of success when refitting from one type to another.

Ocular integrity

The integrity of the cornea and the conjunctiva were examined on lens removal at each stage of the research, at baseline, after wear of the randomised lens and after wear of the crossover lens, as required in standard clinical practice. Although not an outcome measure in this research, it was decided that should any unusual or adverse effects have occurred, these would be reported.

Wolffsohn *et al*., (2015) performed an international survey of eye care practitioners regarding their anterior eye health recording practices to formulate guidelines for best practice. They recommended specifying the grading scales used and record scores to 1 decimal place. They advised that the following conditions are graded in every contact lens examination; bulbar and limbal conjunctiva hyperaemia, limbal neovascularisation, conjunctival papillary redness and roughness, both in white light and with sodium fluorescein (NaFl). They recommended recording the grades of blepharitis, meibomian gland dysfunction and NaFl staining of both the cornea and conjunctiva (Wolffsohn *et al.*, 2015). These recommendations were followed in this research, using the validated grading scale for contact lens complications developed and

validated by Efron et al., (1996), (1997), (1998) and (2001) (Efron *et al.*, 2001; Efron, 1998; Efron, 1997b; Efron, 1996).

There are 16 sets of grading images; these represent the key anterior ocular complications of contact lens wear. The conditions are illustrated in five stages of increasing severity from 0-4, with 'traffic light' colour coding from green (normal) to red (severe) (Table 4.7. Appendix IV.D).

Sample size calculation

For the purpose of sample size calculation in this research the primary outcome measure of ETDRS logMAR BCVA was selected. The calculation was carried out considering the worst-case scenario. This is that a differential carryover effect and / or significant period effect were found, in which case the data would have to be analysed as a parallel group trial instead of a crossover trial. Therefore, the sample size calculation was based on the most conservative approach, calculating the number of participants required if it were just a parallel group trial without crossover. For the calculation, data from previous work by Marsack *et al.*, (2007), Nejabat *et al.*, (2012), Davis *et al.*, (2006), Sabesan *et al.*, (2013), Gumus *et al*., (2011) were used to provide the information of BCVA in CRGPcl and SRGPcl (Table 4.8, Figure 4.4).

Table 4.8 *Research used to establish mean and standard deviation for sample size calculation* (Marsack *et al.*, 2007; Nejabat *et al.*, 2012; Davis *et al.*, 2006; Sabesan *et al.*, 2013; Gumus *et al.*, 2011)

Authors	CRGPcl logMAR mean (StdDev)	SRGPcl logMAR mean (StdDev)
Gumus *et al.*, (2011)		0.09 (±0.10)
Marsack *et al.*, (2007)	0.15 (±0.11)	
Nejabat *et al.*, (2012)	0.04 (±0.04)	
Sabesan *et al.*, (2013)		0.40 (±0.18)
Davis *et al.*, (2006)	0.12 (±0.16)	
Total mean and StdDev	0.10 (±0.10)	0.25 (±0.14)

The required number of subjects (n) can be calculated from the following formula: (Armitage and Berry, 1987); $\mathbf{N > 2\ \{(Z_{2\alpha} + Z_{2\beta})\ \sigma\ /\delta_0\}^2}$

The value $Z_{2\alpha}$ represents the level of result that will be taken as being statistically significant. This will be a two-tailed (*p=0.05*), giving $Z_{2\alpha}$=1.96. $Z_{2\beta}$ represents the desired statistical power, set at 0.80, giving $Z_{2\beta}$=0.842. δ_0 represents the clinically significant difference and σ is the standard deviation of the population.

The key variable in the sample size calculation is high contrast logMAR BCVA, the most widely used and quantitatively rigorous measure of visual performance. The figures were taken from the aforementioned studies in which BCVA with CRGPcl was measured. The studies with CRGPcl only were used for the sample size calculation as these were performed on large numbers of participants with keratoconus who wear CRGPcl as required by the eligibility criteria in the current RCT. Furthermore, the SRGPcl study: Sabesan *et al.,* (2013) was a pilot study with only 11 eyes of 6 participants, and the larger SRGPcl study by Gumus *et al.,* (2011), exhibited similar logMAR BCVA scores to those found in the CRGPcl studies. A single line change (0.10 logMAR) was taken as representing a clinically significant change in logMAR BCVA (Bailey *et al.,* 1991; Brown and Yap, 1995).

Davis *et al.,* (2006) showed a mean logMAR visual acuity with CRGPcl in participants with keratoconus of 0.12 (±0.16), Marscack *et al.,* (2007); 0.15 (±0.11), Nejabat *et al.,* (2012); 0.036 (±0.04). From these studies the average standard deviation obtained was 0.10. The variance of both values was calculated and averaged and the square root of the mean variance calculated to give the common standard deviation. This was used in the above formula with an *alpha* of 0.05 and for power of 80% to give a required sample size of 15 in each group (Table 4.9). This was checked with an online calculator www.stat.ubc.ca/~rollin/stats/ssize/n2.html, which also gave a sample size of 15 in each group. The plan was therefore to continue the study until at least 30 participants have completed the study, 15 starting with CRGPcl and 15 with SRGPcl. Recruitment continued until 30 participants had finished both periods.

Table 4.9 *Sample size calculation*

For power of 80%	Mean	SD	Variance	Mean variance	Common SD	N
CRGPcl	0.10	0.10	0.01	0.01	0.10	**15.70**
SRGPcl	0.20	0.10	0.01			

The fact that the ratio of participants in the 2 experimental groups changed from the planned 15 in each group to 13 in group 1 and 17 in group 2, should have a minimal effect on the significance and power of the study, see discussion in strengths and limitations.

Minimising measurement bias

Blinding is more difficult to achieve in non-pharmacologic trials (Boutron *et al.*, 2004), and participants knew what type of contact lens they inserted every morning. To minimise possible investigator-bias the outcome measures of VA and CS were performed by the research coordinator and the chief investigator's clinical optometrist assistant Mr Daniel Gorjian, both naive to the type of contact lenses worn by the participant at the time of measurement. This was achieved by the chief investigator performing the initial examination of symptoms and history, grading of comfort and vision, visual acuity, over-refraction and contact lens condition and fit evaluation. The visual acuity and contrast sensitivity were measured and recorded by a naïve examiner in a different room. After the completion of these procedures the chief investigator copied the recorded results into the computer-based research database program.

Statistical analysis

The chief investigator ensured that all relevant data were collected and recorded, data from participants who did not participate in both arms of this research were not included in the statistical analysis.

The *IBM-SPSS* version 21 was used for all statistical calculations, *Microsoft Excel* 2010 was used for data storage as well as the generation of some graphs and tables, the data was recorded

in a specially designed database in *LibreOffice* version 5.0.4, prior to being transferred to the Excel files (see below and Appendix IVA, B and C).

The chief investigator carried out all statistical analyses under the guidance and supervision of the research supervisors Prof. Bruce Evans and Dr Martin Benwell. A preliminary statistical analysis was carried out after 12 participants had fully completed their participation; this was done to assess the significance of the carryover effect in this research. The complete statistical analysis was carried out after the data were collected for all participants who completed the research.

Pooling of data

Following the recommendation of Armstrong (2013) and personal communications with Armstrong, experimental data were collected from both eyes in most (Armstrong, 2013).

Keratoconus is a bilateral disease (Gomes *et al.*, 2015), with significant asymmetry between the two eyes (Zadnik *et al.*, 2002), it was therefore hypothesised that it may be appropriate to use the visual scores of each eye as an independent sample to increase sample size and maximally utilise the available data.

The counter argument for pooling the data are that measurements obtained from right and left eyes are usually correlated (Katz *et al.*, 1994), and therefore may not be treated as if they are independent samples, an assumption made in statistical procedures, such as *t-tests*, analysis of variance, confidence intervals and linear regression. When testing hypotheses, the use of inappropriately pooled data from both eyes increases the possibility of a *type 1 error* because the variance between the eyes of the same subject is usually less than that between subjects, the overall variance of a sample of measurements combined from both eyes is therefore likely to be an underestimate of the true variance. Hence, data collected from both eyes from a sample of subjects cannot be combined without taking the correlation into account (Armstrong, 2013). In order to avoid this problem, data from one eye only may be analysed, which would lead to rejection of the valid data from the fellow eye, reduction of the potential power of the study, and may raise ethical questions of subjecting patients to measurements that were not used in a subsequent analysis (Armstrong, 2013).

The decision was taken in this experiment to perform a correlation analysis of the baseline logMAR scores of the right and left eyes of each participant, and a separate analysis of correlation between the scores of the right eye and randomised scores of the left eye. The significantly higher correlation found between the right and left scores taken from the same subject compared with the random correlation, indicated that treating the right and left eyes as independent samples and pooling the data from both eyes would be inappropriate. The statistical analyses for the carryover, period and treatment effects were therefore performed on the mean of the right and left eye's scores of each participant.

Inferential Statistics

In normally distributed data the skewness and kurtosis z values, which are the ratio of skewness and kurtosis values and their respective standard error value, should be between -1.96 to +1.96 and the visual analysis of the data histogram, quantile-quantile plots and box plots should indicate that the data are approximately normally distributed (Cramer, 1998; Doane and Seward, 2011). Analysis for normality was performed on all data and appropriate statistical tests for parametric and non-parametric data were employed in the descriptive and inferential statistics, results sections

Crossover trials have sometimes been analysed using repeated-measures statistical tests, although this approach has been criticised by Wellek and Blettner (2012). A similar point is made in the respected text book on the analysis of crossover trials by Jones and Kenward (2015). Therefore, the inferential statistical analyses of the outcome measures were performed as recommended by the above authors.

Preliminary checks were carried out to ensure that there was no carryover effect from the first to the second treatment periods, as recommended in the literature (Jones and Kenward, 2015; Wellek and Blettner, 2012; Haynes *et al.*, 2006). It was considered unlikely that a significant differential carryover effect would be found because contact lenses do not cure but only manage the optical distortions caused by corneal ectasiae. Furthermore, measurements of visual performance are not affected by previous visual experiences in adult visual systems (Bailey,

2006; Borish and Benjamin, 2006). Additionally, participants who were randomised to SRGPcl all had a one-month washout period of returning to wearing their habitual CRGPcl. Despite the relatively long duration required for corneal stability post CRGPcl prior to measurements for refractive surgery in normal individuals (Tsai *et al.*, 2004), a one-month washout to mitigate against the unlikely significant differential carryover effect was considered adequate, as no corneal recovery is required in RGPcl wear, since RGPcl neutralise corneal irregularities. It was decided that in the unlikely event of a significant differential carryover effect or if a large proportion of participants drop out before the second treatment period then the study would be treated as a parallel group RCT and the data from the first period will be analysed in the usual way as recommended by Haynes *et al.,* (2006). Our conservative sample size calculation allowed for this possibility.

As a precaution, we carried out an unpaired *t-test* to compare any potential confounding variables, e.g., visual acuity and age, in the two randomised groups. It was planned that if these analyses identified any statistically significant differences between the two groups in a confounding variable then further statistical analysis of covariance (ANCOVA) would be carried out to evaluate the treatment effects whilst controlling for these confounding variables.

Compliance and withdrawal

Participants' compliance with wearing of the appropriate contact lenses at each stage was established by interviewing participants during each review appointment. No issues with compliance were anticipated and none were found as expected, since all subjects were experienced contact lens wearers. The chief investigator ensured that compliance with the washout period prior to crossover was complied with by supplying the lenses for the crossover period only after the completion of the one-month washout period.

Data handling and record keeping

Data were collected manually on pre-prepared research clinical records files (CRF) (Appendix IIIA, IIIB, IIIc). These were kept in the CMH in a locked cabinet, with no access except for the chief investigator. The results were later entered into a password protected digital database computer program (see below) which was stored on a password protected computer.

The relevant clinical information contained in these research records was added to the participants' hospital records during the various consultations.

The anonymised data were used for the writing of the doctoral thesis and may be used in professional publications. The only details used in publications may include the participants' gender, age and allocated research serial number, but no personal data. The ethics committee had approved that the anonymised data may be kept for five years after the completion of the research and may be used for further analysis and publications.

The chief investigator is responsible for data collection, recording and data analysis. All research data were collected by the chief investigator the research coordinator and clinical assistant during the scheduled consultations at the hospital eye department's contact lens clinic and community practice. The chief investigator ensured that all data recorded was legible and stored in the correct CRF.

The chief investigator personally double-checked all entries and ensured that correct entries were made into the appropriate sections of the database program.

The database software for research data recording

A customised database was created using the *Base* component of *LibreOffice* version 5.0.4 configured by a software specialist commissioned by the chief investigator for data collection in this research (Appendix IVA, B and C).

When a query is run the output is in the form of a table of data. This is copied and pasted into Excel, for example, and it can then be saved to disk and/or used for basic analysis in Excel. Although Excel is not the right tool for complex data analysis, some basic data manipulation is possible.

An Excel spreadsheet was used for processing NEI-VFQ data. An Excel template spreadsheet has been created, and raw data from a database query is pasted into this template. Cell calculations then flow from these data and the last worksheet of the spreadsheet shows the average scores for each participant, with the raw answers recoded according to Version 2000 of the NEI-VFQ.

Monitoring, quality control and assurance

This research adhered to the tenets of the Declaration of Helsinki and was approved by the NRES Committee London-Camden & Kings Cross NHS Health Research Authority, via the Integrated Research Application System (IRAS) (Appendix IIIB) as well as LSBU REC and Institute of Optometry REC. This research was also reviewed and approved by the North London Hospitals research and development department and has been registered and updated throughout with clinicaltrials.gov. The chief investigator and the research coordinator have received G*ood Clinical Practice* accreditation by examination prior to starting this clinical trial (Appendix IIIA). This accreditation course and examination cover all ethical aspects of clinical research so that researchers possess the knowledge to comply with the requirements for conducting research ethically.

Adverse Events

Although it was considered that adverse events would be unlikely to occur, the potential adverse events which infrequently can occur in individuals with keratoconus when fitted with contact lenses were carefully looked for during the review appointments. These adverse events can be summarised as related to contact lens wear or related to the conditions treated / managed which in this research is mostly keratoconus.

It was considered unnecessary to report the non-serious, commonly encountered contact lens related complications, which include allergic / toxic reactions to contact lens materials and care products and normal resident bacteria as well as minor physical corneal insult during contact lens handling and wear.

Infrequently condition related complications may be the more serious and may result in disease progression or rarely in corneal infection. Corneal abrasion is another possible event which is usually minor but could be extensive and potentiality serious and may lead to complications such as corneal infection and / or scarring. In the unlikely event of the occurrence of a serious adverse event like corneal infection, which requires hospitalisation, immediate clinical action would take place and the event was to be reported to the sponsor within 7 days. This was to be followed to resolution and reported in the annual safety report of the sponsor as well as in publications describing the research. In the unlikely event of serious unexpected suspected adverse reactions reports to the NHS ethics committee, NHS trust and MHRA were to be generated within 15 days. These were to be followed until total resolution and reported in the annual safety report as well as in publications describing the research.

To minimise the risk of adverse events best practice protocols of lens fitting, participant education and instructions in aspects of hygiene, contact lens handling and care as well as appropriate follow up schedules were followed. The participants were carefully instructed regarding the signs and symptoms of these adverse events as well as the actions to take in the event of these occurring. Protocols from Moorfields eye hospital and association of optometrist were used (Appendix ID and IE).

Serious adverse events like corneal infection and the non-serious events were to be treated at the ophthalmology department, CMH and if occurred, were to be reported by the chief

investigator in the participants' clinical record as well as the research records. The consultant ophthalmic surgeon, Mr Simon Levy was the onsite research supervisor and was consulted regarding all aspects of safety issues in this research prior to and during the research process.

The natural progression of keratoconus and related conditions were monitored during this research more vigilantly than during the normal contact lens practice as during this research the participants were reviewed more frequently than during their standard care.

Safety monitoring committee

The persons responsible for the trial safety monitoring, were the chief investigator, the optometrist Anthony Stanton, the onsite supervisor; consultant ophthalmic surgeon Mr Simon Levy and the academic supervisors.

Communication of urgent matters

The protocol was that should any urgent issues arise, which might influence participants' continued participation, it would be conveyed to all participants by e-mail, telephone or by a written letter with appropriate urgency. The participants' contact details are kept on the password protected computers at the hospital clinic. Routine information was to be conveyed to the participants during their routine check-ups.

Summary

This chapter outlined the research design and its rationale in the context of the current research. Important aspects of participants recruitment, informed consent and the ethical accreditation of this research were discussed. The experimental lenses used and the outcome measures to evaluate their performance were outlined and discussed. The sample size calculation and the important statistical considerations pertinent to this research were outlined. Important aspects relating to confidentiality, data handling, record keeping and participants' safety were outlined and discussed.

Chapter 5: Results

Overall 124 patients were approached for consideration of participating in this research. Forty-seven patients did not meet the inclusion criteria, the majority of whom (n=36), did not satisfy the criterion of adequate satisfaction with or performance of CRGPcl: and 43 declined to participate. Thirty-four patients completed the consent procedure, underwent baseline measurements, and randomised to the first arm of the study. Four participants were lost to after-care and were not included in the data analysis. Overall 56 eyes of 30 participants were analysed, 4 participants who required management to one eye only were included in this research because it was considered an appropriate representation of the keratoconus population presenting for contact lens management (Gomes *et al.*, 2015; Zadnik *et al.*, 2002).

During the randomisation 17 participants were randomised to each study arm / group. Group 1, sequence AB, started with CRGPcl and crossed over to SRGPcl and group 2, sequence BA, started with SRGPcl and crossed over to CRGPcl. In group 2 all 17 participants crossed over to CRGPcl, completed their participation and were analysed for primary outcome measures. In group 1, 13 out of the 17 recruited participants crossed over to SRGPcl, completed their participation and were analysed for primary outcome measures (Figure 5.1).

Research flow diagram

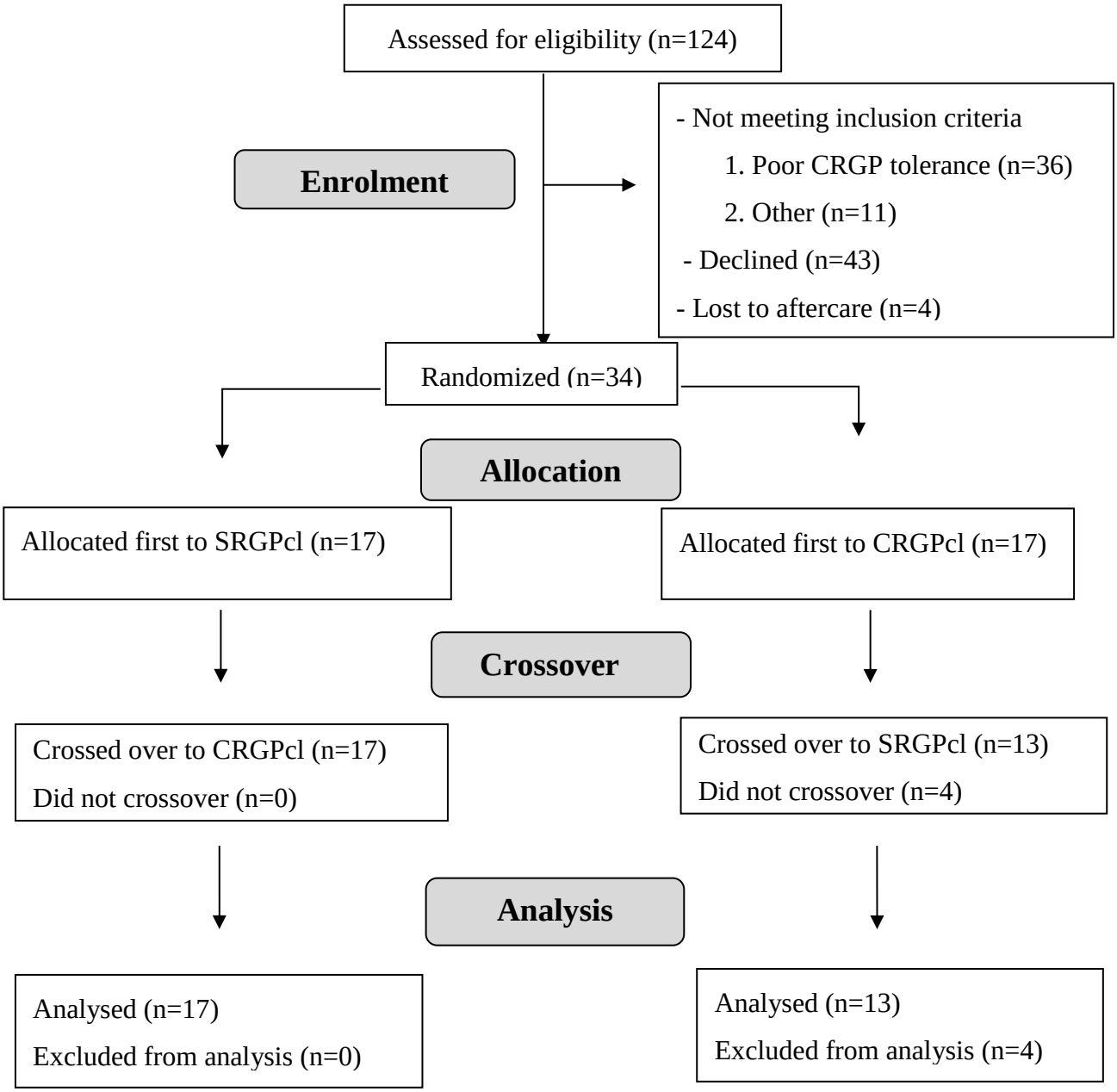


Figure 5.1 *Research flow diagram according to Consolidated Standards of Reporting Trials (CONSORT) (Schulz et al., 2010)*

Baseline Demographics

Gender

Out of the total population of 30 participants entering the study, 77% (n=23) were males and 23% (n=7) were females. The male participants outnumbered the female participants by 3:1.

Age

The population age was not normally distributed; *Shapiro-Wilk* (*p=0.039*), with a range of 46 years (22-68). The median age was 36.0, (IQR=16.0) years, skewness of 0.8 (SE 0.434, *z=1.91*) and kurtosis of -0.01 (SE 0.845, *z=-0.02*) (Table 5.1 and Figure 5.2).

Table 5.1 *Population age demographics.*

Age *Shapiro-Wilk (p=0.039)*	Statistic	Std. Error
Median	36.0	
Interquartile Range	16.0	
Mean	39.1	2.1
95% CI for Mean	34.8 - 43.3	
Std. Deviation	11.5	
Minimum	22.0	
Maximum	68.0	
Range	46.0	
Skewness	0.8	0.4 (z = 1.91)
Kurtosis	0.0	0.8 (z = -0.02)

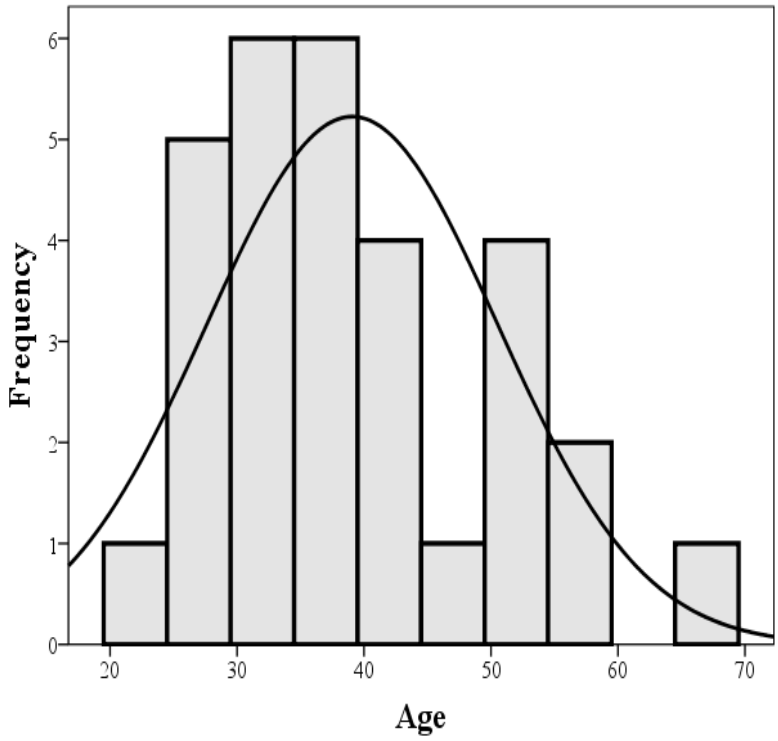


Figure 5.2 *Population age frequency.*

Gender ages

The gender ages were normally (*p=0.697*) and not normally (*p=0.005*) distributed for the female and male genders respectively, with high positive skewness in males of 1.4 (SE=0.5, z=2.9) (Table 5.2). The difference between the male (*Median=34, IQR=13)* and female (*Mean=47.0, ±8.45, Median=45, IQR=14*) ages respectively was statistically significant, *Mann-Whitney U* (*p=0.010*) (Figure 5.3).

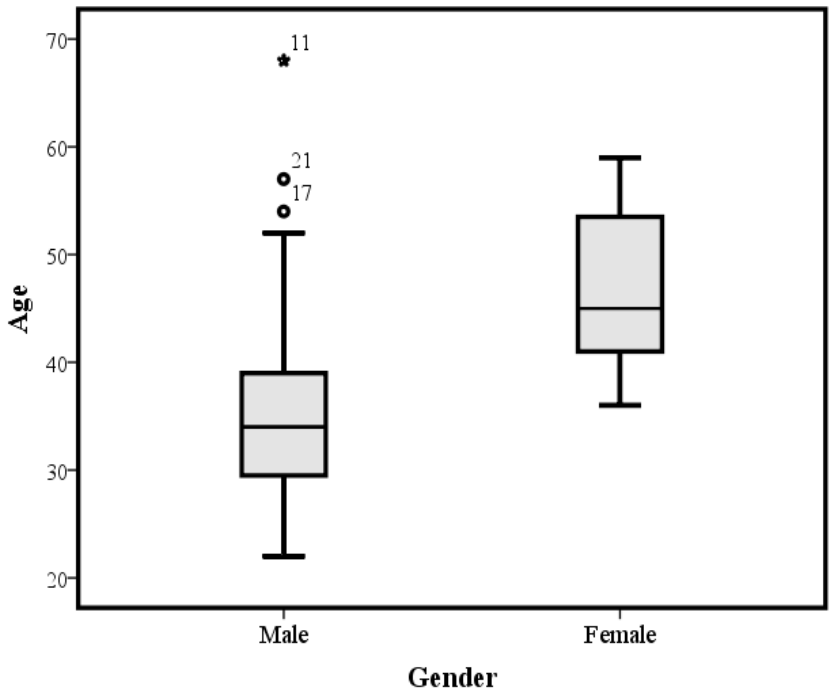


Figure 5.3 *Box plots of age by gender demographics.*

Table 5.2 *Demographic of age by gender.*

Male (n=23) [*Shapiro-Wilk (p=0.005*)]	Statistic	Std. Error
Median	34.0	
Interquartile Range	13.0	
Mean	36.7	2.4
95% CI for Mean	31.8 - 41.5	
Std. Deviation	11.3	
Minimum	22.0	
Maximum	68.0	
Skewness	1.4	0.5 (z = 2.9)
Kurtosis	1.6	0.9 (z = 1.8)
Female (n=7) [*Shapiro-Wilk (p=0.697*)]		
Mean (Median)	47.0 (45.0)	3.2
95% CI for Mean	39.2 - 54.8	
Std. Deviation (IQR)	8.4 (14)	
Minimum	36.0	
Maximum	59.0	
Skewness	0.2	0.8 (z = 0.20)
Kurtosis	-1.5	1.6 (z = -1.0)

Age at diagnosis (AAD)

The AAD was not normally distributed; *Shapiro-Wilk* (*p=0.010*), with significant positive skewness of 1.1 (SE 0.4, *z=2.6*) and a kurtosis of 1.1 (SE 0.8, *z=1.3*). The median AAD for the population was 22 (*IQR=8.0*) years [*Mean=22.7 (± 6.6)*] (Table 5.3, Figure 5.4).

Table 5.3 *AAD population demographics.*

AAD [*Shapiro-Wilk* (*p=0.010*)]	Statistic	Std. Error
Median	22.0	
Interquartile Range	8.0	
Mean	22.7	1.2
95% CI for Mean	20.2 - 25.1	
Std. Deviation	6.6	
Minimum	13.0	
Maximum	40.0	
Range	27.0	
Skewness	1.1	0.4 (*z=2.6*)
Kurtosis	1.1	0.8 (*z=1.3*)

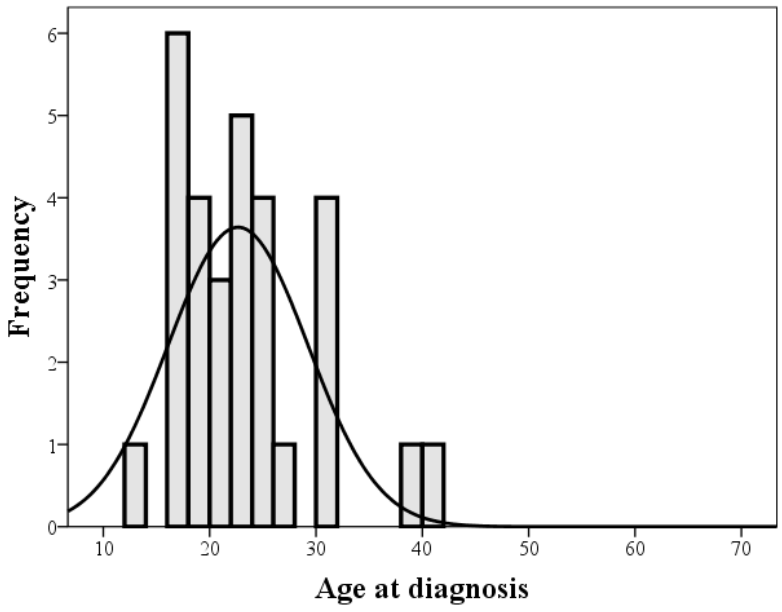


Figure 5.4 *AAD population distribution histogram.*

AAD by gender

The AAD was also not normally (*p=0.016*) and normally (*p=0.541*) distributed in the male and female populations respectively. The male participants exhibited significant positive skewness of 1.3 (SE 0.5, *z=2.7*) and kurtosis of 1.9 (SE 0.9, *z=2.1*) (Table 5.4). The gender AAD were not statistically significantly different *Mann-Whitney U* (*p=0.190*) (Figures 5.5 and 5.6).

Table 5.4. *AAD by Gender Demographics.*

AAD by Gender *Mann-Whitney U* (*p=0.190*)		
Male AAD [*Shapiro-Wilk* (*p=0.016*)]	Statistic	Std. Error
Median	20.0	
Interquartile Range	7.0	
Mean	21.8	1.3
95% CI for Mean	19.1 - 24.5	
Std. Deviation	6.2	
Minimum	13.0	
Maximum	40.0	
Skewness	1.3	0.481 (z=2.7)
Kurtosis	1.9	0.935 (z=2.1)
Female AAD [*Shapiro-Wilk* (*p=0.541*)]		
Mean	25.6	2.8
95% CI for Mean	18.8 - 32.3	
Std. Deviation	7.3	
Minimum	16.0	
Maximum	39.0	
Skewness	0.9	0.794 (z=1.2)
Kurtosis	1.5	1.587 (z=1.0)

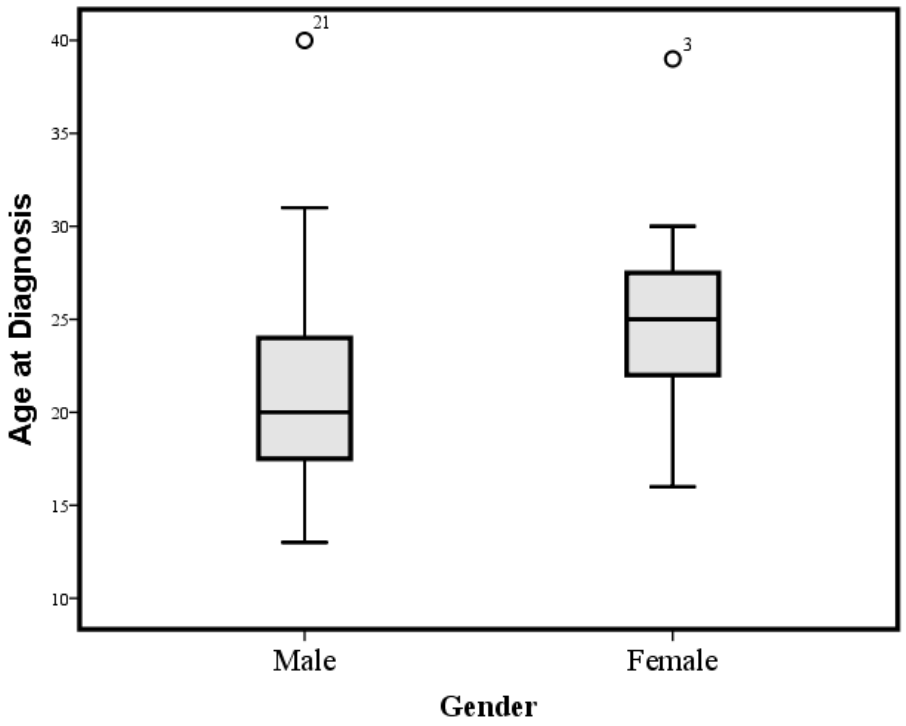


Figure 5.5 *Box plot AAD by gender.*

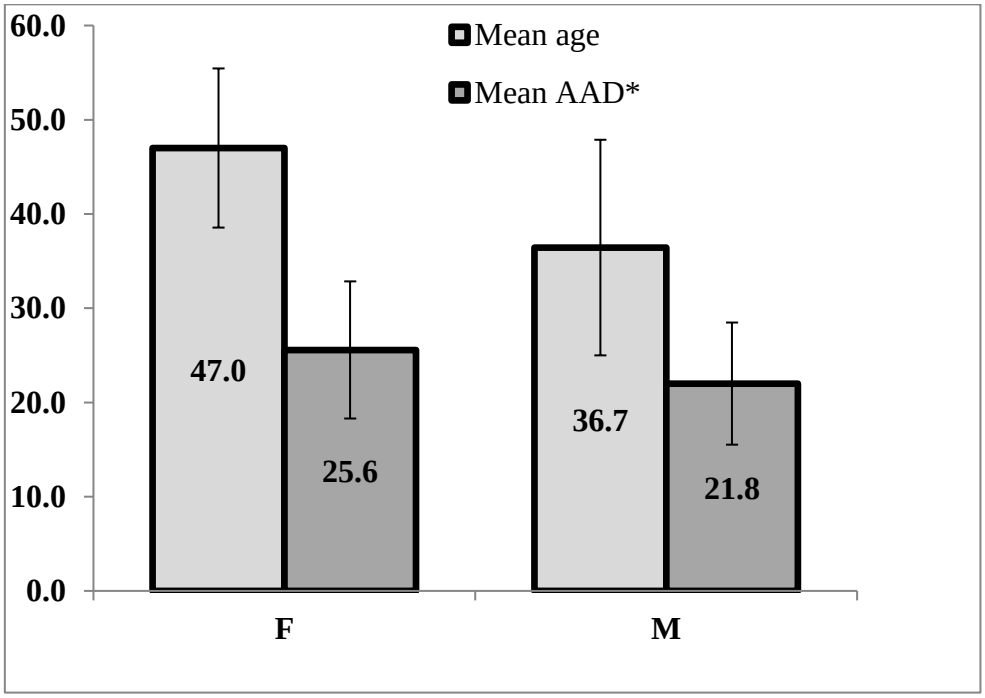


Figure 5.6 *Mean age and age at diagnosis (AAD) by gender, with standard deviations.*

Participants' reported duration of CRGPcl wear at enrolment

The AAD was taken as the date when each participant presented for first hospital consultation and fitting of CRGPcl. The duration of the CRGPcl wear period from the original fitting to the time of enrolment to this study may therefore be estimated from the difference of the age at enrolment and AAD. The estimated length of CRGPcl wear was not normally distributed; *Shapiro-Wilk* (*p=0.014*), had a median length of 14.5 years with an IQR of 12 years, significant positive skewness of 1.2 (SE 0.4, *z=2.8*) and kurtosis of 1.6 (SE 0.8, *z=1.9*) (Table 5.5, Figure 5.7).

Table 5.5 *Participant reported duration of CRGPcl wear at enrolment.*

Duration of CRGPcl Wear [*Shapiro-Wilk* (*p=0.014)*]		
	Statistic	Std. Error
Median	14.5	
Interquartile Range	12.0	
Mean	16.4	1.8
95% CI for Mean	12.7 - 20.1	
Std. Deviation	10.0	
Minimum	4.0	
Maximum	47.0	
Range	43.0	
Skewness	1.2	0.4 (*z=2.8*)
Kurtosis	1.6	0.8 (*z=1.9*)

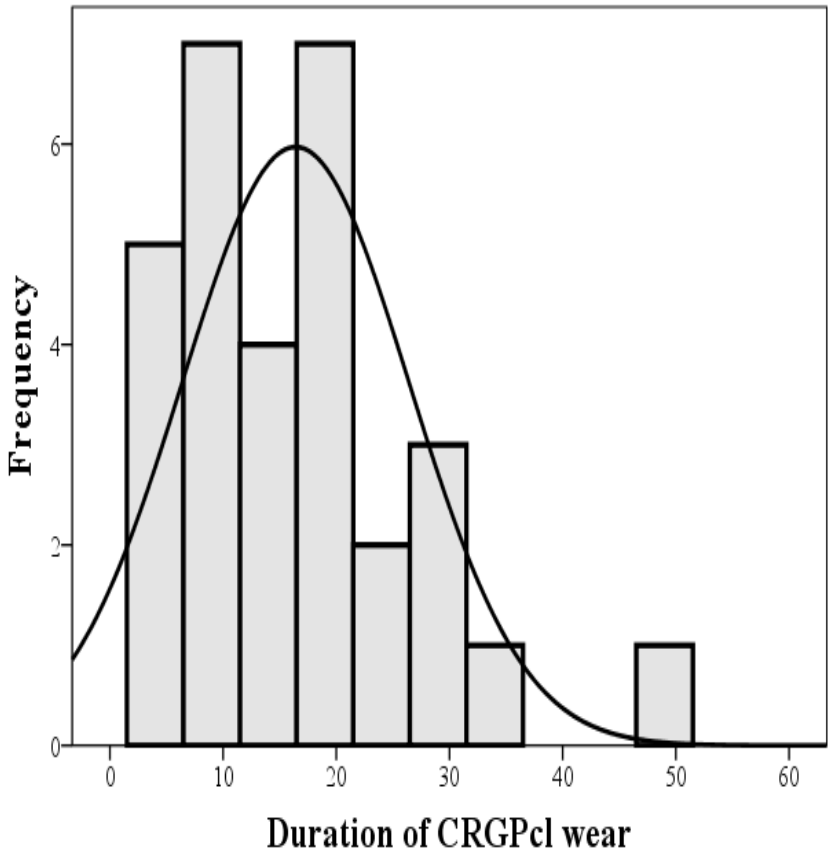


Figure 5.7 *Participant reported duration of CRGPcl wear at enrolment*

With respect to gender, no statistically significant difference in the length of CRGPcl wear was found between male and female participants, *Mann-Whitney U* (*p=0.190*) (Figure 5.8). The distributions of the length of wear of CRGPcl was not normally distributed in the male population; *Shapiro-Wilk* (*p=0.004*) and normally distributed in the female population; *Shapiro-Wilk* (*p=0.790*) (Table 5.6, Figure 5.8).

Table 5.6 *Gender duration of estimated time of where of CRGPcl at enrolment.*

Duration of CRGPcl wear by Gender [*Mann-Whitney U (p=0.190)*]			
		Statistic	Std. Error
Male **[***Shapiro-Wilk* (*p=0.004*)]	Median	12.0	
	IQR	11.0	
	Mean	14.9	2.1
	95% CI for Mean	10.5 - 19.2	
	Std. Deviation	10.1	
	Minimum	4.0	
	Maximum	47.0	
	Range	43.0	
	Skewness	1.6	0.5 (z=3.4)
	Kurtosis	3.5	0.9 (z=3.8)
Female [*Shapiro-Wilk* (*p=0.790)*]	Mean	21.4	3.3
	95% CI for Mean	13.5 - 29.4	
	Std. Deviation	8.6	
	Minimum	10.0	
	Maximum	34.0	
	Range	24.0	
	Skewness	0.4	0.8 (*z=0.5*)
	Kurtosis	-1.0	1.6 (*z=-0.6*)

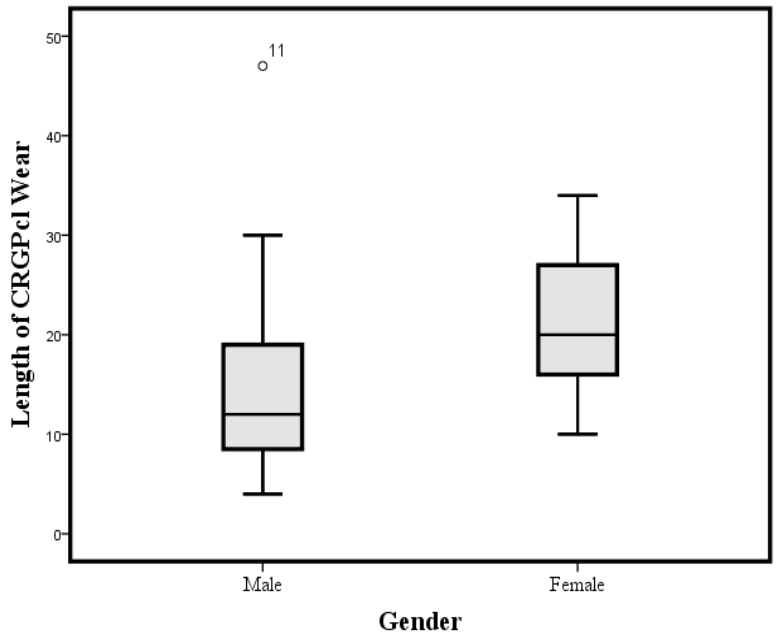


Figure 5.8 *Box plot of duration of CRGPcl wear by gender*

Participant's occupations / education

The number of participants with university education was 17, which constituted 56.7% of the total research population (Table 5.7).

Table 5.7 *The occupations of research participants.*

Participant No	Gender	Occupation	University Education
1	M	Company director	Yes
2	F	Office worker	No
3	M	TV market research	Yes
4	M	Finance	Yes
5	M	Retired sales assistant	No
6	M	Computer programmer	Yes
7	M	Finance	Yes
8	M	Graphic designer	Yes
9	F	Office administrator	No
10	M	Finance	Yes
11	M	Finance, student	Yes
12	M	Engineer	Yes
13	M	Driving instructor	No
14	M	Teacher	Yes
15	F	Book keeper	Yes
16	M	Teacher	Yes
17	M	Administration	No
19	M	Actor	No
20	F	Medical secretary	No
21	M	Business	No
23	M	Customer service	No
24	M	Train station manager	No
26	F	Entertainment Consultant	Yes
27	F	Mother	No
28	M	Manager at MacDonald's	No
30	F	Investment management	Yes
31	M	Accountant	Yes
32	M	Student	Yes
33	M	Truck driver	No
34	M	Electrical engineer	Yes

No of participants with university education	17
Percentage of participants with university education	56.7%

Race / ethnicity

Although racial / ethnic differences were not the subject of this investigation, the role of ethnicity is significant in both the prevalence and incidence of keratoconus (Georgiou *et al.*, 2004; Pearson *et al.*, 2000). Broad race classification was included in this research, in line with the recommendation of the Office of National Statistics, census 2011, which stipulates that: "*Ethnic group classifies people according to their own perceived ethnic group and cultural background*" (Office for National Statistics, ONS., 2013). To broadly classify participant's race, the participants themselves chose, from the office of national statistics listing, their national/geographical origin combined with colour, in groups which were considered relevant for research in which epidemiology of ectatic corneal disorders was important (Senior and Bhopal, 1994). This resulted in 4 groups (Table 5.8, Figure 5.9).

The multiracial profile of the participants is typical of the diverse ethnicity of a London based population. Tables 6 and Figures 9 and 10 exhibit details of race distribution and the relationship between participant's race, age and age at diagnosis.

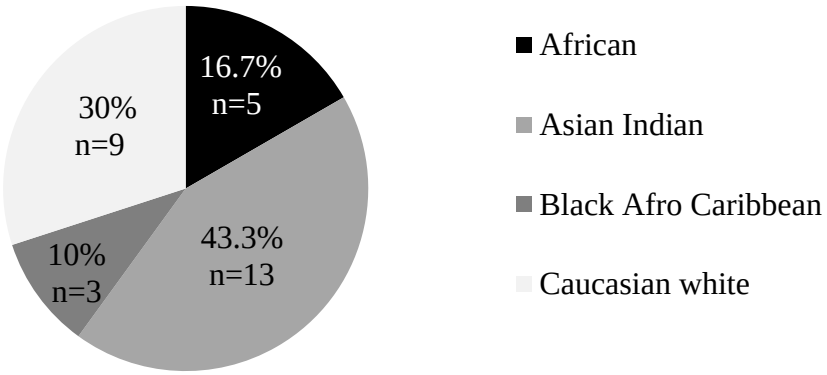


Figure 5.9 *Race frequencies: a number and percentage of participant's ethnicities.*

The mean ages and AAD of the four ethnic groups are specified in Table 5.8 and Figure 5.10. The Caucasian White participants featured the youngest mean age but oldest AAD. The Black African participants exhibited the youngest age at diagnosis.

Table 5.8 *Ethnicity demographics*

Race	N	%	Mean Age	Age StdDev	AAD	AAD StdDev
Black African	5	16.7%	43.8	±16.4	18.8	±3.4
Asian Indian	13	43.3%	36.8	±12.1	22.5	±4.5
Black Afro Caribbean	3	10.0%	32.3	±3.2	22.3	±4.7
Caucasian white	9	30.0%	31.9	±7.0	25.2	±9.9

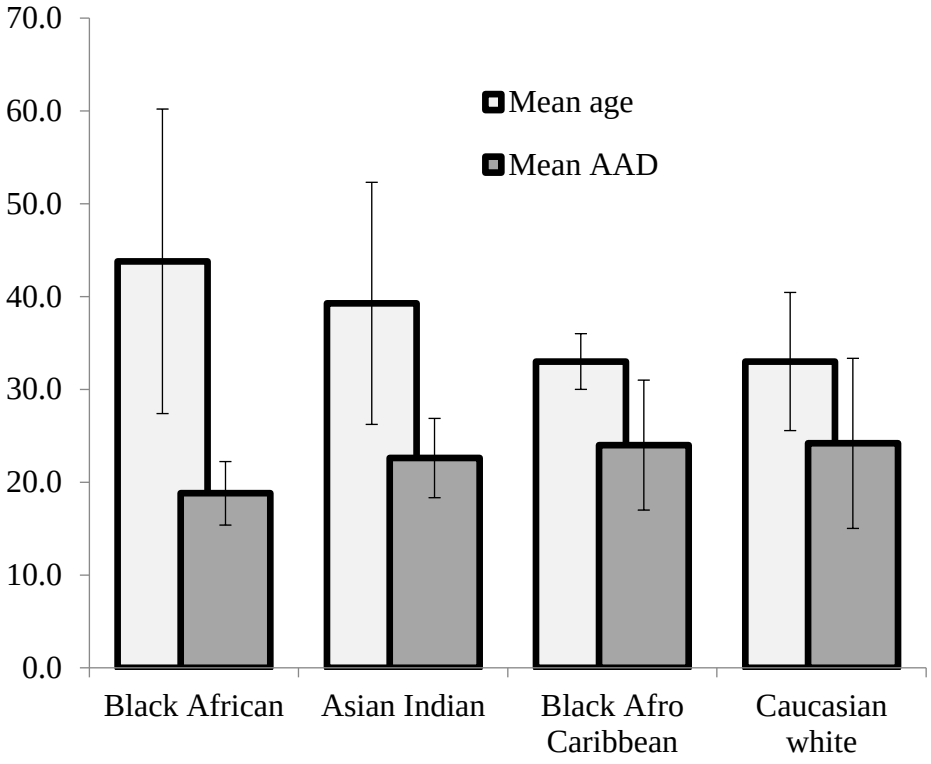


Figure 5.10 *Mean age and mean AAD with respective standard deviations for each ethnicity.*

Corneal characteristics

Keratoconus was the most prevalent corneal ectatic disorder in the study population, featuring in 54 (93.1%) out of the 58 eyes. Two eyes (3.4%) exhibited pellucid marginal degeneration (PMD) and 2 (3.4%) eyes had Deep Lamellar Keratoplasty (DLK) treatments [*corneal transplant due to advanced keratoconus*]. Of the 54 eyes with keratoconus, 33 eyes (56.9%) featured a *nipple* type cone, 21 (36.2%) eyes featured the *oval* type (Perry *et al.*, 1980). Collagen cross-linking (CXL) treatment has been applied to 6 eyes (10.3%), 4 (6.9%) of which featured a nipple shaped keratoconus and 2 eyes (3.4%) an oval type. Two eyes (3.4%) with the oval type cone had been treated with intra-stromal rings (INTACS), eyes with DLK were present in one eye of 2 participants and were not included in this research (Figure 5.11).

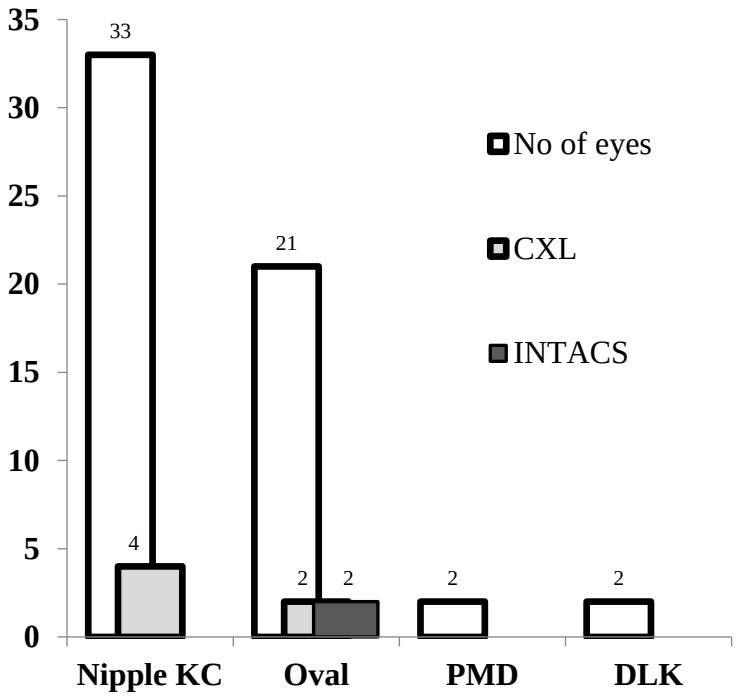


Figure 5.11 *Corneal pathology frequencies, including CXL and INTACS treatments*

Corneal metrics

Ectatic corneal disorders feature corneal metrics which are outside the expected range of normal corneae. Three corneal parameters, which reflect the degree of corneal normality were measured,

1. Corneal curvature, specifically maximal radius of curvature: K_{max}.

2. Corneal thickness: pachymetry.

3 Corneal Surface Regularity Index (SRI).

Maximum corneal curvature (K_{max})

The K_{max}, represents the steepest corneal curvature/radius of the area measured by corneal topography, K_{max} values (in millimetres) of the research population (Table 5.9) were normally distributed, *Shapiro-Wilk* (*p=0.882*) (Figure 5.12).

Table 5.9 *Research participant's K_{max} metrics in mm.*

K_{max} (*Shapiro-Wilk p=0.882)*	N=56	
	Statistic	Std. Error
Mean	6.2	0.1
95% CI for Mean	6.0 - 6.3	
Std. Deviation	0.6	
Minimum	5.0	
Maximum	7.0	
Range	2.0	
Skewness	0.0	0.3 (*z=-0.1*)
Kurtosis	-0.6	0.6 (*z=-0.9*)

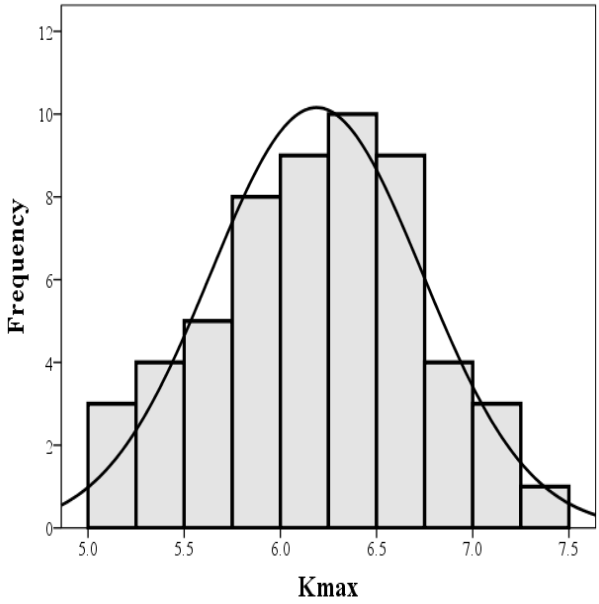


Figure 5.12 *Research participant's K_{max} corneal curvature distribution.*

Corneal thickness (pachymetry)

Corneal pachymetry, measured in micrometres (*µm*), exhibited normal distribution, *Shapiro-Wilk* (*p=0.569*) [*1000µm=1mm*] (Table 5.10, Figure 5.13).

Table 5.10 *corneal thickness (pachymetry in µm) metrics of the research population.*

Pachymetry *(Shapiro-Wilk p=0.569)*	N=56	
	Statistic	Std. Error
Mean	445.11	6.51
95% Confidence Interval for Mean	432 - 458	
Std. Deviation	48.72	
Minimum	309	
Maximum	556	
Range	247	
Skewness	0.02	0.32 *(z=0.6*)
Kurtosis	0.43	0.63 (*z=0.7*)

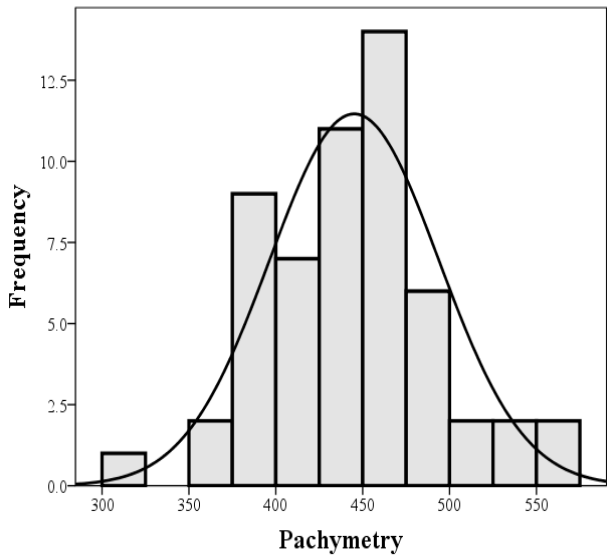


Figure 5.13 *Research population corneal thickness (pachymetry in µm) histogram.*

Corneal surface regularity index

Corneal surface regularity index (SRI) describes corneal optical regularity in the central 4.5 mm area of the cornea. SRI measures the dioptric (DS) optical power differences between adjacent corneal areas in 256 equidistant locations in the central 4.5mm (Cavas-Martinez *et al.*, 2016). SRI correlates well with the measure of BCVA *($r = 0.80, p < 0.001$)*, with normal values below 0.56DS (Wilson *et al.*, 1991; Cavas-Martinez *et al.*, 2016; Liu and Pflugfelder, 1999). The SRI of the research population was not normally distributed: Shapiro-Wilk's (*$p=0.001$*) (Table 5.11 and Figure 5.14).

Table 5.11 *Research population corneal surface regularity index (in dioptres) metrics.*

Surface Regularity Index (n=56) *(Shapiro-Wilk p=0.001)*		
	Statistic	Std. Error
Median	1.53	
Interquartile Range	0.40	
Mean	1.55	0.05
95% CI for Mean	1.45 - 1.65	
Std. Deviation	0.36	
Minimum/Maximum	1.00/3.00	
Skewness	1.00	0.32 (*z=3.14*)
Kurtosis	4.07	0.63 (*z=6.48*)

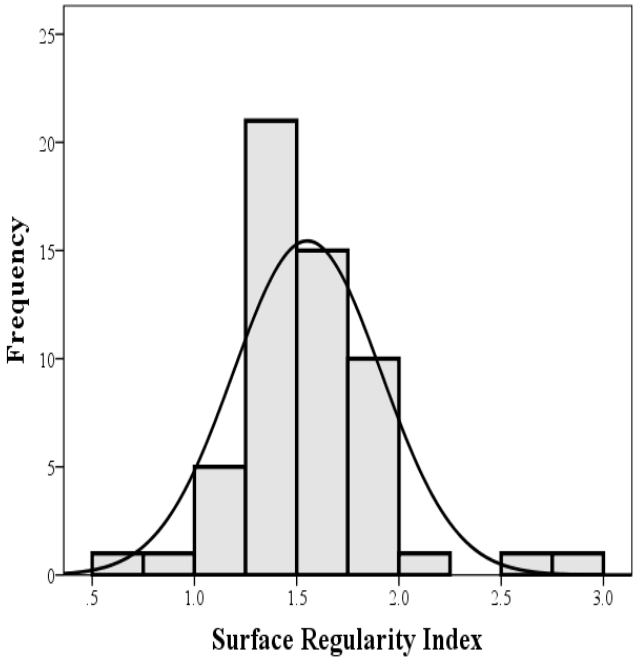


Figure 5.14 *Corneal surface regularity index (in dioptres) of the research population.*

The corneal metrics were normally distributed in the right and left eyes of the study participants with the exception of the right eye SRI index which was not normally distributed; *Shapiro-Wilk* (*p=0.001*). Despite the difference in the mode of distribution, the SRI means of the right (*Median =1.450*) and left (*Median =1.590*) eyes were not statistically significantly different; *Mann-Whitney U* (*p=0.168*). Independent samples *t-test* demonstrated no statistically significant differences between means of the right and left eyes pachymetry and K_{max}, (*p=0.481*) and (*p=0.119*) respectively.

Randomisation demographics

The participants in this research were randomised to the two treatment groups (Table 5.13). The following section presents the analysis and comparison of participant demographics in the two randomised groups (summary Table 5.43a, Appendix V.J).

Table 5.13 *Participant randomisation into the two treatment groups and crossover.*

Crossover study design		**Treatment periods AB/BA**	
Randomisation to treatment groups 1&2		**Period 1**	**Period 2 (Crossover)**
Participant Allocation	Group 1 / Sequence AB	A = CRGPcl	B = SRGPcl
	Group 2 / Sequence BA	B = SRGPcl	A= CRGPcl

Gender, age and age at diagnosis

The gender frequencies after randomisation were as follows: 2 females and 11 males versus 5 females and 12 males in Groups 1 and 2 respectively (Figure 5.15). The Chi-square goodness of fit analysis revealed no significant difference in gender allocation between the 2 groups: χ^2 (1, n=17) = 2.570, (*p=0.109*).

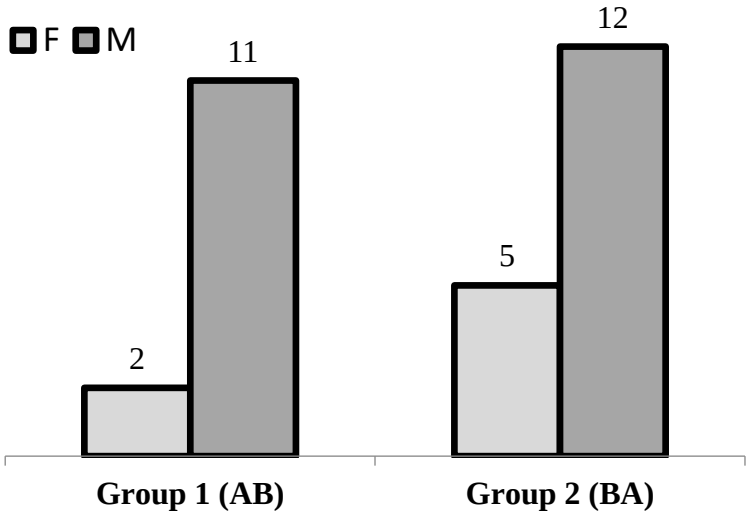


Figure 5.15 *Gender numbers in group 1 (AB) and group 2 (BA).*

The ages of participants randomised to group 1 [*Mean=39.5 (±14.2*)] and group 2 [*Mean=38.8 (±9.3)*] were normally distributed, *Shapiro-Wilk* (*p=0.188*) and (*p=0.147*) respectively (Table 5.14, Figures 5.16 and 5.17). A two tailed independent samples *t-test* showed no statistically significant difference in the means of the ages between the two randomised groups [*p=0.872*, 95% *CI -8.093 – 9.487*].

Table 5.14 *Descriptive statistics of the ages of the randomised groups.*

Age (*t-test p=0.872)*			
Randomised to		Statistic	Std. Error
CRGPcl *(Shapiro-Wilk p=0.188)*			
	Mean	39.5	3.9
	95% CI for Mean	30.8 - 48.1	
	Std. Deviation	14.2	
	Minimum	22.0	
	Maximum	68.0	
	Range	46.0	
	Variance	201.9	
	Skewness	0.8	0.6 (*z=1.3*)
	Kurtosis	-0.4	1.2 (*z=-0.3*)
SRGPcl (*Shapiro-Wilk p=0.147)*			
	Mean	38.8	2.2

	95% CI for Mean	34.0 - 43.5	
	Std. Deviation	9.3	
	Minimum	26.0	
	Maximum	57.0	
	Range	31.0	
	Variance	85.9	
	Skewness	0.7	0.6 (z=1.3)
	Kurtosis	-0.2	1.1 (z=-0.2)

The AAD of participants randomised to Group 1 [*Mean=23.2 (±5.0)*] was normally distributed, *Shapiro-Wilk* (*p=0.439*), the AAD in group 2 (*Median =20.0*) was not normally distributed, *Shapiro-Wilk* (*p=0.008*) (Table 5.15 and Figures 5.16 and 5.17). There was no statistically significant difference in the AAD between group 1 (*Median =22*), and group 2 (*Median =20.0*), *Mann-Whitney U test:* (*p=0.363*), *U=88.50 (z=-0.924)*.

Table 5.15 Descriptive statistics of *AAD of the randomised groups*

AAD (*Mann-Whitney U test p=0.363*)		Statistic	Std. Error
Group 1(Shapiro-*Wilk p=0.43*)	Mean	23.2	1.4
	95% CI for mean	20.1 - 26.2	
	Variance	25.0	
	Std. Deviation	5.0	
	Median	22.0	
	Minimum/maximum	16.0/31.0	
	Skewness	0.3	0.6 (*z=0.5*)
	Kurtosis	-1.0	1.2 (*z=-0.9*)
Group 2 (*Shapiro-Wilk p=0.008*)	Median	20.0	
	Interquartile range	8.0	
	Mean	22.3	1.9
	95% CI for mean	18.3 - 26.3	
	Variance	59.2	
	Std. Deviation	7.7	
	Minimum/maximum	13/40	
	Skewness	1.4	0.6 (*z=2.5*)
	Kurtosis	1.4	1.1 (*z=1.3*)

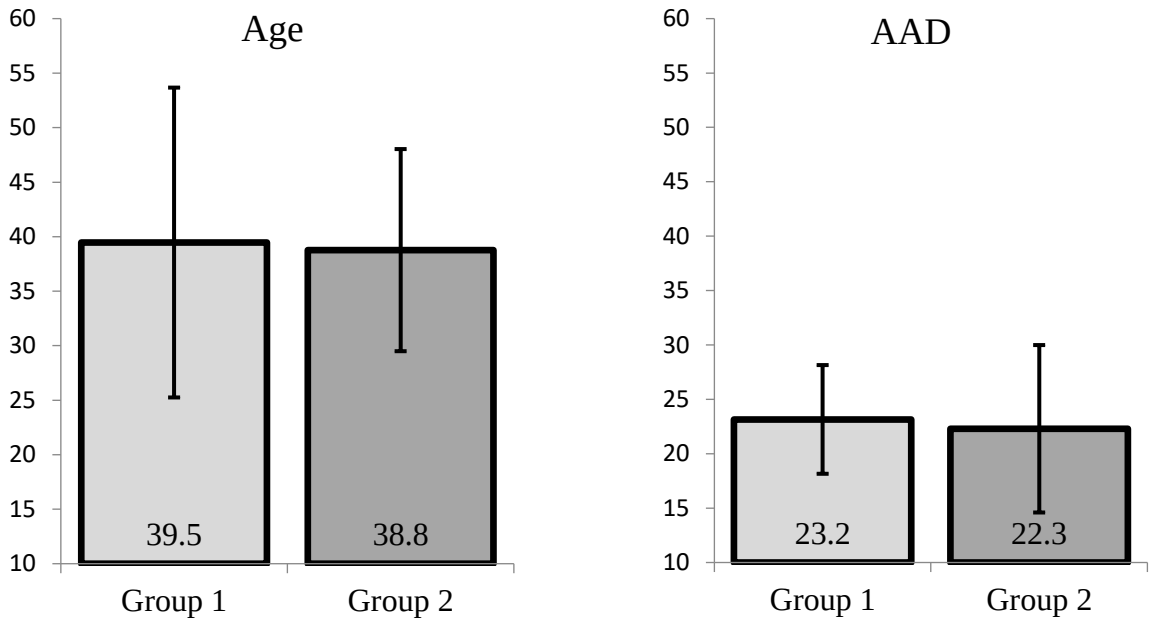


Figure 5.16 *Mean age and AAD and StdDev of the 2 randomised groups. The vertical axis is age in years.*

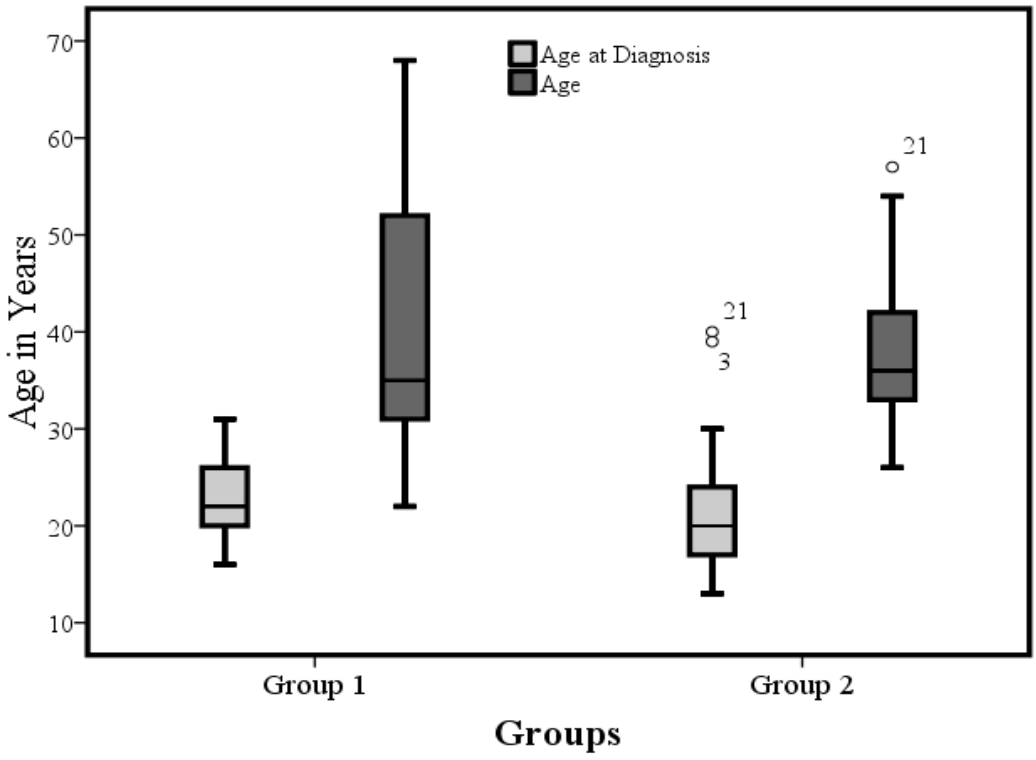


Figure 5.17 *Boxplots of age and AAD in group 1(AB) and group 2 (BA).*

Participant reported duration of CRGPcl wear at enrolment

The estimated duration of CRGPcl wear at enrolment was normally distributed in group 2 *Shapiro-Wilk* (*p=0.214*) [*Mean=16.47, (±6.33)*] and not normally distributed for group 1, *Shapiro-Wilk* (*p=0.022*) [*Median =10.0 IQR=22.0, Mean=16.47 (±13.76)*]. This parameter was not significantly different in the two randomised groups *Mann-Whitney U* (*p=0.363*) [*z=-0.923*], *U=88.50.*

Race / ethnicity in the randomised groups

The distribution of the different races/ethnicities in the randomised groups is presented in Figure 5.18, the Chi-square goodness of fit analysis in the two randomised groups showed no statistically significant difference between the groups: χ^2 (*3, n=13*) =0.810 (*p=0.613*).

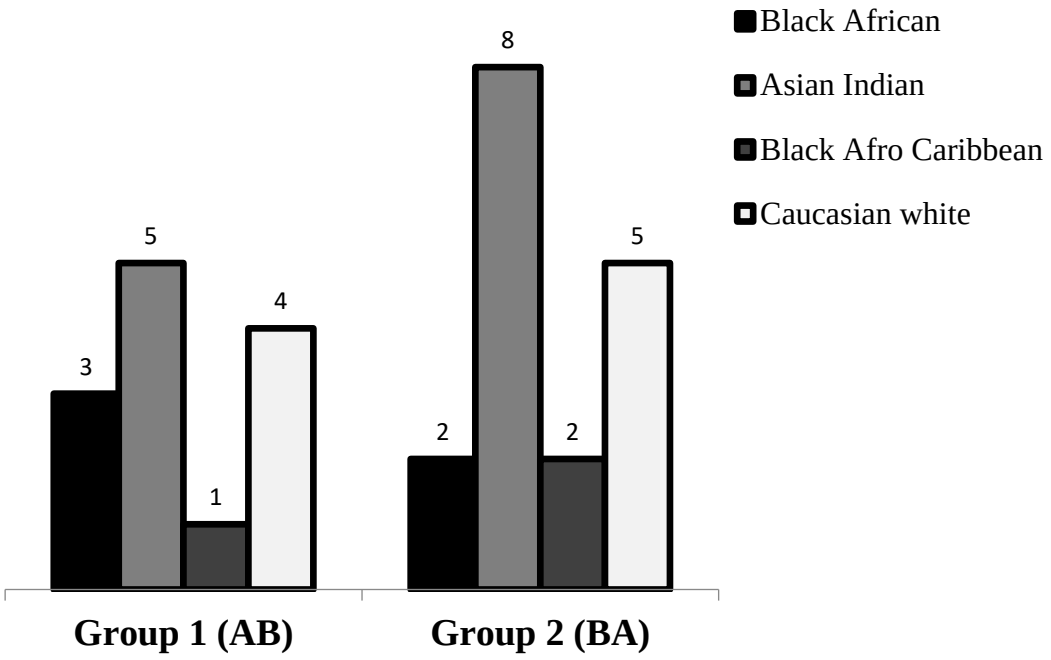


Figure 5.18 *Race frequencies in the randomised groups*

Corneal metrics in the randomised groups

The corneal metrics in this research were measured, analysed and compared to the expected parameters in normal disease free corneae and between the two randomised groups.

K_{max}

The K_{max} values of the corneae in the research population as a whole and in the 2 randomised groups were normally distributed (Table 5.16, Figure 5.19).
Of the K_{max} means analysis of the randomised groups by an independent samples *t-test* showed that the two groups exhibited no statistically significant difference: t (30) =1.898, (*p=0.068*), d =-0.699, 95% CI [-0.0617–0.0235].

Table 5.16 *K_{max} descriptive statistics.*

Corneal K_{max} (*t-test p=0.068)*			
Randomised to		Statistic	Std. Error
Group 1 (*Shapiro-Wilk p=0.301)*	Mean	6.04	0.09
	95% CI for Mean	5.84-6.23	
	Variance	0.22	
	Std. Deviation	0.47	
	Min/Max	5.13/6.72	
	Range	1.59	
	Skewness	-0.12	0.46 (*z=0.26*)
	Kurtosis	-0.98	0.90 (*z=1.09*)
Group 2 (*Shapiro-Wilk p=0.773)*	Mean	6.31	0.11
	95% CI for Mean	6.10-6.53	
	Variance	0.35	
	Std. Deviation	0.59	
	Min/Max	5.0/7.28	
	Range	2.28	
	Skewness	-0.26	0.42 (*z=0.62*)
	Kurtosis	-0.43	0.82 (*z=0.52*)

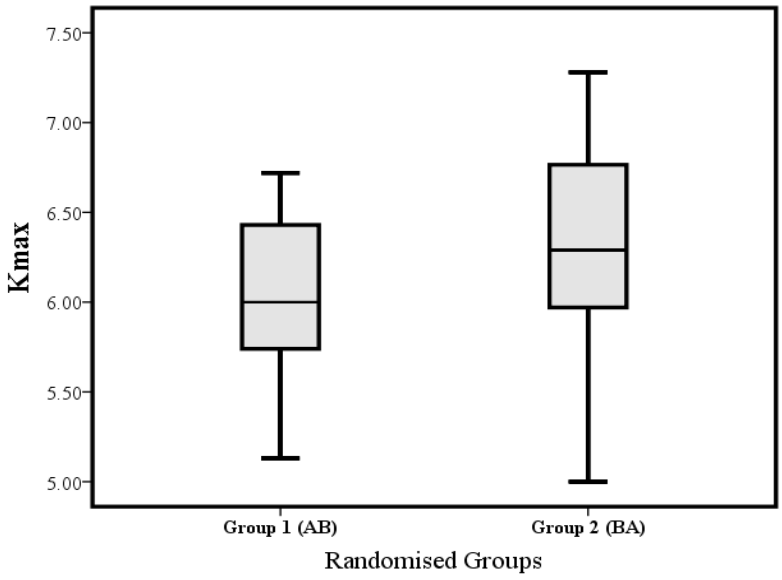


Figure 5.19 a. *Box plot of the K_{max} in the randomised groups.*

Surface regularity index (SRI)

The surface regularity index values of the corneae in group 1 were normally distributed, *Shapiro-Wilk* (*p=0.991*), but not normally distributed in group 2, *Shapiro-Wilk* (*p=0.009*), these variables are summarised in Table 5.17 and Figure 5.19b.

Mann-Whitney U test for independent samples, revealed that the corneal SRI index was not statistically significantly different in the 2 randomised groups, (*p=0.252*) (*z=-1.146*), *U=318.00.*

Table 5.17 *Surface Regularity Index descriptive statistics in the two randomised groups.*

Corneal SRI *(Mann-Whitney U p=0.252)*			
Randomised to		Statistic	Std. Error
CRGPcl *(Shapiro-Wilk p=0.991)*	Mean	1.59	0.05
	95% CI for Mean	1.49-1.69	
	Variance	0.06	
	Std. Deviation	0.24	
	Min/Max	1.11/2.12	
	Range	1.01	
	Skewness	0.2	0.46 (*z=0.44*)

	Kurtosis	-0.15	0.90 (z=*-0.17*)
SRGPcl (*Shapiro-Wilk p=0.009*)	Median	1.47	
	Interquartile Range	0.48	
	Mean	1.52	0.08
	95% CI for Mean	1.36-1.68	
	Variance	0.19	
	Std. Deviation	0.44	
	Min/Max	0.69/2.96	
	Range	2.27	
	Skewness	1.19	0.42 (*z=2.83*)
	Kurtosis	3.46	0.82 (z=*4.22*)

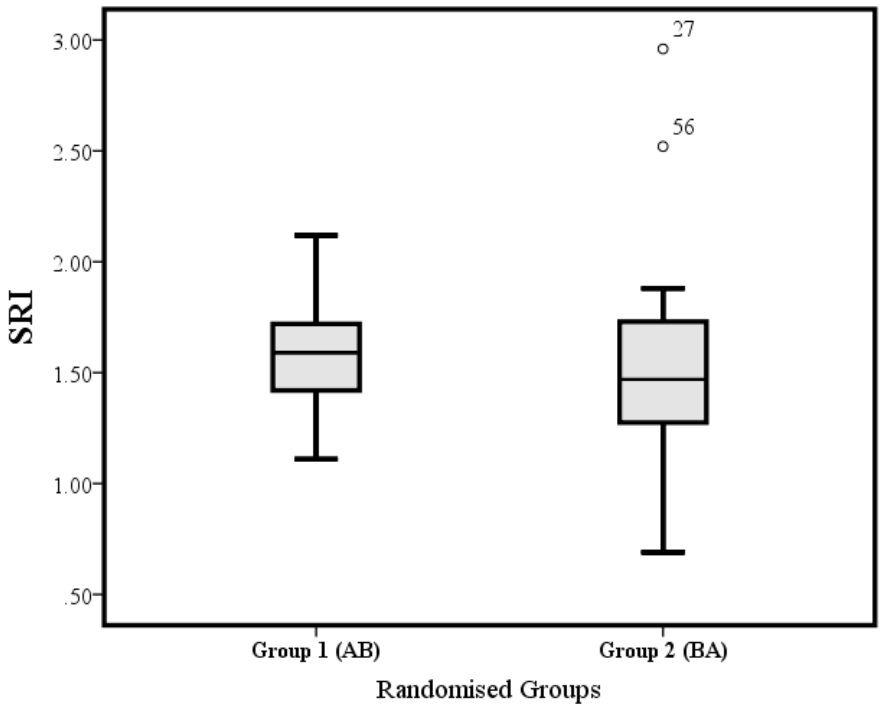


Figure 5.19 b. *SRI Box plot of the randomised groups 1 and 2*

Corneal pachymetry

The analysis of pachymetry values in the corneae of the two randomised groups revealed normal distribution, *Shapiro-Wilk* (*p=0.560*) and (*p=0.227*) in group1 and group 2 respectively, the variables are summarised in Table 5.18 and Figure 5.20.

An independent samples *t-test*, pachymetry means comparison, indicated that the two randomised groups did differ significantly: t (54) = -3.279, (p = 0.002), d = -0.881, 95% CI [-63.77 – -15.38], with group 1 [*Mean= 423.20 (±45.10)*] exhibiting a mean pachymetry thinner than the mean in group 2 [*Mean=462.77 (±44.73)*].

Table 5.18 *Corneal pachymetry descriptive statistics.*

Corneal Pachymetry *(t test p=0.002)*			
Randomised to		Statistic	Std. Error
CRGPcl *(Shapiro-Wilk p=0.560)*	Mean	423.2	9.02
	95% CI for Mean	404.6-441.8	
	Variance	2034.5	
	Std. Deviation	45.1	
	Minimum	309	
	Maximum	498	
	Range	189	
	Skewness	-0.44	0.46 (*z=-0.96*)
	Kurtosis	0.05	0.9 (*z=0.06*)
SRGPcl *(Shapiro-Wilk p=0.227*)	Mean	462.8	8.03
	95% CI for Mean	446.4-479.2	
	Variance	2001.1	
	Std. Deviation	44.7	
	Minimum	389	
	Maximum	556	
	Range	167	
	Skewness	0.46	0.42 (*z=1.10*)
	Kurtosis	-0.17	0.82 *(z=-0.21*)

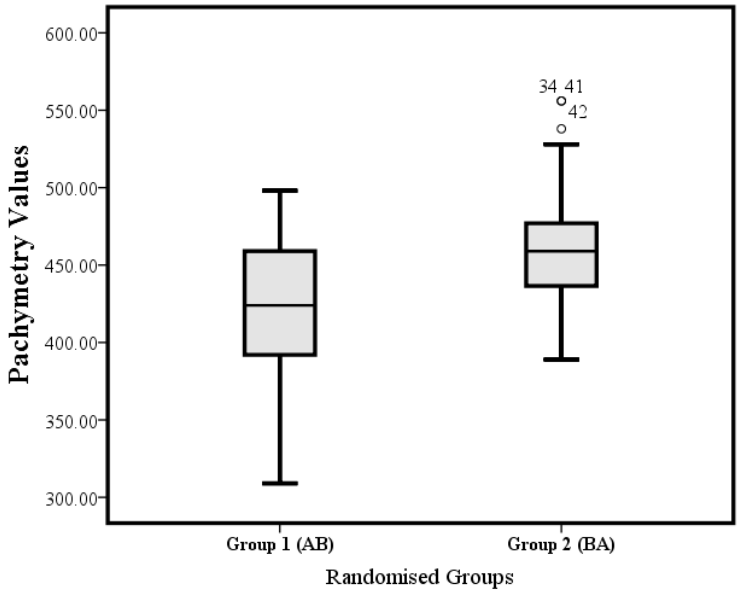


Figure 5.20 *Randomised pachymetry Box and whiskers plot, groups 1 and 2*

The main outcome measures

Thirty participants completed the study. The data collected were analysed for hypothesis testing with respect to the primary and secondary outcome measures (summary Table 5.43b Appendix V.K).

Visual performance, ETDRS logMAR

The logMAR scores of all the measurements [baseline, period 1 and period 2] of the individual eyes of the research population, (n=504) were not normally distributed *Shapiro-Wilk* (*p<0.0001*), positively skewed and leptokurtic, with a median logMAR score of 0.02 and IQR=0.14. These repeated measures data are presented as a demographic of interest and were not used in any other statistical analyses (Figure 5.21, Table 5.19).

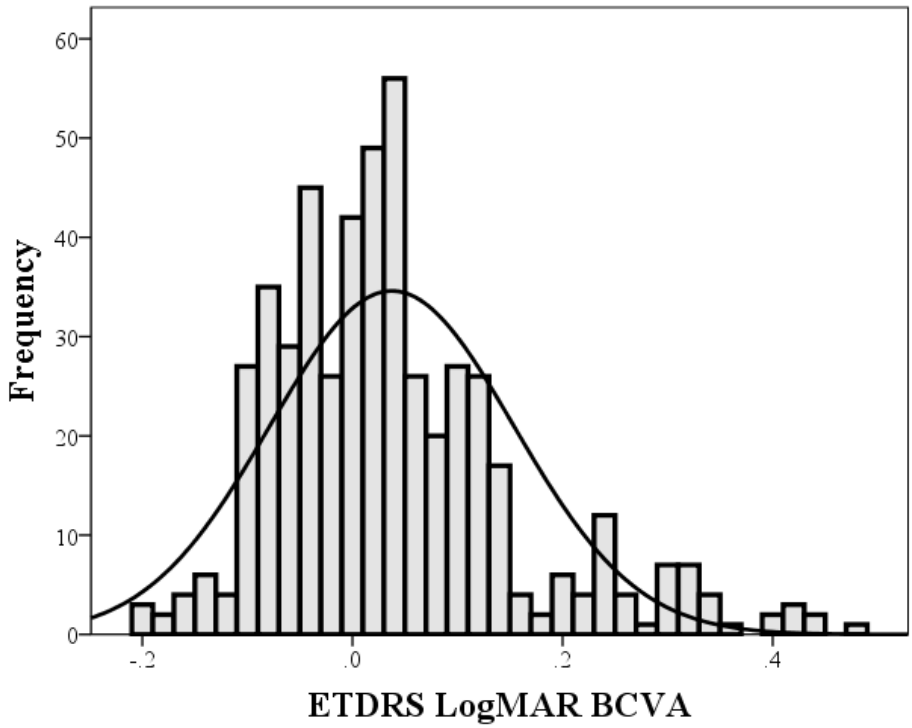


Figure 5.21 *ETDRS logMAR scores all eyes and measurements of the research population*

Table 5.19 *ETDRS logMAR scores of all eyes and measurements of the research population*

ETDRS logMAR BCVA (*Shapiro-Wilk p<0.0001*)		
	Statistic	Std. Error
Mean	0.04	0.01
95% CI for mean	0.03-0.05	
Median	**0.02**	
Variance	0.01	
Interquartile Range	**0.14**	
Minimum	-0.2	
Maximum	0.48	
Range	0.68	
Skewness	1.08	0.11 (*z=9.92*)
Kurtosis	1.49	0.22 (*z=6.88*)

The distributions of the average OD/OS logMAR scores of groups 1(AB) and 2 (BA) were not normally distributed in group 2, *Shapiro-Wilk* (*p<0.0001*), and normally distributed in

group 1, *Shapiro-Wilk* (*p=0.833*). The medians and IQRs (in brackets) of the logMAR scores in group 1 and 2 respectively were, 0.05 (0.13) and 0.01 (0.08) (Tables 5.20, Figure 5.22).

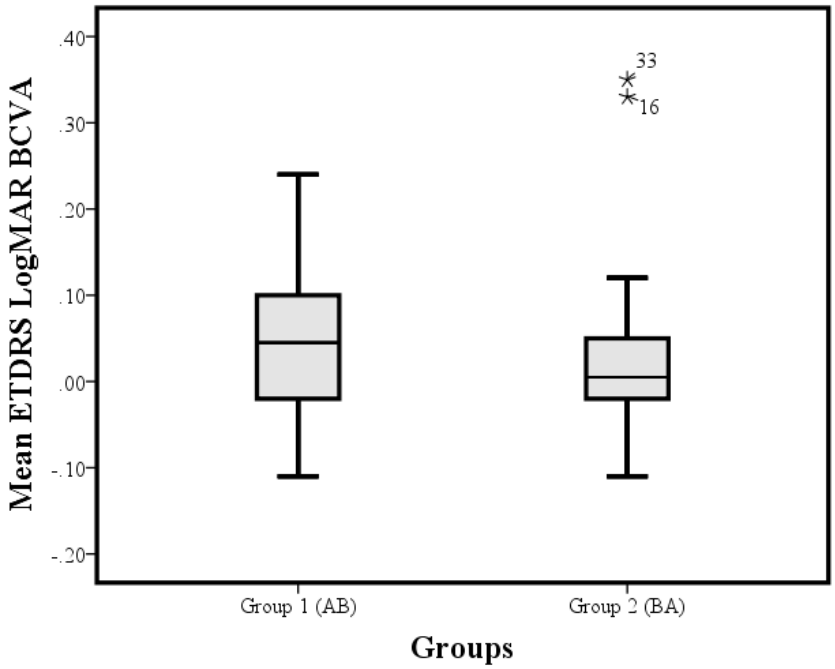


Figure 5.22 *Box Plots ETDRS logMAR BCVA groups 1and 2*

Table 5.20 *ETDRS logMAR BCVA group 1, sequence AB: and group 2 sequence BA*

Log MAR mean OD/OS Scores by Group			
		Statistic	Std. Error
Group 1 (AB)	Mean	**0.05**	0.02
Shapiro-Wilk p=0.833	95% CI for Mean	0.01-0.09	
	Median	0.05	
	Std. Deviation	**0.09**	
	Minimum	-0.11	
	Maximum	0.24	
	Range	0.35	
	Interquartile Range	0.13	
	Skewness	0.24	0.46
	Kurtosis	-0.56	0.89
Group 2 (BA)	Mean	0.02	0.02
Shapiro-Wilk p<0.0001	95% CI for Mean	-0.01-0.06	
	Median	**0.01**	
	Std. Deviation	0.10	
	Minimum	-0.11	
	Maximum	0.35	

	Range	0.46	
	Interquartile Range	**0.08**	
	Skewness	1.80	0.40
	Kurtosis	4.52	0.79

Analysis of the 2x2 crossover trial

Pooling data obtained from the right and left eyes is considered inappropriate in ophthalmic research as discussed in the statistical analysis section in the methods chapter. To determine whether pooling the data obtained from the right and left eyes was appropriate in this research, a correlation analysis of the baseline logMAR scores between OD and OS of all participants who had both eyes fitted, was performed and compared to that between the scores of OD and randomised OS (ROS) (Table 5.21). It was postulated that if the correlation coefficients from both analyses are fairly equal, each eye may be treated as an independent sample, as the differences between the two eyes in the same individual are sufficiently similar to random eyes. The OD logMAR scores from the same individual had normal distribution (*Shapiro-Wilk p=0.25*), the scores of OS and ROS had not normal distribution (*Shapiro-Wilk p=0.006*). The Kendall's tau correlations of the baseline logMAR scores of OD and OS were significantly different to the correlations of OD and ROS: 0.663 (*p=0.01*) and -0.102 (*p=0.478*) respectively. This difference indicates that the logMAR scores may not be pooled data analysis. The statistical analyses for the carryover, period and treatment effects were therefore performed utilising the mean of the right and left eye's scores of each participant.

Table 5.21 *Baseline logMAR scores of OD OS and ROS*

ETDRS logMAR Baseline Scores			
SN	OD	OS	R OS
1	-0.10	-0.10	0.09
2	-0.05	-0.04	-0.02
3	0.03	0.03	0.07
6	-0.02	-0.02	0.10
7	0.03	0.10	0.09
9	0.11	0.11	-0.12
10	0.10	0.07	0.15
11	0.29	0.15	-0.07
12	-0.02	-0.02	-0.04
13	-0.05	-0.04	0.09
14	0.10	0.09	-0.03
15	-0.11	-0.15	-0.04
16	-0.17	-0.12	0.11
17	-0.06	0.09	-0.02
19	0.05	-0.03	-0.10
20	-0.05	-0.04	0.07
21	0.05	0.09	-0.15
23	0.14	-0.01	0.25
24	-0.03	-0.02	0.35
27	-0.03	-0.07	-0.03
28	0.02	0.02	-0.04
30	0.03	0.07	-0.01
31	0.01	-0.03	0.03
32	0.27	0.35	0.45
33	0.16	0.25	-0.02
34	0.05	0.45	0.02

A linear model for the data may be used to derive two-sample *t-tests* or a non-parametric equivalent for testing hypotheses about the direct treatment and carry-over effects (Jones and Kenward, 2015; Wellek and Blettner, 2012).

The general notation to be used in this section is as follows. The participants were randomised into two groups of sizes $n1$=13 and $n2$=17. The $n1$ subjects in group 1 received the lenses in the order CRGPcl-SRGPcl: sequence AB and the $n2$ subjects in group 2 received the lenses in the order SRGPcl-CRGPcl: sequence BA. The outcome of subject k in period j of group i is denoted by $y_{ijk.}$ The group-by-period means for the ETDRS logMAR BCVA data are given in Table 5.22 and Figure 5.23.

Table 5.22 *Group by period means for the mean ETDRS logMAR BCVA*

Group	Mean logMAR Period 1	Mean logMAR Period 2	Mean logMAR
1 (AB) n_1=13	$\bar{y}_{11.}$ =0.06	$\bar{y}_{12}$ =0.04	$\bar{y}_{.1}$ total = 0.05
2 (BA) n_2=17	$\bar{y}_{21.}$ =0.01	$\bar{y}_{22}$ =0.01	$\bar{y}_{.2}$ total. = 0.01
Mean logMAR	$\bar{y}_{.1.}$ = 0.04	$\bar{y}_{.2.}$ =0.03	$\bar{y}_{..}$ total = 0.03

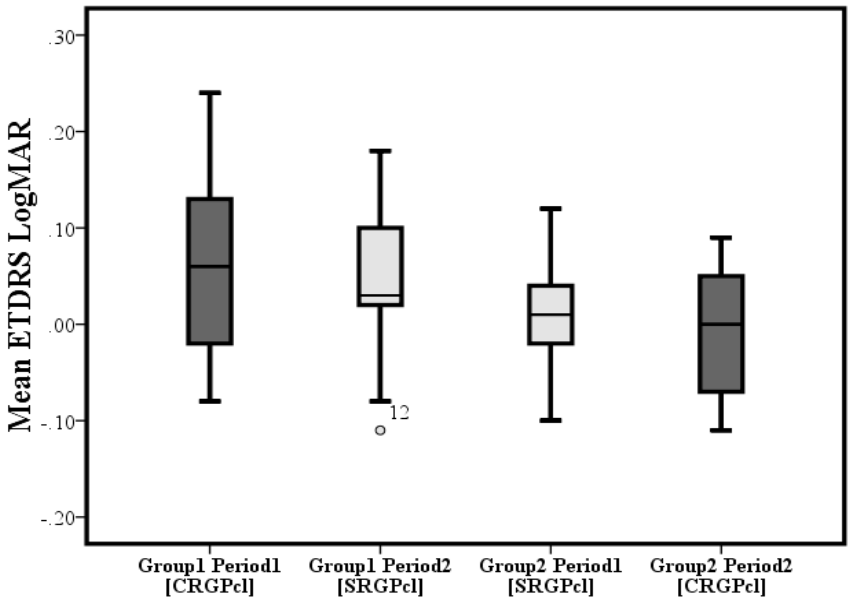


Figure 5.23 *Boxplots of group by period for the mean OD/OS ETDRS logMAR BCVA*

The boxplot in Figure 5.24 exhibits the OD/OS means of the logMAR scores of the 2 experimental lenses of the whole research population. The logMAR scores for CRGPcl [*Mean=0.04, (±0.11*)] were normally distributed; *Shapiro-Wilk* (*p=0.0654*), the SRGPcl logMAR scores [*Mean=0.03, (±0.09), Median=0.02, IQR=0.09*] were not normally distributed; *Shapiro-Wilk* (*p=0.016*).

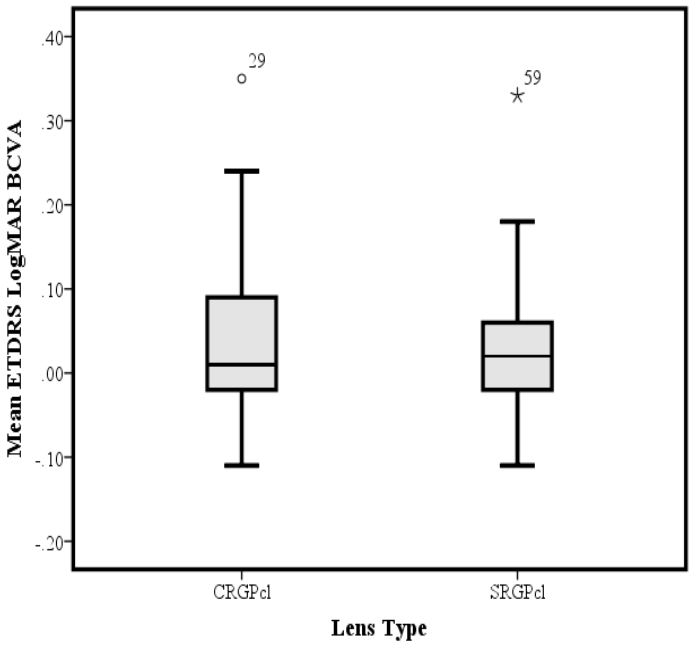


Figure 5.24 *Mean OD/OS logMAR scores of CRGPcl vs SRGPcl*

Group by Period analysis

The plots of the means of OD/OS, ETDRS logMAR scores for each participant in period 1 vs period 2 for group 1(AB) and group 2(BA) are illustrated below (Figures 5.25 and 5.26). The Kendall's tau correlations between the periods were 0.517 and 0.331 for groups 1 and 2 respectively.

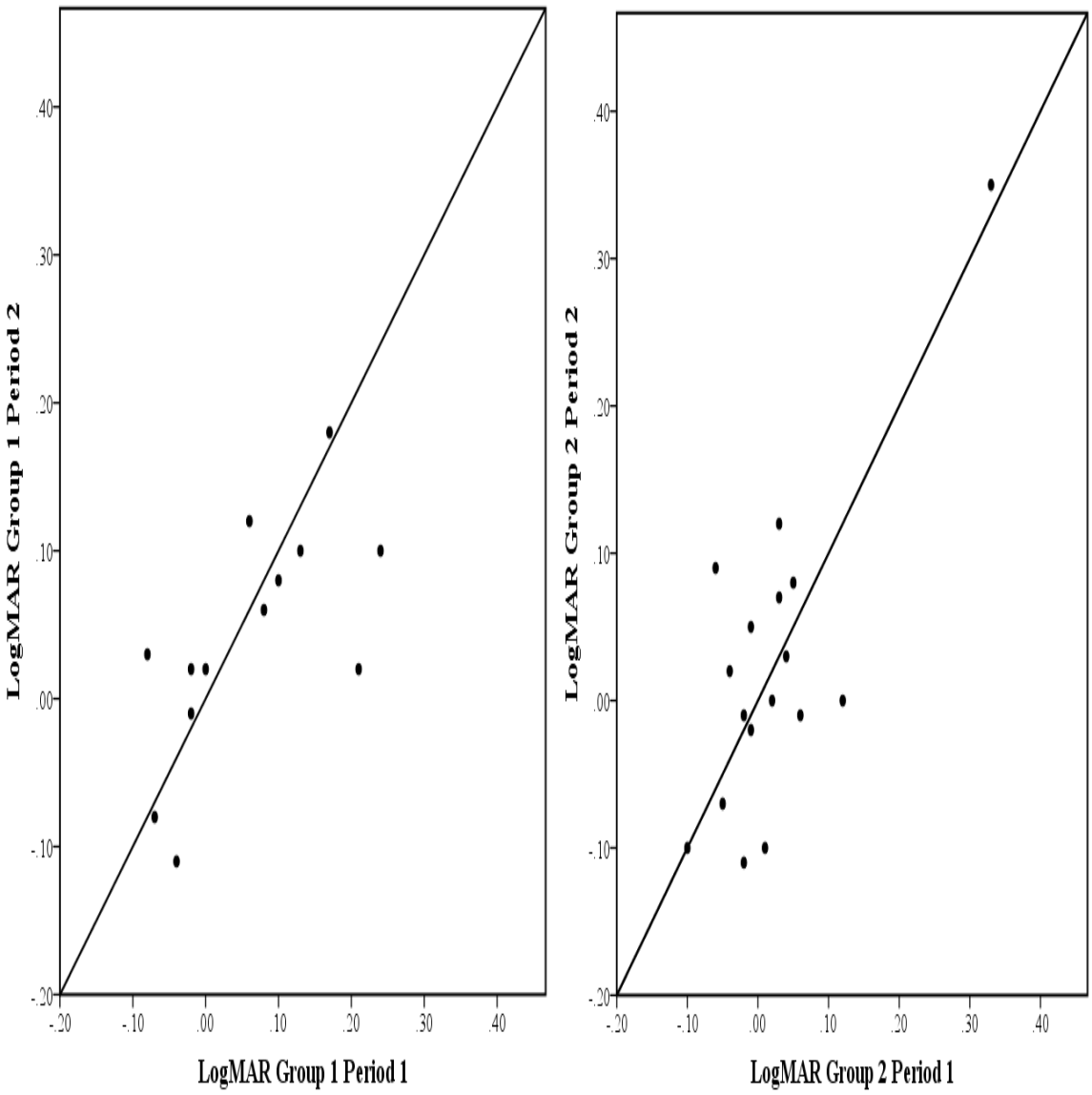


Figure 5.25 and 5.26 *Mean OD/OS ETDRS logMAR BCVA period 1 versus period 2 in both groups*

To determine evidence for a direct treatment effect, Figure 5.27 exhibits the mean OD/OS logMAR scores from both groups on a single graph and indicates the centroid of each group with a solid enlarged character [*centroid is the mean position of all the points/objects in a cluster*]. Kendall's tau correlation between ETDRS logMAR BCVA of period 1 and period 2 of both groups is 0.464 ($p<0.01$).

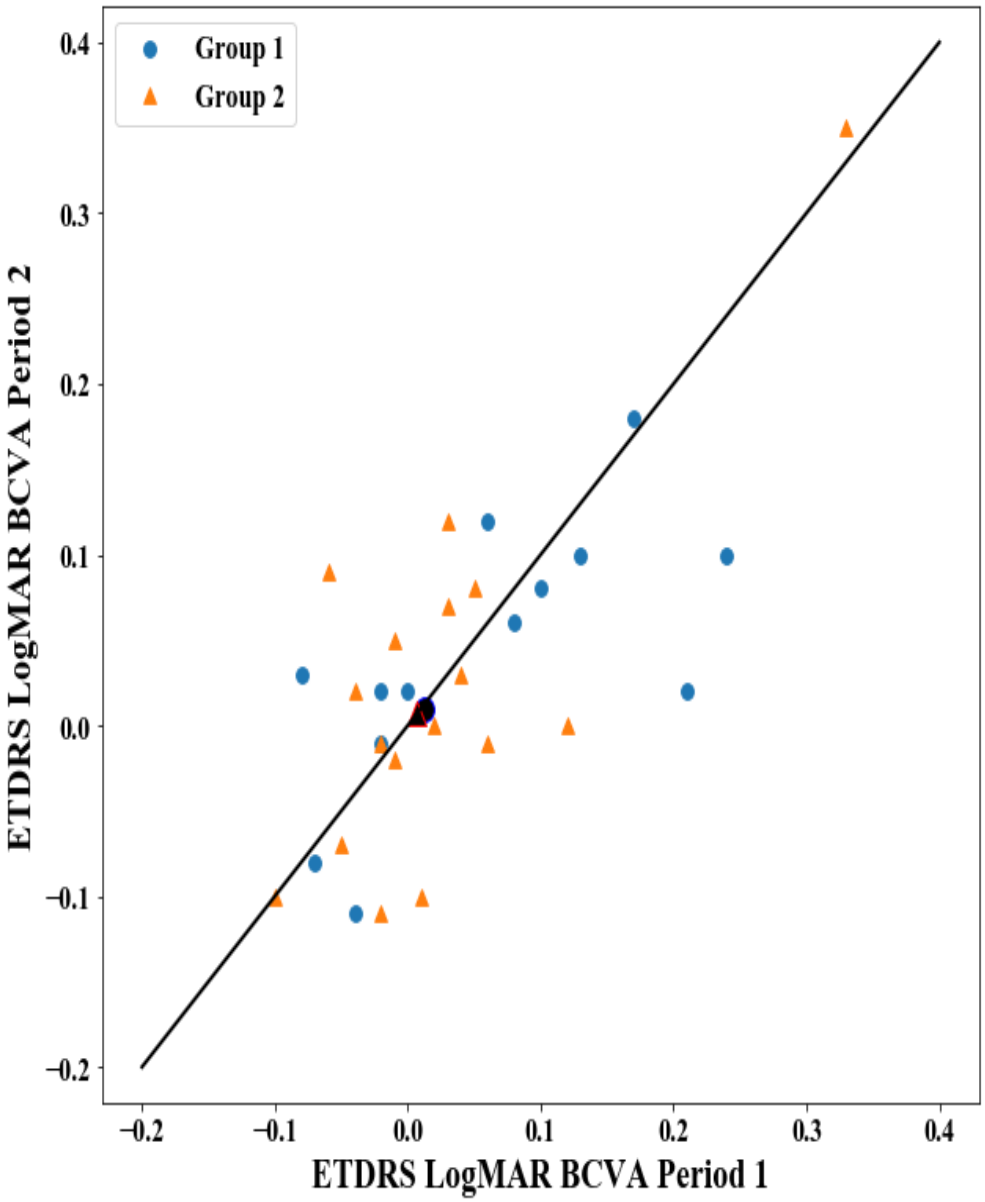


Figure 5.27 *Mean OD/OS logMAR scores period 1 vs period 2 for both groups with centroids (solid black)*

The subject-profile plots illustrate the differences between period 1 and 2, in the mean OD/OS logMAR scores of all participants (inter-subject differences) and in each individual participant (intra-subject difference) in each group (Figure 5.28).

Group 1(AB) **Group 2(BA)**

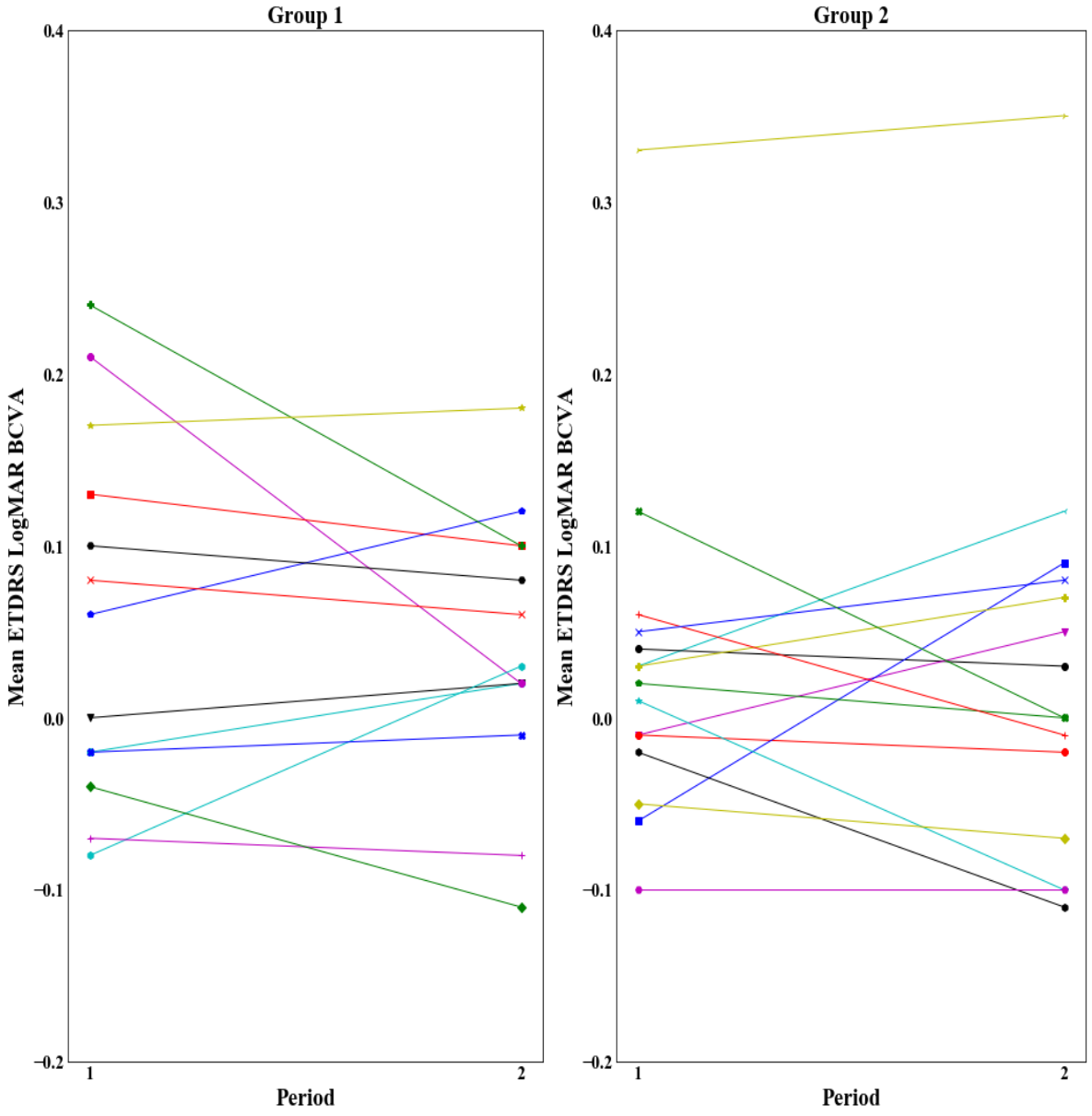


Figure 5.28 *Profiles Plots for ETDRS logMAR by Group intra-participant period difference*

Having looked at the logMAR scores from individual participants, a group-by-period plot, which compares the average logMAR scores of each group in each period, was generated. The four group by period means $\bar{y}_{11}$, $\bar{y}_{12}$, $\bar{y}_{21}$ and $\bar{y}_{22}$ were plotted against their corresponding period labels and joined the means of period 1 of group 1 and period 2 of group 2 [1A and 2A] and period 2 of group 1 with period 1 of group 2 [1B and 2B] (Figure 5.29). The blue and red

circles represent the mean logMAR scores of participants in groups 1 and 2 wearing CRGPcl in periods 1 and 2 respectively and the red and blue triangles represent mean logMAR scores of participants in groups 2 and 1 wearing SRGPcl in periods 1 and 2 respectively.

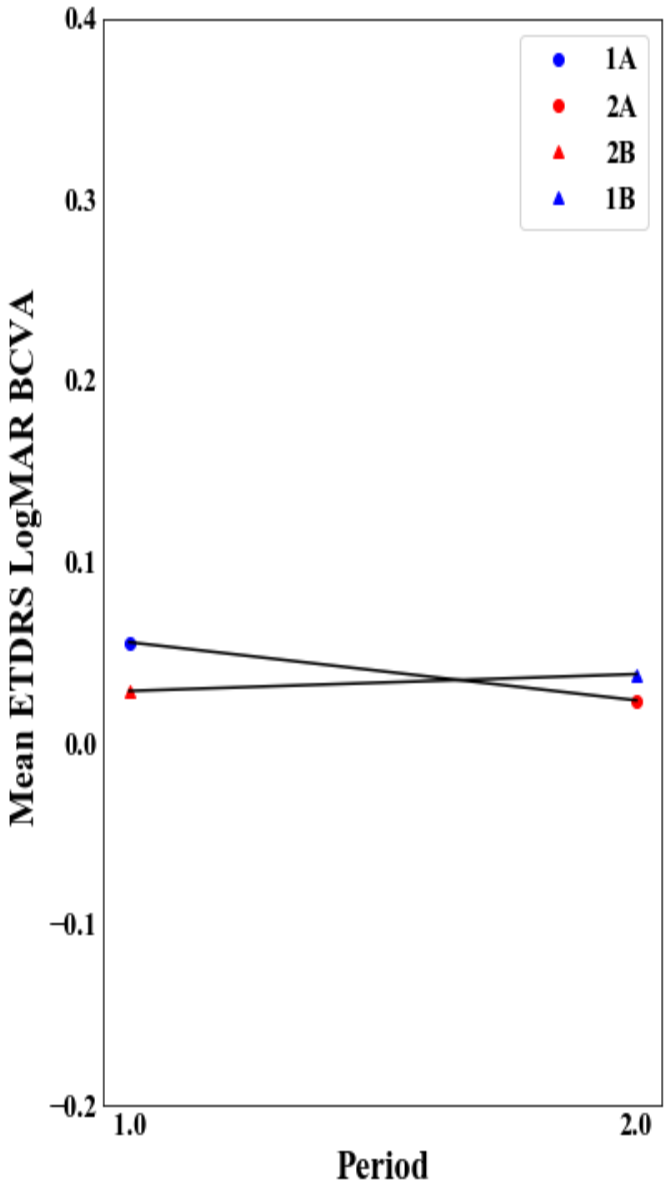


Figure 5.29 *Group-by-period plot for mean ETDRS logMAR data*.

Crossover and treatment effect analysis

A general technique for analysing 2x2 crossover designs [*two treatments with two sequence groups*], involves reducing the two responses / scores of each subject to a single value and comparing the mean of this derived variate between the two groups (Jones and Kenward, 2015). For normally distributed data, an independent two-sample *t*-test is used to compare the group means, for data that are not normally distributed; the *Mann-Whitney U* test for independent samples can be used. The logMAR scores, sums and differences by period in each group are exhibited in Tables 5.23a and 5.23b.

Table 5.23a. *Group 1 ETDRS logMAR scores, sums and differences periods 1 & 2*

Group 1 (Sequence AB)					
SN	Period 1	Period 2	Sum of Periods P1+P2	Δ of Periods (P2-P1)	Crossover Δ (A-B)
1	-0.02	0.02	0.00	0.04	-0.04
2	0.00	0.02	0.02	0.02	-0.02
5	0.13	0.10	0.23	-0.03	0.03
7	0.06	0.12	0.18	0.06	-0.06
10	0.24	0.10	0.34	-0.14	0.14
11	0.17	0.18	0.35	0.01	-0.01
13	-0.08	0.03	-0.05	0.11	-0.11
14	0.10	0.08	0.18	-0.02	0.02
20	-0.07	-0.08	-0.15	-0.01	0.01
23	0.08	0.06	0.14	-0.02	0.02
28	-0.02	-0.01	-0.03	0.01	-0.01
31	-0.04	-0.11	-0.15	-0.07	0.07
33	0.21	0.02	0.23	-0.19	0.19

Table 5.23b. *Group 2 ETDRS logMAR scores, sums and differences periods 1 & 2*

Group 2					
SN	Period 1	Period 2	Sum of Periods P1+P2	Δ of Periods (P2-P1)	Crossover Δ (A-B)
3	0.04	0.03	0.07	-0.01	-0.01
4	-0.01	0.05	0.04	0.06	0.06
6	-0.01	-0.02	-0.03	-0.01	-0.01
8	-0.06	0.09	0.03	0.15	0.15
9	0.02	0.00	0.02	-0.02	-0.02
12	0.03	0.07	0.10	0.04	0.04
15	0.01	-0.10	-0.09	-0.11	-0.11
16	-0.02	-0.11	-0.13	-0.09	-0.09
17	-0.10	-0.10	-0.20	0.00	0.00
19	0.06	-0.01	0.05	-0.07	-0.07
21	0.05	0.08	0.13	0.03	0.03
24	0.12	0.00	0.12	-0.12	-0.12
26	-0.05	-0.07	-0.12	-0.02	-0.02
27	-0.04	0.02	-0.02	0.06	0.06
30	-0.02	-0.01	-0.03	0.01	0.01
32	0.33	0.35	0.68	0.02	0.02
34	0.03	0.12	0.15	0.09	0.09

Carryover and period effects analysis

A preliminary analysis, after the first 12 participants completed their participation, for carryover effect was performed as recommended by Wellek and Blettner (2012) and Jones and Kenward (2015), by an independent sample *t-test*. The results exhibited no significant difference: t (12) = 2.228, df = 10, ($p=0.056$), 95% CI [-0.29087, 0.0042] NS, *Cohen's d* = -1.250. The mean sum of BCVA, of the better eye for participants randomised to SRGPcl [*Mean =0.10, ±0.112*] was not significantly different to that of participants randomised to CRGPcl [*Mean =0.04, ±0.048*]. This finding does not support the presence of a significant carry over effect in that group of participants, indicating that it is appropriate to progress with analysing for treatment effects based on the crossover data.

A similar analysis was carried out once the study was completed for the full study population. The comparison of the sums of the mean OD/OS logMAR scores of the 2 periods between groups 1 and 2 of the whole population, by the *Mann-Whitney U* test indicated that there was no statistically significant difference between the period sums of group 1 (*Median=0.14, IQR= 0.27*) and group 2 (*Median=0.03, IQR=0.17*), *U=84.5* (*p=0.281*) [*z=-1.089*], which confirmed the absence of a carryover effect (Table 5.24a. and b).

Table 5.24 *Carryover effect statistics Mann-Whitney U test*

Sum P1+P2			
Group	N	Mean Rank	Sum of Ranks
Group 1 (AB)	13	17.5	227.5
Group 2 (BA)	17	13.97	237.5
Total	30		

a.

Test Statistics	Sum of Means
Mann-Whitney U	84.5
Wilcoxon W	237.5
Z	-1.089
Exact. Sig. [2-(1-tailed Sig.)]	0.281

b.

To calculate the period effect as recommended by Wellek and Blettner (2012) and Jones and Kenward (2015), the crossover period differences [Crossover Δ (A-B), Tables 5.23 a and b] were compared between the two randomised groups. The crossover period differences were normally distributed, *Shapiro-Wilk* (*p=0.417*) and (*p=0.853*) group 1 and 2 respectively. An independent samples *t-test* means comparison of the period crossover differences between group 1 [*Mean=0.0177*, (*±0.08*)] and 2 [*Mean=0.0006*, (*±0.07*)] revealed no significant difference between the two groups, *t (0.62), df 28, (p=0.541)*, 95% CI (-0.04 -0.07), *d=0.23*. This finding indicated that there was no significant period effect in the logMAR scores in this research.

ETDRS logMAR BCVA treatment effect analysis

To establish whether a statistically significant difference exists between the ETDRS logMAR BCVA of the eyes wearing CRGPcl compared with SRGPcl, the nonparametric independent samples *Mann-Whitney U* test was applied, to the period differences; (period 2 - period 1) between group 1; sequence AB and group 2; sequence BA. *Mann-Whitney U* test indicated that despite the slightly better (numerically lower) logMAR score of SRGPcl in group 1, there was no statistically significant difference between the period differences of group 1 *(Median=-0.01, IQR=0.08)* and group 2 *(Median=0.00, IQR=0.10), U=96.5,* (*p=0.563*) [*z=-0.588*] (Table 5.25a and b, Figure 5.30 and 5.31). In other words, as stipulated by the H_0, the ETDRS logMAR BCVA with CRGPcl was not statistically significantly different to that with SRGPcl.

Table 5.25 *Mann-Whitney U test logMAR scores period differences between groups 1 and 2.*

Ranks				
Group		N	Mean Rank	Sum of Ranks
logMAR Difference (P2-P1)	Group 1 (AB)	13	14.42	187.50
	Group 2 (BA)	17	16.32	277.50
	Total	30		

a.

Test Statistics	Difference P2-P1
Mann-Whitney U	96.500
Wilcoxon W	187.500
Z	-0.588
Exact. Sig. [2 (1-tailed Sig.)]	0.563

b.

Figures 5.30 and 5.31 show the mean OD/OS logMAR values of all participants in CRGPcl and SRGPcl and the frequency distribution of the logMAR scores with CRGPcl and SRGPcl in the research population respectively.

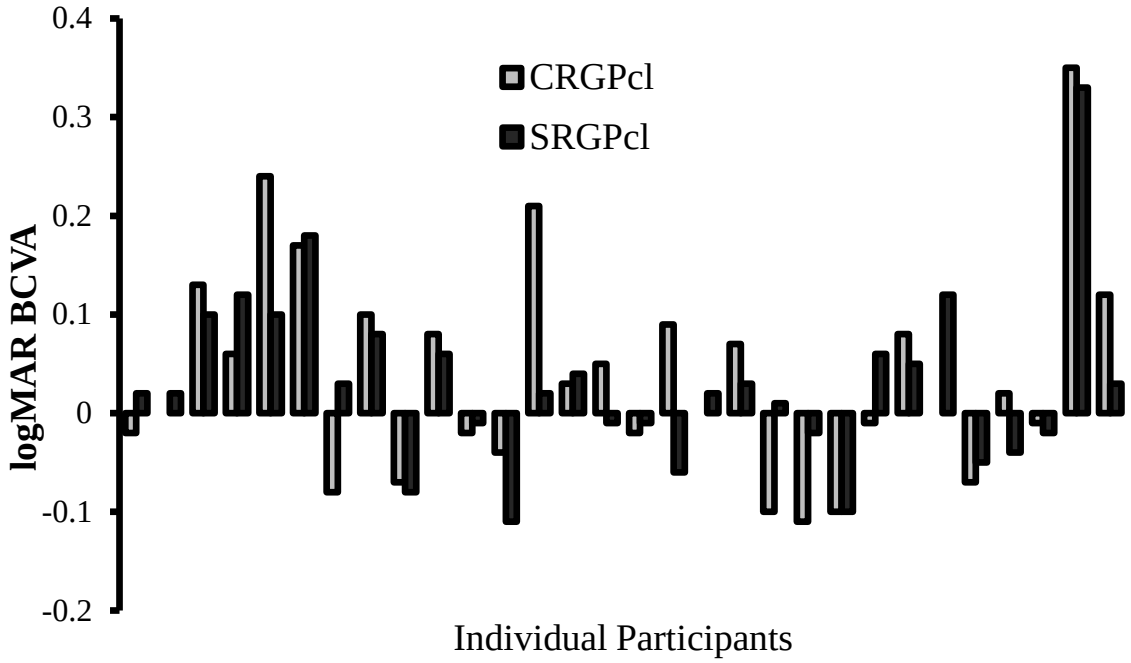


Figure 5.30a. *Individual logMAR scores in CRGPcl and SRGPcl of the research population*

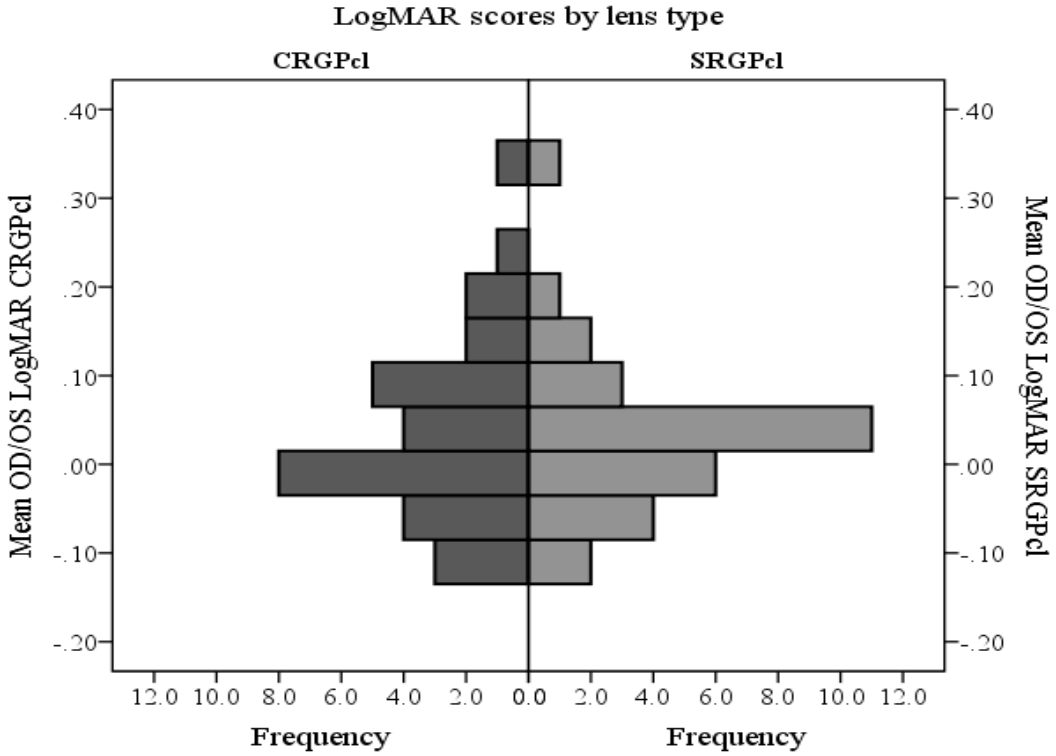


Figure 5.30b. *Frequency distribution logMAR BCVA with CRGPcl and SRGPcl*

Contrast sensitivity function (CSF) visual performance outcomes

The OD/OS mean numerical CS scores of the four CPD tests of the research population were not normally distributed and are exhibited in Table 5.26 (Appendix V.H) and Figure 5.31b. The CSF per CPD data for all eyes is exhibited in Figure 5.31a.

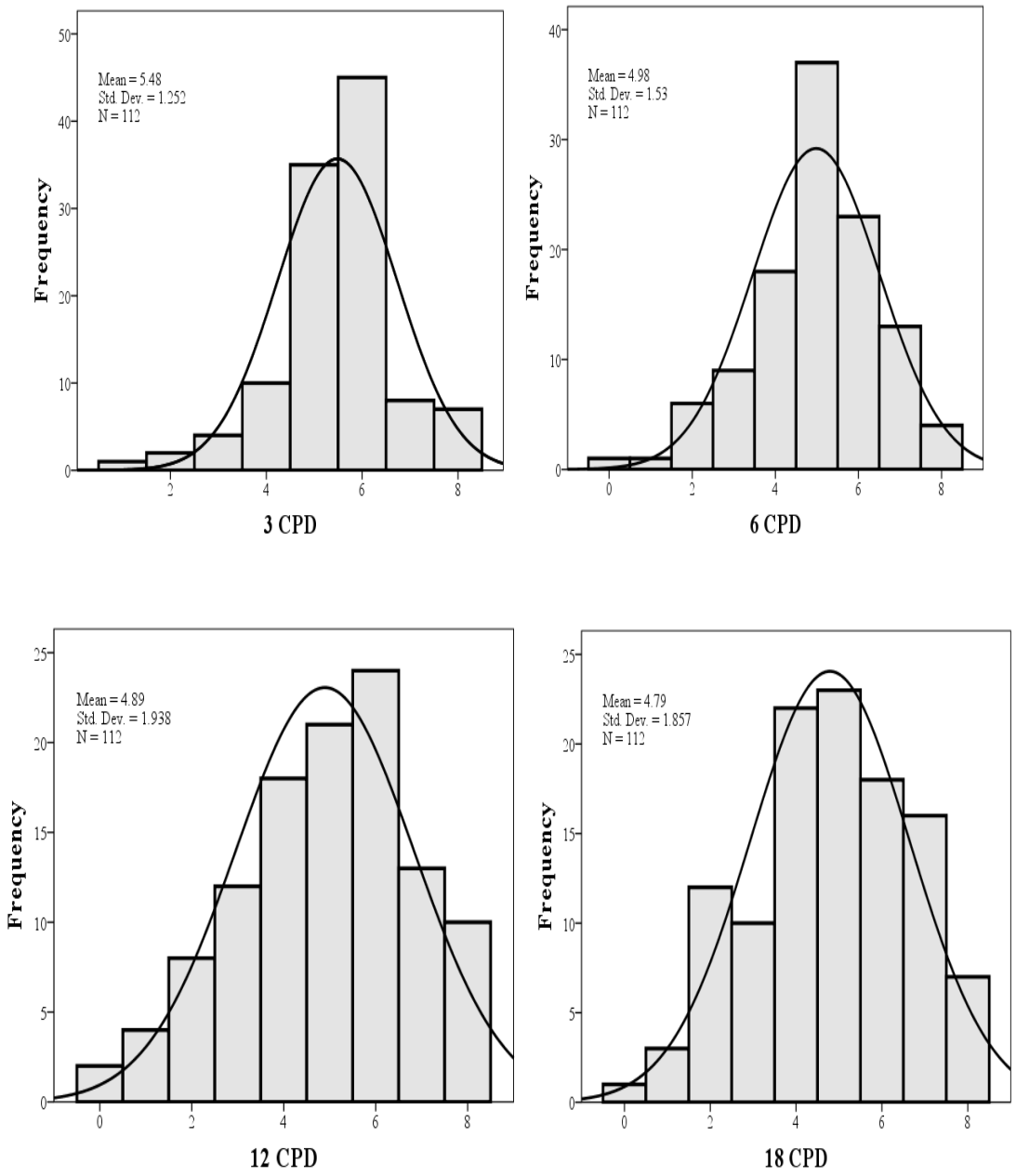


Figure 5.31a. *Numeric values of experimental CS scores distribution by CPD of OD and OS of the research population*

The OD/OS averages of the CS numerical scores for CRGPcl and SRGPcl are shown in table 5.27.a (Appendix V.A), total means per CPD in Table 5.27.b. and Figure 5.31b and 5.33.

Table 5.27.b *CS numerical means and StdDev. for averages of OD/OS scores in CRGPcl and SRGPcl for the research population*

	Mean 3 CPD	Mean 6 CPD	Mean 12 CPD	Mean 18 CPD	Total Mean
CRGPcl	5.39 (±1.46)	4.79 (±1.58)	5.00 (±1.96)	4.61 (±1.98)	4.95 (±1.75)
SRGPcl	5.57 (±1.01)	5.18 (±1.47)	4.79 (±1.92)	4.96 (±1.73)	5.13 (±1.53)
Mean Population	5.48 (±1.25)	4.98 (±1.53)	4.89 (±1.93)	4.79 (±1.86)	5.03 (±1.64)

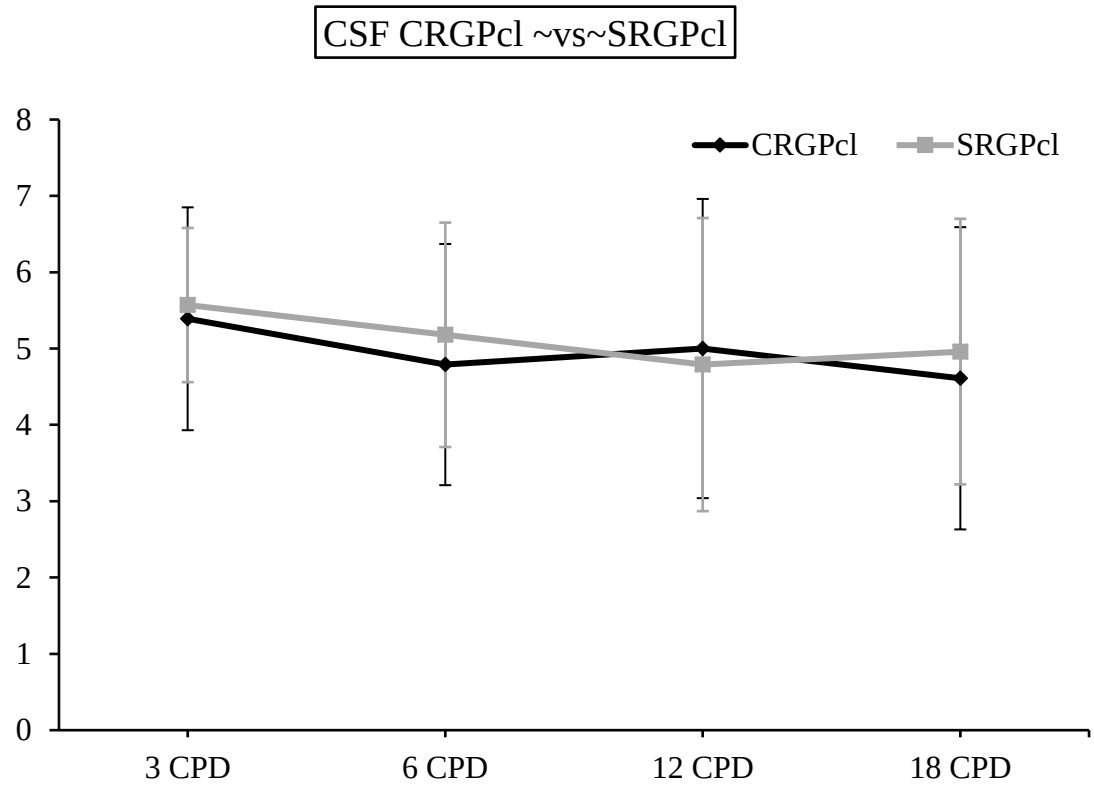


Figure 5.31b. *OD/OS means of numeric CSF scores and standard deviations; CRGPcl vs SRGPcl of the research population*

The normative means of the general population (Table 5.28) for photopic light conditions are exhibited below; these data were collected as base-line in an FDA clinical trial for refractive surgery [unpublished data quoted in (VectorVision, 2013)]. These results are based on the evaluation of 79 patients with an age range of 21–55 years, mean 36.6 (±9.02) years. Mean pre-operative acuity for these patients was logMAR -0.10 (±0.06). Another population-based study, evaluated 370 subjects with normal 20/20 [*logMAR 0.00*] visual acuity (Hashemi *et al.*, 2012). A comparison of CSF values of the research population to participants with keratoconus from a study by Wei *et al*., (2011) is exhibited in Figure 5.32c.

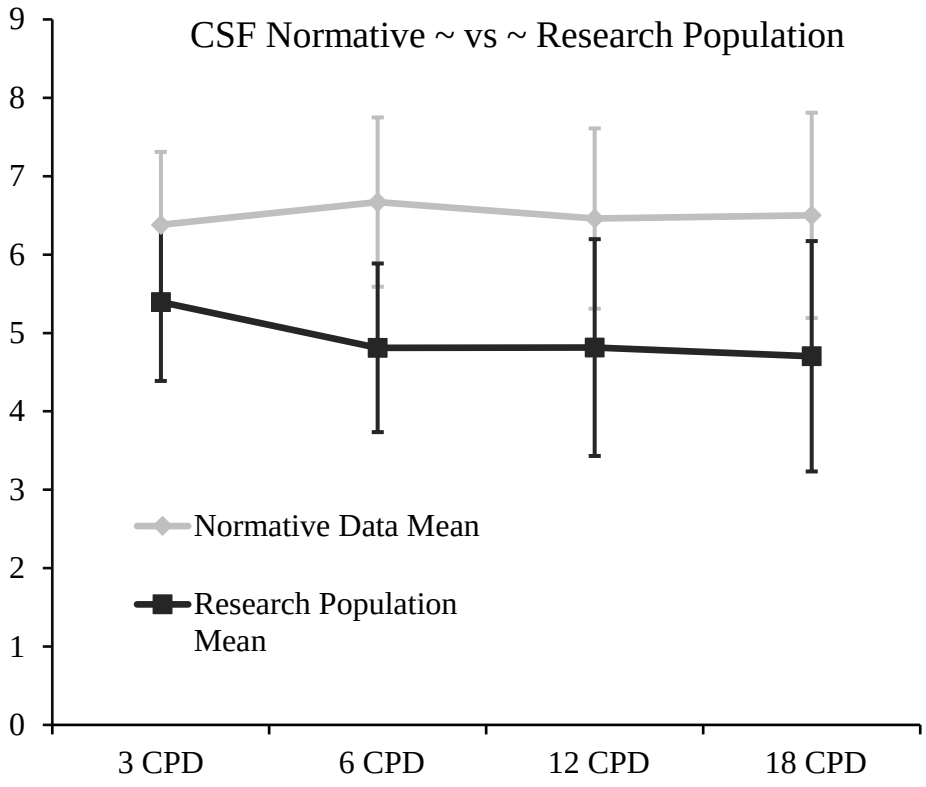
Table 5.28 *Normative data ages 21-51 FDA study and Hashemi et al., (2012) italicised.*

Spatial Frequency	Log Average (Contrast Level Numeric)	Standard Deviation
Row A (3 CPD)	1.84 (6.38) / *1.63 (5.0)*	0.14 (0.93) / *0.18 (1.2)*
Row B (6 CPD)	2.09 (6.67) / *1.90 (5.4)*	0.16 (1.08) / *0.20 (1.3)*
Row C (12 CPD)	1.76 (6.46) / *1.58 (5.3)*	0.17 (1.15) / *0.23 (1.5*)
Row D (18 CPD)	1.33 (6.50) / *1.14 (5.3)*	0.19 (1.31) / *0.24 (1.6)*

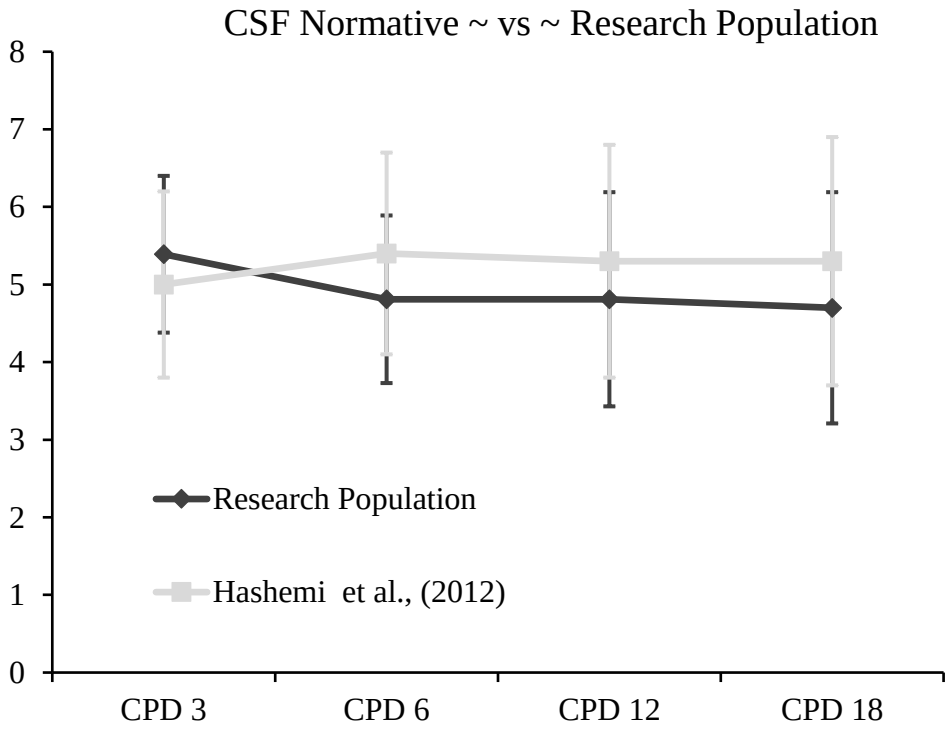
Plotting the CSF of the whole research population together with normative data from the sources described above is presented in Table 5.29 and Figure 5.32a-c.

Table 5.29 *CS normative vs research population data*

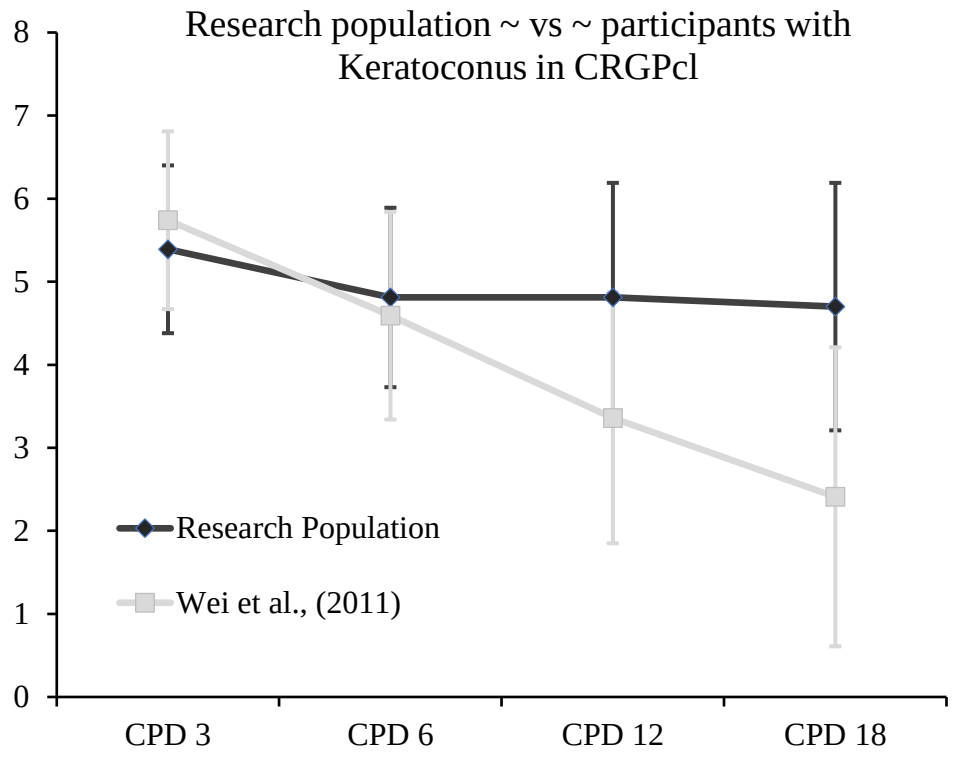
	3 CPD	6 CPD	12 CPD	18 CPD
Normative data (FDA)	6.38 (±0.93)	6.67 (±1.08)	6.46 (±1.15)	6.50 (±1.31)
Hashemi *et al*., (2012)	5.00 (±1.20)	5.40 (±1.30)	5.30 (±1.30)	5.30 (±1.60)
Research population data	5.48 (±1.25)	4.98 (±1.53)	4.89 (±1.93)	4.79 (±1.86)


CSF Normative ~ vs ~ Research Population
9
8
7
6
5
4
3
2
1
0
Normative Data Mean
Research Population Mean
3 CPD
6 CPD
12 CPD
18 CPD

a


CSF Normative ~ vs ~ Research Population
8
7
6
5
4
3
2
1
0
Research Population
Hashemi et al., (2012)
CPD 3
CPD 6
CPD 12
CPD 18

b.



c.

Figure 5.32 *CSF mean and std. deviation of the research population data versus:* ***a.*** *FDA normative data,* ***b.*** *Hashemi et al., (2012) normative data,* ***c****. Wei et al., (2011).*

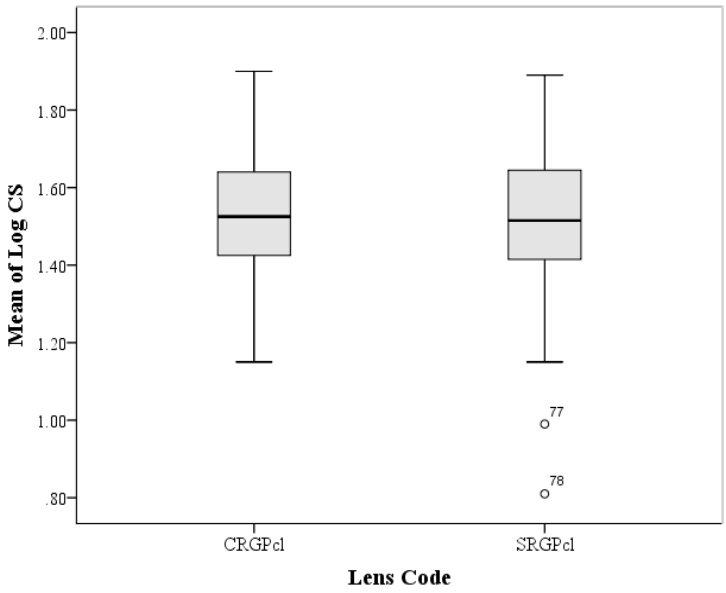


Figure 5.33 *Boxplots mean logCS experimental lenses current research*

The average OD/OS mean of 3,6,12,18 CPD, logCS scores in the experimental lenses were normally distributed, *Shapiro-Wilk* (*p=0.731*) and (*p=0.144*) in CRGPcl and SRGPcl respectively. The logCS scores for CRGPcl were [*Mean 1.53, (±0.14)*] and SRGPcl [*Mean=1.50, (±0.20)*] (Figure 5.33).

Crossover data analysis

The summary of the average OD/OS mean of the 4 CPD scores logCS, by group and period are exhibited in Table 5.30. The sums and differences of the mean OD/OS logCS scores for the 2 groups are exhibited in Table 5.31. The descriptive statistics of the periods in the two groups are exhibited in Table 5.32. The logCS period data are normally distributed, *Shapiro-Wilk p>0.30* in periods 1 and 2 of groups 1(AB) and 2(BA) respectively.

Table 5.30 *Summary of CS scores by group and period*

Group	Mean logCS Period 1	Mean logCS Period 2	Mean logCS
1 (AB) n_1=13	$\bar{y}_{11.}$ =1.46	$\bar{y}_{12}$ =1.42	$\bar{y}_{.1}$ total = 1.44
2 (BA) n_2=17	$\bar{y}_{21.}$ =1.56	$\bar{y}_{22}$ =1.59	$\bar{y}_{.2}$ total. = 1.58
Mean logCS	$\bar{y}_{.1.}$ = 1.51	$\bar{y}_{.2.}$ =1.51	$\bar{y}_{..}$ total = 1.51

Table 5.31 *logCS all CPD period scores, sums and differences of OD/OS means, group 1(AB) and 2 (BA)*

Group 1 (AB) Mean OD/OS logCS							Group 2(BA) Mean OS/OS logCS					
SN	P1(A)	P2(B)	P1+P2	ΔP2/P1	ΔA/B		SN	P1(B)	P2(A)	P1+P2	ΔP2/P1	ΔA/B
1	1.53	1.47	3.00	-0.06	0.06		3	1.42	1.40	2.81	-0.02	-0.02
2	1.62	1.63	3.25	0.01	-0.01		4	1.63	1.49	3.12	-0.14	-0.14
5	1.40	1.28	2.67	-0.12	0.12		6	1.50	1.53	3.03	0.02	0.02
7	1.43	1.68	3.12	0.25	-0.25		8	1.58	1.52	3.10	-0.06	-0.06
10	1.27	1.27	2.54	-0.01	0.01		9	1.44	1.55	2.99	0.11	0.11
11	1.51	1.21	2.73	-0.30	0.30		12	1.47	1.40	2.87	-0.07	-0.07
13	1.54	1.49	3.03	-0.05	0.05		15	1.77	1.78	3.55	0.01	0.01
14	1.38	1.30	2.68	-0.08	0.08		16	1.57	1.58	3.14	0.01	0.01
20	1.63	1.52	3.15	-0.11	0.11		17	1.80	1.80	3.61	0.00	0.00
23	1.42	0.90	2.32	-0.52	0.52		19	1.52	1.57	3.09	0.05	0.05
28	1.41	1.57	2.97	0.16	-0.16		21	1.59	1.53	3.12	-0.06	-0.06
31	1.64	1.72	3.36	0.08	-0.08		24	1.72	1.69	3.40	-0.03	-0.03
33	1.21	1.48	2.69	0.27	-0.27		26	1.75	1.70	3.46	-0.05	-0.05
							27	1.41	1.65	3.06	0.24	0.24
							30	1.68	1.68	3.37	0.00	0.00
							32	1.33	1.41	2.74	0.08	0.08
							34	1.32	1.76	3.08	0.44	0.44

Table 5.32 *Descriptive statistics of Mean OD/OS logCS in the 2 periods in both groups*

	Group 1(AB)				Group 2(BA)			
	Period 1		Period 2		Period 1		Period 2	
	Statistic	StdEr	Statistic	StdEr	Statistic	StdEr	Statistic	StdEr
Shapiro-Wilk *p*	***0.522***		***0.35***		***0.632***		***0.348***	
Mean	1.46	0.04	1.42	0.06	1.56	0.04	1.59	0.03
95% CI	1.38-1.54		1.29-0.56		1.48-1.64		1.52-1.66	
Std. Deviation	0.13		0.23		0.15		0.13	
Minimum	1.21		0.90		1.32		1.4	
Maximum	1.64		1.72		1.80		1.8	
Range	0.43		0.82		0.48		0.4	
Skewness	-0.33	0.62	-0.91	0.62	0.05	0.55	0.1	0.6
Kurtosis	-0.51	1.19	0.96	1.19	-1.07	1.06	-1.1	1.1

Average OD/OS, mean of CPDs: 3,6,12 and 18, logCS scores of period 1 versus period 2 in groups 1 and 2 separately and together with centroids are exhibited in Figures 5.34 and 5.35 respectively. Individual participant scores in both periods are exhibited in Figure 5.36 [noticeable outlier in group 1, with poor logCS scores in period 2, results confirmed in participant 23].

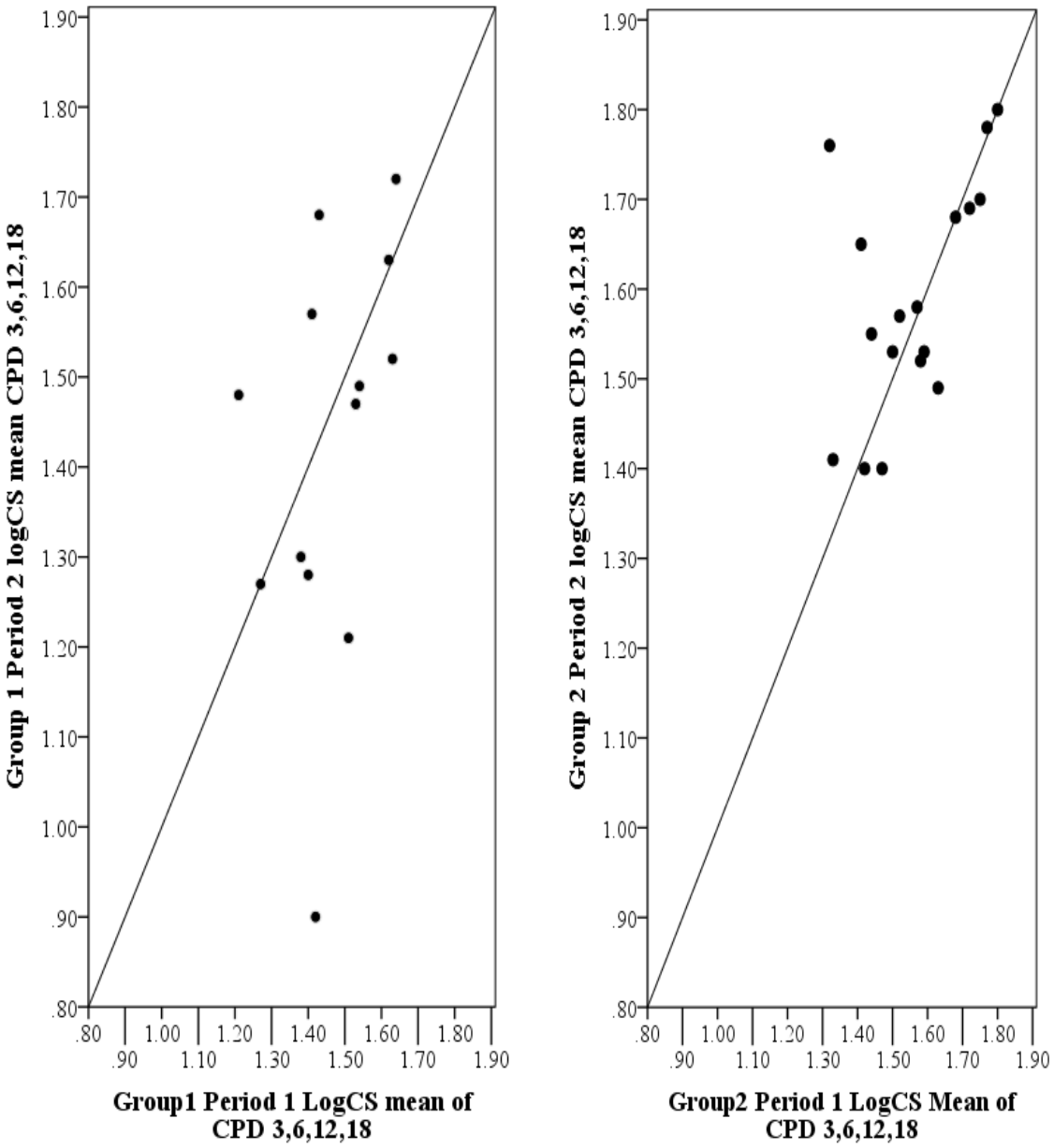


Figure 5.34 *Mean OD/OS logCS period 1 versus period 2 in both groups*

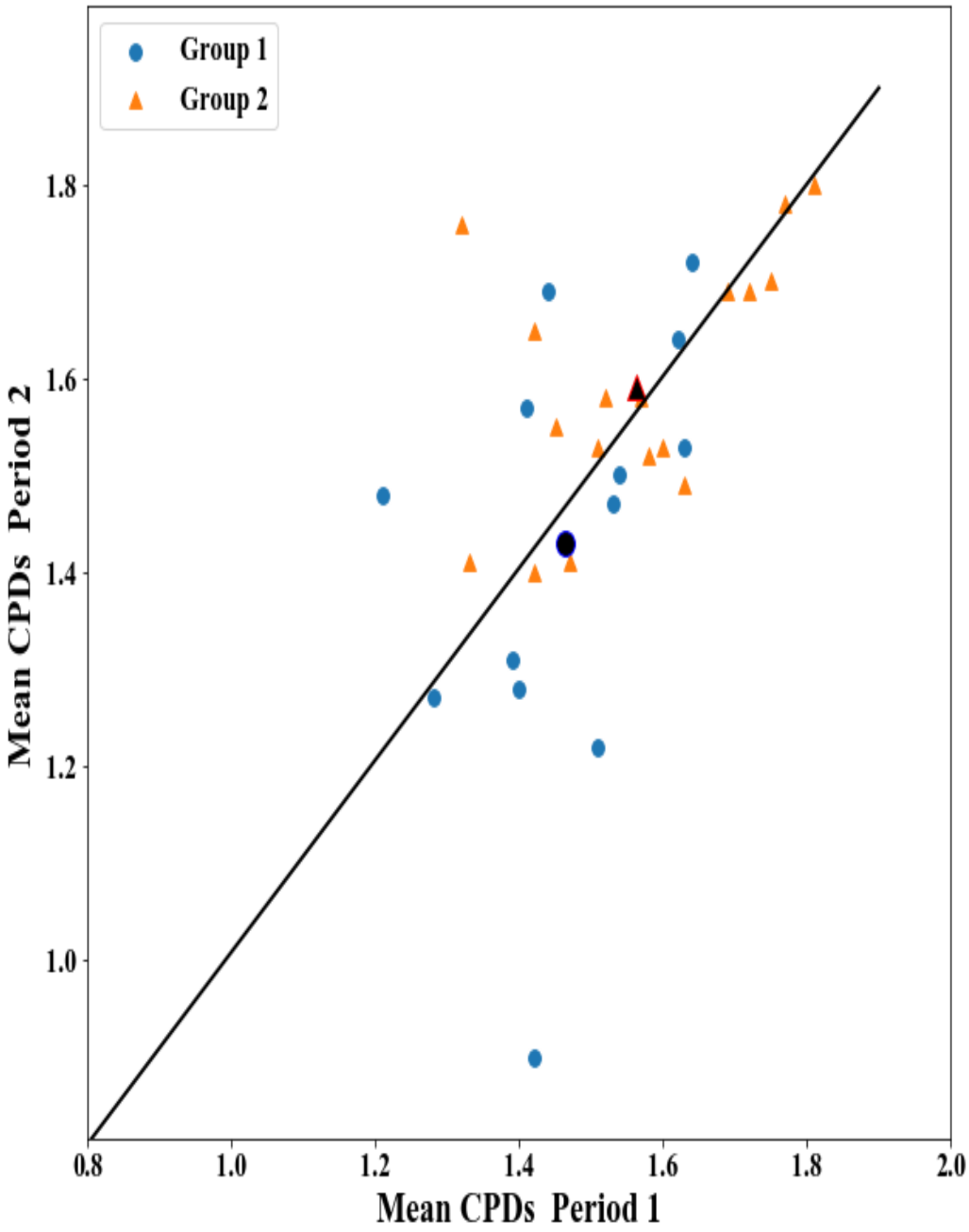


Figure 5.35 *Average OD/OS logCS mean of CPD 3,6,12,18 scores period 1 vs period 2 for both groups with centroids (solid black)*

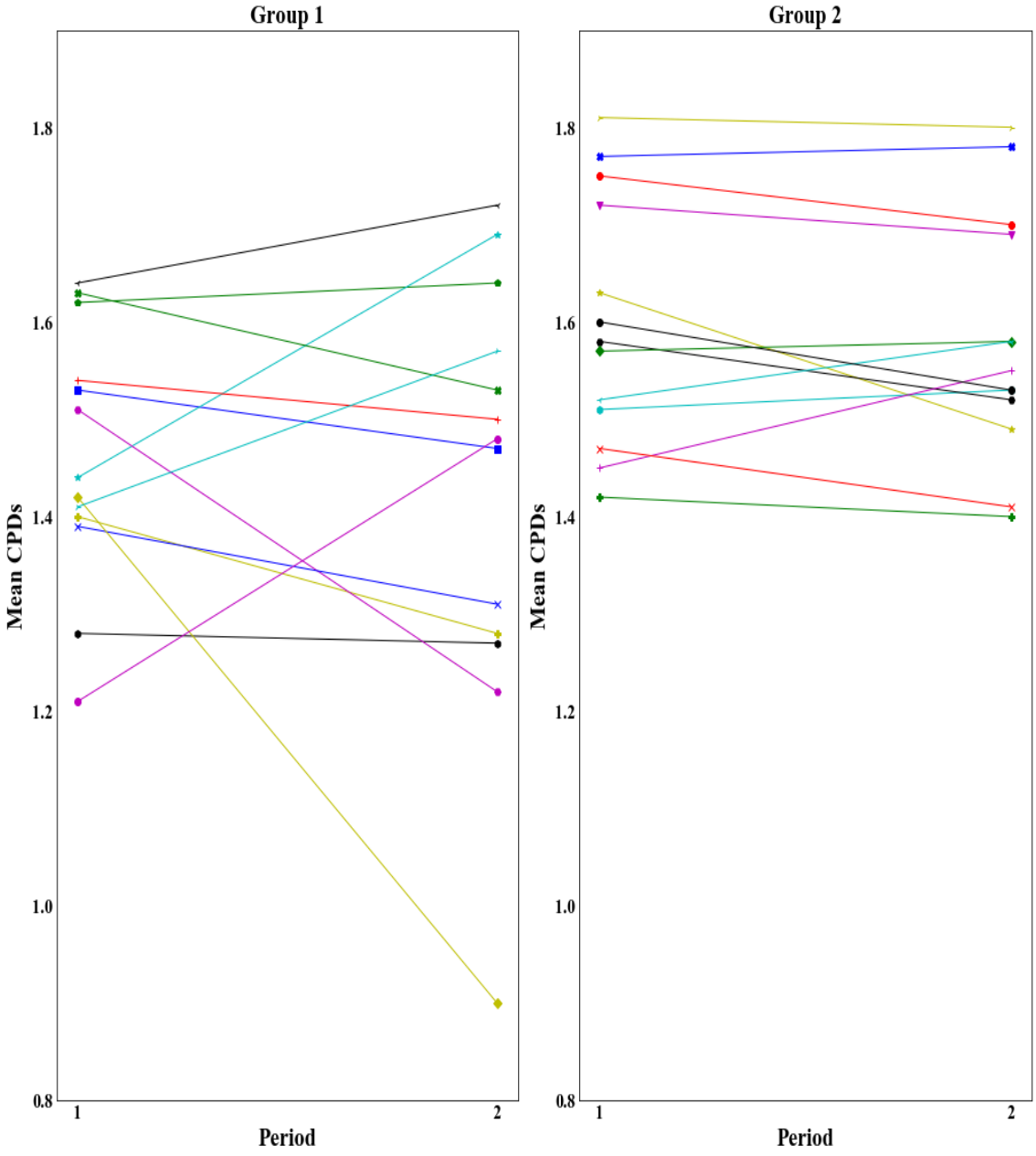


Figure 5.36 *Individual participant's logCS scores in group 1 and 2, periods 1 and 2*

Having looked at the logCS scores from individual participants, a groups-by-period plot, which compares the average logCS scores of each group in each period, was generated. The four group by period means $\bar{y}_{11}$, $\bar{y}_{12}$, $\bar{y}_{21}$ and $\bar{y}_{22}$ were plotted against their corresponding period labels and joined the means of period 1 of group 1 and period 2 of group 2 [1A and 2A] and period 2 of group 1 with period 1 of group 2 [1B and 2B] (Figure 5.37). The blue and red circles represent the mean logCS scores of participants in groups 1 and 2 wearing CRGPcl in periods

1 and 2 respectively and the blue and red triangles represent mean logCS scores of participants in groups 1 and 2 wearing SRGPcl in periods 2 and 1 respectively.

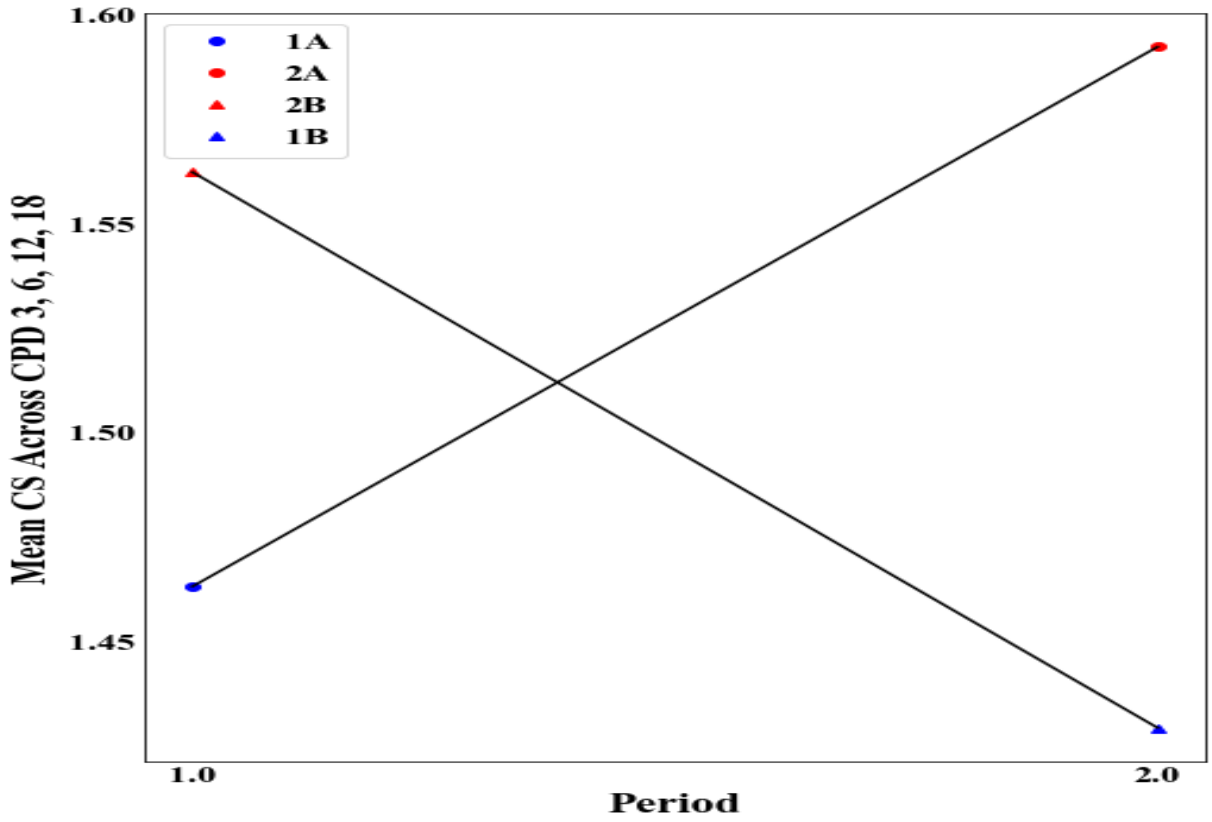


Figure 5.37 *Group-by-periods plot for mean logCS data*.

Carryover and period effect analysis

Independent samples *t-test* comparing the means of the period sums of the two groups found a statistically significant difference between the period sums in group 1 [*Mean=2.89, (±0.31)*] and the period sums in group 2 [*Mean=3.15, (±0.25)*], (*p=0.019*), 95% CI [*-0.45* -

-0.47]. This result indicates that because the mean of period sums in group 2 is significantly higher than that in group 1, there is a possibility of the presence of a differential carryover effect. Owing to this finding, the analysis of the data with respect to the treatment effect was performed in two ways: as a crossover trial, using data from both periods and as a parallel group trial, using data from the first period only.

To calculate the period effect as recommended by Wellek and Blettner (2012) and Jones and Kenward (2015), the crossover period differences [Crossover Δ (A-B), Tables 5.31] of the logCS scores were compared between the two randomised groups. The crossover period differences were normally distributed in group 1 and not normally in group 2, *Shapiro-Wilk* (*p=0.464*) and (*p=0.002*) respectively. A *Man-Whitney U* test comparison of the period crossover differences between group 1 [*Mean=0.369,* (*±0.214*), *Median=0.050, IQR=0.24*] and group 2 [*Median=0.00, IQR=0.12*)] revealed no significant difference between the two groups, *U=101.50,* (*p=0.711*). This finding indicated that despite the significant carryover effect, there was no significant period effect in the logCS scores in this research.

Crossover analysis of the treatment effect

The determination whether there was a difference between the two experimental lenses in the visual performance with respect to logCS scores, analysis was performed as recommended by Wellek and Blettner (2012) and Jones and Kenward (2015), by comparing the period score differences of the two randomised groups with an independent samples *t-test.*

The mean OD/OS logCS mean of the four CPD period difference of groups 1 and 2 [*Mean=-0.0354, SD=0.21469*] and [*Mean=0.0300, SD=0.13500*] respectively, showed that the higher scores of logCS achieved with CRGPcl in both groups did not reach statistical significance: (*p=0.316*), *t(30)=-1.022, df=28, d=-0.258, 95%* CI [*-0.1965-0.0657*] (Figure 5.38). This result indicates that there was no statistically significant difference between the two experimental lenses with respect to the logCS scores achieved with each contact lens as stipulated by the H_0.

Due to the indication of a differential carryover effect in the analysis of the period sums of both groups, the study protocol required a treatment effect analysis by an independent samples *t-test*

comparing the logCS mean of the four CPDs scores of the two contact lens types in the two groups in period 1only (without the crossover scores), as performed in a parallel group RCT. This means comparison also supported the H_0, as it showed no statistically significant difference between the logCS mean scores of the two lens types (*p=0.070*), *t(30)=-1.881, df=28,* 95% CI [*-0.20739 - 0.00884*]. The SRGPcl exhibited a higher mean logCS score [*Mean=1.5624, SD ±0.5127*] than the CRGPcl [*Mean=1.4631, SD ±0.13181*], a difference of 0.10 logCS, which is less than the smallest; 0.15 logCS score increment.

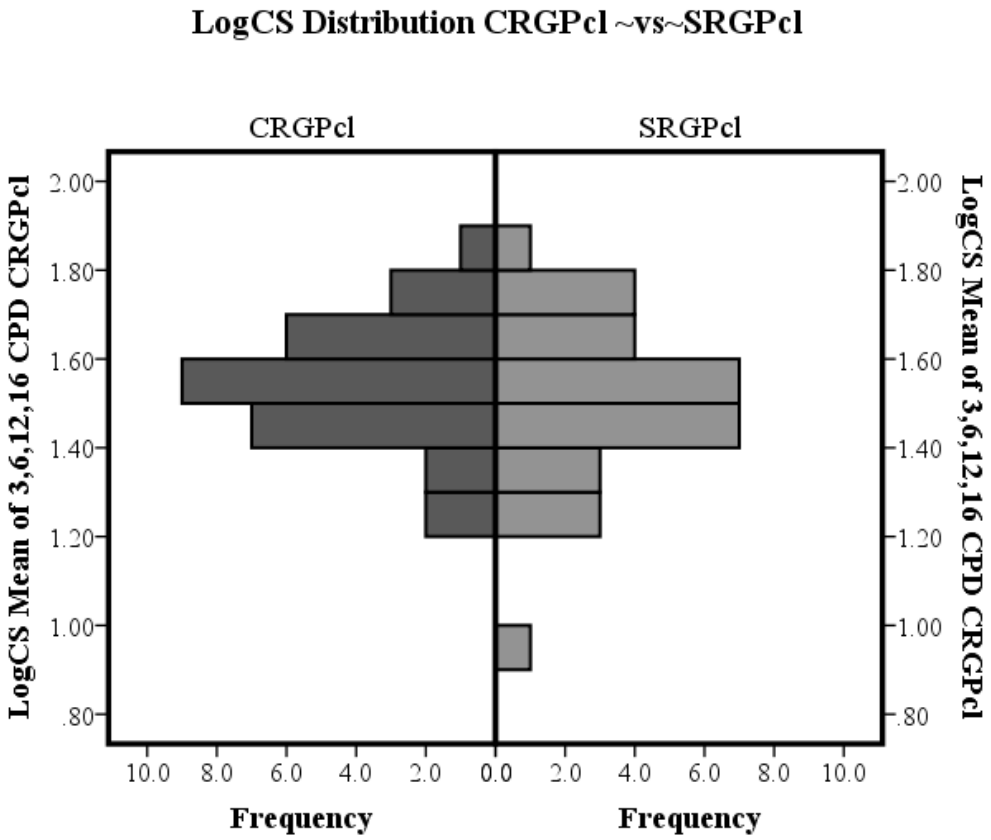


Figure 5.38 *Average OD/OS logCS mean of all CPDs distribution CRGPcl ~vs~ SRGPcl*

The logCS scores at 6 CPD are of interest because normative data suggests that the highest scores are achieved at 6 CPD compared with the other three, because it represents visual detail of a relatively large size: x2 and x3 larger than 12 and 18 CPD respectively and

because the score difference between the two experimental lenses of the research population was largest at 6 CPD (Figure 5.31b). It was therefore decided to compare by an independent samples *t-test*, the means of the period differences of the average OD/OS logCS scores at 6 CPD in the two randomised groups (Table 5.33, Appendix V. G). Group 1 [*Mean=-0.0285, SD ±0.1579*] and group 2 [*Mean=0.0641, SD ± 0.1431*], showed that the higher levels of logCS at 6 CPD achieved with CRGPcl in both groups did not reach statistical significance: t (30) = -1.68, df =28, d = -0.435, ($p = 0.104$), 95% CI [-0.2055 – 0.0203]. This therefore indicates that there was no statistically significant difference in the performance of the two experimental lenses, supporting the H_0.

Due to the indication of a differential carryover effect in the analysis of the period sums of both groups, the study protocol required a treatment effect analysis by an independent samples *t-test* comparing the logCS mean of 6 CPD scores of the two contact lens types in the two groups in period 1only, as performed in a parallel group RCT. This means comparison also showed no statistically significant difference between the two lens types with respect to the logCS mean scores at 6 CPD, supporting the H_0. The higher scores of SRGPcl [*Mean=1.84, SD ±0.16*] compared with CRGPcl [*Mean=1.75, SD ±0.17*] in period 1 did not reach statistical significance: t (30) =-1.651, df=28, d=-0.435, ($p=0.110$), 95% CI [-0.2069–0.0222].

The National Eye Institute-Visual Function Questionnaire (NEI-VFQ)

The summary of the descriptive statistics of the twelve domains measured by the NEI-VFQ are exhibited in Table 5.34 (Appendix V.I.) and Figure 5.40a. All domains were not normally distributed, but means and SD are included for comparison with the literature (previous workers seem to have assumed that NEI-VFQ data are normally distributed).

Research population vs CLEK study population

Figure 5.40 exhibits the the NEI-VFQ means and StdDev of the current study in both the experimental lenses and the CLEK study (Kymes *et al.*, 2004)

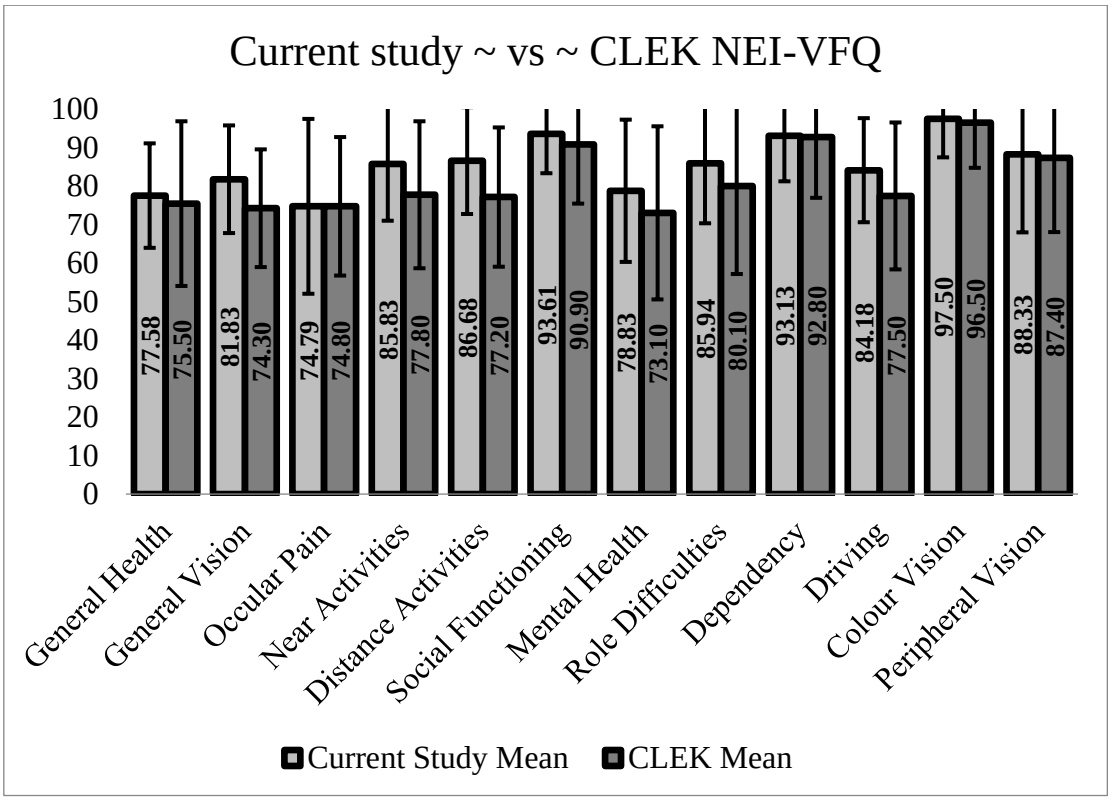


Figure 5.40a *NEI-VFQ means and StdDev; current study vs CLEK*

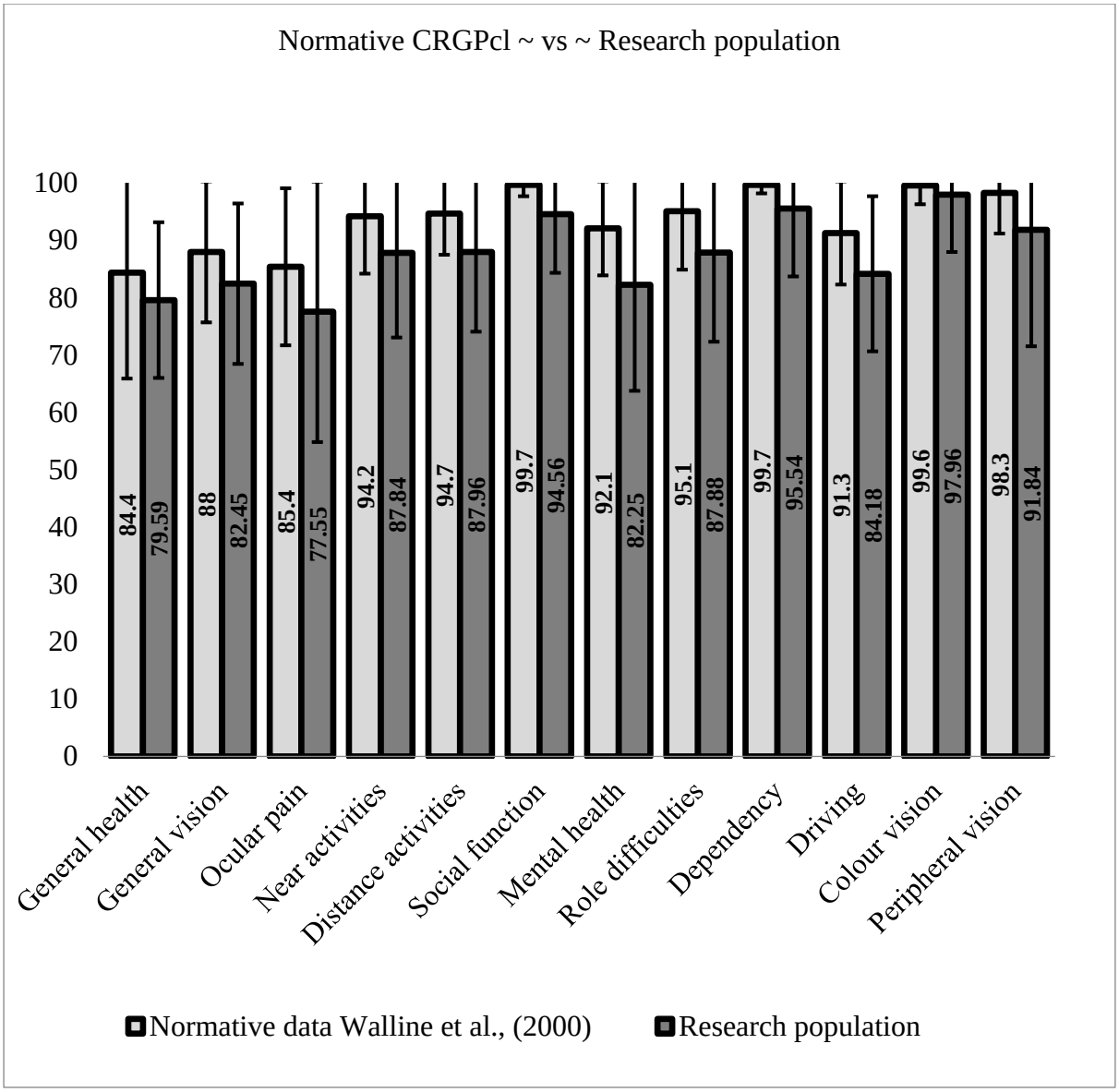
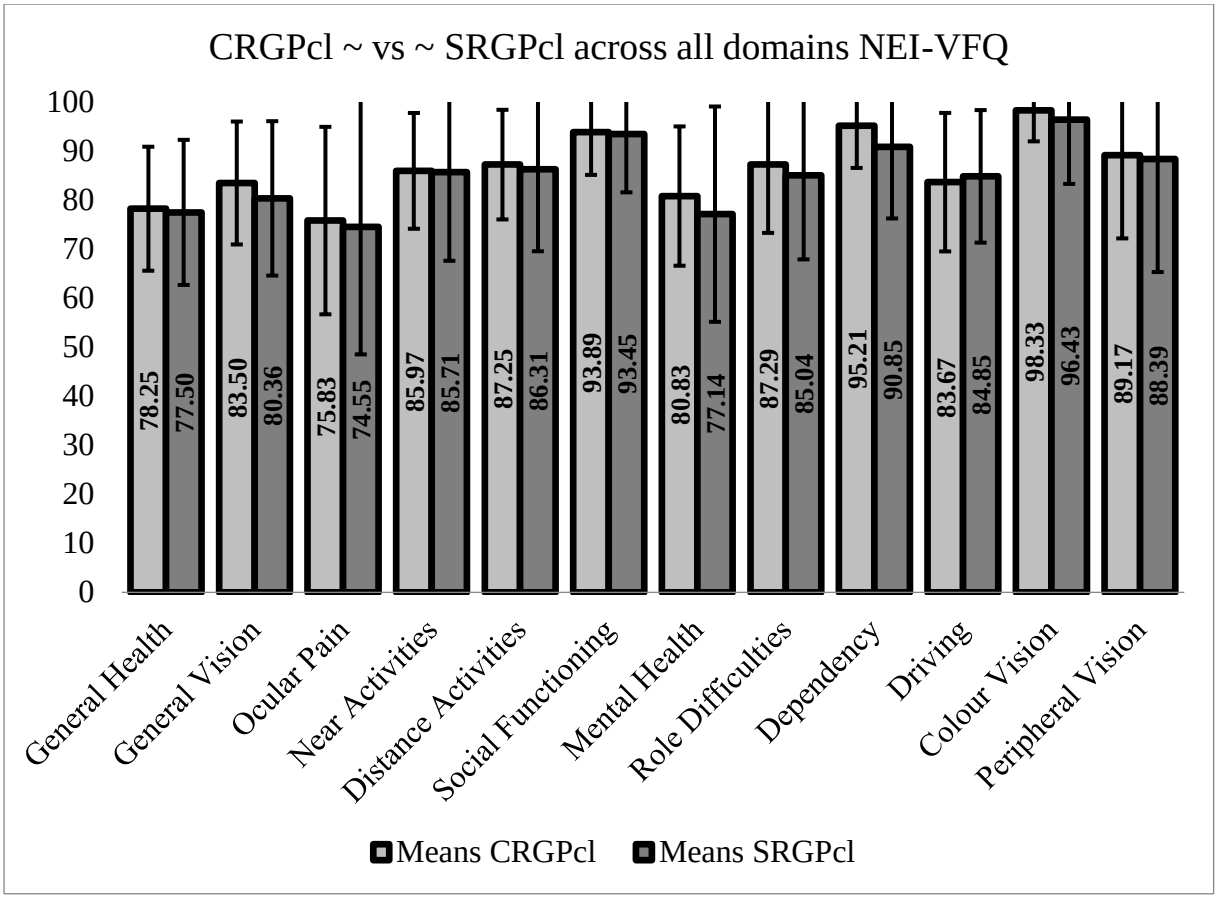


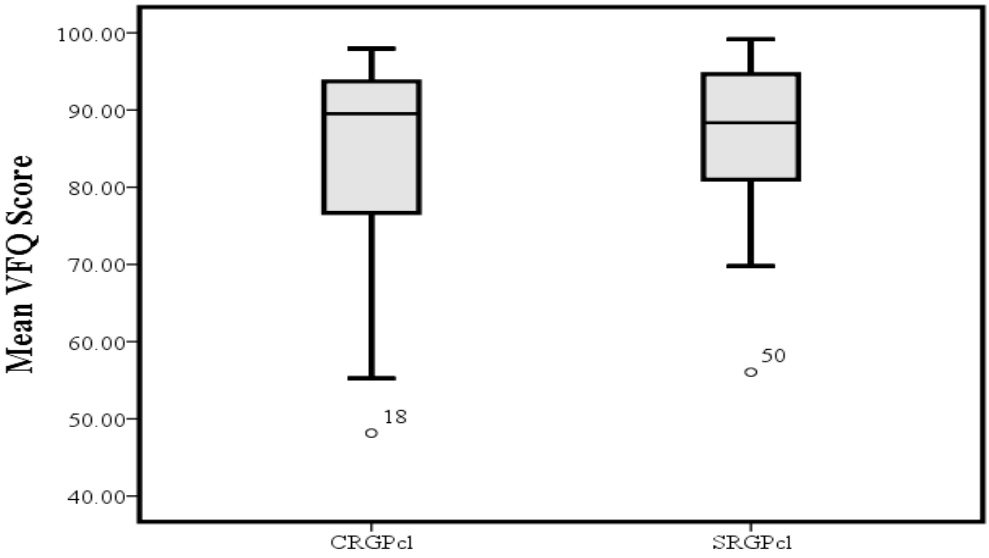
Figure 5.40b *NEI-VFQ current study vsNormative CRGPcl wearers* Walline *et al.,* (2000) *(Kymes et al., 2004)*

CRGPcl vs SRGPcl

The means and standard deviations of the mean scores of the NEI-VFQ 12 domains for CRGPcl vs SRGPcl for the whole research population are shown in Figure 5.41a. The NEI-VFQ scores were not normally distributed, Shapiro-Wilk (*p=<0.0001*) and (*p=0.014*) for CRGPcl and SRGPcl respectively, the medians and IQRs of all 12 domains in CRGPcl and SRGPcl were [*Median=89.53, IQR=17.38*], [*Median=88.35, IQR=14.04*] respectively (Figure 5.41b).



a.



b.

Figure 5.41. a *NEI-VFQ 12 domains means and StdDev, CRGPcl vs SRGPcl.* ***b****. Boxplots CRGPcl vs SRGPcl.*

NEI-VFQ group 1 vs group 2

The means and standard deviations of the scores of the NEI-VFQ 12 domains of group 1 vs group 2 are exhibited in Figure 5.42.

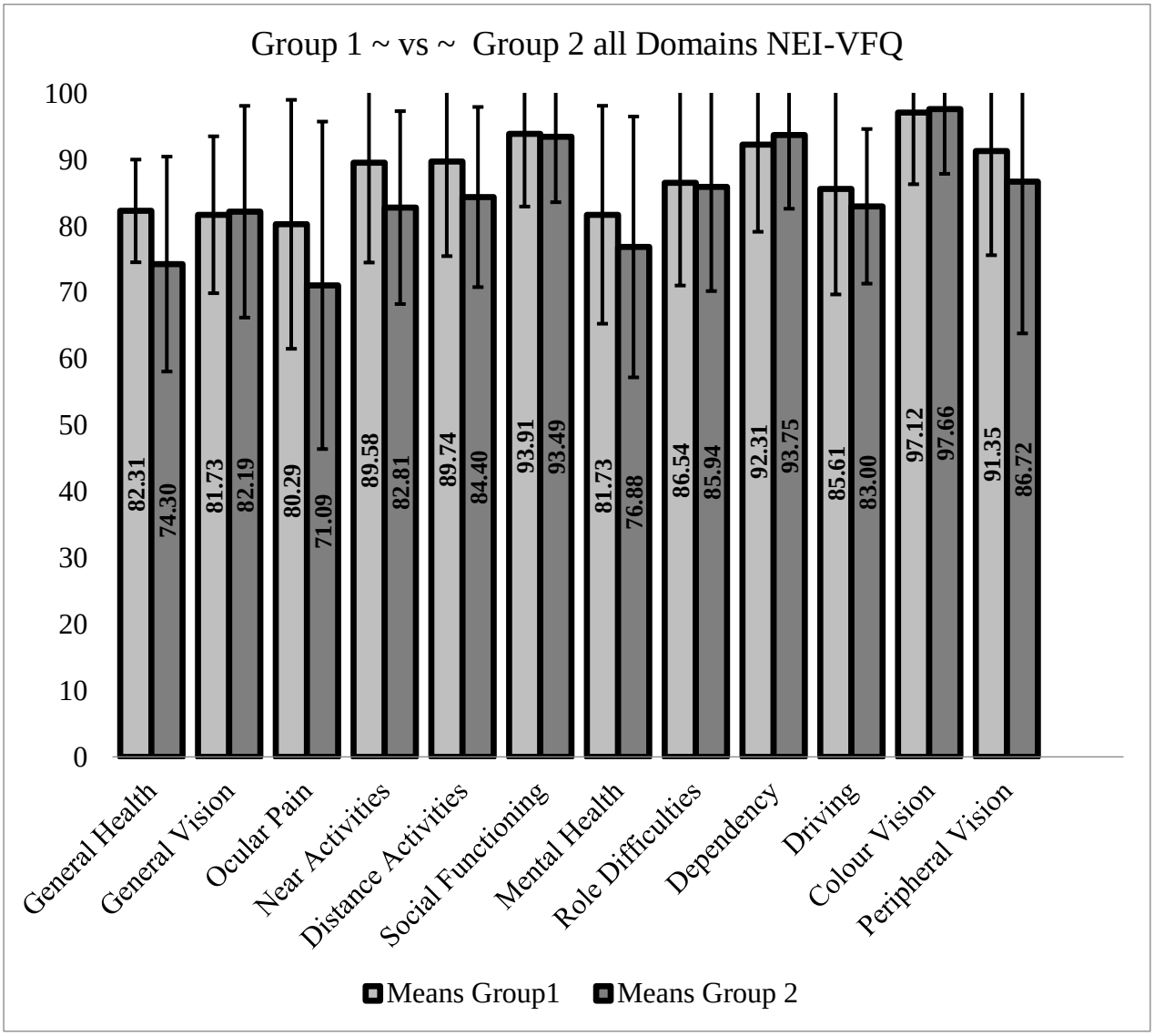


Figure 5.42. *NEI-VFQ 12 domains group 1 vs group 2 with means and standard deviations*

Carryover and treatment effects

The mean scores of the 12 domains of NEI-VFQ of groups 1 and 2 in periods 1 and 2, as well as the period sums and differences for the purpose of calculation of period and treatment effects are exhibited in Table 5.35 (Appendix V B).

The comparison of the period sums between group 1 (*Median=182.0, IQR=20.23*) and group 2 (*Median= 178.1, IQR=32.97*) by *Mann-Witney U* test, indicated that there was no statistically significant difference between the two groups; U=82.0, (*p=0.245*) [*z=-1.193*] (Table 5.36a, b).

Table 5.36 *Statistics of Sum of periods, carryover effect.*

Sum P1P2			
Group	N	Mean Rank	Sum of Ranks
Group 1 (AB)	13	17.69	230
Group 2 (BA)	17	13.82	235
Total	30		

a.

Test Statistics	Sum P1P2
Mann-Whitney U	82
Wilcoxon W	235
Z	-1.193
Exact Sig. [2(1-tailed Sig.)	0.245

b.

This indicates that there was no evidence for a carryover effect with respect to visual quality of life levels measured by the NEI-VFQ.

To calculate the period effect as recommended by Wellek and Blettner (2012) and Jones and Kenward (2015), the crossover period differences [Crossover Δ (A-B), Tables 5.35] of the NEI-VFQ scores were compared between the two randomised groups. The crossover period differences were normally distributed, *Shapiro-Wilk* (*p=0.442*) and (*p=0.082*) group 1 and 2 respectively. An independent samples *t-test* means comparison of the period crossover

differences between group 1 [*Mean=-0.9231*, (±*1.37*)] and 2 [*Mean=-1.2353*, (±*1.98*)] revealed no significant difference between the two groups, *t (0.965), df 28, (p=0.343),* 95% CI (-3.965 - 11.025), *d=0.35*. This finding indicated that there was no significant period effect in the NEI-VFQ scores in this research

The treatment effect was calculated by analysing the period differences in the means of all NEI-VFQ domains in the randomised groups by the *Mann-Whitney U* test, as recommended by (Wellek and Blettner, 2012; Jones and Kenward, 2015). This analysis showed that there was no significant difference in the period differences between group 1 (*Median=1.67, IQR=10.53*) and group 2 (*Median=-1.74, IQR=9.23*), *U=93.0*, (*p=0.483*) [*z=-0.732*] (Table 5.37 a and b). This result therefore supports the H_0, despite slightly higher Qol scores in SRGPcl, there was no statistically significant difference between the experimental contact lenses with respect to their effect on the total (across all domains) visual Qol, measured by the NEI-VFQ instrument.

Table 5.37 *Statistics of period differences; treatment effect.*

Difference P2P1			
Group	N	Mean Rank	Sum of Ranks
Group 1 (AB)	13	16.85	219
Group 2 (BA)	17	14.47	246
Total	30		

a.

Test Statistics	Difference P2P1
Mann-Whitney U	93
Wilcoxon W	246
Z	-0.732
Exact Sig. [2 (1-tailed Sig.)]	0.483

b.

Subjective measures of comfort and vision

The subjective measures of comfort and vision with the two experimental lenses were elicited after each period of lens wear and graded on LSCS and the LSVS. These are Likert-like scales from 1-10, with 1 constituting the worst and 10 the best SPC and SPV scores.

The LSVS in the experimental lenses were not normally distributed, both CRGPcl, *Shapiro-Wilk* (*p=0.024*), [*Median=8.0, IQR=2.0)*] and in SRGPcl, (*p=0.007*), [*Median=8.0, IQR=2.0*]. The LSCS were normally distributed in CRGPcl, *Shapiro-Wilk* (*p=0.091*), [*Mean=7.78, (±1.45)*] and not normally distributed in SRGPcl, (*p=0.001*), [*Median=9.0, IQR=2.0, Mean=8.88, (±1.10)*].

The total LSCS and LSVS were not normally distributed in both periods. The LSCS in periods 1 and 2 respectively were [*Median=9.0, IQR=1.13*] (*p=0.016*) and [*Median=8.5, IQR=3.00*] (*p=0.009*). LSVS in periods 1 and 2 respectively were [*Median=8.0, IQR=2.00*] (*p=0.007*) and [*Median=8.0, IQR=2.00*] (*p<0.0001*).

The LSCS for each participant in periods 1 and 2 are exhibited in Figures 5.43 and 5.44 for groups 1 and 2 respectively and the LSVS in each participant are exhibited in Figures 5.45 and 5.46 for groups 1 and 2 respectively (Appendix V C).

The scatter plots below exhibit the individual scores for SPC and SPV in periods 1 and 2 in each group (Figure 5.47a and 5.48). The LSCS period by group comparisons in Figures 5.47a exhibit higher scores in group 1, period 2 (SRGPcl) and group 2, period 1 (SRGPcl). Figure 5.47b exhibits the LSCS of both groups on a single graph, with group1 concentration above the diagonal and group 2 below, indicating better results for SRGPcl, with centroids on opposite side of the diagonal, indicating the possibility of treatment effect. Figure 5.47c exhibits the individual participants LSCS profiles in both groups, with larger inter-subject variation in group 2 and noticeable difference in the slope directions in both groups, indicating higher LSCS in SRGPcl, more noticeable in group 2.

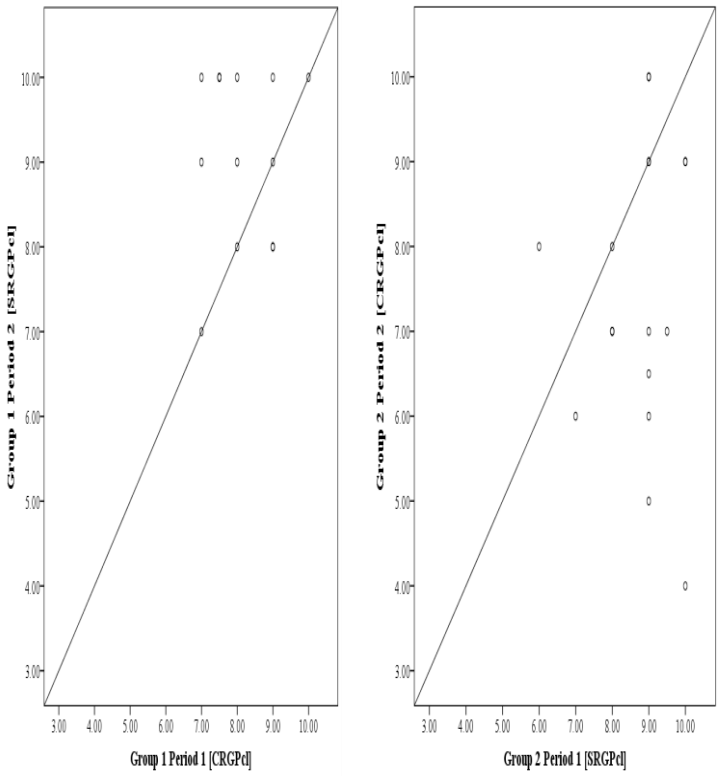


Figure 5.47a *Individual LSCS in periods 1 and 2 in groups 1 and 2*

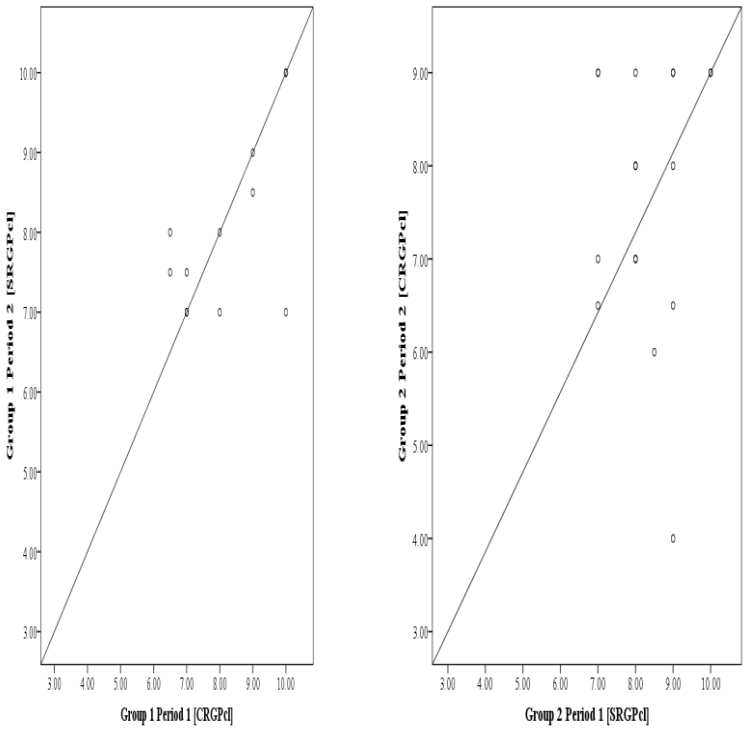


Figure 5.48 *Individual LSVS in periods 1 and 2 in groups 1 and 2*

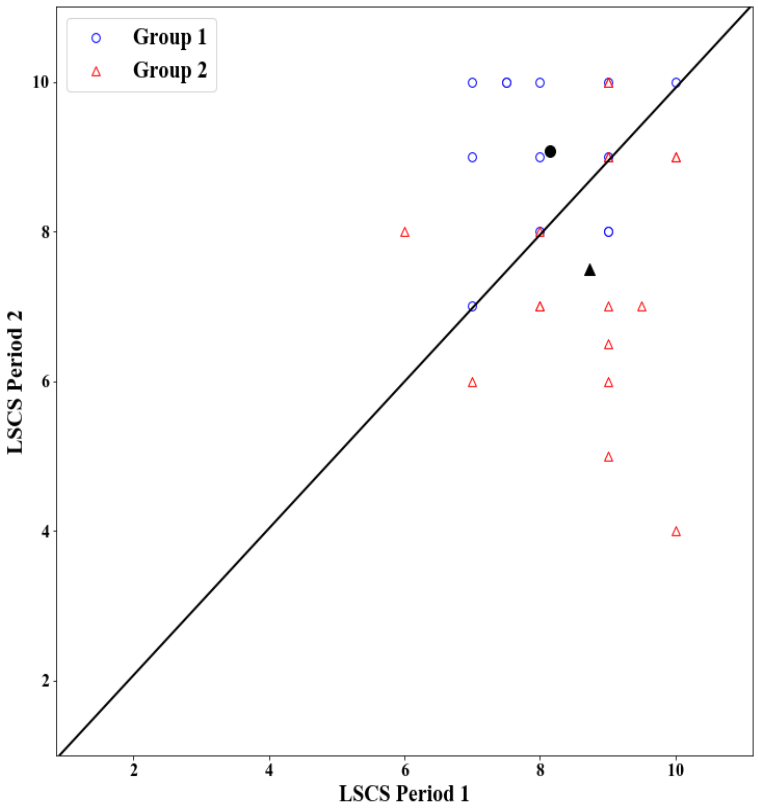


Figure 5.47b. *LSCS both groups with centroids*

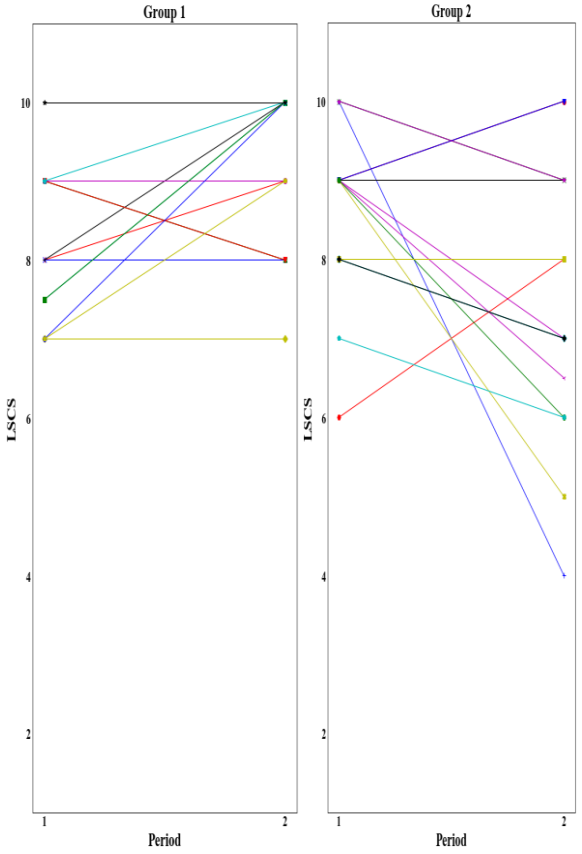


Figure 5.47c. *LSCS individual profiles groups 1 and 2*

To calculate the likelihood of a period carryover effect and the treatment effect, the scores for the SPC and SPV as well as the sums of periods and period differences of these scores for each participant were calculated and are exhibited in Tables 5.38 and 5.39.

Table 5.38 *LSCS by period and sums and differences of periods in both groups*

Comfort Quality												
Group 1							Group 2					
SN	P1	P2	P1+P2	P2-P1	A-B		SN	P1	P2	P1+P2	P2-P1	A-B
1.0	8.0	9.0	17.0	1.0	-1.0		3.0	9.0	7.0	16.0	-2.0	-2.0
2.0	8.0	8.0	16.0	0.0	0.0		4.0	6.0	8.0	14.0	2.0	2.0
5.0	9.0	8.0	17.0	-1.0	1.0		6.0	10.0	4.0	14.0	-6.0	-6.0
7.0	7.0	7.0	14.0	0.0	0.0		8.0	10.0	9.0	19.0	-1.0	-1.0
10.0	7.5	10.0	17.5	2.5	-2.5		9.0	9.0	5.0	14.0	-4.0	-4.0
11.0	8.0	10.0	18.0	2.0	-2.0		12.0	8.0	7.0	15.0	-1.0	-1.0
13.0	9.0	9.0	18.0	0.0	0.0		15.0	9.0	9.0	18.0	0.0	0.0
14.0	9.0	8.0	17.0	-1.0	1.0		16.0	9.0	6.5	15.5	-2.5	-2.5
20.0	7.0	10.0	17.0	3.0	-3.0		17.0	9.0	10.0	19.0	1.0	1.0
23.0	7.5	10.0	17.5	2.5	-2.5		19.0	9.0	10.0	19.0	1.0	1.0
28.0	7.0	9.0	16.0	2.0	-2.0		21.0	9.0	6.0	15.0	-3.0	-3.0
31.0	9.0	10.0	19.0	1.0	-1.0		24.0	8.0	8.0	16.0	0.0	0.0
33.0	10.0	10.0	20.0	0.0	0.0		26.0	7.0	6.0	13.0	-1.0	-1.0
							27.0	8.0	7.0	15.0	-1.0	-1.0
							30.0	10.0	9.0	19.0	-1.0	-1.0
							32.0	9.5	7.0	16.5	-2.5	-2.5
							34.0	9.0	9.0	18.0	0.0	0.0

Table 5.39 *LSVS by period and sums and differences of periods in both groups.*

Vision Quality												
Group 1							Group 2					
SN	P1	P2	P1+P2	P2-P1	A-B		SN	P1	P2	P1+P2	P2-P1	A-B
1.0	10.0	7.0	17.0	-3.0	3.0		3.0	8.0	-8.0	0.0	-16.0	-16.0
2.0	8.0	8.0	16.0	0.0	0.0		4.0	7.0	7.0	14.0	0.0	0.0
5.0	8.0	7.0	15.0	-1.0	1.0		6.0	7.0	9.0	16.0	2.0	2.0
7.0	7.0	7.5	14.5	0.5	-0.5		8.0	9.0	9.0	18.0	0.0	0.0
10.0	9.0	9.0	18.0	0.0	0.0		9.0	8.5	6.0	14.5	-2.5	-2.5
11.0	6.5	8.0	14.5	1.5	-1.5		12.0	8.0	7.0	15.0	-1.0	-1.0
13.0	10.0	10.0	20.0	0.0	0.0		15.0	9.0	4.0	13.0	-5.0	-5.0
14.0	7.0	7.0	14.0	0.0	0.0		16.0	9.0	6.5	15.5	-2.5	-2.5
20.0	10.0	10.0	20.0	0.0	0.0		17.0	9.0	9.0	18.0	0.0	0.0

23.0	7.0	7.0	14.0	0.0	0.0		19.0	8.0	9.0	17.0	1.0	1.0
28.0	10.0	10.0	20.0	0.0	0.0		21.0	10.0	9.0	19.0	-1.0	-1.0
31.0	9.0	8.5	17.5	-0.5	0.5		24.0	7.0	9.0	16.0	2.0	2.0
33.0	6.5	7.5	14.0	1.0	-1.0		26.0	8.0	8.0	16.0	0.0	0.0
							27.0	8.0	8.0	16.0	0.0	0.0
							30.0	10.0	9.0	19.0	-1.0	-1.0
							32.0	9.0	8.0	17.0	-1.0	-1.0
							34.0	7.0	6.5	13.5	-0.5	-0.5

Subjective perception of comfort and vision carryover and period effects

The analyses to establish the presence of period and differential carryover effects were performed as recommended by Wellek and Blettner (2012) and Jones and Kenward (2015), by the comparison of the LSCS period sums between group 1 (*Median=17.0, IQR=1.50*) and group 2 (*Median=16.0, IQR=4*). A *Mann-Witney U* test indicated that with respect to SPC there was no statistically significant difference between the two groups; *U=78.5*, (*p=0.183*) [*z=-1.349*].

With respect to LSVS the comparison of the period sums between group 1 (*Median=16.0, IQR=4.75*) and group 2 (*Median=16.0, IQR=3.25*) by *Mann-Witney U* test, indicated that with respect to SPV there was no statistically significant difference between the two groups; *U=97.0*, (*p=0.592*) [*z=-0.568*].

This indicates that there is no evidence for the presence of a differential carryover effect with respect to the scores of these outcomes.

To calculate the period effect as recommended by Wellek and Blettner (2012) and Jones and Kenward (2015), the crossover period differences [Crossover Δ (A-B), Tables 5.38, 5.39] of the subjective comfort and vision scores were compared between the two randomised groups. The crossover period differences of the LSCS were normally distributed, *Shapiro-Wilk* (*p=0.204*) and (*p=0.526*) group 1 and 2 respectively. An independent samples *t-test* means comparison of the period crossover differences between group 1 [*Mean=-0.9231*, (*±1.37*)] and

2 [*Mean=-1.2353*, (±*1.98*)] revealed no significant difference between the two groups, *t (0.486), df 28, (p=0.630)*, 95% CI (-1.003 - 1.627), *d=0.18*. This finding indicated that there was no significant period effect in the LSCS in this research.

The crossover period differences of the vision scores were not-normally distributed, *Shapiro-Wilk* (*p=0.009*) and (*p=0.000*) group 1 and 2 respectively. A *Man-Whitney U* test comparison of the period crossover differences in subjective vision scores between group 1 [*Median=0.00, IQR=0.50*] and 2 [*Median=-0.50, IQR=1.75*)] revealed no significant difference between the two groups, *U=76.500,* (*p=0.157*). This finding indicated that there was no significant period effect in the SPV scores in this research.

Subjective comfort and vision treatment effect

The comparison of the two groups with respect to the treatment effect was performed as recommended by (Wellek and Blettner, 2012; Jones and Kenward, 2015) by the analysis of the difference in the period scores of the two randomised groups. This was performed by the *Mann-Whitney U* test, which revealed that with respect to subjective comfort, the period difference in group 1 (*Median=1.0, IQR=2.25*) and the period difference in group 2 (*Median=-1.0, IQR=2.50*), were significantly different, (*p=0.002*) [*z=-2.993*], *U=40.0*. This result rejects the H_0 and indicates that the higher subjective comfort score achieved with SRGPcl was statistically significant (Figure 5.49a).

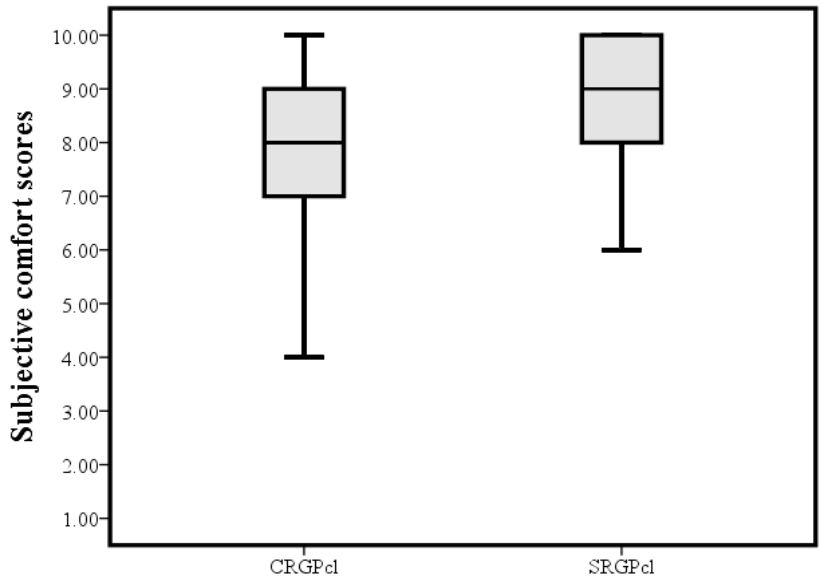


Figure 5.49a. *Boxplots of subjective comfort scores in CRGPcl and SRGPcl*

With respect to the subjective vision score, the comparison of the score differences in the two periods in group 1 (*Median=0.0, IQR=0.50*) and group 2 (*Median=-0.5, IQR=1.75*), by *Mann-Whitney U* test indicates that there was no significant difference, (*p=0.213*) [*z=-1.301*], *U=80.50*. This result therefore supports the H_0 with respect to the subjective perception of the participant's quality of vision (Figure 5.49b).

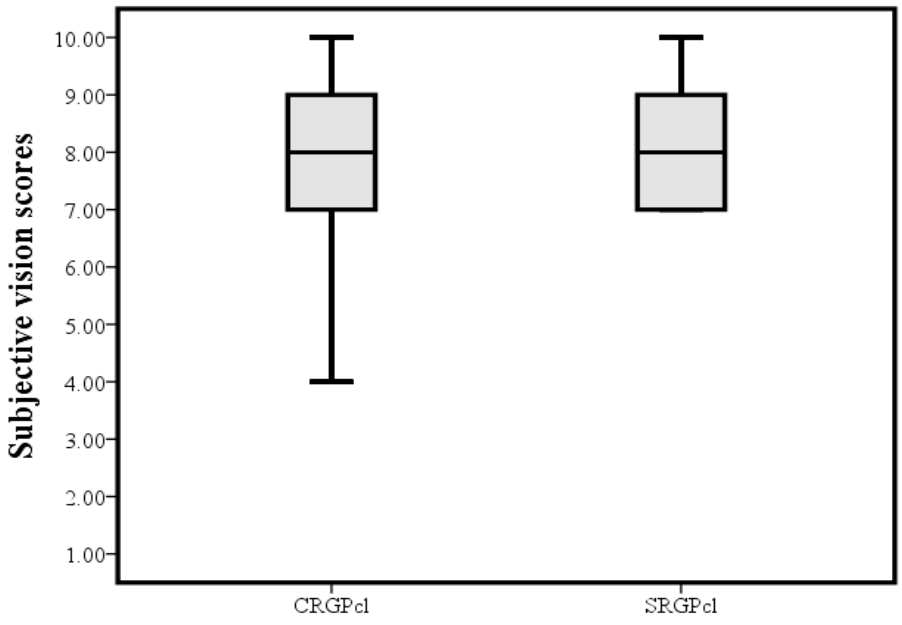


Figure 5.49b. *Boxplots of subjective vision scores in CRGPcl and SRGPcl*

NEI-VFQ ocular pain domain

Due to the statistically significant difference between the two experimental lenses in the SPC, an analysis of the period and treatment effects of the NEI-VFQ *ocular pain* domain was performed. The only normally distributed scores in this domain were of group 1 period 1; *Shapiro-Wilk* (*p=0.095*), the rest of the scores were not normally distributed; (*p=0.019, 0.005* and *0.034*) in Group 1 period 2, group 2 period 1 and period 2 respectively.

The analyses of the two groups with respect to period carryover and treatment effects were performed as recommended by (Wellek and Blettner, 2012; Jones and Kenward, 2015). The *Mann-Whitney U* analysis of the period sums of group 1 (*Median=175.0, IQR=56.25*) and group 2 (*Median=150.0, IQR=75.0*) indicated that here was no differential carryover effect (*p=0.263*), [*z=-1.141*] *U=83.50*. The crossover differences were normally distributed in group 2 (*p=0.015*) and not normally in group 1 (*p=0.467*). The *Mann-Whitney U* analysis of the crossover differences of group 1 (*Median=0.02, IQR=0.21*) and group 2 (*Median=0.04, IQR=0.16*) indicated that there was no significant period effect (*p=0.563*).

The treatment effect analysis by *Mann-Whitney U* test of the period differences of group 1 (*Median=12.5, IQR=37.5*) and group 2 (*Median=0.00, IQR=25.0*), indicated that the better *ocular pain* scores with SRGPcl in group 1, did not reach statistical significance (*p=0.170*) [*z=-1.423*], *U=77.00*, which supports the $H_{0.}$

Final lens choice

At the end of the second experimental sequence participants were asked to choose either CRGPcl or SRGPcl as their habitual contact lens. Fourteen (46.7%) participants chose SRGPcl and 16 (53.3%) chose CRGPcl as their preferred habitual lens.

The only statistically significant outcome in this experiment was the better SPC in SRGPcl compared to CRGPcl, which was supported by the better scores in the *ocular pain* domain of the NEI-VFQ (statistical significance not reached). Therefore, it was decided to determine

whether there is a significant correlation between the scores of SPC in the experimental lenses and final lens choice.

The participants' SPC and SPV in the experimental CRGPcl and the final lens choice are presented in table 5.40 (Appendix V D).

The LSCS approximated a normal distribution *Shapiro-Wilk* (*p=0.091*), with a mean of 7.78 (±1.45), range of 6.0 [4.0 – 10], 95 CI for mean 7.24–8.33 (Figure 5.51).

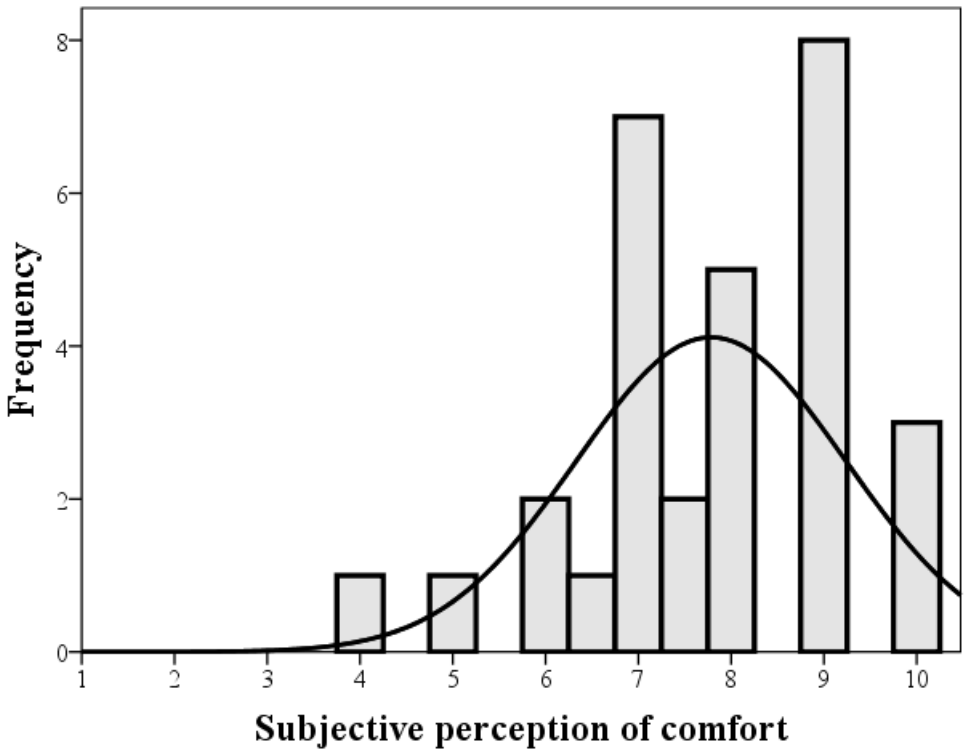


Figure 5.51. *Distribution of the scores of SPC in experimental CRGPcl*

The LSCS in CRGPcl means / *medians* and SD / *IQR* for the participants who selected CRGPcl and SRGPcl were 8.44 (±1.03) / *9.00 (1.75)* and 7.04 (±1.54) / *7.00 (1.54)* respectively, with non-normal distribution of the scores of CRGPcl selectors and normal distribution of scores of SRGPcl selectors, *Shapiro-Wilk* (*p=0.019*) and (*p=0.980*) respectively. A means comparison between the subjective comfort scores (Table 5.41) of those participants who selected CRGPcl

and SRGPcl as their habitual lenses, was performed by the independent samples *t-test*, due to the non-significant variance between the scores [Levene's test for equality (*p=0.426*)].

Due to the not-normal distribution of the SPC scores of the 16 participants who selected CRGPcl an additional analysis was performed by the non-parametric *Mann-Whitney U* test, to confirm agreement between the parametric and non-parametric analyses regarding this important outcome (Figure 5.52).

Table 5.41 *Mean, median, StdDev and IQR scores of subjective comfort for final lens choice*

Final Lens choice	CRGPcl	SRGPcl
Comfort in CRGPcl mean and (StdDev)	8.44 (±1.03)	7.04 (±1.54)
Comfort in CRGPcl median and (IQR)	9.00 (1.75)	7.00 (2.00)

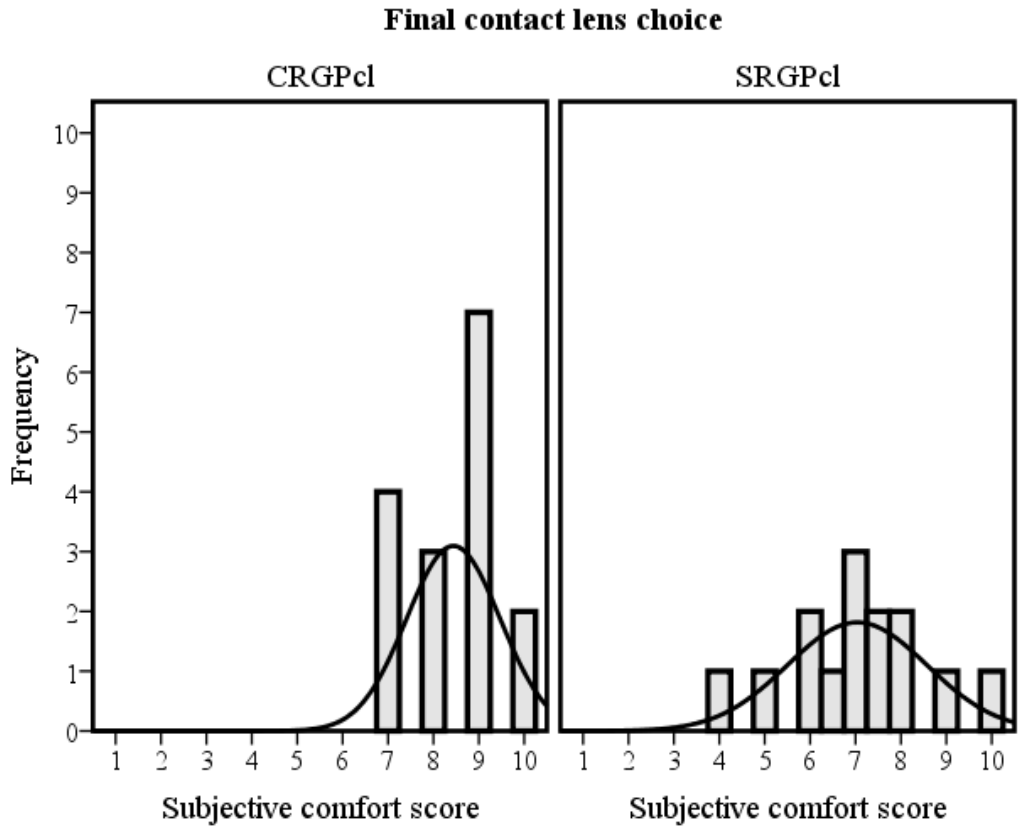


Figure 5.52 *Subjective comfort scores in CRGPcl in participants who chose CRGPcl and SRGPcl*

Both these analyses showed a significant difference in the CRGPcl SPC scores between the participants who chose CRGPcl and those who chose SRGPcl; *t=2.967, (df=28),* (*p=0.006*), *d=1.086,* 95% CI [0.434-2.37]. *Mann-Whitney U* test: (*p=0.009*), *(z=-2.605), U=50.5, Wilcoxon W=155.5.*

The expected better LSCS in SRGPcl in participants who chose SRGPcl [*Median=9.750, IQR=1.3*] compared to participants who chose CRGPcl [*Median=9.00, IQR=1.0*], did not reach statistical significance regarding the LSCS difference *(p=0.052).*

These results indicate that the subjective score of perceived comfort in the experimental CRGPcl was significantly lower in the participants who selected SRGPcl [*Mean=7.04, (±1.54)*] than those who selected CRGPcl [*Mean=8.44, (±1.03)*], (*p=0.006*) and (*p=0.009*) by independent samples *t-test* and *Mann-Whitney U* test respectively, thus rejecting the H_0. It is of note that no participant who selected to remain in CRGPcl scored their SPC lower than 7.0.

Despite the absence of statistically significant carryover effect in the subjective comfort, it was decided to explore whether the sequence of contact lens wear had an effect on the subjective comfort in CRGPcl. Such an effect could for example occur in group 2, after wearing the first sequence SRGPcl. It is possible that some loss of tolerance to CRGPcl could occur, which may have contributed to the lower score in the washout period and sequence 2, when the habitual and experimental CRGPcl were worn.

Group 1 [*Mean=8.15, (±0.97)*] and group 2 [*Mean=7.5, (±1.71)*] were normally distributed with respect to subjective comfort scores in the experimental CRGPcl, *Shapiro-Wilk* (*p=0.139*) and (*p=0.481*) respectively. An independent samples *t-test* comparison of means exhibited no statistically significant difference in the subjective score of comfort of the two groups: *t=1.322,* (*df= 26*), (*p=0.198*), *d= 0.454,* 95% CI [*-0.363 – 1.670*]. This result indicates that the sequence of wear did not have a significant effect on the subjective score of comfort reported by the participants in two randomised groups.

A χ^2 analysis was performed to also establish whether the sequence of lens wear had any effect on the final lens choice for the same reason as stipulated regarding the subjective comfort scores. The results of this analysis (Table 5.42) indicate that there was no significant difference between the participants in the 2 groups in their choice of preferred habitual lens $\chi^2=0.475$, (n=30), (*p=0.713*).

Table 5.42 *χ2 analysis of final lens choice by randomised groups*

Final lens choice					
Group		CRGPcl	SRGPcl		Total
Group 1 (AB)	Count of participants	6	7		13
	% within group	46.20%	53.80%		100.00%
	% within final lens choice	37.50%	50.00%		43.30%
Group 2 (BA)	Count of participants	10	7		17
	% within group	58.80%	41.20%		100.00%
	% within final lens choice	62.50%	50.00%		56.70%
Total	Count	16	14		30
	% within group	53.30%	46.70%		100.00%
	% within final lens choice	100.00%	100.00%		100.00%

Chapter 6: Discussion

In this RCT with a 2x2 crossover, 34 participants entered the study and 17 participants were randomised to each of the 2 experimental groups. The participants randomised to group 1 (sequence AB), started with CRGPcl (lens A) in period 1 and after completing period 1 and a 1-month washout period, crossed over to wear SRGPcl (lens B) in period 2 (Figure 4.1). Participants in group 2 (sequence BA), started with SRGPcl (lens B) in period 1 and after completing period 1 and a 1-month washout period, crossed over to wear CRGPcl in period 2 (lens A). All 17 participants in group 2 completed their participation, whereas in group 1, thirteen participants completed the study (see limitations) (Figure 5.1). Data collected from 56 eyes of the 30 participants who completed this research were analysed, with right and left eye data averaged for participants who wore lenses in both eyes. The inclusion of 4 participants who were fitted in one eye only, was considered appropriate representation of the population in the clinic, as keratoconus is a bilateral disease (Gomes *et al.*, 2015) and patients may present for contact lens management with significant asymmetry between the two eyes (Zadnik *et al.*, 2002).

Descriptive statistics of the study population

Gender

Epidemiological studies regarding keratoconus gender preponderance are inconclusive, with reported female dominance of 53% (Jonas *et al.*, 2009), 65% (Amsler, 1961) and 66% (Hammerstein, 1972) and reported male dominance of 62% (Ertan and Muftuoglu, 2008), 53% (Fatima *et al.*, 2010), 57% (Pouliquen *et al.*, 1981) and 59% (Owens and Gamble, 2003). Others have demonstrated no significant gender differences (Kennedy *et al.*, 1986).

The overall consensus appears to be that keratoconus has similar prevalence in both genders (Ramez *et al.*, 2017).

The progression of keratoconus in the CLEK study was found to be equivalent in both genders; however, gender differences were found in patient history, vision and ocular symptoms (Fink *et al.*, 2010). Women were older, more likely to report symptoms of dryness, reported less hours per day of contact lens wear and more hours of near work and scored significantly lower with respect to driving ($p<0.0001$), distance activities ($p=0.0001$) and general health ($p=0.003$) domains of the NEI-VFQ (Fink *et al.*, 2010).

The male population in this research, n=23 (77%) outnumbered the female population n=7 (23%), 3:1. This ratio is different to the expected 1:1 gender ratio of individuals affected by keratoconus (Feder and Gan, 2011; Ramez *et al.*, 2017). The reason for this discrepancy is unclear.

Gender ages

The 10-year age difference between the genders, male (*Median=34.0*) and female (*Median=45*) (Table 5.2, Figure 5.3) was significant: *Mann-Whitney U* ($p=0.010$), with older females, as found by (Fink *et al.*, 2010).

The gender numbers and age imbalance in this research may be important, because female gender, estrogen therapy in postmenopausal women, androgen deficiency and older age are all risk factors in dry eye disease (DED) (Stapleton *et al.*, 2015). Dry eye symptoms, especially in DED have a detrimental effect on contact lens tolerance, and SRGPcl may be indicated to alleviate these symptoms and increase contact lens tolerance in patients with keratoconus (Visser *et al.*, 2016). This could bias the female participants to choose SRGPcl over CRGPcl due to improved comfort, which may increase the scores of the SPC and the scores of the NEI-VFQ. This potential bias however, may have been minimised in this study by the relatively small number of female participants and by the fact that at the time of enrolment all participants were successful CRGPcl wearers and were therefore unlikely to suffer significantly from DED. The crossover study design is another important aspect which minimises bias due to inter-subject variability, as each participant acts as his or her own control.

Age and age at diagnosis (AAD)

Keratoconus is a disease with a typical onset at adolescence and young adulthood (Feder and Gan, 2011), with some delay between onset and time of diagnosis and management with RGPcl. Keratoconus is typically diagnosed between the ages of 20 and 30 years (Galvis *et al.*, 2015) and rarely after age 35 (Krachmer *et al.*, 1984). The age of the research population [*Median=36.0, IQR=16.0, Mean=39.1 (±11.5)*] was not normally distributed (*p=0.039*), due to skewness towards younger age [*0.8 (SE 0.4)*] normally found in individuals with keratoconus (Feder and Gan, 2011; Ramez *et al.*, 2017).

It has been hypothesised that the surprisingly low numbers of patients diagnosed with keratoconus over the age of 50 years, given the chronic nature of this disorder (Gordon-Shaag *et al.*, 2015), may be due to association of keratoconus with such conditions as mitral valve prolapse (Beardsley and Foulks, 1982), obesity, obstructive sleep apnoea (Pihlblad and Schaefer, 2013) and Down syndrome, although the mortality rate in individuals with keratoconus is similar to that of the general population (Moodaley *et al.*, 1994). The reason for this is therefore unclear, but could in my opinion be because significant keratoconus is diagnosed early in life and if keratoconus remains insignificant, it is unlikely to progress and therefore unlikely to be diagnosed later in life.

The non-normal distribution of the AAD of the research population (Figure 5.4), is most likely due to the significant positive skewness (*1.1, SE 0.4*), with 80% of participants diagnosed before age 30, as expected in a population affected by keratoconus (Krachmer *et al.*, 1984). The female AAD was normally distributed, the male AAD featured positive skewness and kurtosis and had a non-normal distribution (Table 5.4). The research population did not exhibit a statistically significant difference between the genders in the AAD (Figure 5.5), *Mann-Whitney U* (*p=0.190*), which is consistent with the impression that keratoconus exhibits no clear gender preponderance (Alio, 2017; Fink *et al.*, 2010).

Participants' reported duration of CRGPcl wear at enrolment

An essential selection criterion in this study required that all participants were experienced and successful CRGPcl wearers. The length of CRGPcl wear prior to enrolment was not normally distributed, with a total range of 43 years, a minimum of 4 and a maximum of 47 years [*Median=14.5, IQR=12, (mean=16.4, ±10)*]. There was no statistically significant difference between the genders in the duration of CRGPcl wear at enrolment (Figure 5.8); *Mann-Whitney U test:* (*p=0.190*).

The duration of contact lens wear may have implications on the visual acuity scores because in the longitudinal assessment of visual acuity in 925 CLEK subjects over a seven-year period, high-contrast and low-contrast visual acuity decreased by 10 or more letters (logMAR ≥0.2) in 19.0% and 30.8% of subjects, respectively (Davis *et al.*, 2006). The NEI-VFQ scores also reduced over a 7 year follow up in all domains except ocular pain and mental health (Kymes *et al.*, 2008).

Occupation / education

All participants were either employed or in an education programme, with 56% of the participants having university education (Table 5.7).

Ethnicity

Ethnicity may be an important factor in this research since aspects of keratoconus such as disease incidence, may vary from 25 cases per 100,000, per year for Asians compared with 3.3 cases per 100,000, per year for Caucasians ($p < 0.001$) (Georgiou *et al.*, 2004). In the UK

keratoconus incidence in Asians Indians vs white Caucasians is respectively: 19.6 vs 4.5 cases per 100,000 population, per year (Pearson *et al.*, 2000).

Ethnicity also plays a role in the progression and severity of keratoconus; with the Asian Indian ethnicity presenting at a significantly younger age and progressing to more severe levels than the Caucasian white population (Georgiou *et al.*, 2004). The 13 Asian Indian participants constituted 43.3% of all participants and exhibited an earlier mean AAD of 22.5 (±4.5), compared with the 30% (n=9) of white Caucasian participants, whose mean AAD was 25.2 (±9.9), consistent with Georgiou *et al.*, 2004. The 10% (n=3) black Afro Caribbean participants, whose AAD was 22.3 (±4.7), were second only to the black African participants 14.7% (n=5) of the sample, who exhibited the earliest mean AAD of 18.8 (±3.4) and who also featured the oldest mean age of 43.8 (±16.4) years (Tale 5.8, Figures 5.9, 5.10).

The confounding aspects of age, gender and ethnicity were also minimised in this research by participant randomisation and the crossover research design (Wellek and Blettner, 2012; Jones and Kenward, 2015).

Corneal characteristics

As noted in the methods section of this thesis, this research was designed to study corneal ectatic disorders in general, as would typically be encountered in a hospital "keratoconus clinic". It was anticipated that the vast majority of participants would have keratoconus because this is the preeminent ectatic disorder. Other ectatic disorders such as keratoglobus and pellucid marginal degeneration (PMD) are considered variations of keratoconus. In a *pilot for the global consensus on ectasias*, there was a 94% agreement among experts that these are ectatic corneal disorders and 100% agreed that the only aspects that distinguish between keratoconus, PMD and keratoglobus were the thinning location and pattern (Ambrósio *et al.*, 2014).

The purpose of the present research was to study a population which is managed with CRGPcl as a consequence of being affected by corneal ectatic disorders. Analysis revealed that keratoconus was indeed the main corneal ectatic disorder in the study population affecting 93%

(n=54) of the eyes, 2 eyes (1 participant) exhibited PMD. Two eyes had previously undergone deep lamellar keratoplasty (DLK) [*corneal transplant surgery*] due to severe keratoconus. Minor treatments such as collagen crosslinking (CXL) and intra-stromal corneal ring segments (INTACS) were previously applied to 6 eyes and 2 eyes respectively, more than 1 year prior to participation in this research (Figure 5.11). Individuals with keratoconus commonly undergo the various treatments such as CXL to slow down / arrest the disease progression, INTACS to improve the optical integrity and DLK to replace severely distorted corneae (Bao *et al.*, 2017; Kılıç *et al.*, 2017; O'Brart, 2017; del Barrio *et al.*, 2017). These treatments were not expected to materially affect contact lens management of the participants, all of whom were successful CRGPcl wearers. Although INTACS may be indicated to contact lens intolerant individuals, they are not contraindicative to contact lens wear, and have even been reported in previous studies to facilitate contact lens fitting and comfortable wear (Ertan and Colin, 2007; Hladun and Harris, 2004). Contact lens wear post CXL is indicated for the management of the visual disability caused by keratoconus (Michaud and Breton, 2018) and significant regular and irregular astigmatism post keratoplasty may often be best managed with RGPcl (van Dijk *et al.*, 2014).

Research Population Corneal Metrics

Pathological corneal irregularity was an inclusion criterion in this research. Objective measures of corneal topography indices confirmed that the research population exhibited pathological levels of corneal irregularity. The three indices measured are now discussed in turn.

K_{max}

K_{max} represents the maximum (steepest) corneal radius of curvature, which in keratoconus would normally exhibit values below 7.03mm (above 48D), significantly steeper [*shorter*

radius of curvature in mm and larger magnitude in dioptres] than the value of 7.85mm (±0.31) expected in a normal cornea (Sorbara *et al.*, 2010).

Sorbara *et al*., (2010) analysed the corneae of 40 normal eyes and found corneal curvature to be normally distributed with a mean radius of 7.85mm (±0.31), 95% CI: 8.70-7.24 mm (Sorbara *et al.*, 2010). Corneal radius values between 7.03mm (48D) and 6.75mm (50D) are considered suspect for keratoconus, and values below 6.75mm denote abnormally steep corneal curvature (Cavas-Martinez *et al.*, 2016; Pinero *et al.*, 2010). The analysis of K_{max} in the research population exhibited a normal distribution (*p=0.882*), [*Mean=6.20mm (±0.6)*] (Table 5.9, Figure 5.12), which is more than 3 standard deviations steeper than the steepest value of the 95% CI of normal corneae found in Sorbara *et al.*, (2010). Means comparison by an independent sample *t-test* with the normative data presented in Sorbara *et al.*, (2010) confirmed that the research population exhibited a statistically significantly steeper radius of curvature than normal corneae (*p<0.0001*), with a mean difference of 1.62mm, *95% CI 1.43–1.80mm*.

Pachymetry

Corneal ectasiae, such as keratoconus are by definition associated with corneal thinning. Pinero *et al.*, (2010) evaluated 51 eyes with various degrees of keratoconus and 20 normal eyes, of 29 male and 22 female patients, aged 16-54. Pachymetry readings were progressively lower in eyes with subclinical, early, or moderate keratoconus compared with the normal mean value of 549.90µm (±28.48) (*p<0.01*) (Pinero *et al.*, 2010). In the moderate to advanced keratoconus they found a mean pachymetry value of 457.61µm (±38.77).

The central corneal thickness in the research population (Table 5.10, Figure 5.13) was normally distributed, (*p=0.569*) and an independent samples *t-test* comparison with the mean pachymetric values reported in Pinero *et al*., (2010), confirmed that this research population exhibited significantly thinner values than both the normal; *Mean=544.74, ±42.42),* (*p<0.0001*) and the moderate and advanced keratoconus groups; *Mean=475.19, ±48.4* (*p=0.020*).

Surface regularity index (SRI)

SRI describes central corneal optical regularity; it is a measure of the dioptric optical power differences in 256 equidistant locations in the 4.5mm central corneal area. SRI correlates well with the measure of BCVA *(r=0.80, p<0.001*), with normal values below 0.56DS (Wilson *et al.*, 1991; Cavas-Martinez *et al.*, 2016; Liu and Pflugfelder, 1999). The SRI index in a normal cornea is expected to be below 0.56DS (Wilson *et al.*, 1991; Cavas-Martinez *et al.*, 2016). Liu and Pflugfelder (1999) confirmed this assertion in their comparison of the SRI index in 64 eyes of 33 normal and 42 dry eye subjects (Liu and Pflugfelder, 1999). Burns *et al.*, (2004) analysed a total of 13 different corneal topographic indices in 73 patients with keratoconus and found mean SRI indices in the right and left eyes of 1.24 (±0.83) [*range 0.10-4.59*] and 1.24 (±0.82) [*range 0.02-4.02*] respectively (Burns *et al.*, 2004).

The SRI of the research population (Table 5.11 , Figure 5.14) is almost 3 times higher than the SRI value of 0.56DS expected in normal corneae (Wilson *et al.*, 1991; Cavas-Martinez *et al.*, 2016; Liu and Pflugfelder, 1999).

Right eye vs left eye corneal metrics

Keratoconus is a bilateral disease (Gomes *et al.*, 2015), with significant asymmetry between the two eyes (Zadnik *et al.*, 2002), the SRI index difference between the right and left eyes in the population of this study exhibited no significant difference, Mann-Whitney U (p=0.168). Independent samples t-test analysis of the means of the right and left eye's pachymetry and K_{max} values also showed no statistically significant difference between the two eyes, *(p=0.481)* and *(p=0.119)* respectively.

In summary all three corneal indices were consistent with the abnormal indices found in populations with pathological, ectatic corneal disorders such as keratoconus and were statistically significantly different to the indices found in populations with normal corneae. These objective measures of corneal topography parameters confirm the presence of corneal

pathology consistent with keratoconus in the research participants and the appropriateness of the optical management with rigid contact lenses, of the visual disability caused by this pathology.

Randomisation demographics

Gender

The gender allocation to the two groups did not exhibit gender bias with 2 versus 5 females and 11 versus 12 males randomised to group 1and 2 respectively (Figure 5.15). The Chi-square (χ^2) goodness of fit analysis confirmed that there was no statistically significant difference between the two randomised groups with respect to gender allocation (*p=0.109*).

Age

The age distributions in the two randomised groups (Table 5.14, Figures 5.16 and 5.17) were normal and the mean ages of 39.82 and 28.12 years in Group 1 and 2 respectively, were not statistically significantly different when compared by an independent samples *t-test*, (*p=0.872*).

AAD

The research participants' 95% CI for mean age spanned a substantially larger time period: 30.8-48.1 than that of the 95% CI for mean AAD: 18.3-26.3 (Figures 5.16 and 5.17). This is

consistent with the nature of keratoconus, which is normally diagnosed in early life and persists throughout life (Ramez *et al.*, 2017; Galvis *et al.*, 2015).

Estimated duration of CRGPcl wear at the time of enrolment

The estimated duration of CRGPcl wear at enrolment was not statistically significantly different between the randomised groups (*Mann-Whitney U* test $p=0.363$). This aspect of the population demographics is important because both visual acuity and quality of life scores may significantly reduce in a substantial proportion of keratoconic contact lens wearers over a period of 7 years (Davis *et al.*, 2006; Kymes *et al.*, 2008a). The equivalence of the estimated duration of CRGPcl wear was therefore unlikely to reduce the validity of the visual and NEI-VFQ outcomes in this study.

Ethnicity

The race/ethnicity frequency in the two randomised groups exhibited a balanced distribution (Figure 5.18) and the χ^2 goodness of fit test indicated that there was no significant difference between the two randomised groups with respect to the distribution of ethnicities ($p=0.613$). The validity of this analysis however, is sub-optimal because of the small number of participants: less than 5, in 3 of 4 ethnic groups. The possibility of some bias in the randomisation groups with respect to ethnicity was considered insignificant due to the crossover research design, as discussed above.

Corneal metrics in the randomised groups

K_{max} and SRI did not differ significantly in group 1 and 2 (Figures 5.19a and 5.19b). An independent samples *t-test* revealed a significantly thinner mean corneal thickness in group 1 than in group 2 (*p=0.019*), (Figure 5.20). The actual difference between the means was 37µm, which is unlikely to be clinically significant, because both groups mean values are higher than 400µm. Estrada *et al.*, (2017) described grading systems of keratoconus, which include more than one corneal feature for characterizing the disease (Estrada *et al.*, 2017). They reviewed the anatomical grading system of Amsler-Krumeich and the optical grading of Alio-Shabayek, both systems stipulate that corneal thickness >400µm is considered as grade II; early to moderate keratoconus. This indicates that the means of both randomised groups fall into the same grade category of keratoconus. The more recent visual function-based grading system developed by Estrada *et al.*, (2017) uses narrower pachymetry bands of 20µm from grade *I* to *IV* and 80µm for the most severe keratoconus grade *IV plus*, which based on pachymetry alone may allocate a different grade to group 1 and 2. However, with respect to the other 6 parameters of this grading system, one of which is corneal radius, the 2 groups are not statistically significantly different.

The difference in the pachymetry values may suggest that the level of the ectatic disease in group 1 was somewhat more advanced despite statistical equivalence with respect to the other 2 indices; K_{max} and SRI. This possible difference in the severity of keratoconus between the two groups may be a confounding element in the data analysis of a parallel groups RCT. However, the crossover RCT design of this research should minimise the effect of this difference, as each participant performs as his own control with respect to confounding parameters including disease severity. Furthermore, the selection criterion of good tolerance of CRGPcl of all participants supports the premise that there was no clinical indication for refitting with SRGPcl due to disease severity in any of the participants.

The four participants who had one eye fitted were 3 males and 1 female, three fitted eyes were right and one eye left. Two participants SN 4 and 8 had a corneal transplant in the other eye, due to severe keratoconus and wore daily SRGPcl and glasses, with intermittent SRGPcl respectively. The other two, SN 5 and 26 wore CRGPcl and soft disposable lenses respectively. Randomisation was 1 to group 1 and 3 to group 2, resulting in 25 eyes fitted in group 1 and 31 eyes in group 2.

Summary of demographics in the randomised groups

In summary with respect to the effectiveness of randomisation it could be concluded that overall there were no marked differences in the demographics of the 2 randomised groups and the randomisation achieved its purpose.

Main outcome measures

Visual acuity, ETDRS logMAR BCVA

It is well established that visual quality may be significantly improved in individuals with irregular corneal disorders such as keratoconus, with both CRGPcl and SRGPcl compared to unaided vision, spectacle and regular soft contact lenses corrections. These improvements may be demonstrated by subjective logMAR scores of improved visual resolution at 100% contrast and improved contrast sensitivity scores at progressively reduced levels of contrast (Zhou *et al.*, 2003; Wei *et al.*, 2011; Chaudhary *et al.*, 2017; Visser *et al.*, 2013b; Sabesan *et al.*, 2013; Picot *et al.*, 2015; Ozek *et al.*, 2018).

LogMAR demographics

The mean and standard deviation of the logMAR scores in CRGPcl and SRGPcl in this study were similar to the published research used for the sample size calculations. This equivalence

confirms the appropriateness of the sample size calculation and the reliability of the logMAR data collection in this research.

The ETDRS logMAR demographics of the 2 groups are exhibited in Figure 5.21 and Table 5.19. ETDRS logMAR BCVA scores in individuals with keratoconus are expected to show good repeatability of measurements. Gordon *et al.,* (1998) examined the repeatability of ETDRS logMAR scores of 134 participants (74.6% CRGPcl wearers) from the CLEK study, who exhibited a wide range of keratoconus. Good test retest repeatability, especially for same examiners, was demonstrated in both low and high contrast visual acuities, measured monocularly and binocularly, with inter-class correlation coefficient range of *0.757-0.853* (Gordon *et al.*, 1998).

Pooling the data obtained from the right and left eyes could, in theory not only increase the power and significance of a study, but also optimally use the data obtained from the study population. However, in this research population, the significantly higher correlation of the logMAR scores of the two eyes from same individuals compared to randomised eyes means that pooling the data from both eyes as independent samples was inappropriate (table 5.21). The statistical analyses for the carryover and treatment effects of the visual outcome measures was therefore performed using the mean scores of the right and left eyes of each participant.

Differential carryover and period effects analyses

In a 2x2 crossover RCT the efficacy of treatments A and B is assessed on the basis of the comparisons of the within-subject difference between the two treatments with regard to the outcome variable. The recommended approach (Wellek and Blettner, 2012; Jones and Kenward, 2015) is to use a standard independent samples *t-test* for normally distributed data or a non-parametric equivalent such as the *Mann-Whitney U test*, using the within-subject differences between the outcomes in both periods as the raw data (Wellek and Blettner, 2012; Jones and Kenward, 2015).

Prior to the analysis of the treatment effect, the possibility of a differential carryover and period effect must be tested for (discussion in the *methods* chapter). In the current research a carryover

effect was considered unlikely because visual acuity, which is the spatial resolving capacity of the visual system, is limited mainly by optical and neural factors or their combination (Bailey, 2006). The neural factors are subject (eye) specific and are expected to be well controlled by randomisation, especially with a crossover, which controls for individual idiosyncrasy. The only significant variables to visual performance in this research are therefore the integrity and quality of the optical correction at the time of the examination. In a fully developed, adult visual system, when the quality of the visual correction is sub-optimal visual performance will be impaired irrespectively of the quality and timescale of previous visual experiences as may be demonstrated by the blur confirmation test performed during normal refraction. When the quality of the visual correction at the time of examination is optimised, the visual performance will be optimised irrespectively of the previous visual experience (Borish and Benjamin, 2006). Despite this accepted clinical wisdom, to conform to the crossover design analysis, it was considered prudent to perform the appropriate statistical analysis for a differential carryover and period effects, prior to performing the analysis of the treatment effect, as recommended in the literature (Wellek and Blettner, 2012; Jones and Kenward, 2015).

The analysis of a carryover effect should include a pre-test confirmatory analysis, which consists of comparing the sums of means of the 2 periods for each subject in the two groups / sequences by means of another appropriate test for independent samples (Wellek and Blettner, 2012; Jones and Kenward, 2015). If this test yields a statistically significant result, the usual crossover analysis which compares the intra-subject differences of the effects of the two treatments between the randomised groups, should not be applied and the analysis should be performed as in a parallel study using the data from the first period only, in each randomised group (Wellek and Blettner, 2012).

A preliminary assessment was performed on the logMAR data as soon as the first 12 participants completed the study. An independent sample *t-test* comparing the sums of the logMAR period scores revealed no significant difference, ($p=0.056$), which indicated an absence of a significant carry over effect. At the end of the study, a similar analysis of the full dataset (Table 5.23a and 5.23b), also revealed no statistically significant difference between the period sums of the two randomised groups, ($p=0.281$) (Table 5.24). This result indicates that there was no evidence for a carryover effect and enables the utilisation of the full crossover data in the analysis for treatment effect on visual performance measured by the ETDRS logMAR.

The period effect was also considered unlikely due to the relatively short period of the research. Period effect was calculated by an independent samples *t-test* means comparison of the period crossover differences (A-B) between the randomised groups (Tables 5.23 a and b), this finding indicated that there was no significant period effect in the logMAR scores in this research *(p=0.541)*.

Treatment effect, ETDRS logMAR

The objective of a crossover trial is to determine whether within-subject treatment effect differences exist. This may be achieved by the comparison of the within participant score differences in periods 1 and 2, between the two randomised groups (Wellek and Blettner, 2012; Jones and Kenward, 2015).

The summary table of the period means of the mean OD/OS logMAR scores in the two groups (Table 5.22) and the box plots of group by period logMAR scores (Figure 5.23) illustrate the similarity in the means of the scores and the differences in the interquartile range and total range in the two periods of the two groups. The logMAR scores with CRGPcl [group 1 period 1, group 2 period 2] exhibit a larger interquartile range then the SRGPcl [group 1 period 2, group 2 period 1]. The wider interquartile and total range of the logMAR scores with CRGPcl compared with SRGPcl is also apparent in Figure 5.24, which exhibits the box plots of the whole population mean OD/OS logMAR scores in CRGPcl versus SRGPcl.

The group by period analysis exhibited in Figures 5.25 and 5.26 highlights the logMAR score differences between participants and the subtle differences between the two groups, by the spread of scores along the diagonal (Jones and Kenward, 2015). Group 1 exhibits a larger inter-subject variability, group 2 exhibits a single low scoring outlier (top of the graph), which is responsible for the lower *Kendall's tau_b* correlation of *0.331* in group 2 versus *0.517* in group 1. The majority (7 versus 6) of the plotted scores in group 1 are below the diagonal, which indicates a tendency for better logMAR scores (lower values) in period 2 (SRGPcl). The periods in group 2 exhibits more equal scores, 8 under and above the diagonal. The fairly

symmetrical distribution of the plotted scores in relation to the diagonal in both groups indicates an absence of a significant period effect (Jones and Kenward, 2015).

To illustrate treatment effect, both groups were plotted on the same graph with their respective centroids plotted in Figure 5.27. The fact that both centroids are on the diagonal, at essentially the same position, indicates an absence of a significant treatment effect, or period score equivalence in both groups (centroids on the diagonal) and equivalence in the logMAR scores between group 1 and 2 (same position of centroids) (Jones and Kenward, 2015).

A good plot for displaying within-participant treatment / period differences is the subject-profiles plot (Figure 5.28) (Jones and Kenward, 2015). These plots exhibit the logMAR scores in the two periods for each participant. Larger inter-subject variability is apparent in group 1, with an obvious outlier with poorer scores in group 2 (top of the graph). The majority of logMAR score changes (slopes) are relatively small, 3 participants in each group exhibited significant changes of five or more letters. There is no clear trend (direction of slopes) which also indicates an absence of a significant treatment effect.

Plotting the four groups by period means $\bar{y}_{11,}$ $\bar{y}_{12,}$ $\bar{y}_{21}$ and $\bar{y}_{22}$ against their corresponding period labels and joining the mean logMAR scores achieved in CRGPcl [periods 1 group 1 with period 2 group 2] and joining the scores achieved in SRGPcl [period 2 group 1 with period 1 group 2] (Figure 5.29) exhibits the difference in the mean logMAR scores between participants in groups 1 and 2 wearing CRGPcl and the difference between participants in groups 2 and 1 wearing SRGPcl (Jones and Kenward, 2015). In period 1 the mean logMAR score difference (A vs B) is 0.03 (1.5 letters) in period 2 (B vs A) is 0.02 (one letter), the crossing of the graph lines indicates that the participants in group 2 (red triangle and dot) exhibited lower logMAR scores (better visual acuity) in both CRGPcl and SRGPcl than the participants in group 1.

To establish whether a statistically significant difference existed between the ETDRS logMAR scores of participants wearing CRGPcl compared with participants wearing SRGPcl a comparison of the logMAR score period differences between the two experimental groups (Table 5.23a and 5.23b) was performed by the non-parametric *Mann-Whitney U test*. This analysis confirmed the null hypothesis (H_0) that despite the slightly better logMAR score in SRGPcl in group 1, there was no significant difference between group 1 *(Median=-0.01)* and

group 2 *(Median=0.00)*, period differences: *U=96.5*, (*p=0.563*) *[z=-0.588]* (Tables 5.25 a, b, Figures 5.30 and 5.31).

Summary of the ETDRS logMAR outcome measure

The ETDRS logMAR results indicate that in patients with irregular cornea disorders such as keratoconus, who are successful CRGPcl wearers, with no clinical indications for refitting with alternative contact lenses such as SRGPcl, the logMAR visual acuity is expected to be equivalent in both CRGPcl and SRGPcl. With respect to logMAR visual acuity, no advantage is expected in refitting a successful CRGPcl wearer with SRGPcl and no disadvantage in refitting with SRGPcl, if and when this is clinically indicated.

Contrast sensitivity measure of visual performance

The second aspect of visual performance measured and compared in CRGPcl versus SRGPcl was the contrast sensitivity function (CSF), which measures the visual system's resolution of 4 different grating spatial frequencies, expressed in cycles per degree (CPD), at 8 levels of gradual contrast reduction. These scores may be expressed by a numerical value of contrast on a scale from 0-8, for each grating size, which may be plotted on a contrast sensitivity chart and also expressed in log contrast sensitivity (logCS) for statistical analysis.

The research population's numerical scores of CS (Table 5.26, Figure 5.31a) were lower at all four spatial frequencies (poorer performance) than normative data collected by the FDA researchers [unpublished data quoted in (VectorVision, 2013)] (Table 5.28, Figure 5.32a) and also poorer performance in CPD 6, 12 and 18 compared with the published normative data by Hashemi *et al.,* (2012) (Table 5.29, Figure 5.32b). The reduced CSF of keratoconic CRGPcl wearers was found in other research; (Wei *et al.*, 2011) (Figure 5.32c). The mean numerical

CS scores in this research (Tables 5.27.a (Appendix IV.A) and 5.27b) were similar to the Wei *et al.,* (2011) scores at 3 and 6 CPD. However, at 12 and 18 CPD, the mean scores in this research were higher (≥1.0 CS scores) than in Wei *et al.,* (2011). The reason for this difference is not clear, it is possible that in the Wei *et al.,* (2011) study there were more eyes with advanced keratoconus, which negatively affected the higher resolution demands (Zadnik *et al.,* 2002; Wagner *et al.*, 2007; Wei *et al.,* 2011) at 12 and 18 CPD [logMAR 0.5 and 0.20 respectively (Sukha and Rubin, 2013)].

Numerical average OD/OS CSF scores means at 3, 6, 12 and 18 CPD in CRGPcl and SRGPcl and whole population are presented in Tables 5.27a and b and Figure 5.32. The two experimental lenses exhibit similar mean and StdDev numeric CSF scores at all four CPD (Figure 5.31b).

Crossover data analysis

The analysis of the CS data was performed in a similar manner to that of the ETDRS logMAR scores, the logCS scores of the right and the left eyes were averaged and a mean CPD score was calculated for each participant in periods 1 and 2, in group 1 (AB) and group 2 (BA) (Tables 5.30, 5.31 and 5.32).

Plotting the logCS scores in periods 1 and 2, in groups 1 and 2 (Figure 5.34), highlights the larger inter-subject logCS score variation (spread of the scores along the diagonal) in group 1 and the overall slightly higher (better) logCS scores in group 2 (higher concentration of scores in the upper part of the graph). In group 1 the logCS scores were higher in period 1 (CRGPcl) (more points under the diagonal) and in group 2 the scores were higher above the diagonal, period 2 (CRGPcl). Group 1 exhibited a single outlier (participant 23), with a significantly better score in period 1 (CRGPcl). The fairly symmetrical distribution of the plotted points in relation to the diagonal in both groups is an indication for the absence of a period effect (Jones and Kenward, 2015).

To illustrate evidence of treatment effect both groups were plotted on the same graph with their respective centroids (Figure 5.35). The centroids are close to and on the opposite sides of the

diagonal, which indicates that there was a slight (proximity to diagonal) difference between the two periods in both groups and that in both groups, participants had higher logCS scores with CRGPcl (group 1 period 1, group 2 period 2). The higher overall performance was in group 2, indicated by the higher location of the group 2 centroid, is not indicative of a period carryover effect since the lens in period 1 in that group was SRGPcl, which had lower scores than CRGPcl. The fact that the centroids are placed either side of the diagonal line with some vertical separation may be an evidence of a direct treatment effect. (Jones and Kenward, 2015).

The subject-profiles plot displays within-participant treatment / period differences, by displaying and connecting the logCS scores in the two periods for each participant (Figure 5.36). Larger inter-subject variability is apparent in group 1 compared with group 2, with an outlier with poorer scores in group 1 period 2 (participant 23). The majority of logCS score changes are relatively small (less than 0.1 log units), four participants in group 1 and two participants in group 2, exhibited significant logCS score changes of ≥0.10 log units. The trend for higher logCS scores in period 1 of group 1 can be detected in the general direction of slopes, in group 2, no obvious trend is apparent.

Plotting the four group by period means $\bar{y}_{11,}$ $\bar{y}_{12,}$ $\bar{y}_{21}$ and $\bar{y}_{22}$ against their corresponding period labels and joining the mean logCS scores achieved in CRGPcl [period 1 group 1 with period 2 group 2] and joining the scores achieved in SRGPcl [period 2 group 1 with period 1 group 2] (Figure 5.37), illustrates the small difference in the mean logCS scores between participants in groups 1 and 2 wearing CRGPcl and the difference between participants in groups 1 and 2 wearing SRGPcl. In period 1 the mean logCS score difference (A vs B) is 0.10 logCS; better scores for SRGPcl: [*CRGPcl Mean=1.46, SRGPcl Mean=1.56*]. In period 2 (B vs A) the difference is 0.17 logCS, better scores for CRGPcl [*CRGPcl Mean=1.59, SRGPcl Mean=1.42*]. The crossing of the graph lines highlights the higher logCS of participants in group 2 in both lenses (red triangle and a red circle). A significant difference between the scores of groups may be indicative of a treatment-by-period interaction (carryover effect) (Jones and Kenward, 2015).

Carryover and period effects analysis

Analysis of period carryover effect by an independent samples *t-test* indicated that due to the significantly higher mean of period sums in group 2 there is a possibility of a period carryover effect (*p=0.019*). The most likely explanation for this finding may be related to the absolute differences in the logCS scores between the two groups and not due to period interaction. As discussed above regarding carryover effect in the logMAR scores these arguments are equally applicable to the logCS scores (Bailey, 2006; Borish and Benjamin, 2006). However, despite this accepted clinical wisdom and the absence of a statistically significant difference in the period sums of the logMAR visual scores, it was decided to analyse the treatment effect both according to a crossover study protocol (ignoring the statistically significant finding regarding the sum of periods) and more conservatively as a parallel group RCT protocol, in which the results of period 1 only in both groups will be compared (Wellek and Blettner, 2012).

The period effect was calculated by a *Mann-Whitney U* test comparison of the period crossover differences between the randomised groups (Tables 5.31), this finding indicated that there was no significant period effect in the logCS scores in this research *(p=0.711).*

LogCS treatment effect

An independent samples *t-test* comparing the means of the period differences between group 1 and group 2 confirmed the H_0, that the higher logCS scores achieved in CRGPcl in both groups were not significantly different to the logCS scores achieved in SRGPcl (*p=0.316*), (Figure 5.38).

The parallel group analysis was performed by an independent samples *t-test* comparing the logCS means of the four CPD scores achieved with the two contact lens types in period 1 of group 1 and period 1 in group 2. The 0.10 logCS higher scores achieved in SRGPcl (<0.15, single logCS increment, Figure 6.1) did not reach statistical significance and therefore also supported the H_0, (*p=0.070*).

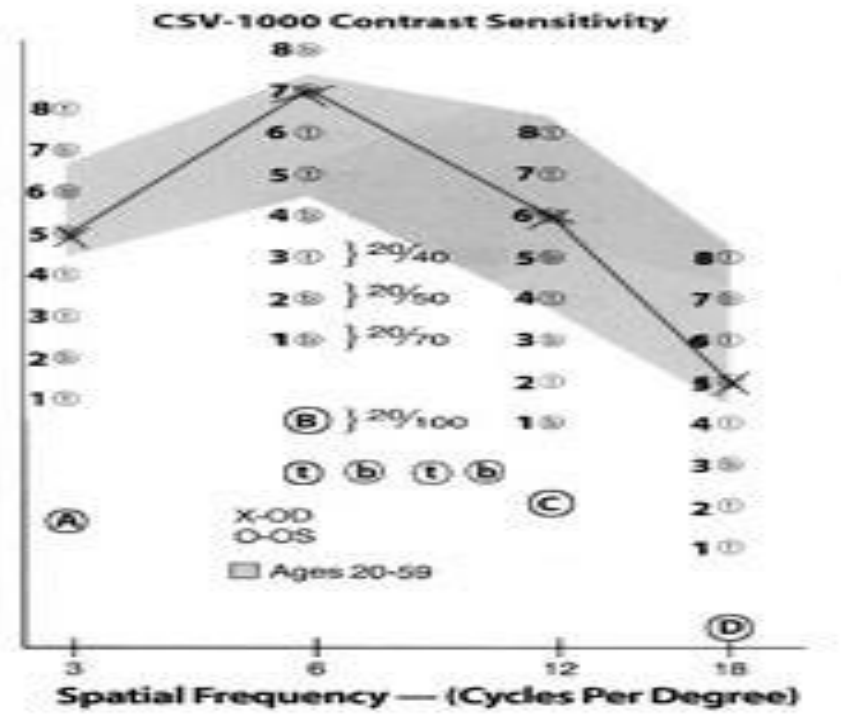


Figure 6.1. *CSF score chart, 1 level difference between numbers in each row is equivalent to approximately 0.15logCS.* (reproduced with permission of VectorVision)

The magnitude of 0.10 logCS difference did not constitute a statistically significant difference in visual performance between the two experimental lenses. To determine whether this difference is clinically significant, it would be instructive to refer to clinical research in which CS scores are used to evaluate visual improvement due to therapeutic treatment.

Bland and Altman (1986) suggested that for normally distributed data, the coefficient of repeatability (COR) describes the 95% CI for the variability of these data [*COR=SD of test retest difference x 1.96*] (Bland and Altman, 1986). Reeves *et. al.*, (1993) suggested that COR may be a useful criterion to determine the minimum change in test performance necessary to indicate a significant change in vision on a particular test. If the ratio of the score difference and COR is higher than 1, it would indicate that the difference in scores is higher than the normal variation between measurements and therefore significant, if lower than 1 then insignificant, as may be due to a normal measurement variability (Reeves *et al.*, 1993). Pomerance and Evans (1994) used the CSV-1000 to measure the effect of glaucoma therapy

on vision. They compared the normative COR for each spatial frequency to the change in vision before and after therapy in glaucoma patients (Pomerance and Evans, 1994). They found that the average COR of normal subjects was 0.191 and that vision differences / COR ratios, were significant for CPDs 3, 6 and 12: *1.98, 1.15, 1.30, respectively* and not significant for 18 CPD: *0.64*. Using the same normative data to establish the clinical significance of the logCS difference in the current research, the ratio of the mean score difference between the two groups: 0.10 and normative COR: 0.191 from Pomerance and Evans (1994), was lower than 1: [*0.1/0.191=0.52*], which confirms that this difference is unlikely to be clinically significant.

LogCS scores at 6 CPD

It was decided to compare the logCS scores of CRGPcl and SRGPcl at 6 CPD specifically, because the score difference between the experimental lenses was largest at 6 CPD (Figure 5.31b) and because the resolution required for 6 CPD target is 6/30 / logMAR 0.70 (Sukha and Rubin, 2013). This level of resolution is relatively low and has been achieved by all eyes in this research. Another reason for choosing 6 CPD was that normative data indicate that the highest CS scores are achieved at 6 CPD compared with the other three and therefore could provide useful insight into visual performance in addition to that provided by the mean logCS and ETDRS logMAR.

Due to the possibility of a period carryover effect the treatment effect analysis was again performed for the whole data of the crossover and the data from period 1 of both groups, ($p= 0.104$) *and* ($p=0.110$) respectively. Analyses by both these methods supports H_0.

Summary of subjective visual outcomes

Both methods of assessing visual performance in this research, the ETDRS logMAR and the logCS, indicated that there was no statistically significant difference between the two experimental lenses with respect to the research participants' visual performance. Similar results may be found in published research, such as was used in the sample size calculation (Davis *et al.*, 2006; Marsack *et al.*, 2007; Nejabat *et al.*, 2012; Gumus *et al.*, 2011; Sabesan *et al.*, 2013). Other research exploring CSF visual performance in both lens types, Wei *et al*., (2011) in CRGPcl and Ozek *et al*., (2018) in 28 keratoconic, 4 PMD and 8 corneal grafts SRGPcl wearers, reported an identical mean logCS to this study, in CRGPcl and SRGPcl respectively (Wei *et al.*, 2011; Ozek *et al.*, 2018).

In summary, no statistically or clinically significant differences were found in the visual performance, measured by logMAR and LogCS, between CRGPcl and SRGPcl in the participants in this research. The visual outcomes in this research therefore do not support the findings in other studies such as Baran *et al.*, (2012) and Bergmanson *et al.*, (2016), who found superior visual performance in SRGPcl compared with CRGPcl.

The most likely explanation for this difference is the study design and the population demographics. The present research is a crossover RCT, whereas Baran *et al.*, (2012) and Bergmanson *et al.,* (2016) are retrospective analyses of participants who were refitted with SRGPcl due to clinical needs and therefore may have had more advanced levels of keratoconus. The suggestion that:

> "*Given the here reported comfort and vision advantage, it may be argued that the scleral contact lenses should be tried at an earlier stage and possibly be the first rigid lens prescribed for keratoconus cases*" (Bergmanson *et al.,* 2016).

is not supported by this research at least with respect to achieving better visual performance, when no other clinical indication for refitting CRGPcl wearers with SRGPcl are present.

The visual outcome results in this research also indicate that patients who may require a refitting from CRGPcl to SRGPcl due to nonvisual clinical indications, such as reduced lens tolerance, should not be disadvantaged with respect of their vision from being refitted with SRGPcl.

National Eye Institute Visual Function Questionnaire (NEI-VFQ)

The third outcome analysed was the National Eye Institute Visual Function Questionnaire (NEI-VFQ). Assessment of visual quality of life has been widely used in the monitoring of treatment efficacy in ocular disorders. The NEI-VFQ developed and validated by Mangione *et al.,* (1998) evaluates the vision-related health status, and the impact of ocular diseases on individuals' social function, emotional well-being and daily routine activities (Mangione *et al.*, 1998; (Mangione, 2000).

Keratoconus has a significant detrimental effect on quality of life (Qol), which is equivalent in its severity to categories 3 and 4 (advanced stages) macular degeneration (Kymes *et al.*, 2004). Baran *et al.,* (2012) re-fitted 49 selected participants (43 with keratoconus) with SRGPcl from their habitual CRGPcl and found 27.6/100 points improvement in NEI-VFQ scores, across the 12 domains ($p < 0.001$).

Changes in the NEI-VFQ scores of 925 keratoconus patients were evaluated by the CLEK study over a 7-year follow-up period. The researchers reported a decrease in scores of all NEI-VFQ domains, except ocular pain and mental health. These decreases in vision related Qol were associated with exacerbation of keratoconus and reduction in visual quality (Kymes *et al.,* 2008). Nevertheless, Aydin Kurna *et al.,* (2014) suggested that the higher visual acuity afforded by RGPcl may improve vision related Qol, which was supported by the finding that patients with keratoconus expressed higher levels of satisfaction after being fitted with CRGPcl than patients with normal corneae, who were fitted with CRGPcl for myopia correction (Lee *et al.*, 2017).

NEI-VFQ demographics

From the 12 domains of the NEI-VFQ in this research (Table 5.34) ocular pain featured the lowest (worst) mean score of 77.6 (±21.19) followed by the participant perception of their

general health 79.55 (±12.45). These results were similar to the CLEK study by Kymes *at al.,* (2004), the 1166 participants with keratoconus reported mean scores of 74.8 (±18.0) and 75.5 (±21.4) for ocular pain and general health respectively. Both these populations graded the ocular pain and general health status lower than the normative population of CRGPcl wearers reported in Kymes *et al.,* (2004); 85.4 (± 13.7) and 84.4 (±18.5) respectively (Figures 5.40a. and 5.40b).

The NEI-VFQ score differences between the keratoconic participants and the normative CRGPcl participants, reach statistical significance for all 12 domains, ($p<0.05$), in the Kymes *et al.,* (2004) study. The current study exhibited slightly higher (better) NEI-VFQ scores compared with Kymes *et al.,* (2004), except in the domain of ocular pain (Figure 5.40a). However, the results in the current study were also lower in all domains than the normative data published by Kymes *et al*., (2004) taken form Walline *et al.,* (2000) (Kymes *et al.,* 2004; Walline *et al.,* 2000) (Figure 35b).

Kymes *et al*., (2008) followed the 1166 participants for 7 years and found a modest decline in all NEI-VFQ domains except *ocular pain* and *mental health*. The drop in these scores was associated with a significant decline of 10 letters in logMAR scores and a 3.00D increase in corneal curvature (0.6mm steeper). This finding is significant for the current research because of the association of contact lens wear duration with decline in logMAR scores and exacerbation of keratoconus, both of which may be associated with reductions in NEI-VFQ scores. This aspect however, should have been well controlled in this research due to randomisation and the overall equivalence between the two randomised groups with respect to age at diagnosis and equivalence with respect to the estimated reported duration of CRGPcl wear at enrolment (Figure 5.16 and 5.17).

Summary NEI-VFQ demographics

The comparison of the mean scores of individual domains between the two experimental lenses (Figures 5.41a and 5.41b) shows that the participants reported slightly higher scores in CRGPcl

[*Median=89.53, IQR=17.38*], than in SRGPcl [*Median=88.35, IQR=14.04*], except in the *driving* domain, in which SRGPcl featured slightly higher scores.

Carryover and period effects analysis of NEI-VFQ

The mean of the scores of the 12 domains of NEI-VFQ for each participant, in each period was calculated as well as period sums and crossover differences in the two groups [Table 5.35, (Appendix IV B)]. The absence of carryover effect was confirmed by *Mann-Whitney U* test (*p=0.245*). An independent samples *t-test* means comparison of the period crossover differences between the randomised groups confirmed the absence of a period effect *(p=0.343)* in the NEI-VFQ scores in this research.

Treatment effect analysis

The two randomised groups exhibited similar scores in all 12 domains of the NEI-VFQ with slightly higher mean scores in group 1, in 9 of 12 domains (Figure 5.42). To establish the treatment effect of the experimental lenses on the VFQ scores, data analysis was conducted as in previous outcome measures according to recommendations of Wellek and Blettner (2012) and Jones and Kenward (2015). The mean of the scores of the 12 domains of NEI-VFQ for each participant, in each period was calculated as well as period sums and differences in the two groups [Table 5.35, (Appendix IV B)].

The absence of carryover effect was confirmed by *Mann-Whitney U* test (*p=0.245*).

The treatment effect analysis revealed that the higher scores reported by the participants in SRGPcl did not reach statistical significance (*p=0.483*). These results indicated that with respect to the mean score of the 12 domains of the NEI-VFQ there was no statistically significant difference between the experimental lenses, confirming H_0.

The NEI-VFQ results in this research did not support the findings of other research which found higher NEI-VFQ scores in participants wearing SRGPcl compared with CRGPcl, such as Baran *et al.*, (2012). This difference in results is most likely due to the difference in the research design with Baran *et al.*, (2012) being a retrospective analysis of participants who were refitted with SRGPcl for clinical reasons. The current research design is a crossover RCT, of participants who had no clinical indications for refitting with SRGPcl.

Summary of NEI-VFQ outcome measure

The conclusion which may be drawn from the NEI-VFQ results of the current research are, that there would most likely be no significant improvement in the vision related Qol if patients with keratoconus and other irregular cornea disorders, who are successful CRGPcl wearers, with no clinical indications for refitting, are refitted with SRGPcl. There would also be no likelihood of a disadvantage with respect to vision related Qol if patients who wear CRGPcl are refitted with SRGPcl and vice versa, when clinically indicated.

Subjective measures of comfort and vision

Optometrists use grading scales in their daily practice for a variety of purposes. A study by Efron *et al.*, (2011) concluded that grading scales for contact lens complications may "*be considered as an expected norm in contact lens practice"*, they further advocated *"the incorporation of such grading scales into professional guidelines and standards for good optometric clinical practice"* (Efron *et al.*, 2011). Grading scales are also used in optometric practice for the recording of symptoms such as comfort levels due to ocular dryness (Begley *et al.*, 2001). Numerical rating scales were found to be useful, repeatable and accurate when the visual quality is generally high (Papas and Schultz, 1997), as in the current research.

The measurement of contact lens discomfort is complex; the sensation experienced is inherently variable, and existing measurement scales may not be optimal. Appropriately designed questionnaires undergo a rigorous process of item development and validation. Interval scales (e.g. numerical rating scale and visual analogue scale) are frequently used to measure temporal characteristics of contact lens discomfort and remain useful in assessing qualities such as duration, onset and chronicity. Jalbert *et al.*, (2015) reviewed the instruments used to assess contact lens comfort and stipulated that the majority of studies have used questionnaires designed and validated for use in dry eye patients, most commonly the *ocular surface disease index* (Schiffman *et al.*, 2000) was used in 13 studies, the *contact lens dry eye questionnaire* (Begley *et al.*, 2001) was used in 7 studies. The authors pointed out the questionable nature of such practice as the characteristics; epidemiology and underlying mechanisms of contact lens wearers differ from those reported by dry eye patients. They recommended that improved instruments need to be developed, but until then, interval scales and the short version of the *contact lens dry eye questionnaire* are the best validated instruments available for measuring contact lens discomfort (Jalbert *et al.*, 2015).

Wirth *et al.*, (2016) initiated the development of the *Contact Lens User Experience* system. They interviewed 86 healthy adult, soft disposable contact lens wearers and identified three key areas patients consider important when describing their experience with contact lenses. These were: comfort, vision and contact lens handling. The authors claim that these instruments exhibit excellent psychometric properties (Wirth *et al.*, 2016). To my best knowledge these instruments have not to date been used in research and because they were developed for healthy soft lens wearers are unlikely to be suitable for the current research.

It was therefore decided to follow the advice of Jalbert *et al.*, (2015) and develop a Likert-like interval scale from 1-10, (1=worst comfort and vision, 10= perfect comfort and vision) to grade personal perception of vision and comfort in the experimental contact lenses. This instrument was designed for this study by the chief investigator, with a view that if appropriate, it may after further validation be used in both specialist and standard contact lens practice.

The individual scores for SPC and vision of each participant in periods 1 and 2 in both groups are presented in Figures 5.43, 5.44, 5.45 and 5.46 (Appendix IVC). Significant differences are apparent in some individuals in their scores of the subjective comfort such as in group 1; participants 10, 11, 20, 23, 28; scoring their comfort in SRGPcl higher by 2.5, 2, 3, 2.5 and 2 points respectively. In group 2 smaller differences in subjective comfort scores were apparent

with participants 6 and 34 reporting a 3 and 2-point better comfort in SRGPcl, with the rest reporting differences of less than 2-points. Subjective grading of vision showed less obvious differences between the two experimental lenses in group 1: participant 1 reporting a 3 points better vision in CRGPcl, with the rest of the participants in that group reporting equivalence or differences smaller than 2 points. Participants in group 2 also reported equivalent results except participant 15, who reported 5-point better vision in SRGPcl, and participants 9, 16 and 24 reporting differences of 2.5, 2.5 and 2-points respectively, the first 2 reported better vision with SRGPcl and the latter with CRGPcl.

Crossover analysis of subjective scores of vision and comfort

The analyses of the subjective scores of vision and comfort were performed in the same manner as the other outcome measures, as recommended by Wellek and Blettner (2012) and Jones and Kenward (2015).

The period by group comparisons in Figures 5.47 and 5.48 highlight an important finding which shows that subjective comfort was better in period 2 in group 1 and period 1 in group 2, this finding indicates that overall participants reported better comfort in SRGPcl.

Subjective grading of vision was fairly equally symmetrical around the diagonal in group 1, with 3 participants reporting better vision in period 2 (SRGPcl) and 3 participants reporting better vision in period 1 (CRGPcl), 7 participants reported equal SPV. In group 2, five participants reported better vision in period 1 (SRGPcl) and 6 reported better vision in period 2 (CRGPcl), the remaining 5 participants reported equal vision.

The *Mann-Whitney U* tests indicated that there was no statistically significant carryover effect in SPC and vision scores reported by the participants (*p=0.183*) and (*p=0.592*) respectively. The period effect analysis by an independent samples *t-test* means comparison of the period crossover differences between the randomised groups (Tables 5.38, 5.39), indicated that there was no significant period effect in the SPC and SPV scores in this research *(p=0.630), (p=0.157)* respectively.

The comparison of the two groups with respect to the treatment effect of the two experimental lenses was performed as recommended by Wellek and Blettner (2012) and Jones and Kenward (2015). The *Mann-Whitney U* tests indicated that the slightly higher (better) SPV scores achieved with SRGPcl did not reach statistical significance, (*p=0.213*), which supports the $H_{0,}$ (Figure 5.49b). The participants' subjective grading of their own vision is also in agreement with the experimental visual findings that there was no significant difference between the two experimental lenses with respect to the visual performance measured by logMAR and logCS.

Participants' perception of their subjective comfort in the two experimental lenses, was also evaluated for treatment effect by the *Mann-Whitney U* test comparing the period difference in group 1 (*Median = 1.0*) to the period difference in group 2 (*Median = -1.0*). The group by period and individual profile plots reveal higher scores with SRGPcl (Figures 5.47a, b and c) and were confirmed as statistically significant (*p=0.002*). This result rejects the H_0 and indicates that in this research population significantly higher subjective comfort scores were achieved with SRGPcl (Figure 5.49a).

After establishing the statistically significantly higher SPC scores in SRGPcl, it was decided to explore whether other factors, unrelated to the lens type could have influenced the participants' scoring of subjective comfort. The sequence of contact lens wear was considered as a possibility, because the loss of adaptation to CRGPcl after wearing SRGPcl [group 2, sequence: BA] could have detrimental effects on the perception of comfort on resumption of CRGPcl wear in the washout and experimental periods. If this assumption is true, the comfort score of the experimental CRGPcl in group 2 would be lower (worse) than in group 1 [CRGPcl worn first, sequence: AB]. An independent samples *t-test* comparing the means of the subjective comfort in experimental CRGPcl between group 1 and group 2 revealed no statistically significant difference between two groups: (*p=0.198*). This excluded the sequence of wear as a factor with significant influence on the subjective comfort scores.

The other outcome measure which assesses participants' comfort in this experiment may be found in the *ocular pain* domain of the NEI-VFQ. It was decided to evaluate this domain in isolation to determine whether a statistically significant difference between the two experimental lenses might be found with respect to ocular pain as well. The analysis was performed as recommended by Wellek and Blettner (2012) and Jones and Kenward (2015), after establishing the absence of significant period and differential carryover effects, the higher (better) ocular pain scores achieved with SRGPcl, supported the finding of the subjectively

reported levels of comfort in the experimental lenses, but this difference did not reach statistical significance (*p=0.170*). Therefore, still supported the H_0 in this regard.

Final lens choice

Lens choice for future habitual use was the final outcome measure. Fourteen (47%) of participants chose the SRGPcl and 16 participants chose the CRGPcl (53%) as their habitual lens. The chosen habitual lenses of the four participants who had one eye fitted were: participants 4, 5 and 8 chose to remain in CRGPcl and participant 26 chose SRGPcl. Interestingly, participants 4 and 8 chose to remain in CRGPcl despite successfully wearing a SRGPcl in the other, non-experimental eye.

Based on the absence of statistically significant differences in the participants' visual performance or in their scores across the 12 domains of the QoL, it was of interest that almost 50% of participants chose to abandon their habitual CRGPcl and wear SRGPcl, despite exhibiting no statistically significant visual or Qol advantages in these lenses.

The only statistically significant difference found in this experiment was in the participants' perception of comfort in the two experimental lenses, with better comfort scores in SRGPcl. It may be postulated that the significantly better perception of comfort in SRGPcl was the main reason for 47% of the participants to switch to SRGPcl from their habitual lens design, CRGPcl.

The participants' SPC and SPV together with the final lens choice are presented in Table 5.40 (Appendix IV D) and Figure 5.51.

To try and understand why a high proportion (47%) of successful CRGPcl wearers chose to change to SRGPcl, it was decided to analyse and compare the scores of the perceived subjective comfort in the experimental CRGPcl between the participants who chose CRGPcl and those who chose SRGPcl.

A means comparison of the subjective comfort scores reported in the experimental CRGPcl of the participants who selected CRGPcl [*Mean=8.44 (±1.03)*] and SRGPcl [*Mean=7.04 (±1.54)*] was performed by two independent samples methods, the *t-test* and *Mann-Whitney U* test (Figure 5.52).

Both analyses revealed significantly higher scores of reported subjective comfort by the participants who selected CRGPcl as their habitual lens compared with participants who selected SRGPcl, (*p=0.006*) and (*p=0.009*) by independent samples *t-test* and *Mann-Whitney U* test respectively, thus rejecting the H_0.

These results indicate that there is a significant difference in the subjective comfort perception in CRGPcl between the participants who chose CRGPcl and those who chose SRGPcl as the preferred habitual contact lenses. This significance indicates that the difference in the subjective comfort in CRGPcl may be an important measure of the performance of CRGPcl in the wider population of patients with keratoconus managed by these lenses.

After establishing the statistically significantly higher score of SPC in participants who chose CRGPcl as their future habitual lenses, it was decided to explore whether other factors, such as the sequence of contact lens wear could influence the final lens choice. Sequence was considered important due to the possibility of loss of adaptation to CRGPcl after wearing SRGPcl in group 2 [sequence BA]. Alternatively, the possibility of preferring the latest lens worn; SRGPcl in group 1 [sequence: AB] and CRGPcl in group 2 [sequence BA]. This analysis compared the number of participants selecting CRGPcl and SRGPcl in the two randomised groups. The non-significant $\chi 2$ results, (*p=0.713*), indicate that neither lens wear sequence nor the final lens worn by the participants had a significant influence on the choice of the final habitual lens (Table 5.42).

It is of note that 12 (75%) of the 16 participants who chose CRGPcl scored their subjective comfort in these lenses as ≥8 and none scored their comfort level in these lenses at < 7, which seems reasonable for successful contact lens wear. Nevertheless, 8 (57%) out of the 14 previously successful CRGPcl wearers scored their comfort level in these lenses at ≤7, and given an alternative choice selected SRGPcl. The other 6 (43%) participants, who chose SRGPcl, scored their subjective comfort in CRGPcl at ≥7.5, switched to SRGPcl most likely due to a combination of other factors, such as improved vision and equal or better comfort.

Summary of statistically significant results

This research revealed statistically significantly higher subjective comfort scores in SRGPcl than in CRGPcl and also found that participants who chose CRGPcl as their habitual lenses, had statistically significantly higher subjective comfort scores in CRGPcl. Furthermore, no participant chose to remain in CRGPcl with subjective comfort scores <7. These findings indicate that for some wearers SRGPcl afford superior comfort to CRGPcl and habitual wearers of CRGPcl are likely to prefer SRGPcl if their subjective comfort score with CRGPcl are lower than 7.

These results indicate that the LSCS instrument may be appropriate for use in patients with keratoconus and other irregular cornea disorders managed by CRGPcl, to determine the degree of their perceived comfort. Based on the findings of this research a comfort score <7 may indicate that despite reported satisfaction, and no clinical indications for refitting with alternative lenses, the contact lens experience may be improved with alternative contact lenses, such as SRGPcl. If the findings of this research regarding preference of SRGPcl by CRGPcl wearers with subjective comfort scores <7 are replicated and validated, the LSCS instrument may be used routinely to establish whether an alternative lens management may be appropriate to further improve contact lens tolerance of successful CRGPcl wearers, by refitting with SRGPcl.

Strengths and limitations

The main strength of this research is the RCT with a crossover design, employed to answer the research questions regarding the performance of the two experimental lenses in the specific research population. The causal inferences afforded by an RCT provide the strongest empirical evidence of a treatment's efficacy. The randomisation of participants and concealment of their allocation ensured that allocation bias and confounding of unknown variables were minimised. This was further enhanced by minimisation of the *detection bias* by performing visual data

collection by practitioners who were naive to the type of lenses worn at the time, this masking was possible for all participants assessed, with both experimental lens types.

The chronicity of the corneal pathology and the non-curative nature of the experimental lenses evaluated were appropriate for the crossover aspect of this research (Armitage and Hills, 1982), which minimised the confounding of individual idiosyncrasies such as gender, age, race, disease severity et cetera (Wellek and Blettner, 2012; Jones and Kenward, 2015).

It is inevitable with research of this type that participants cannot be masked to the lens type. However, the research team took care to use neutral language in describing the lens options and not to make any comment that could lead participants to expect that one of the lens types may be preferable to the other.

The potential disadvantages of RCT were not significant in this research, dropout / attrition rate was low (4 participants; 12%), the ethical considerations were appropriately addressed prior to the study commencement and there was sufficient prior knowledge about the clinically meaningful levels of improvement and expected variation of improvement in the sample size calculation (Levin, 2007). The sample size was calculated conservatively to allow for the possibility of analysing the results from period 1 only (50% of data) as in a parallel RCT, in the unlikely event of discovering a significant differential carryover effect.

The imbalance between the two randomised groups in the number of participants who completed the study (13 and 17 participants, in group 1 and 2, respectively) occurred by chance and not due to any inherent differences between the two lens types. Two participants SN 18 and 25 have emigrated. Participant 29 underwent a corneal cross-linking intervention after enrolling to this research and therefore could not continue participation. Participant 22, did not return to the CMH clinic and could not be reached by the clinic staff, therefore presumed to have moved away.

The fact that the ratio of participants in the 2 experimental groups changed from the planned 15 in each group to 13 in group 1 and 17 in group 2, should have no effect on the significance and power of the study because the sample size was calculated conservatively to enable analysis of results from period 1 only as in a parallel RCT design, if a significant differential carryover effect was established. The statistical power in this scenario, assigning group 2 as experimental (n=17) and group 1as control (n=13), the power of the study would change from 0.80 to 0.75, α=0.05. However, in this research all outcomes except logCS, demonstrated no

significant differential carryover effect and were therefore analysed as a crossover RCT, which is considered more powerful than a parallel group analysis (Wellek and Blettner, 2012; Jones and Kenward, 2015).

The specialist clinical setting of this research has both strengths and limitations. The strengths of such a setting are, the access to the specific population required for this research and minimisation of bias associated with non-specialist clinical settings with respect to disease severity range and experience of the treating professionals. The limitations of this setting are the challenges of allocating the extra time required for the additional examinations stipulated by the research protocol and the reliance on the contact lens fitting skills of a single practitioner, the chief investigator.

Other limitations of this study are the inequality between the genders in the population, which may be significant due to poorer contact lens tolerance by older female participants (Stapleton *et al.*, 2015; Fink *et al.*, 2010) and alleviation of these symptoms by SRGPcl (Visser *et al.*, 2016).

The variation / range of the scores of the reported subjective comfort in CRGPcl in the research population, although probably reflecting the different contact lens experience to that expected in normal myopic individuals (Kymes *et al.*, 2004; Walline *et al.*, 2000), may have contributed to the high proportion (47%) of participants who chose SRGPcl as their final habitual lens. Furthermore, the LSCS instrument has not been validated and the conclusions regarding participants' comfort may be applied only to successful CRGPcl wearers and may not be applicable to neophytes. Other factors such as the relatively limited period of SRGPcl wear by the participants in this research and the relatively moderate severity of keratoconus, amenable to successful management with CRGPcl, may also have influenced the outcomes.

Conclusions

The use of SRGPcl to manage patients with corneal disorders such as keratoconus who progress to advanced disease and /or fail to tolerate CRGPcl is well recognised and described in the literature (Tan *et al.*, 1995; Pullum and Buckley, 1997; Segal *et al.*, 2003; Pullum *et al.*, 2005; Baran *et al.*, 2012; Severinsky *et al.*, 2014; Schornack, 2015; Bergmanson *et al.*, 2016; Maharana *et al.*, 2016).

Due to significant advances in technology the use of SRGPcl has undergone a revival in specialist contact lens practice in recent years (van der Worp *et al.*, 2014; Schornack, 2015). However, their use remains mainly in the realm of management of advanced keratoconus and as a problem-solving modality when CRGPcl and other lens options fail to appropriately manage the visual disability caused by the various irregular cornea disorders (Visser *et al.*, 2007b; Bergmanson *et al.*, 2016).

This research attempted to determine whether the role of SRGPcl may be expanded beyond the important but limited scope of current use to, as suggested by Bergmanson *et al.*, (2016) a first-choice lens for a neophyte keratoconic and/or a better option for a successful CRGPcl wearer.

To address this question the participants in this research were successful CRGPcl wearers, which is considered the gold standard contact lens management of the visual disability caused by ectatic corneal disorders such as keratoconus (Robertson and Cavanagh, 2011). Refitting this population with SRGPcl in this experiment was not a problem-solving exercise but an exposure of experienced contact lens wearers to a significantly different, alternative contact lens type. The importance of successful CRGPcl wear experience was that it ensured a relatively straightforward transition and adaptation to the alternative contact lens *wear and care* and with the help of randomisation and crossover research design, facilitated a comparison of performance of these two lenses, in a non-problem-solving clinical scenario.

The crossover RCT method was considered ideal due to the chronic nature of the disorder and the non-curative management of contact lenses. Additionally, it afforded the control of confounding variables such as gender, age, race, disease severity and other personal idiosyncrasies of contact lens wearers, because the comparisons in a crossover analysis are of the within-subject differences between the two randomised groups.

The analysis of the demographics of the research population confirmed that the population was consistent with that expected in a specialist contact lens clinic in a metropolitan city such as London. The demographics of the two randomised groups confirmed that the randomisation achieved its purpose with respect to age, gender, race and disease severity in the two randomised groups.

The only statistically significant outcome in this research was a better subjective perception of comfort in SRGPcl compared to comfort in CRGPcl, measured by the LSCS. This finding was supported by the significantly lower LSCS in CRGPcl in participants who chose CRGPcl as their final habitual lens, compared with those who chose to remain in CRGPcl.

The analysis of the main outcome measure, the ETDRS logMAR BCVA revealed no statistically significant difference between the two experimental lenses.

The analysis of the CSF, revealed no statistically significant differences between the two experimental lenses in the logCS scores across the 4 CPD range and no significant difference in the logCS at specifically 6 CPD.

The analysis of the NEI-VFQ revealed that the two experimental lenses did not differ in a statistically significant manner across the 12 domains investigated by this Qol tool, nor did the two experimental lenses exhibit a statistically significant difference in the specific domain of *ocular pain.*

The score of SPV in the two experimental lenses, revealed no significant differences in the participants' subjective score of their vision between the two experimental lenses.

The score of the SPC revealed significantly higher (better) comfort scores in SRGPcl. This finding is of significance because although SRGPcl are better tolerated by patients who are unable to tolerate CRGPcl (Schornack, 2015; Bergmanson *et al.*, 2016; Yan *et al.*, 2017), this research indicates that 47% of successful CRGPcl wearers, who demonstrate equivalent visual and Qol outcomes in both experimental lenses, preferred SRGPcl for their future habitual use. The most likely explanation for this, is that even in individuals who are successful and well adapted CRGPcl wearers, the particular SRGPcl fitting features, corneal clearance and therefore absence of lens cornea interaction, minimal lens mobility and eyelid interaction and the continued lubrication of the ocular surface covered by the lens, may all contribute to the significantly better comfort and high participant proportion choice of SRGPcl as their habitual lens.

The final outcome measure in this research was the participants' choice of one of the two experimental lenses as their habitual lens for future use. Sixteen participants chose to remain in CRGPcl and 14 chose to switch to SRGPcl. The finding that 47% preferred SRGPcl to their habitual well performing CRGPcl, may indicate that a significant proportion of keratoconic patients who are satisfied with CRGPcl, may prefer SRGPcl, most likely if they experience superior comfort levels in these lenses.

The clinical conundrum of how to effectively identify those successful CRGPcl wearers who are most likely to benefit from being refitted with SRGPcl may to some degree have been answered by the findings in this research. The analysis of the subjective comfort scores in experimental CRGPcl indicated that participants who chose to remain in CRGPcl had significantly higher comfort scores of ≥7.0, than those participants who switched to SRGPcl. These findings indicate that a routine use of the LSCS tool designed for this research, may identify those patients who would benefit from a refit with SRGPcl even if no other clinical indications for refitting are apparent. If this research's results can be replicated and the LSCS is validated, then this method may be considered appropriate for the selection of patients for refitting with SRGPcl if their LSCS score in CRGPcl is < 7, even if no other indication for refitting is apparent.

The findings in this research that SRGPcl are significantly more comfortable than CRGPcl and that the two experimental lenses perform equally with respect to vision and visual quality of life, may support a practitioner's decision to refit an existing CRGPcl wearer with SRGPcl or to fit a neophyte with either contact lens type, knowing that lens performance should be equivalent with respect to vision and quality of life and may be better with respect to comfort and therefore base their choice of lens on other clinical aspects. In a neophyte such clinical aspects may include an existing high ocular sensitivity, the presence or absence of allergies, ocular surface disorders, dry eye disease, environmental dryness or other idiosyncratic features of ocular sensitivity or factors which may adversely affect it.

This research also demonstrates that there are unlikely to be visual or visual Qol advantages or disadvantages in refitting existing successful CRGPcl wearers with SRGPcl, or fitting a neophyte with SRGPcl even if CRGPcl are also appropriate.

This research further supports a practitioners' clinical decision to refit a CRGPcl wearer with SRGPcl and vice versa, by the indication that there should be no significant disadvantage in

either scenario with respect to their visual performance and visual Qol, provided that CRGPcl demonstrate equivalent comfort levels when patients are refitted from SRGPcl.

The above conclusions and recommendations may extend the scope of SRGPcl fitting not only beyond the role of a problem solver but also in addition to the recommendations by Visser *et al.,* (2016) who developed a flowchart for contact lens selection in a specialist contact lens practice. The authors recommended that SRGPcl may achieve better vision and longer wearing time / comfort when factors which cause reduced lens tolerance, such as advanced corneal irregularity, significant tear film deficiency or elevated corneal scar, are present (Visser *et al.*, 2016). This may be extended to include reduced subjective comfort in CRGPcl to a level <7 on the LSCS.

The equivalence of the two lens types with respect to visual performance and visual Qol is important considering the challenge of fitting CRGPcl in a way that does not risk compromising corneal integrity in corneal ectatic disorders (Chapter 3). Over a number of years, it may not be possible to avoid a flat CRGPcl fit, which may cause or exacerbate corneal scarring resulting in visual loss due to corneal morbidity. Alternatively, a steep, cone vaulting CRGPcl fit, attempted to prevent corneal damage associated with excessive cone bearing, can cause progression of keratoconus. Due to complete corneal vaulting it is reasonable to expect that SRGPcl will be more likely to avoid these problems. If there are long-term physiological advantages to SRGPcl, then the short-term equivalence in visual performance and visual Qol of SRGPcl and CRGPcl demonstrated in the present research may lead to the conclusion that SRGPcl may indeed be considered as the lens option of first choice in corneal ectatic disorders management.

An additional recommendation which may be formulated from the results of this research is that existing well adapted and satisfied CRGPcl wearers, may benefit from routine, quick and straightforward assessment of their SPC with the LSCS instrument. If no clinical indications for a refitting exist, it would be an evidence-based conclusion that it is appropriate to continue wearing CRGPcl if comfort level on the LSCS are ≥7.0. However, if comfort level is <7, the evidence in this research suggests that refitting with SRGPcl may be of benefit, even when no other indications are present.

Other considerations when fitting with or re-fitting to SRGPcl, with respect to patients, are the higher cost of lenses and additional care products and the considerable dexterity required for lens handling. From the perspective of the treating clinicians a consideration of the steep

learning curve required to achieve competence in this complex field of contact lens practice and the appreciation of the potential for complications associated with long term SRGPcl wear is also necessary. Recent research raised concerns regarding compromised corneal physiology due to reduced tear exchange in the sealed, post lens fluid reservoir and the considerable barrier to oxygen posed by the thickness of SRGPcl and the post lens tear layer (Michaud *et al.*, 2012; Vincent *et al.*, 2019). Concerns have also been raised regarding the physical pressure exerted by the haptic portion on the sclera causing increased intra-ocular pressure increasing the risk of glaucomatous optic neuropathy (Fadel and Kramer, 2019; Michaud *et al.*, 2019).

Further research is suggested to validate the LSCS in CRGPcl wearers, managed for corneal ectatic disorders. In addition, due to the significantly better comfort achieved in SRGPcl in the population of this research, a crossover RCT comparing CRGPcl to SRGPcl in neophytes requiring contact lens management for corneal ectatic disorders, would more specifically clarify the viability of using SRGPcl as a lens of first choice.

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Appendix

Appendix I

A. Participant Information

The Eye Department
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Participant Information

Investigation of the performance of Scleral and Corneal Rigid Gas Permeable (RGP) contact lenses in participants with keratoconus and other irregular cornea disorders

You are being invited to take part in a research study comparing different types of contact lenses for a condition called keratoconus. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information and ask any questions before deciding whether or not you wish to take part.

Introduction

The cornea is the transparent layer at the front of the eye. The cornea's shape should be regular for good vision. Keratoconus is a condition in which the cornea gradually develops an irregular shape. This causes reduced vision which cannot be effectively corrected by spectacles and soft contact lenses. The usual management of keratoconus is Corneal RGP contact lenses (corneal lenses). Sometimes corneal lenses work well, but in other cases wearers can develop discomfort and scarring of the cornea.

For many years people who experience problems with corneal lenses have been fitted with a different type of lens, called scleral lenses. These are larger than corneal lenses and sit on the sclera (the white part of the eye) so that they completely bridge over the cornea. Scleral lenses can be more comfortable and are thought to reduce the risk of scarring of the cornea.

The Aim of the Research

The aim of this research is to compare the performance of scleral and corneal lenses in adults with keratoconus who usually wear corneal lenses.
We want to discover whether modern scleral lenses should be considered not only if problems occur with corneal lenses, but potentially as a lens of first choice in the management of keratoconus and related conditions.

What would taking part involve?

If you decide to take part in this research, you will be given additional information and be asked to sign a consent form. You are free to withdraw any time without giving a reason. A decision to take part, withdraw or not to take part, will not affect the level of care and treatment you receive.
During the trial you will wear a pair of corneal lenses and a pair of scleral lenses, one after the other. We will decide (randomly) which pair you start with. We will ask you to attend for a fitting appointment so that both types can be fitted, ordered, and manufactured.

During the collection session these lenses would both be assessed in your eyes and detailed training and instructions in lens handling will be given.
After 6-8 weeks you will return to wearing your own original lenses for a period of one month after which you will wear the other type of experimental lenses for 6-8 weeks.
After each 6-8 weeks period of experimental lens wear we will check your eyes and vision and a quality of life questionnaire will be completed.

Your involvement in the study is anticipated to last for approximately 6-7 months.
Please note that compared with a new contact lens wearer, you will need 2-3 more appointments than would usually be expected.

During the period of the study you will be able to contact the investigator Mr Levit directly (details below) if you have any questions or concerns.

What are the possible advantages or disadvantages?

An advantage is that you will be able to try different types of contact lenses and keep any that work well for you.

It is not anticipated that you will be at any disadvantage or suffer any risk from this study, as these lenses are of high quality and are CE marked as well as approved for clinical use by the American Food and Drug Agency (FDA). These lenses are used in specialist contact lens practice and are routinely fitted to patients with keratoconus and other irregular corneal disorders.

If for any reason you pull out of the research, for example due to health issues unrelated to your eyes, the research team would retain research data collected and continue to use it confidentially.

Please note all information received from you will be held until the publication of the doctoral thesis in 2017 and will be handled in a confidential manner and stored at the hospital premises and on a password protected computer in an environment locked when not occupied.

At the completion of the study you may obtain a summary of the anonymous results from the Institute of Optometry website: www.ioo.org.uk. Any participants who do not have web access can contact the researchers for a paper version.

This study is being completed as part of a Professional Doctorate in Optometry at London South Bank University and the Institute of Optometry. It has been reviewed and ethically approved by NHS Integrated Research Ethics Committee, the London South Bank University Research Ethics Committee and the Institute of Optometry Research Ethics Committee.

If you have a concern about any aspect of this study, you should ask to speak with the researcher (details below) who will do his best to answer your questions.
Alex Levit Bsc. (Hons) FCOptom (CL CVP)
The Eye Department,
Central Middlesex Hospital.
Acton Lane
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e mail: Alexander.Levit@nwlh.nhs.uk

If you wish for any further information regarding this study or have any complaints about the way you have been dealt with during the study or other concerns you can contact: Professor Bruce Evans who is an Academic Supervisor for this study, on 0207 7407 4183 or email bjwe@bruce-evans.co.uk.

Finally, if you remain unhappy and wish to complain formally, you can contact the Chair of the University Research Ethics Committee, by phone, email or write a letter to: Professor Nicola Crichton
London south Bank University

103 Borough Road
London SE1 0AA
phone 02078156742, email crichtnj@lsbu.ac.uk

Participants can also contact the Patients Advisory Liaison Service (PALS) 02084532569.

B. Participant Informed Consent

Corneal RGP contact lenses Versus Scleral RGP contact lenses for the irregular cornea (e.g., keratoconus)

Invitation to Participate

You have been invited to participate in this study because you have keratoconus and habitually wear corneal rigid Gas Permeable (RGP) contact lenses (corneal lenses). If you are a suitable candidate it is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw anytime without giving a reason up to the time when the dissertation is submitted. A decision to take part, withdraw or not to take part, will not affect the level of care and treatment you receive. Before you decide I would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you may have**.** This should take no longer than 10-15 minutes. Please talk to others about the study if you wish.

Part 1 tells you about the purpose of this study and what will happen to you if you choose to take part.

Part 2 gives you more detailed information about the conduct of the study.
After the verbal discussion please take time to read the information below and to contact Mr Levit (details below) if you have any further questions about this research.

What is the purpose of the study?

The aim is to investigate the visual quality and vision related quality of life whilst wearing scleral contact lenses compared with corneal lenses in participants with keratoconus (or a similar condition) who wear corneal lenses. Our objective is to discover whether modern scleral lenses should be considered not only as a problem solver but potentially as a lens of first choice in the management of keratoconus and related conditions.

Why have I been invited?

You have been invited because you have keratoconus and wear corneal lenses successfully.

Do I have to take part?

It is up to you to decide whether to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

If you are willing to participate your involvement in the study will last for approximately 8 months. The number of participants required to complete this research is 30. Please note that the frequency and nature of the check-ups is similar to that required in the first 6 months of wearing a new type of contact lens. The differences are that the fitting appointments will last longer because two sorts of contact lens are being fitted and that additional measurements of visual quality of life will be performed. This will involve completing a form prior to the beginning of the study and at the end of the two lens wearing periods. This form takes 10-15 minutes to complete.

You will be invited for contact lens fitting as well as the measurement of your vision with the contact lenses worn. The whole procedure will last approximately 40-60 minutes. Two types of lenses will be ordered, the corneal lens and the scleral lens.

A few weeks later the new lenses and your vision with them will be checked and you will be instructed on how to insert, remove contact lenses and given one pair to wear. A review 3 weeks after this initial fitting appointment will be booked which will take approximately 30 minutes.

Please note that this is a randomized experiment, which means that neither you nor the researcher will know which lenses you will be given to start with. If your practitioner needs to find out for clinical reasons he can do so. The type of lens given to you will be randomly allocated with a 50% chance of receiving the experimental scleral lens and 50% the control corneal lens. The reason for this way of researching is because sometimes we do not know which way of treating patients is best. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). After 8-12 weeks of wear you will be asked to return to wearing the contact lenses that you wore before starting in the research. About a month later you will be given the other research lenses to use for 8-12 weeks, this is the crossover stage. The reason for the break between the different types of lenses is so that any effects of the first type of lens are cleared before you start the new treatment.

What are the possible disadvantages and risks of taking part?

It is not anticipated that you will be at any disadvantage or suffer any risk specifically from taking part in this study, as the lenses used are of the highest quality and are CE marked. There is a slight risk of complications associated with contact lens wear, but as far as we know there is not any additional risk with the types of contact lenses used in the research compared with the contact lenses you already wear. The opportunity of trying two different types of lenses will allow you to choose which is better. But this opportunity involves more appointments and inconvenience for you and this is a disadvantage.

What are the possible benefits of taking part?

If you prefer the comfort and vision of the experimental or the control lens you will be able to keep these lenses for your continued personal use. Otherwise it is unlikely that you will gain any personal benefit from participating in this research. However, the information gained from this research will help develop effective approaches for people who suffer from visual difficulties due to Keratoconus or similar conditions.

What happens when the research study stops?

If you wish you will be allowed to keep the lenses used in the research free of charge and will continue to be reviewed in the contact lens clinic in the regular manner.

Will my taking part in the study be kept confidential?

All information received from you will be handled in a confidential manner and stored in the hospital records and on a password protected computer in an environment locked when not occupied. Only the researcher and research supervisors will have direct access to the information. Any reference to you will be coded into a number and your name and contact details will not be taken away from the hospital. The research data will be held until the publication of the doctoral thesis, which is anticipated in 2017.

This study is being completed as part of a Professional Doctorate degree in Optometry at London South Bank University and the Institute of Optometry. It has been reviewed and ethically approved by NHS Integrated Research Ethics Committee and the London South Bank University Research Ethics Committee. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If you wish for any further information regarding this study or if you have a concern about any aspect of this study, you should ask to speak with the researcher who will do his best to answer your questions.

Alex Levit Bsc. (Hons) FCOptom (CL CVP)
The Eye Department,
Central Middlesex Hospital.
Acton Lane
London NW10 7NS
Mobile 07813160631
e mail: Alexander.Levit@nwlh.nhs.uk

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researcher who will do his best to answer your questions.

Contact details: Alex Levit (details above)

If you have any complaints about the way you have been dealt with during the study or any possible harm you might suffer will be addressed by the researcher Mr A. Levit, you can also contact the academic supervisor of this research: Professor Bruce Evans on 0207 7407 4183.

If you remain unhappy and wish to complain formally, you can contact the Chair of the University Research Ethics Committee. Details can be obtained from the university website:

http://www.lsbu.ac.uk/rbdo/external/index.shtml

Participants can also contact the Patients Advisory Liaison Service (PALS) 02084532569

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

Sometimes new information becomes available about the treatment being studied. If this happens, your research optometrist will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research optometrist will make arrangements for your care to continue. If you decide to continue in the study, he may ask you to sign an agreement outlining the discussion he had with you.

Or your research optometrist might consider you should withdraw from the study. He will explain the reasons and arrange for your care to continue.

Or if the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I do not want to carry on with the study?

You are free to withdraw from the study at any time up to the time of the completion of the dissertation. Information collected about you to the point when you decide to withdraw, will be retained and used by the researcher. The information collected will not identify you in any way, confidentiality and anonymity will be maintained at all times. You are free to withdraw at any time during the study without your normal standard of care being affected.

Are there circumstances and/or reasons under which my participation in the trial may be terminated?

Your participation is unlikely to be terminated unless you do not comply with the study protocol of the correct wear and care of your contact lenses and / or do not attend the required check up appointment without a good reason for non-attendance. You will be allowed to keep the contact lenses prescribed during the study even if your participation is terminated for any reason.

Harm

In the unlikely event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in this study be kept confidential?

During the approximately 9 months of your participation, the data of visual performance and visual quality of life will be collected during the consultations in the contact lens clinic.

For the proper maintenance of anonymity and confidentiality all research information will be recorded on specially designed separate records which would be stored on a password protected computer. Hard copies would be kept in the Hospital in a locked cabinet, with no access except for the research personnel. These records will contain no personal data but only allocated research numbers.

The clinical information contained in these research records may be later added to the patients Hospital records.

The data will be used for the writing of the doctoral thesis and in professional publications. The only details used will be the participants' gender, age and allocated research serial number.

Involvement of the General Practitioner/Family doctor (GP)

Your GP will be informed about the treatment you receive in the usual manner.

What will happen to the results of the research study?

The results of the research will be published in professional literature in a manner which does not in any way identify the participants. Should you wish, you may have access to copies of the publications relating to this research.

Who is organizing and funding the research?

This study is done as a part of professional doctorate in Optometry at the department of Allied Health Sciences at the School of Health and Social Care London South Bank University and the Institute of Optometry. The researcher and the Institutions involved have no conflicts of interests in this research.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests.

Further information and contact details

1. General and specific information about research. Please see part 1 of this document or contact Mr A. Levit.

2. Advice as to whether they should participate: see information of personnel below as well as your own GP.
3. Emergency contact during the study: Mr A. Levit. Mobile 07813160631.
4. Other personnel: Sister in charge 020 8963 7195 Mon - Fri 9-5

Professor Bruce Evans on 0207 7407 4183.

Chair of the University Research Ethics Committee: http://www.lsbu.ac.uk/rbdo/external/index.shtml

C. Consent form

The Eye Department
Central Middlesex Hospital
Acton Lane
London NW10 7NS

CONSENT FORM

Title of Project: Corneal RGP vs. Scleral RGP contact lenses for the irregular cornea

Name of Researcher: Mr A. Levit

Ethics ref No: 11122014

Please initial box

1. I confirm that I have read and understand the information sheet dated 1/12/14 version 1, for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by responsible individuals from the London South Bank University, the Ophthalmology department at Central Middlesex Hospital, from regulatory authorities or from the NHS Trust, and where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree to take part in the above study. ☐

Name of Patient ..... Date..... Signature.....

Name of researcher..... Date..... Signature.....
CC copies to: 1. participant 2. participant's medical records.

D. Participant Information on Receipt of Contact Lenses

In this research we aim to investigate the effect of contact lenses on your vision and visual quality of life. These lenses are of high quality and were fitted and manufactured with great precision to fit your eyes and correct their optical anomalies.

If you are new to contact lenses or wore a different type of lenses, please note that a period of adaptation of 3-5 days may be required. If no contraindications are found by your contact lens practitioner, you may be able to wear these lenses daily from 10-16 hours.

Contact lens wear is safe and comfortable if proper hygiene and lens care are followed meticulously. However, in the unlikely event of developing any of the following symptoms;

-Eyes stinging, burning, itching (irritation), or other eye pain

-Lenses are less comfortable than when first placed on eye

-Feeling of something in the eye such as a foreign body or scratched area

-Excessive watering (tearing) of the eyes

-Unusual eye secretions

-Redness of the eyes

-Reduced sharpness of vision (poor visual acuity)

-Blurred vision, rainbows, or halos around objects

-Sensitivity to light (photophobia)

-Unusually dry eyes

REMOVE YOUR LENSES IMMEDIATELY.

If the discomfort or problem stops, then look closely at the lens. If the lens is in any way damaged, **DO NOT** put the lens back on your eye. Place the lens in the storage case and contact Mr Levit. If the lens has dirt, an eyelash, or other foreign objects on it, or the problem stops and the lens appears undamaged, you should thoroughly clean, rinse and disinfect the lens; then reinsert it. If the problem continues, you should IMMEDIATELY remove it and contact Mr Levit.

If you have any questions regarding any aspect of contact lens wear contact Mr Levit at; The Ophthalmology Department, Central Middlesex Hospital, Acton Lane

London NW10 7NS. Tel 07813160631, e mail Alexander.Levit@nwlh.nhs.uk
Please read and learn the written contact lens handling instructions enclosed. Please view the video of contact lens handling and care on http://icdlens.com/icd-a&r-video.html

E. Handling and Care of Scleral Contact Lenses

You will be given full instruction by Alex Levit and plenty of time to practice handling under his supervision. This document is intended to reinforce the verbal instructions that you receive.

As with all contact lenses, the maintenance of proper hygiene procedures is essential. The surface of gas permeable scleral lenses is subject to deterioration with use and handling. Please take good care of your lenses in order to maintain the optimal surface integrity as long as possible.

• Always wash your hands with antibacterial soap and dry your hands thoroughly with lint free towel or tissue, before inserting or removing your lenses.

• Take care not to catch the lens or your eye with your fingernails – keep them short

• Work over a clean, flat surface, put in the plug if you are working over a wash basin

• Use saline solution to rinse your lenses – do **not** rinse them with tap water as this can cause serious eye infections.

• Remember **Contact lens case hygiene** is important as infections can occur due to poor lens case cleaning. The rubber insert in the lens case and all rubber or plastic lens applicators should be scrubbed with a dedicated clean toothbrush on a weekly basis with cooled boiled water and then left to air dry. Do not use soap in case it is not fully rinsed away. The lens case should be replaced with a new one at least every six months

• To minimise the possibility of mixing your lenses up, it is a good practice to always insert and remove the same lens first.

• Prior to lens application, remove the lens from its soaking / conditioning solution, rinse it well with non-preserved saline.

• Fill the lens with **non-preserved sterile** saline and insert (see handling instructions below).

Lens Application / Insertion

• Rinse the lens well with preservative-free saline, never use tap water.

• Place the lens, bowl side up, on the large plunger supplied with your lenses.

• Fill the bowl of the lens completely with **preservative-free sterile** saline. It is important that the saline is non-preserved and sterile as it will remain in contact with the cornea through the day. Tear circulation with a scleral lens is minimal therefore, preservatives or contaminants in the bowl of the lens remain in contact with the cornea for the duration of wear and this increases the chance of toxicity, infection and inflammation.

• Lean forward with your face parallel to the floor. Hold both lids open wide.

• Look at the hole in the plunger while guiding the lens on to the eye

• Apply the lens to the surface of the eye, take care to spill as little saline in the bowl of the lens as possible, in order to avoid trapping an air bubble.

• If an air bubble gets under the lens, remove, rinse, refill with saline and reapply the lens as instructed above.

Lens removal:

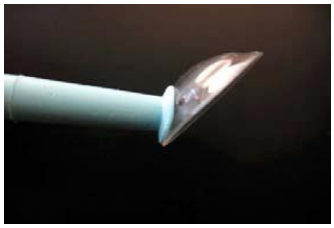
Since the scleral lens is large, the capillary forces which hold the lens on the eye are powerful. Removal is always best done by first lifting the edge to eliminate this force. Attempting to pull the lens from the centre will create negative pressure and will rarely be successful.

• First, moisten the small plunger with a few drops of saline solution.

• Place the small plunger on the lens at the lower edge at the 6 o'clock position. (Near the bottom), so that the plunger is just inside the lens.

• Lift or tilt the lens of the eye and remove. You may have to gently push on the eye or eyelid next to the lens to break the seal.

Method 1. Plunger



Method 2. Fingers

Alternatively, the lens may be removed as follows (Method 2);

Look down, but keep your chin upwards

• Take your upper lid on the side nearest your nose with your index finger so that the lid is above the upper rim of the lens

• Press downwards, then tighten the lid by drawing your finger towards the temple. This action will push the lid underneath the edge of the lens, relieving the suction. Now, look up to eject the lens from your eye and catch it with your other hand, or do this over a table covered with a towel to prevent the lens from falling onto the floor

Lens Care and cleaning:

Always use the care system recommended to you by your contact lens practitioner

• Once the lens is removed from your eye, rinse the lens with saline

• Apply your contact lens cleaning solution (Eyeye Crystal cleaner) to the front and back surfaces, while gently rubbing between your fingers

• Rinse again with saline until all of the cleaning solution is removed

• Store in fresh conditioning solution (Boston or Menicare plus) in the case provided taking care not to introduce any water or residual cleaning solution into the case.

• Once every 2 weeks, after cleaning, soak in Progent (protein cleaner) for 30 minutes. Than in saline for 30-60 seconds. Clean once again with cleaning solutions, rinse well and store overnight in the conditioning solution.

General Information Regarding Scleral Lens Wear

If you are new to contact lenses or wore a different type of lenses, please note that a period of adaptation of 3-5 days may be required. If no contraindications are found by your contact lens practitioner, you may be able to wear these lenses daily from 10-16 hours.

Contact lens wear is safe and comfortable if proper hygiene and lens care are followed meticulously. However, in the unlikely event of developing any of the following symptoms;

-Eyes stinging, burning, itching (irritation), or other eye pain
-Lenses are less comfortable than when first placed on eye
-Feeling of something in the eye such as a foreign body or scratched area
-Excessive watering (tearing) of the eyes
-Unusual eye secretions
-Redness of the eyes
-Reduced sharpness of vision (poor visual acuity)
-Blurred vision, rainbows, or halos around objects
-Sensitivity to light (photophobia)
-Dry eyes

REMOVE YOUR LENSES IMMEDIATELY

If the discomfort or problem stops, then look closely at the lens. If the lens is in any way damaged, **DO NOT** put the lens back on your eye. Place the lens in the storage case and contact Mr Levit. If the lens has dirt, an eyelash, or other foreign objects on it, or the problem stops and the lens appears undamaged, you should thoroughly clean, rinse and disinfect the lens; then reinsert it. If the problem continues, you should IMMEDIATELY remove it and contact Mr Levit.

Contact Details

If you have any questions regarding any aspect of contact lens wear contact Mr Levit at;
The Ophthalmology Department
Central Middlesex Hospital
Acton Lane London NW10 7NS
Tel 07813160631, email; Alexander.Levit@nwlh.nhs.uk

Appendix II

Appendix II. A. Baseline clinical information

Baseline information CRF

Scleral Vs Corneal RGP lenses

Date:	Examiner: A. Levit
General Information	
Participant's Serial Nr.	
DOB	Age
Gender	
Occupation	

Race					
Condition Information					
Cornea irregularity type OD	KC Nipple	PMD	Globus	Post KC	Graft DLK
	KC oval				Graft PK
	KC mixed				INTACS
Cornea irregularity type OS	KC Nipple				Graft DLK
	KC oval				Graft PK
	KC mixed				INTACS
Diagnosis age:					
Pachymetry:	OD	OS			
K_{max}	OD	OS			
Surface Regularity Indices:	OD	OS			

Lens Information of participants own lens

	OD					OS				
Lens type	Type	Material	Spherical	toric	quadrant	Type	Material	Spherical	toric	quadrant
Lens parameters	OZR	OZD	TD	BVP	edge	custom	OZR	OZD	TD	BVP	edge	custom
Lens fit central	bearing	Alignment	clearance			bearing	alignment	clearance		
Lens fit periph	inadequate	Optimal	excessive			inadequate	Optimal	excessive		
Lens Condition 0-10	0-2 unacceptable	3-4 Poor	5-6 adequate	7-8 good	9-10 New	1-2 unacceptable	3-4 Poor	5-6 adequate	7-8 good	9-10 New

Comfort 0-10	1 unbearable, 10 cannot feel		1 unbearable, 10 cannot feel	
Vision 0-10	1 very poor, 10 excellent		1 very poor, 10 excellent	
Visual Acuity				
Over refraction				
sphere				
cyl				
axis				
VA				

Eye	OD				OS			
Visual Measures	1.	2.	3.	Ø	1.	2.	3.	Ø
LogMAR BCVA								
CSF Row A 3cpd								
CSF Row B 6cpd								
CSF Row C 12cpd								
CSF Row D 18cpd								

Clinical findings on lens removal. Efron Scale from 0-5 in 0.1 steps

Condition	OD	OS
Blepharitis		
MGD		
SLK		
Corneal Infiltrates		
Corneal Ulcer		

Endothelial Polymegathism		
Endothelial Blebs		
Corneal Distortion		
Conjunctival Redness		
Bulbar		
Limbal		
Conjunctival NaFl Staining		
Bulbar		
Limbal		
Tarsal Conjunctival Papillae		
Corneal NaFl Staining		
central		
Peripheral (limbal)		
Limbal Vascularisation		
Epithelial Microcysts		
Corneal Oedema		

Detail of QOL Questionnaire (1-10 scale in steps of 1)

Question No	Score	Appendix Q No	Score
1		A1	
2		A2	
3		A3	
4		A4	
5		A5	
6		A6	
7		A7	
8		A8	
9		A9	

10		A10	
11		A11a	
12		A11b	
13		A12	
14		A13	
15		Total	
15a			
15b			
15c			
16			
16a			
17			
18			
19			
20			
21			
22			
23			
24			
25			
Total			

Appendix II.B. Data collection CRF

Data Collection (naive data collector) CRF

Scleral Vs Corneal RGP lenses

Date:	Examiner:
Participant's Serial No	
Details	
Average Days per week:	Hours per day:

Eye	OD		OS	
Visual Acuity				
Over-Refraction				
Sphere				
Cylinder (-ve)				
Axis				
VA				
Comfort 0-10	1 unbearable, 10 cannot feel		1 unbearable, 10 cannot feel	
Vision 0-10	1 very poor, 10 excellent (perfect)		1 very poor, 10 excellent (perfect)	

Visual Quality Outcome Measures								
Eye	OD				OS			
	1.	2.	3.	Ø	1.	2.	3.	Ø
LogMAR BCVA								
CSF A 3cpd								
CSF B 6cpd								
CSF C 12cpd								
CSF D 18cpd								
Clinical Findings on Lens Removal from 0-5 in 0.1 steps								

Eye	OD	OS
Blepharitis		
MGD		
SLK		
Corneal Infiltrates		
Corneal Ulcer		
Endothelial Polymegathism		
Endothelial Blebs		
Corneal Distortion		
Conjunctival Redness		
Bulbar		
Limbal		
Conjunctival Staining		
Bulbar		
Limbal		
Tarsal Conjunctival Papillae		
Corneal Staining		
central		
Peripheral (limbal)		
Limbal Vascularisation		
Epithelial Microcysts		
Corneal Oedema		

Appendix II. C. Fitted Lens Information

Patient Serial No		Randomised to		Fitter	
Corneal RGP				Scleral RGP	
Lens Type	RK2	date	Material	Zenlens	date	Material
OD		OS		OD	OS
Type					
OZR					
OZR2 (toric)					
SAG					
Diameter					
Power (Sphere)					
Power (cyl)					
Axis (negative cyl)					
LCD (limbal sag)					
APS (edge spec)					
Edge lift					
Custom Quadrant fit					
Comfort 1-10					
Vision 1-10					
Over refract Sphere					
OR cylinder					
OR axis					
VA					
No fitted for best fit					
No exchanged					

Appendix III

Appendix III. A. Good clinical practice certificate

EPIGEUM

Certificate

Number: Prog925030002

This is to certify that

Alex Levit

of North West London Hospitals NHS Trust

Successfully completed the course

Good Clinical Practice Online

Protocol and Associated Documents	90%
Applications, Agreements and Approvals	75%
Trial Master Files	81%
Conducting the trial	87%
Safety Reporting	86%

as part of the Epigeum Online Course System course programme.
Dated 08 May 2014

Appendix III.B. IRAS approval certificate

NHS
Health Research Authority

NRES Committee London - Camden & Kings Cross
Room 001
Jarrow Business Centre
Rolling Mill Road
Jarrow
Tyne & Wear
NE32 3DT

Telephone: 0191 4283545

05 August 2015

Mr Alexander Levit
The Eye Department Central Middlesex Hospital
Acton Lane,
London
NW10 7NS

Dear Mr Levit

Study title: **A randomised controlled research to compare the visual quality, clinical performance and effect on vision related quality of life of Rigid Gas Permeable (RGP)Scleral contact lenses to Corneal RGP contact lenses in participants with Keratoconus and other Irregular Cornea disorders (IC)**
REC reference: **15/LO/1067**
Protocol number: **11122014**
IRAS project ID: **162888**

Thank you for your letter of 4 August 2015. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 31 July 2015

Documents received

The documents received were as follows:

Document	*Version*	*Date*
IRAS Checklist XML [Checklist_04082015]		04 August 2015
Other [Informed Consent Document]	V2	23 July 2015
Participant consent form [Consent Form]	3	04 August 2015
Participant information sheet (PIS) [Participant information sheet]	4	04 August 2015

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		30 March 2014
GP/consultant information sheets or letters [Letter to GP]	1.0	01 December 2014
Instructions for use of medical device [Handling and Care of Scleral Contact Lenses]	1	15 April 2015
Instructions for use of medical device [Patient Information on receipt of Contact Lenses]	1	18 April 2015
IRAS Checklist XML [Checklist_04082015]		04 August 2015
Letters of invitation to participant [Participant Information Research Details]	1	18 April 2015
Other [Martin Benwell CV]		09 May 2014
Other [NWLH NHS Trust R&D Project Registration Form]	4	24 August 2014
Other [NWLH NHS Trust R&D Project Registration Form - Simon Levy signature]		24 August 2014
Other [Anthony Stanton CV]		01 December 2014
Other [Informed Consent Document]	V2	23 July 2015
Participant consent form [Consent Form]	3	04 August 2015
Participant information sheet (PIS) [Participant information sheet]	4	04 August 2015
REC Application Form [REC Form 19052015]		19 May 2015
Research protocol or project proposal [Research Protocol]	V4	05 February 2015
Summary CV for Chief Investigator (CI) [Alexander Levit]		18 April 2015
Summary CV for supervisor (student research) [Bruce Evans]		09 May 2014
Validated questionnaire [National Eye Institute Visual Functioning Questionnaire - 25 (VFQ-25)]		01 January 2000

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

15/LO/1067 **Please quote this number on all correspondence**

Yours sincerely

Mrs Helen Wilson
REC Manager (Covering)

E-mail: nrescommittee.london-camdenandkingscross@nhs.net

A Research Ethics Committee established by the Health Research Authority

Copy to: Professor Nicola Crichton

Dr Simon Lewis, North West London Hospitals NHS Trust

Appendix IV

Appendix IV. A. Database Libre Office, data entry, extraction and analysis

Data Entry Methodology

Introduction

The data generated by the experiments needs to be entered into a computer for statistical analysis, and it is important to use a tool that makes it as simple as possible to enter the data correctly. The best tool to use for this purpose is a database, using a graphical user interface to enter data into the underlying database tables.

We developed a simple database using the open-source LibreOffice office productivity software suite (https://www.libreoffice.org/). This software provides a relational database (named 'Base'), and includes tools to create forms and queries – these are respectively windows that can be used to view and enter data, and database commands that extract specific subsets of the data in the system. The various forms in the database are managed by a small amount of programming using LibreOffice's Basic macro language. This is required to configure the forms to display the correct data when they are opened.

LibreOffice Base is very flexible – it can be configured so that the underlying data and forms/queries are stored in separate files, and it can be used as the front-end to manipulate data stored in other vendors' databases. However, in this case the scope of the database is small enough that it makes sense to keep everything in a single file – including the data, forms and queries. The database can be opened simply by double-clicking on the file (provided the LibreOffice software is installed).

The LibreOffice suite is available for a wide range of platforms, including all recent versions of Microsoft Windows, Apple Macintoshes, and common Linux distributions. Therefore, the database file is portable between different systems simply by copying the file from one computer to another – and no special installation is required to configure the database on a new machine.

Database Purpose

The function of the database is to simplify data entry, not to analyse the data. However, although visual acuity data is entered into the database in Snellen format, the data is stored in the underlying tables using its equivalent LogMAR value. This allows the user to enter data in the more intuitive Snellen format, and automatically convert it to the LogMAR format which is more useful for statistical analysis.

Where possible the database uses drop-down selection boxes and tick boxes for data entry rather than allowing manual typing. This reduces as far as possible the opportunity for typographical errors in the entered data. Drop-down selections are used for fields such as Gender, Race, and lens fit information. Tick boxes are used for all questions that are essentially Boolean in nature – i.e. yes/no or true/false data items.

Database Workflow

Data entry follows a simple workflow, starting from the main form used for entering data about each subject. The data entry fields are laid out to match the format of the raw data captured in the handwritten forms used during examinations.

The top-level form is shown below. It contains basic data about the subject, including the condition of their eyes and their own contact lens parameters. On the right-hand side the buttons can be clicked to open forms containing baseline data and results for each phase of the experiment.

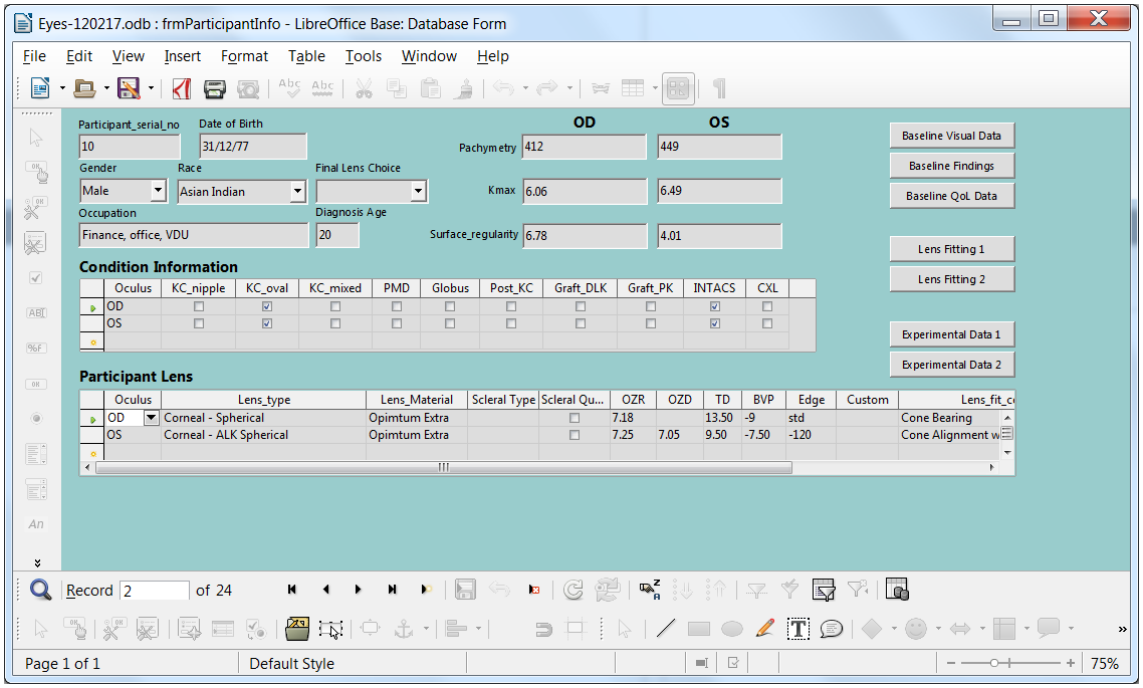


Figure 1. Top-level data entry form.

When the buttons on the right-hand side are clicked, the forms that open are set up to show data for the same subject as shown in the main form. This is achieved using LibreOffice Basic macro programming that runs when buttons are pressed, and it ensures that data entered on linked forms refers to the correct individual, without any effort on the part of the database user.

For example, when the button on the top right of the above form is clicked, the form shown below opens, displaying data for the same used as was selected in the main form.

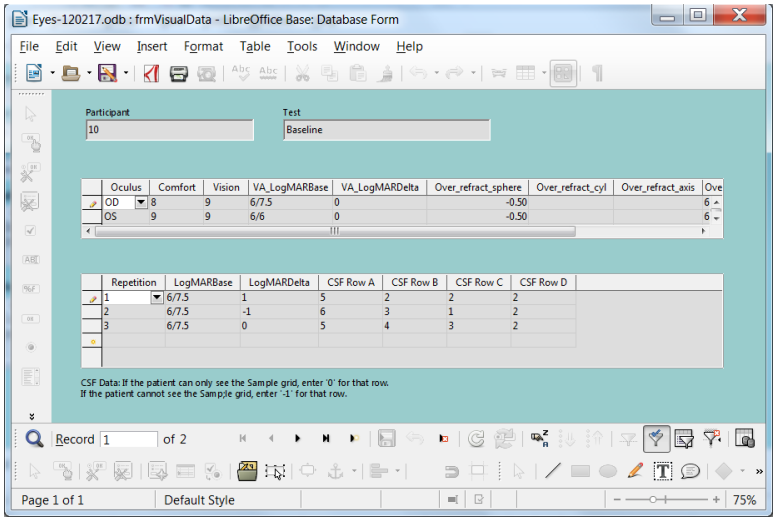


Figure 2. Baseline Visual Data form.

Running Queries

Queries are run using the SQL database query language. Although this is fundamentally a text-based query language, LibreOffice Base provides a graphical tool to automatically create the SQL commands required to pull data out of the database. Queries can contain parameters to be entered by the user when the query runs, so a single query can be used to extract equivalent data for different experimental phases, for example.

The figure below shows an example of the graphical tool used to create queries. The top half of the window contains tables defined in the database, and the lines drawn between them indicate the relationships between the tables (the key feature of this type of software, hence the name relational database). The bottom half of the window shows the fields that will be present in the output data from this query, drawn from the three tables included in the query. The database will automatically collate the correct data from the linked fields in the tables to generate the result from the query.

Although the fundamental purpose of queries is to extract subsets of data from the database, some basic data manipulation is also used. This includes:

splitting the date into separate day/month/year fields so that the date is not presented to analysis tools as a text string that has to be processed to pull out the individual fields

Sorting the data in ascending order of participant ID.

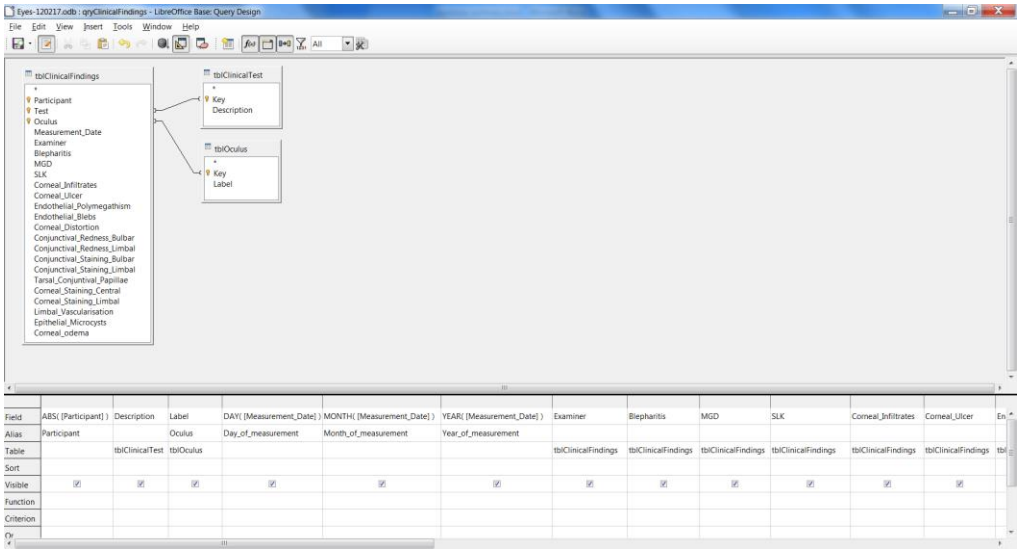


Figure 3. Graphical tool for generating database queries.

Data Analysis

When a query is run the output is in the form of a table of data. This is copied and pasted into Excel, for example, and it can then be saved to disk and/or used for basic analysis in Excel. Although Excel is not the right tool for complex data analysis, some basic data manipulation is possible.

Currently an Excel spreadsheet is used for processing VFQ-25 Quality-of-Life data. An Excel template spreadsheet has been created, and raw data from a database query is pasted into the top-left of the first worksheet of this template. Cell calculations then flow from this data and the last worksheet of the spreadsheet shows the average scores for each participant, with the raw answers recoded according to Version 2000 of the VFQ-25.

Appendix IV. B. NEI-VFQ Spreadsheet information

QoL Spreadsheet Information

Introduction

The database contains raw data from the Quality-of-Life questionnaire, with individual answers scored in different ranges. Reference [1] provides an algorithm for recoding these answers onto a scale of 0 to 100, and for grouping individual questions together into "sub-scales".

The Excel spreadsheet template "QoL Recode" is used to recode the results of Quality-of-Life questionnaire according to reference [1]. The steps involved are as follows:

-Extract raw QoL data from the database and copy into the spreadsheet.

-Recode individual answers onto a scale of 0 to 100

-Count how many questions within each 'sub-scale' have been answered, so that missing answers can be accounted for.

-Generate average scores for each 'sub-scale'

Extracting Raw Data from the Database

The database has a query called qryQualityOfLife which is used to extract QoL data from the database. Double-click the query to run it, and enter the experiment for which QoL data is required – one of Baseline, Experimental_1, or Experimental_2.

Copy all the data that appears in the query results window, then paste it into the top-left cell of the first worksheet of a new spreadsheet document created from the Excel template "QoL Recode". This first worksheet is called 'Raw data'. It is important to paste the data correctly, as all calculations flow from this first page.

Recoding Individual Answers

Reference [1] defines how the scores from individual questions map onto the scale of 0 to 100. The second worksheet in the spreadsheet (called 'Recoded data') implements this recoding, for individual questions.

The worksheet is split into two sections. The top section runs the recoding calculation for each question, setting the result to zero if the answer to the question is missing (this is required as part of the algorithm specified in [1].

Accounting for Missing Answers

The lower section of the worksheet 'Recoded data' fills a table with one value for each question – a zero if the data is missing for that question, and a one if the data is present. This data is used when calculating sub-scales, so that missing data is handled correctly. The score for each sub-scale ignores missing data – i.e. the calculation has to keep count of how many valid answers are present in each sub-scale.

Generating Average Scores

Each sub-scale score is the average of a number of individual questions – i.e. the sum of those individual scores divided by the number of scores. The top section of the worksheet 'Summed data' contains the summed values, taken from the 'Recoded data' worksheet.

Each cell in the top section of the worksheet contains the sum of the question scores for that sub-scale. If a question is missing its value is zero in 'Recoded data', so it doesn't affect the average. Therefore, there's no need to check at this point which individual questions are present.

The lower section of the worksheet 'Summed data' contains the count of valid answers present for each sub-scale. This is done by summing the values for each sub-scale in the lower section of worksheet 'Recoded data' – where each cell contains a zero if the data is missing and a 1 if it's present. Therefore, this sum of ones and zeros adds up to the number of valid questions that make up the sub-scale.

The worksheet 'Processed data' pulls all the information together to give the final scores for each sub-scale. For each sub-scale score, the worksheet checks whether there are any valid data for the sub-scale. If not, the cell is left blank. If there is at least one valid answer, the sub-scale is calculated as the sum of the valid answers divided by the number of valid answers.

References

[1] "The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25)", Version 2000.

Appendix IV.C. NEI-VFQ data entry, coding and analysis

The scores from the NEI-VFQ questionnaire were entered into the specially prepared database software as raw data, with individual answers scored in different ranges. The NEI-VFQ manual (Mangione, 2000) provides an algorithm for recoding these answers onto a scale of 0-100, and for grouping individual questions together into "sub-scales".

The Excel spread sheet template "QoL Recode" was developed to recode the results of the NEI-VFQ questionnaire according to (Mangione, 2000) as follows:

1. Extract raw QoL data from the database and copy into the spread-sheet.
2. Recode individual answers onto a scale of 0-100
3. Count how many questions within each 'sub-scale' have been answered, so that missing answers can be accounted for.
4. Generate average scores for each 'sub-scale'.

Data extraction

The database has a query called *qryQualityOfLife* which is used to extract NEI-FVQ data from the database. The query is run by double-clicking it, entry of the required experimental QoL data; one of Baseline, Experimental_1 (first lens in sequence), or Experimental_2 (second lens in sequence). The data that appears in the query results window is copied and pasted into the top-left cell of the first worksheet of a new spread sheet document created from the Excel template "QoL Recode". This first worksheet is called 'Raw data'.

Recoding individual answers

Mangione (2000) defines how the scores from individual questions map onto the scale of 0-100 (Mangione, 2000). The second worksheet in the spread-sheet (called 'Recoded data') implements this recoding, for individual questions. The worksheet is split into two sections. The top section runs the recoding calculation for each question, setting the result to zero if the answer to the question is missing (this is required as part of the algorithm specified in Mangione (2000).

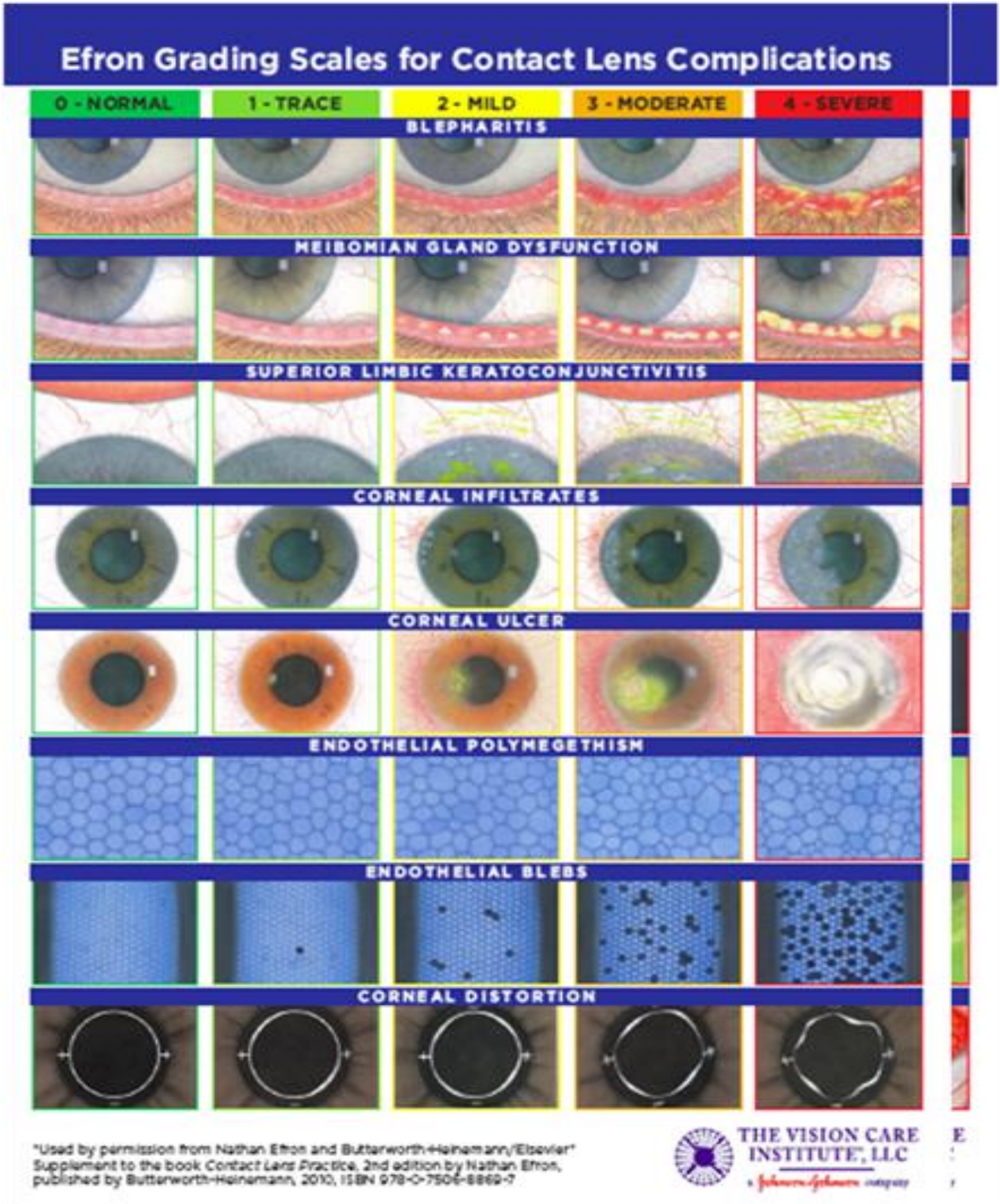
Accounting for missing answers

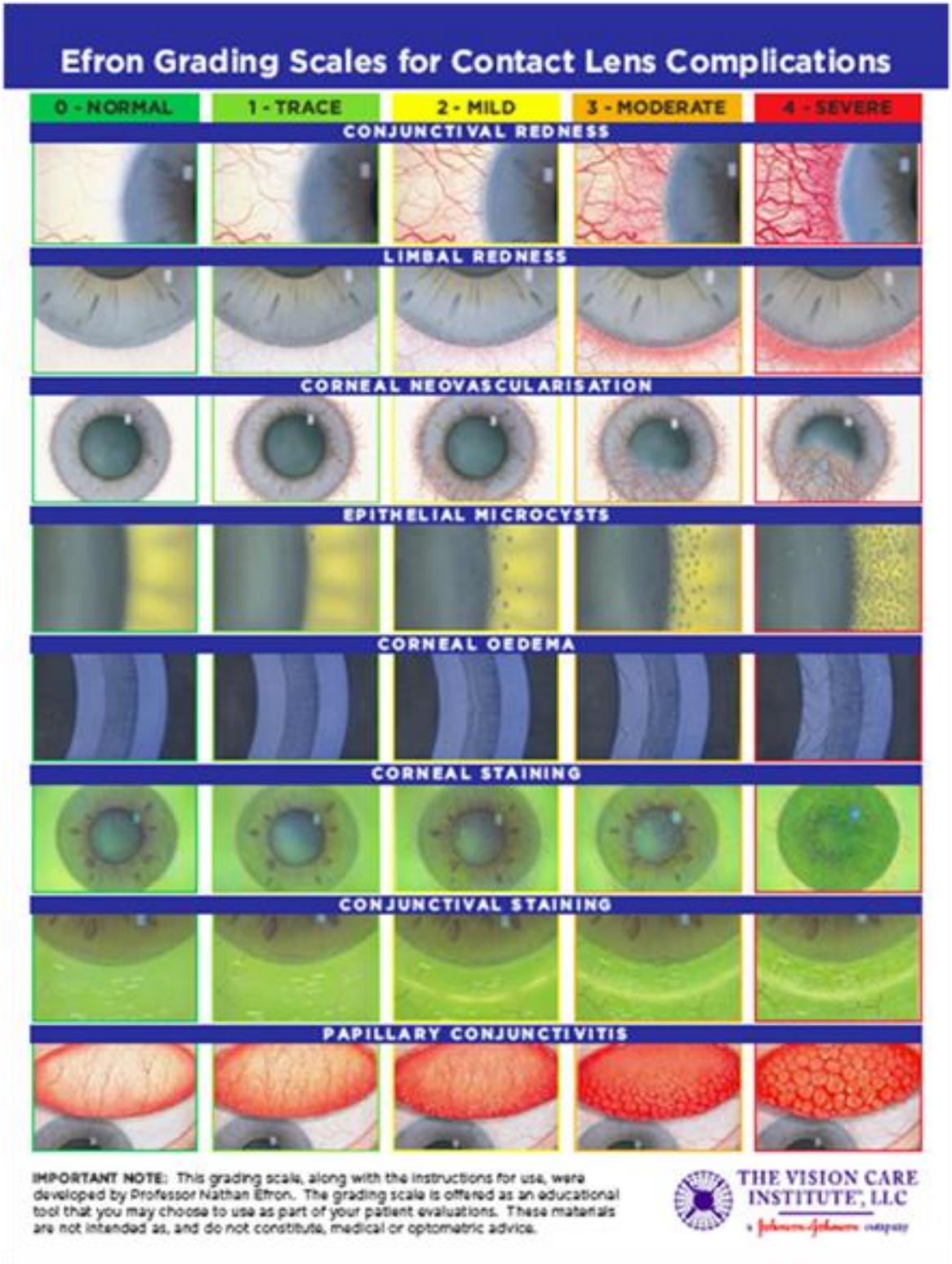
The lower section of the worksheet 'Recoded data' fills a table with one value for each question – a zero if the data are missing for that question, and a one if the data are present. These data are used when calculating sub-scales, so that missing data are handled correctly. The score for each sub-scale ignores missing data – i.e. the calculation has to keep count of how many valid answers are present in each sub-scale.

Generating average scores

Each sub-scale score is the average of a number of individual questions (Table 4.6) – i.e., the sum of those individual scores divided by the number of scores. The top section of the worksheet 'Summed data' contains the summed values, taken from the 'Recoded data' worksheet. Each cell in the top section of the worksheet contains the sum of the question scores for that sub-scale. If a question is missing its value is zero in 'Recoded data', so it doesn't affect the average. The lower section of the worksheet 'Summed data' contains the count of valid answers present for each sub-scale. This is done by summing the values for each sub-scale in the lower section of worksheet 'Recoded data' – where each cell contains a zero if the data are missing and a 1 if it the data are present. Therefore, this sum of ones and zeros forms the number of valid questions that make up the sub-scale. The worksheet 'Processed data' pulls all the information together to give the final scores for each sub-scale. For each sub-scale score, the worksheet checks whether there are any valid data for the sub-scale. If not, the cell is left blank. If there is at least one valid answer, the sub-scale is calculated as the sum of the valid answers divided by the number of valid answers.

Appendix IV. D. **Table 4.7.** *The Efron grading scales contact lens complications (J&J vision care institute)*




Efron Grading Scales for Contact Lens Complications
0 - NORMAL
1 - TRACE
2 - MILD
3 - MODERATE
4 - SEVERE
CONJUNCTIVAL REDNESS
LIMBAL REDNESS
CORNEAL NEOVASCULARISATION
EPITHELIAL MICROCYSTS
CORNEAL OEDEMA
CORNEAL STAINING
CONJUNCTIVAL STAINING
PAPILLARY CONJUNCTIVITIS
IMPORTANT NOTE: This grading scale, along with the instructions for use, were developed by Professor Nathan Efron. The grading scale is offered as an educational tool that you may choose to use as part of your patient evaluations. These materials are not intended as, and do not constitute, medical or optometric advice.
THE VISION CARE INSTITUTE, LLC

Appendix V

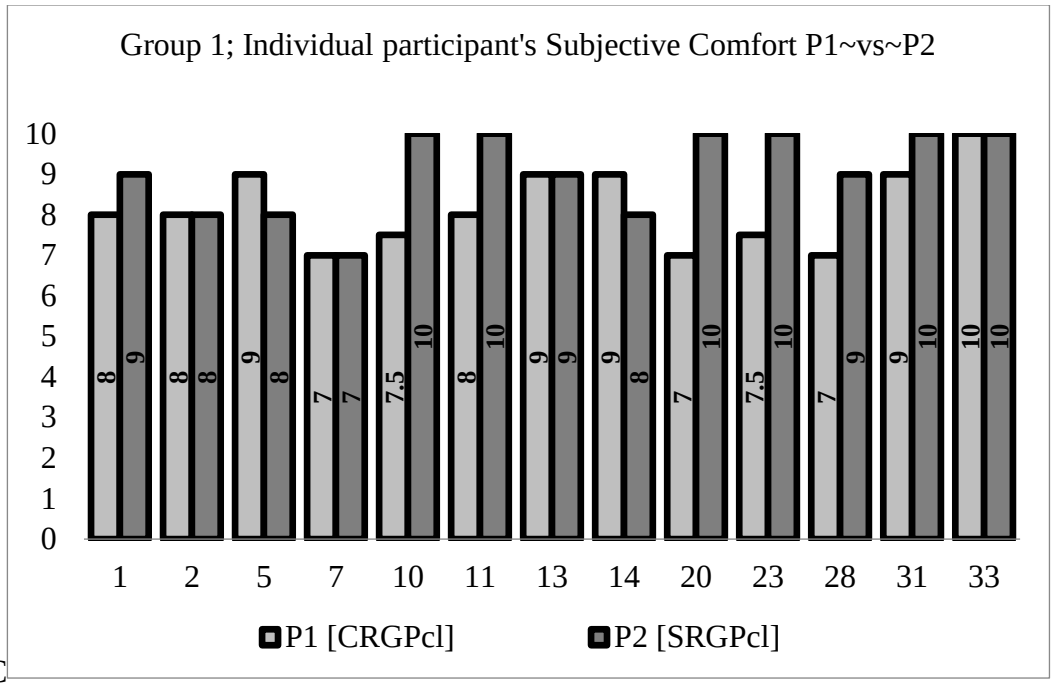
Appendix V.A. Table 5.27.a *OD/OS averages of the CS numerical scores for CRGPcl and SRGPcl*

	CRGPcl					SRGPcl			
SN	3 CPD	6 CPD	12 CPD	18 CPD		3 CPD	6 CPD	12 CPD	18 CPD
1	5.34	5.00	5.67	5.17		4.34	3.67	4.50	4.67
2	4.84	5.00	5.50	6.00		5.50	5.50	6.00	6.67
3	5.34	5.17	4.67	5.34		3.17	3.50	3.17	3.00
4	4.00	4.67	5.33	5.00		6.00	4.33	5.67	6.67
5	4.00	4.00	3.67	4.67		3.00	3.67	3.33	3.00
6	5.84	4.84	4.67	4.33		6.00	4.50	4.50	4.33
7	5.00	5.34	4.67	5.50		4.84	5.17	5.50	5.50
8	6.00	5.00	4.67	4.00		6.00	4.33	5.67	5.33
9	5.84	6.50	4.00	3.50		5.50	4.50	3.83	4.50
10	5.33	3.34	2.00	2.17		3.67	1.67	4.83	3.67
11	3.84	3.84	4.50	2.50		4.67	5.00	3.50	3.33
12	5.50	4.17	4.34	3.34		4.34	4.34	4.17	4.67
13	4.67	4.67	5.50	5.84		5.00	5.17	3.17	5.34
14	5.84	4.50	4.67	3.17		3.50	4.00	2.00	2.50
15	7.00	7.17	6.34	7.50		6.17	6.33	6.34	6.34
16	6.84	5.17	3.33	4.17		5.50	5.67	5.50	6.17
17	6.84	7.33	7.84	7.84		5.67	5.84	6.17	7.17
19	6.00	5.50	4.50	4.84		5.00	5.00	5.00	5.00
20	5.33	5.84	5.50	5.84		5.50	4.50	5.00	5.00
21	6.50	5.34	4.67	2.34		6.84	5.34	6.17	4.50
23	3.84	2.84	3.00	3.00		3.50	3.17	1.00	2.00
24	6.50	6.50	6.50	5.67		6.84	5.33	6.67	5.17
26	6.00	5.67	6.00	7.00		6.00	6.33	6.33	7.33
27	5.50	4.50	4.84	5.00		6.17	3.34	6.00	4.84
28	6.17	4.67	4.17	4.00		6.00	4.33	4.00	4.34
30	6.00	6.00	6.67	7.00		5.50	5.84	5.50	5.84
31	6.50	5.17	7.00	5.00		6.50	5.34	7.17	5.34
32	4.67	4.50	2.67	2.67		6.17	4.67	3.34	2.83
33	4.84	3.17	3.34	2.84		5.17	3.17	4.17	3.50
34	6.83	6.17	6.50	4.84		5.00	3.67	4.00	3.67

Appendix V. B. Table 5.35 *Period sums and differences of means of all domains of NEI-VFQ in group 1&2*

Group 1							Group 2					
SN	P1	P2	P1+P2	P2-P1	A-B		SN	P1	P2	P1+P2	P2-P1	A-B
1	94.58	84.62	179.20	-9.97	9.97		3	88.40	90.35	178.75	1.94	1.94
2	96.53	96.11	192.64	-0.42	0.42		4	83.13	96.32	179.44	13.19	13.19
5	72.74	56.04	128.78	-16.70	16.70		6	94.31	88.47	182.78	-5.83	-5.83
7	90.87	90.94	181.81	0.07	-0.07		8	94.83	90.49	185.31	-4.34	-4.34
10	91.46	94.65	186.11	3.19	-3.19		9	82.80	48.14	130.95	-34.66	-34.66
11	93.71	88.30	182.01	-5.42	5.42		12	78.61	80.10	158.72	1.49	1.49
13	97.50	99.17	196.67	1.67	-1.67		15	76.84	88.68	165.52	11.84	11.84
14	75.76	79.66	155.42	3.90	-3.90		16	94.10	88.26	182.36	-5.83	-5.83
20	89.62	96.39	186.01	6.77	-6.77		17	89.93	94.79	184.72	4.86	4.86
23	76.22	70.49	146.70	-5.73	5.73		19	97.36	97.95	195.32	0.59	0.59
28	89.44	95.45	184.90	6.01	-6.01		21	80.98	76.67	157.65	-4.32	-4.32
31	83.19	93.06	176.25	9.86	-9.86		24	85.66	92.47	178.13	6.81	6.81
33	90.28	92.60	182.88	2.33	-2.33		26	81.18	62.57	143.75	-18.61	-18.61
							27	86.18	86.04	172.22	-0.14	-0.14
							30	96.32	94.58	190.90	-1.74	-1.74
							32	69.77	55.23	125.00	-14.55	-14.55
							34	74.41	69.51	143.92	-4.90	-4.90

Appendix V. C. Subjective comfort and vision of participants in group 1, period 1 vs period 2



C

Figure 5.43 *Subjective comfort of each participant in group 1, period 1 vs period 2*

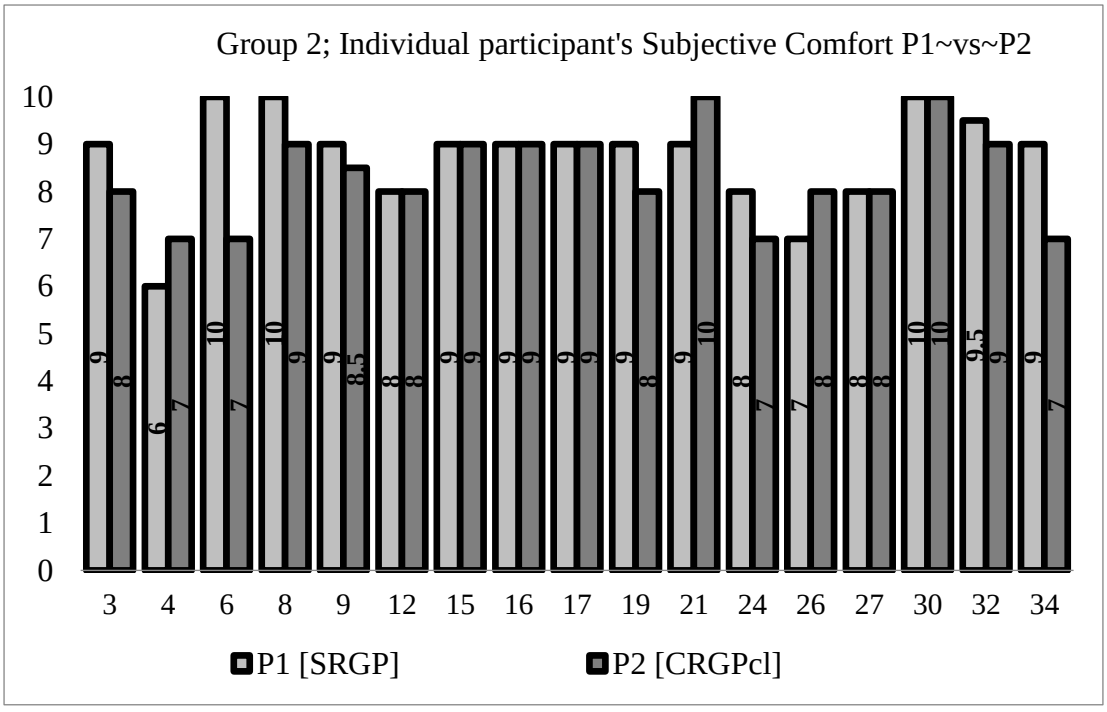


Figure 5.44 *Subjective comfort of each participant in group 2, period 1 vs period 2*

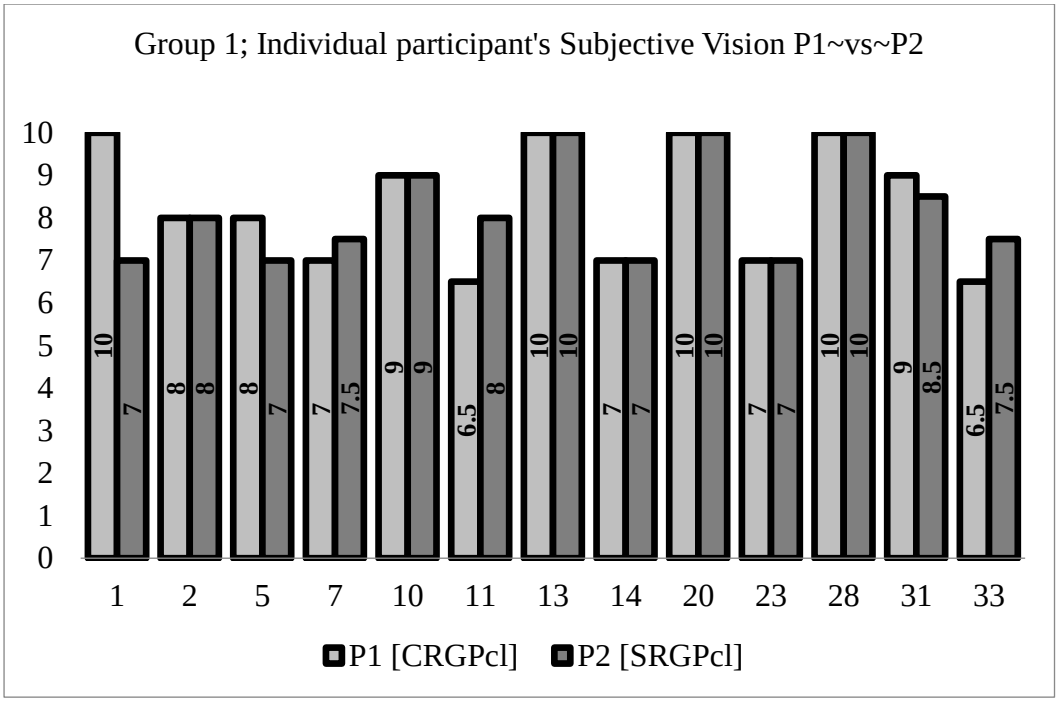


Figure 5.45 *Subjective vision of each participant in group 1, period 1 vs period 2*

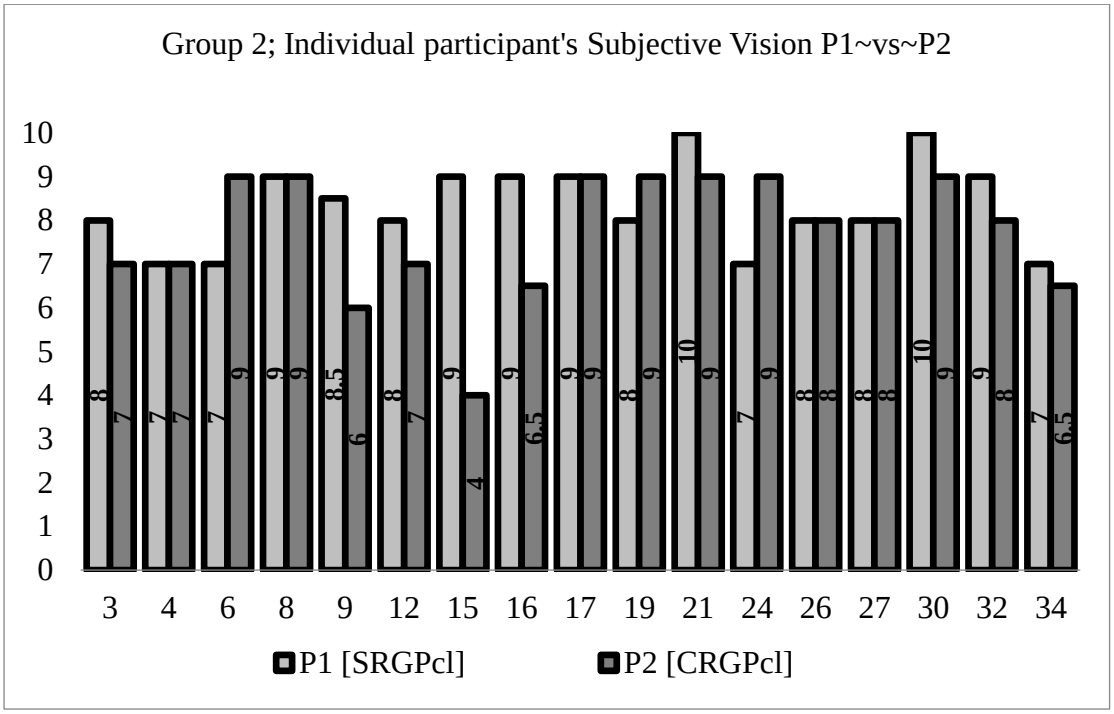


Figure 5.46 *Subjective vision of each participant in group 2, period 1 vs period 2*

Appendix V. D. Table 5.40 *SPC and vision CRGPcl and final lens choice*

SN	Comfort	Vision	Final lens choice
1	8	10	CRGPcl
2	8	8	SRGPcl
3	7	7	CRGPcl
4	8	7	CRGPcl
5	9	8	CRGPcl
6	4	9	SRGPcl
7	7	7	CRGPcl
8	9	9	CRGPcl
9	5	6	SRGPcl
10	7.5	9	SRGPcl
11	8	6.5	SRGPcl
12	7	7	SRGPcl
13	9	10	CRGPcl
14	9	7	CRGPcl
15	9	4	CRGPcl
16	6.5	6.5	SRGPcl
17	10	9	CRGPcl
19	10	9	CRGPcl
20	7	10	SRGPcl
21	6	9	SRGPcl
23	7.5	7	SRGPcl
24	8	9	CRGPcl
26	6	8	SRGPcl
27	7	8	CRGPcl
28	7	10	CRGPcl
30	9	9	CRGPcl
31	9	9	SRGPcl
32	7	8	SRGPcl
33	10	6.5	SRGPcl
34	9	6.5	CRGPcl

Appendix V. E Table 4.10. *Randomisation order*

Number	Randomised to	Comments
1	C	
2	C	
3	S	
4	S	
5	C	
6	S	
7	C	
8	S	
9	S	
10	C	
11	C	
12	S	
13	C	
14	C	
15	S	
16	S	
17	S	
18	C	Lost to aftercare
19	S	
20	C	
21	S	
22	C	Lost to aftercare
23	C	
24	S	
25	C	Lost to aftercare
26	S	
27	S	
28	C	
29	C	Lost to aftercare
30	S	
31	C	Sequential
32	S	Sequential
33	C	Sequential
34	S	Sequential

Appendix V. F. Table 4.5. *Item number translation from the 51-Item field test version to the VFQ 25* Mangione (2000).

Field Test	Sub-scale	Status	VFQ-25	Field Test	Sub-scale	Status	VFQ-25
1	General health	S	1	29	Social Function	-----	-----
2	General health	A	A1	30	Social Function	A	A9
3	General vision	S	2	31	Social Function	S	13
4	Expectations	-----	-----	32	Distance Vision	A	A8
5	Wellbeing/distress	S	3	33	Distance Vision	A	A7
6	Wellbeing/distress	-----	-----	34	Distance Vision	S	14
7	Ocular pain	S	19	35	Driving (filter item)	S	15
8	expectations	-----	-----	35a	Driving (filter item)	S	15a
9	expectations	-----	-----	35b	Driving (filter item)	S	15b
10	expectations	-----	-----	35c	Driving	S	15c
11	Wellbeing/distress	S	25	36	Driving	-----	-----
12	Ocular Pain	S	4	37	Driving	S	16
13	Wellbeing/distress	-----	-----	38	Driving	S	16a*
14	General Vision	A	A2	39a	Role limitations	S	17
15	Near Vision	S	5	39b	Role limitations	A	A11a
16	Near Vision	A	A3	39c	Well-being/distress	-----	-----
17	Near Vision	S	6	39d	Role limitations	-----	-----
18	Near Vision	-----	-----	39e	Role limitations	A	A11b
19	Near Vision	S	7	39f	Role limitations	S	18
20	Distance Vision	S	8	40	Well-being/distress	A	A12
21	Distance Vision	-----	-----	41	Dependency	S	20
22	Distance Vision	S	9	42	Well-being/distress	S	21
23	Peripheral Vision	S	10	43	Well-being/distress	S	22
24	Distance Vision	A	A6	44	Dependency	-----	-----
25	Social Function	S	11	45	Dependency	A	A13
26	Near Vision	A	A4	46	Dependency	S	23
27	Colour Vision	S	12	47	Dependency	S	24
28	Near Vision	A	A5				

Table 45. Terms: S=retained in the VFQ-25, A=retained in the appendix should be used for the VFQ-39, -----=deleted from the VFQ-25 & VFQ-39. *=VFQ-25 item 16a was listed in previous versions as part of the appendix of supplemental items (#A10).

Appendix V. G. Table 5.33 *OD/OS logCS, 6CPD scores and period sums and differences group 1 and 2*

6 CPD Sums and Differences										
Group 1 (AB) CS 6 CPD						Group 2 (BA) CS 6 CPD				
P1(A)	P2(B)	P1+P2	P2-P1	A-B		P1(B)	P2(A)	P1+P2	P2-P1	A-B
1.79	1.69	3.48	-0.10	0.10		1.80	1.70	3.50	-0.10	-0.10
1.84	1.92	3.76	0.08	-0.08		1.75	1.79	3.54	0.04	0.04
1.70	1.65	3.35	-0.05	0.05		1.77	1.82	3.59	0.05	0.05
1.79	1.97	3.76	0.18	-0.18		1.74	1.84	3.58	0.10	0.10
1.41	1.50	2.90	0.09	-0.09		1.84	1.99	3.83	0.15	0.15
1.84	1.67	3.51	-0.17	0.17		1.77	1.70	3.47	-0.07	-0.07
1.84	1.82	3.66	-0.02	0.02		2.12	2.09	4.21	-0.03	-0.03
1.77	1.70	3.47	-0.08	0.08		1.82	1.99	3.81	0.17	0.17
1.94	1.79	3.73	-0.15	0.15		2.07	2.09	4.16	0.02	0.02
1.73	1.33	3.06	-0.40	0.40		1.85	1.92	3.76	0.07	0.07
1.75	1.79	3.54	0.04	-0.04		1.87	1.92	3.78	0.05	0.05
1.80	1.97	3.76	0.17	-0.17		1.99	1.97	3.96	-0.02	-0.02
1.55	1.59	3.14	0.04	-0.04		2.04	1.94	3.98	-0.10	-0.10
						1.48	1.87	3.34	0.39	0.39
						1.99	1.97	3.96	-0.03	-0.03
						1.78	1.79	3.57	0.02	0.02
						1.64	2.02	3.65	0.38	0.38

Appendix V. H. Table 5.26 *Numeric CS scores of the research population*

CSF Numeric Scale		Statistic	Std. Error
3 CPD	Median	6.0	
Shapiro-Wilk (p<0.0001)	Interquartile Range	1.0	
	Mean	5.48	0.12
	95% CI for Mean	5.25-5.72	
	Std. Deviation	1.25	
	Skewness	-0.59	0.23 (z=-2.59)
	Kurtosis	1.67	0.45 (z=3.68)
6 CPD	Median	5.0	
Shapiro-Wilk (p<0.0001)	Interquartile Range	2.0	
	Mean	4.98	0.15
	95% CI for Mean	4.70-5.27	
	Std. Deviation	1.53	
	Skewness	-0.49	0.23 (z=-2.16)
	Kurtosis	0.51	0.45 (z=1.12)

12 CPD	Median	5.0	
Shapiro-Wilk (p=0.0001)	Interquartile Range	2.0	
	Mean	4.89	0.18
	95% CI for Mean	4.53-5.26	
	Std. Deviation	1.94	
	Skewness	-0.38	0.23 (z=-1.68)
	Kurtosis	-0.37	0.45 (z=-0.83)
18 CPD	Median	5.0	
Shapiro-Wilk (p=0.0002)	Interquartile Range	2.0	
	Mean	4.79	0.18
	95% CI for Mean	4.44-5.13	
	Std. Deviation	1.86	
	Skewness	-0.23	0.23 (z=-1.01)
	Kurtosis	-0.57	0.45 (z=-1.26)

Appendix V.I. Table 5.34 *NEI-VFQ 12 domains measured in the research population*

NEI-VFQ Descriptive Statistics						
	Shapiro-Wilk	Median	IQR	Min	Max	Mean (StdDev)
General health	*p < 0.0001*	77.50	5.00	45.00	100.00	79.59 (±12.45)
General vision	*p < 0.0001*	80.00	20.00	30.00	100.00	82.45 (±14.37)
Ocular pain	*p < 0.0001*	87.50	37.50	37.00	100.00	77.55 (±21.19)
Near activities	*p < 0.0001*	91.67	18.75	50.00	100.00	87.84 (±12.89)
Distance activities	*p < 0.0001*	91.67	20.83	50.00	100.00	87.96 (±12.38)
Social function	*p < 0.0001*	100.00	8.33	66.67	100.00	94.56 (±9.40)
Mental health	*p < 0.0001*	90.00	20.00	40.00	100.00	82.25 (±16.04)
Role difficulties	*P< 0.0001*	93.75	21.88	43.75	100.00	87.88 (±14.51)
Dependency	*p < 0.0001*	100.00	6.25	50.00	100.00	95.54 (±9.11)
Driving	*p < 0.0001*	83.33	16.67	41.67	100.00	84.18 (±13.53)
Colour vision	*p < 0.0001*	100.00	0.00	50.00	100.00	97.96 (±8.60)
Peripheral vision	*p < 0.0001*	100.00	0.00	25.00	100.00	91.84 (±17.22)
Total		**91.29**	**14.60**	**44.09**	**100.00**	**87.47 (±6.53)**

Appendix V.J.

Table 5.43a *Randomised demographics (*significant difference between the groups)*

Measure		**Groups**						**Difference** ***p value***
		Group 1			Group 2			
		N	Mean (*StdDev*)	Median (*IQR*)	N	Mean (*StdDev*)	Median (*IQR*)	
Gender	Male	11			12			*0.109*
	Female	2			5			
Age			39.5 (*14.2*)			38.8 (*9.3*)		*0.872*
Age at Diagnosis			23.2 (*5.0*)				20.0 (*8.0*)	*0.363*
Duration	CRGPcl wear			10.0 (*22.0*)		16.47 (*6.63*)		*0.363*
Ethnicities	Black African	3			2			*0.613*
	Asian Indian	5			8			
	Black Afro Caribbean	1			2			
	Caucasian white	4			5			
Corneal metrics	Kmax		6.04 (*0.47*)			6.31 (*0.59*)		*0.068*
	*****Pachymetry		423.2 (*45.1*)			462.8 (*44.7*)		*******0.002*
	SRI		1.59 (*0.24*)				1.47 (*0.48*)	*0.252*

Appendix V. K

Table 5.43b *Inferential crossover statistics summary*

		Group 1		Group 2		
Measure		**Mean (*StdDev*)**	**Median (*IQR*)**	**Mean (*StdDev*)**	**Median (*IQR*)**	***P***
ETDRS logMAR	Treatment effect		-0.01 (0.08)		0.00 (0.10)	0.563
	Carryover effect		0.14 (0.27)		0.03 (0.17)	0.281
	Period effect	0.0177 (0.08)		0.0006 (0.07)		0.541
CSF logCS all CPD	Treatment effect *crossover*	-0.035 (0.215)		0.03 (0.135)		0.316
	Treatment effect P1 (G1)	1.46 (0.13)				0.070
	Treatment effect P1 (G2)	1.56 (0.51)				
	Carryover effect	2.89 (0.31)		3.15 (0.25)		0.019*
	Period effect		0.05 (0.24)		0.00 (0.12)	0.711
CSF logCS 6 CPD	Treatment effect *crossover*	-0.0285 (0.16)		0.0641 (0.14)		0.104
	Treatment effect P1 (G1)	1.75 (0.17)				0.110
	Treatment effect P1 (G2)	1.84 (0.16)				
NEI-VFQ all Domains	Treatment effect		1.67 (10.53)		-1.74 (9.23)	0.483
	Carryover effect		182.0 (20.23)		178.1 (32.97)	0.245
	Period effect	-0.92 (1.37)		-1.235 (1.98)		0.343
NEI-VFQ Ocular pain	Treatment effect		12.5 (37.5)		0.00 (25.0)	0.170
	Carryover effect		175 (56.25)		150.0 (75.0)	0.263
	Period effect		0.02 (0.21)		0.04 (0.16)	0.563
LSCS	Treatment effect		1.0 (2.25)		-1.0 (2.50)	0.002*
	Carryover effect		17.0 (1.50)		16.0 (4.0)	0.183
	Period effect	-0.923 (±1.37)		-1.235 (1.98)		0.63
LSVS	Treatment effect		0.00 (0.50)		-0.50 (1.75)	0.213
	Carryover effect		16.0 (4.75)		16.0 (3.25)	0.592
	Period effect		0.00 (0.50)		-0.50 (1.75)	0.157
Final lens choice	CRGPcl	16 (53.3%)				
	SRGPcl	14 (46.7%)				
LSCS CRGPcl	CRGPcl chosen 16 (53%)		Median (IQR) 9.0 (1.75)			0.009*
	SRGPcl chosen 14 (46.7%)		Median (IQR) 7.0 (1.54)			

*Statistically significant *p<0.05*