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An Investigation of Computer Vision Syndrome with Smart Devices

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By

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Copyright Statement

Abstract

AN INVESTIGATION OF COMPUTER VISION SYNDROME WITH SMART DEVICES

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The overarching theme of the thesis was to investigate the association between smart device use and computer vision syndrome. The initial study designed and developed the Open Field Tear film Analyser (OFTA) enabling a continuous, real-time assessment of the tear film and blink characteristics during smart device use. The monocular OFTA prototype was validated and showed good intra- and inter-observer repeatability relative to the Oculus Keratograph 5M and Bausch and Lomb one position keratometer. Subsequently, tear osmolarity following engagement with reading and gaming tasks on smart device and paper platforms was investigated. Discrete measures of osmolarity pre- and post-engagement with the tasks were obtained with the TearLab osmometer; osmolarity values differed between platforms when participants were engaged in a gaming task but no such difference was observed with the reading task. In addition, the influence of repeated measurements on tear osmolarity was also explored. To simulate the habitual binocular viewing conditions normally associated with smart device use, the binocular OFTA was developed. The device was used to assess the tear film and blink characteristics whilst engaging with reading and gaming tasks on smart device and paper platforms. The results revealed differences in blink characteristics and non-invasive tear break up time between the different platforms and tasks assessed. In addition, the thesis also reports on an investigation examining the real-time accommodative response to various targets displayed on smart devices using an open-field autorefractor with a Badal lens system adaptation. The results showed that accommodative latency, accommodative lag, mean velocity of accommodation, speed of disaccommodation and mean velocity of disaccommodation varied across the different platforms. Through the use of validated subjective questionnaires and smartphone apps, the relationship between duration of smartphone use and symptoms of dry eye were examined. The findings of this study demonstrated that longer duration of smartphone and personal computer use were associated with higher risk of dry eyes as indicated by subjective questionnaire outcomes.

Dedication

For the benefit of mankind.

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Author's Declaration

At no time during the registration for the degree of Doctor of Philosophy has the author been registered for any other University award without prior agreement of the Doctoral College Quality Sub-Committee.

Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment.

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Abbreviation List

Abbreviation	Meaning
%	Per cent
±SD	Plus minus standard deviation
ØD	Outside diameter
µL	Microliter
µl/min	Microliter per minute
µm	Micrometre
^{0}C	Degree Celsius
2-DE	Two-dimensional gel electrophoresis
3D	Three dimensions
ADDE	Aqueous deficient dry eye
ADHD	Attention deficit hyperactivity disorder
AFU	Arbitrary fluorescence units
ALag	Accommodative lag
ALat	Accommodation latency
ANOVA	Analysis of variance
AP	Associated Phoria
apps	Applications
AR	Accommodation response
ASRC	Accommodative Stimulus–Response Curve
blinks/min	Blinks per minute
BOS	Badal optical stimulator
BOSHWS	Binocular open-view Hartmann-Shack wavefront sensor
BR	Blink rate
BUT	Break Up Time
CAD	Computer Aided Design
CANDEES	Canada Dry Eye Epidemiology Study
Cells/mm^2	Cells per millimetre square
cd/m^2	Candela per meter square
cm	Centimetre
cm/s	Centimetre per second
CRF	Case Reference File
CsA	Cyclosporine-A
CVS	Computer Vision Syndrome
D	Diopter
DALat	Disaccommodation latency
DDS	Decreasing distance series
DEEP	Dry eye epidemiology projects
DEQ	Dry eye questionnaire
DiES	Digital eye strain
DoT	Distance of travel
dpi	Dots per inch
DSE	Display screen equipment

EDE	Evaporative dry eye
ELISA	Enzyme linked immunosorbent assay
EMG	Electromyogram
EMR	Electromagnetic radiation
EOG	Electrooculography
fMRI	Functional magnetic resonance imaging
FPD	Freezing point depression
FVAM	Functional visual acuity measurement
g/cm^2	Grams per centimetre square
GCP	Good clinical practice
HD	High definition
HPLC	High performance liquid chromatography
IBI	Interblink interval
ICC	Intraclass correlation coefficient
ICH	International conference of harmonisation
IDC	International Data Corporation
IgA	Immunoglobulin A
IR	Infrared
KCS	Keratoconjunctivitis sicca
kDa	Kilo Dalton
kHz	Kilohertz
LASIK	Laser-assisted in situ keratomileusis
LCD	Liquid crystal display
LE	Left eye
LED	Light emitting diode
LoA	Limits of agreement
LogMAR	Log Minimum Angle of Resolution
LPS	Levator palpebral superioris
LT	Light tape
MAR	Minimum angle of resolution
MATLAB	Matrix Laboratory
MEM	Monocular Estimate Method
mg	Milligram
MGD	Meibomian Gland Dysfunction
mg/ml	Milligram per millimetre
mm	Millimetre
MMP	Matrix metalloproteinase
MOD	Modulus
mOsm/L	Milliosmol per litre
ms	Millisecond
MSC	Magnetic Search Coil
MUC	Mucin-like glycoprotein
NEI	National Eye Institute
NEI-VFQ	National Eye Institute-Visual Function Questionnaire
NIBUT	Non-invasive tear break up time
nL	Nanolitre

NLS	Negative lens series
nm	Nanometre
NRA	Negative relative accommodation
Non-SSDE	Non Sjogren syndrome dry eye
OFTA	Open Field Tear film Analyser
OOC	Orbicularis oculi
OPI	Ocular Protection Index
OSDI	Ocular surface disease index
PAHC	Peninsula Allied Health Centre
PCA	Principal Component Analysis
PCD	Pitch circle diameter
PDF	Portable Document Format
PDM	Portable, slit-lamp mounted digital meniscometer
PeWE	Pediatric wavefront evaluator
PLS	Positive lens series
PPI	Pixels per inch
PRA	Positive relative accommodation
PRT	Phenol red thread
Q_1	First quartile
Q_3	Third quartile
RE	Right eye
RGP	Rigid gas permeable
RH	Relative humidity
RX	Relative humidity
s	Seconds
SAI	Surface Asymmetry Index
SEBR	Spontaneous Eyeblink Rate
SF	Spatial frequency
SOA	Speed of accommodation
SODA	Speed of disaccommodation
SPSS	Statistical Package for Social Science
SRI	Surface Regularity Index
SSDE	Sjogren syndrome dry eye
SVST	Standardized Visual Scale Test
t	Teeth
TBUT	Tear break up time
TMH	Tear meniscus height
TSAS	Tear stability analysis system
UV	Ultra violet
V1	Visit one
V2	Visit two
V3	Visit three
VA	Visual acuity
VDA	Velocity of disaccommodation
VDT	Visual display terminal
VDU	Visual display unit

vs.	Versus
×	Times
χ	Friedman test
Z	Wilcoxon signed-rank tests

Chapter 1: Literature Review

1.1 History of Smartphones

Smartphones have revolutionised how humans communicate and access information across the world. These pocket-sized electronic devices provide the means to communicate via voice calls, video calls, text messages and even emails (Long et al., 2017; Duggan, 2013; Cloud, 2014). Moreover, smartphones are now the primary devices for accessing the internet and provide a convenient interface for engagement with electronic media (Xu et al., 2011; Falaki et al., 2010; Jeong et al., 2016; Lee et al., 2014).

The trends in ownership and usage of smartphones have changed significantly over the last decade. In 2009, 25% of the population of the United States of America (USA) owned a smartphone; 14% of worldwide phone shipments were smartphones (Chetan, 2009). It was reported that worldwide mobile phone sales amounted to 455.6 million units in the third quarter of 2013 (of which 55% were smartphones), showing an increase of 5.7% from the same period in 2012 (Rob & Janessa, 2013). Furthermore, according to the International Data Corporation (IDC), smartphone manufacturers shipped a total of 1,004.2 million smartphones worldwide; an increase by 38.4% from the 725.3 million units in 2012 (Ramon et al., 2014).

More recently, it was a reported that in 2016, 77% of Americans owned a smartphone; this increase is more than double the number reported in 2011 when only 35% of the population were in possession of a smartphones (Smith, 2017). The country that has the most smartphone users is China, with approximately 717 million users in 2017 (Newzoo, 2017). Whilst in the UK in 2017, Deloitte, (2017) reported that 85% of the population owned a smartphone and the number was expected to reach 90% by 2020 or earlier. These statistics

clearly highlight the rapid increase in smartphone demand in the last 6 years that has led to their ubiquitous use in modern society.

In addition to their use for communication and accessing the internet, smartphones have also been utilized as research apparatus; examples include monitoring sleep related disorders (Natale et al., 2012; Behar et al., 2013), assessment of posture in smartphone users (Lee et al., 2013) and detecting fatigue in drivers (He et al., 2013) . Furthermore smartphones have also been used in clinical trials as a method of communicating subjective data (Woods et al., 2011). In the clinical setting, smartphones have also been used to assess patient's visual acuity (Vision, 2015), colour vision (VizMeter, 2015; Ozgur et al., 2018), fundus examination (Zvornicanin et al., 2014; Russo et al., 2015; Bastawrous et al., 2016) and contrast sensitivity (Kingsnorth et al., 2016). Other investigators have developed smartphone-based identification system that uses visible iris recognition software for biometric identification (Raja et al., 2014).

The effect of smartphone use has been extensively investigated in the field of human psychology (Parasuraman et al., 2017; Zhang et al., 2018; Schweizer et al., 2017; Carbonell et al., 2018; Višnjić et al., 2018; Elhai et al., 2017; Long et al., 2016; Cha & Seo, 2018; Wang et al., 2017; Lee et al., 2014; Oulasvirta et al., 2012; Plaza et al., 2011; van Deursen et al., 2015) and the evidence seems to suggest a link between excessive smartphones usage and negative behaviour. Electromagnetic radiation (EMR) emanating from common electrical items such as mobile phones have been classified as a potential health hazard (Genuis, 2008). Although the relationship between EMR from mobile phones and its effect on human health has been investigated (Aydin et al., 2011; Frei et al., 2011; Kwon et al., 2011; Volkow et al., 2011; Benson et al., 2015; SCENIHR, 2015), as yet, there is lack of research addressing the long term

effects on health of EMR from smartphones. In an animal model study, it was shown that EMR from mobile phones caused an increase in the amount of free radicals which could lead to oxidative stress (Ozguner et al., 2005). It has also been reported that regular and long term exposure to EMR from mobile phones plays an important role in the development of metabolic and neurodegenerative disease (Kesari et al., 2013). In mice, chronic exposure to EMR from smartphone was found to induce delayed hyperactive behaviour (Choi & Choi, 2016). Thus, it is unsurprising that several investigators have expressed concerns over the potential impact of mobile phones on humans (Repacholi, 2001; Patrick et al., 2008; Ahamed et al., 2008).

In contrast to smart devices (i.e. smartphones, tablets and wearable technology), the health effects of visual display terminals (VDT) such as computers and laptops have been extensively investigated (Table 1.1). The majority of these studies report on the association between VDT use and visual fatigue, discomfort, dry eye and blinking (see Table 1.1. for further details). On review of the literature, it is apparent that the term Computer Vision Syndrome (CVS) is frequently used to describe eye and vision-related problems resulting from prolonged use of computers, tablets, e-readers and smartphones.

Reference and Sample Size (n)	Environment	Type of VDT¥ Screen	Size of VDT Screen	Key Findings
Dainoff et al., (1981) 121 participants	Office	CRT	Not specified	A high incidence of symptoms relating to eye fatigue, including dry eyes and glare were reported in a cohort of VDT workers.
Läubli et al., (1981) 295 participants	Office	CRT	Not specified	VDT workers were associated with a higher incidence of eye fatigue and ocular burning sensation compared to non-VDT workers.
Grandjean et al., (1983) 68 participants	Laboratory	CRT	Not specified	VDT users did not maintain an upright trunk posture and tend to lean backwards with a trunk inclination angle between 97 and 121 degree.
Shahnavaz & Hedman, (1984) 29 participants	Office	CRT	Not specified	In workplace with high luminance contrast, 6 hours of VDT work caused over accommodation.
Garciai & Wierwille, (1985) 10 participants	Laboratory	CRT	Not specified	Glare from VDT screen was found to increase the amount of time required to read relatively easy passages.
Tanahashi et al., (1986) 8 participants	Laboratory	CRT	14-inch	The mean number of complaints of eye strain and fatigue increased significantly during VDT task.
Rossignol et al., (1987) 1,545 participants	Office	Not specified	Not specified	There was an increased prevalence of eye strain, sore eyes, blurred vision, red eye, musculoskeletal discomfort and headaches among clerical workers who used VDT.
Oborne et al., (1988) 16 participants	Laboratory	CRT	Not specified	No significant difference was found in reading speed or comprehension between the monitor and paper, or between dark and light character displays.
Miyao et al., (1989) 10 participants	Laboratory	CRT	IBM PC-AT	For very small alphabets, higher resolution VDT display screen improved readability when compared to lower resolution VDT display screen.
Yeow & Taylor, (1989) 105 participants	Office	CRT	Not specified	VDT work does not have a significant impact on visual function compared to non-VDT work.

Yaginuma et al., (1990) 7 participants	Laboratory	Not specified	Not specified	Two hours of VDT work reduced blink rate and TBUT. VDT group exhibit lower lacrimation compared to control group.
Collins et al., (1990b) 98 participants	Office	Not specified	Not specified	The legibility of letters on the VDT screen significantly influenced the occurrence of symptoms of ocular discomfort; vertical head movement significantly affected the incidence of postural/headache symptoms.
Collins et al., (1990a) 98 participants	Office	Not specified	Not specified	Tired eyes and headache were the most common symptoms related to VDT use.
Yeow & Taylor, (1991) 178 participants	Office	CRT	Not specified	Significantly greater near point of accommodation was evident in VDT users compared to non-VDT users.
Murata et al., (1991) 24 participants	Office	Not specified	Not specified	Approximately 2.5 hours of VDT work was associated with an increased number of complaints related to fatigue (drowsiness and lack of interest in performing VDT work).
Jaschinski-Kruza, (1991) 20 participants	Laboratory	CRT	Not specified	During VDT use, visual strain at a working distance of 50 cm was worse than at 100 cm (even with the characters on the display screen being twice the size at 50 cm).
Patel & Port, (1991) 10 participants	Laboratory	Not specified	Not specified	No significant difference in tear film stability was found between VDT users and non-VDT users. Tear volume of VDT users was significantly higher than non-VDT users.
Patel et al., (1991) 16 participants	Laboratory	Not specified	Not specified	VDT use does not affect tear film stability but caused a 5-fold reduction in blink rate.
Wiggins & Daum, (1991) 12 participants	Laboratory	Not specified	Not specified	Small amount of uncorrected astigmatism tends to cause eyestrain during VDT use.
Bergqvist et al., (1992) 535 participants	Office	Not specified	Not specified	VDT use was related to the risk of developing ocular discomfort as well as hand and wrist problems.
Sheedy, (1992) 1,307 participants	Office	Not specified	Not specified	Uncorrected refractive errors, irritated eyes, accommodative disorders, binocular vision disorders and spectacle design problems were the most common problems associated with VDT users.

Wiggins et al., (1992) 12 participants	Laboratory	CRT	23.5 x 18 cm	Significant relationship was identified between presence of residual astigmatism and reported visual discomfort.
Lie & Watten, (1994) 18 participants	Laboratory	CRT	14-inch	After 3 hours of continuous VDT work, participants displayed significant transient myopia.
Collins et al., (1994) 6 participants	Laboratory	CRT	14-inch	Under binocular conditions, reflections on the VDT did not significantly influence the accuracy of the accommodative response. However, under monocular conditions, reflections on the VDT caused small accommodative errors.
Bergqvist & Knave, (1994) 327 participants	Office	Not specified	Not specified	The occurrence of eye discomfort increases as the extent of VDT work increased.
Collins et al., (1994) 7 participants	Laboratory	CRT	Not specified	Accommodation response to a wide range of screen conditions were relatively accurate and stable during short-term VDT screen viewing.
Saito et al., (1994) 5 participants	Laboratory	CRT	Not specified	Visual fatigue symptoms were reported by participants after performing a VDT task for 4 hours; findings were confirmed by a reduction of the critical fusion frequency.
Salibello & Nilsen, (1995) 324 participants	Office	Not specified	Not specified	Five hours of VDT use per day caused symptoms such as eyestrain, headache, loss of focus at near and neck pain.
Tsubota et al., (1996) 10 participants	Laboratory	CRT	Not specified	Blinks rate decreased as participants read with reduced room illuminations which resulted in increased desiccation of the ocular surface; this was thought to be responsible for the symptoms of eye fatigue.
Cole et al., (1996) 1360 participants	Office	Not specified	Not specified	In a 6 year epidemiological study, there was a small but significant differences between VDT users and non-VDT users in the prevalence of myopia and asthenopic symptoms (sore eyes).

Jaschinski et al., (1998) 24 participants	Office	Not specified	Not specified	VDT workers reported more eyestrain when they were asked to work at a shorter working distance compared to their preferred longer working distance.
Ziefle, (1998) 14 participants	Laboratory	CRT	19-inch	Reaction time (visual search task) was found to be longer in low resolution CRT monitor (62 dpi) compared to higher resolution CRT monitor (89 dpi).
Acosta et al., (1999) 20 participants	Laboratory	CRT	12-inch	VDT task was associated with ocular discomfort and reduced blink rate.
Wolska & Śwituta, (1999) 66 participants	Laboratory	Thin Film Transistor Liquid Crystal Display with (TFT-LCD) and Cathode Ray Tube (CRT)	10.5-inch (TFT-LCD) and 14-inch (CRT)	Luminance ratio did not significantly influence asthenopic symptoms for either type of display.
Shieh & Lin, (2000) 48 participants	Laboratory	CRT and TFT-LCD	17-inch (CRT) and 12.1-inch (TFT-LCD)	Participants performed better letter identification task with TFT-LCD compared to CRT. Visual performance was better under 450 lux ambient illumination vs. 200 lx. Blue letters on a yellow background provided the best performance and purple-on-red was the worst.
Mocci et al., (2001) 212 participants	Office	Not specified	Not specified	A total of 68 participants reported at least 1 symptom of asthenopia during or soon after their work shift, 3 or more times in a week.
Fogleman & Lewis, (2002) 292 participants	Office	Not specified	Not specified	Hours spend on VDT was the most consistent risk factor associated with self-reported musculoskeletal discomfort.
Nakazawa et al., (2002) 25,964 participants	Office	Not specified	Not specified	Physical symptoms (headache, eye strain, stiff shoulder, lower back pain, arthralgia and general fatigue) were elevated with increased duration of daily VDT use.

Bernard et al., (2003) 35 participants	Laboratory	CRT	17-inch	Twelve-point size text was much easier to read compared to 10-point size text. Arial font were much easier to read compared to Times New Roman.
Seghers et al., (2003) 16 participants	Laboratory	CRT and TFT	17-inch (CRT) and 15-inch (TFT)	During prolonged (89 minutes) VDT work at different screen height settings, lowering of screen height decreased the ear – eye angle, increased the viewing angle, increased the viewing angle relative to the ear – eye line, and increased the muscle activity of the neck extensor muscles.
Freudenthaler et al., (2003) 51 participants	Laboratory	Not specified	17-inch	There was increased variability of the individual blink rate during VDT task. A significant reduction in blink rate occurred during VDT use.
Daum et al., (2004) 39 participants	Laboratory	CRT	15-inch	Uncorrected astigmatism was found to reduce work productivity and increase visual discomfort.
Sheedy et al., (2005) 37 participants	Laboratory	LCD	17-inch	During 5 minutes of reading from an LCD screen, surrounding luminance does not affect participant's discomfort ratings.
Treaster et al., (2006) 16 participants	Laboratory	Not specified	Not specified	Neck and shoulder muscle pain manifested after continuous typing on a computer for a time period as short as 30 minutes.
Nahar et al., (2007) 31 participants	Laboratory	Not specified	Not specified	Blink rate reduced with smaller font size and lower contrast.
Hayes et al., (2007) 638 participants	Office	Not specified	Not specified	An average of 6 hours per day was spend on VDT work. Eye related VDT symptoms were found to be significantly correlated with length of time of VDT use, job demands and ergonomics.
Bhanderi et al., (2008) 419 participants	Office	Not specified	Not specified	Asthenopia is common among computer operators, particularly in those who started its use at an early age (15 years old).
Lin et al., (2008) 20 participants	Laboratory	TFT-LCD	15-inch	Performing a dynamic visual information processing task on a VDT induced visual fatigue. Both time-based and environmental-based factors (screen type, viewing distance) significantly and independently affected visual fatigue.

Himebaugh et al., (2009) 32 participants	Laboratory	Not specified	Not specified	Blink rate was found to be reduced when playing video games on a computer monitor when compared to looking at a small fixation point on an other- wise blank computer monitor.
Bababekova et al., (2011) 229 participants	Laboratory	Smartphones	Not specified	Mean working distance when using a smartphone is shorter compared to the typical near working distance of 40 cm when viewing hardcopy text.
Shrestha et al., (2011) 76 participants	Office	Not specified	Not specified	The most common abnormalities and symptoms reported by VDT users were accommodative infacility and tired eyes. Dry eye was also found to be correlated with ocular symptoms.
Collier & Rosenfield, (2011) 20 participants	Laboratory	LCD	14.1-inch	Symptoms related to VDT use may be associated with an increased vergence response during VDT use but were unlikely to results from a change in the accommodative response.
Chu et al., (2011) 30 participants	Laboratory	LCD	17-inch	Symptoms post-VDT task were significantly worst compared to hard copy version of the task.
Cardona et al., (2011) 25 participants	Laboratory	TFT-LCD	20-inch	Blink amplitude, blink rate and tear film stability were reduced when playing computer games. Larger percentage of incomplete blinks were also evident when playing computer games.
Hoyle et al., (2011) 20 participants	Laboratory	Not specified	Not specified	Postural and visual demands during computer work plays a role in myofascial muscle activation and causes musculoskeletal discomfort.
Kojima et al., (2011) 171 participants	Office	Not specified	Not specified	Office workers who wore contact lenses and spent >4 hours of VDT work had a lower tear meniscus volume and higher dry eye symptom score compared to non-contact lens wearers.
Paulo et al., (2012) 476 participants	Office	Not specified	Not specified	The presence of computer vision syndrome (CVS) was associated with being female, lack of recognition at work, the organization of work in call centres and high demand at work.
Gowrisankaran et al., (2012) 33 participants	Laboratory	Not specified	Not specified	Under the same visual stress level, the presence of cognitive load exaggerates the asthenopic symptoms.

Rosenfield, Hue, et al., (2012) 12 participants	Laboratory	LCD	17-inch	2 Dioptres of induced oblique astigmatism produced a significant increase in CVS symptoms during computer use.
Thorud et al., (2012) 20 participants	Laboratory	LCD	15-inch	Two hours of visually demanding VDT work increases eye-related pain, tiredness, blurred vision, itchiness, gritty eyes, photophobia, dry eyes, tearing and the orbicularis oculi muscle load.
Siegenthaler et al., (2012) 10 participants	Laboratory	LCD and Backlit LED (e-Ink)	9.7-inch (LCD) and 7-inch (e-Ink)	Reading on the 2 display types was not significantly different in terms of visual fatigue, visual search task, reading speed and the latency of pupillary light reflex.
Teoh et al., (2012) 31 participants	Laboratory	LCD	Not specified	VDT work significantly reduced post-task NIBUT. VDT work induced lower blink rate and larger vertical aperture size while non-VDT work did not change the blink rate but is associated with a smaller vertical aperture size.
Portello et al., (2012) 520 participants	Office	Not specified	Not specified	Significant positive correlation was observed between the symptom score and the number of hours spent working on a computer. Most prevalent symptoms were tired eye, dry eye and discomfort.
Agarwal et al., (2013) 150 participants	Office	CRT and LCD	Not specified	Eye strain, itching and burning sensation was the most common ocular complaints among computer users working for >6 hours per day.
Portello et al., (2013) 21 participants	Laboratory	LCD	15-inch	Increased symptoms during VDT use was associated with both a reduction in blink rate and an increased percentage of incomplete blinks.
Benedetto et al., (2013) 12 participants	Laboratory	LCD and e-Ink	7-inch (LCD) and 6-inch (e-Ink)	Reading on Kindle Fire HD (LCD) triggers higher visual fatigue compared to both Kindle Paperwhite (e-Ink) and the paper book. The absence of differences between E-ink and paper suggests that, concerning visual fatigue, the E-ink is very similar to actual paper.

Chu et al., (2013) 20 participants	Laboratory	Not specified	Not specified	Prolonged daily computer usage (>6.55 hours) can cause an increase in tear osmolarity which may contribute to the symptoms of CVS.
Uchino et al., (2013) 561 participants	Office	Not specified	Not specified	Female, increased age and VDT use of >8 hours were identified as risk factor for definite and probable dry eye.
Cardona et al., (2014) 11 participants	Laboratory	LCD	20-inch	A combination of white screen and blinking instructions has been shown to result in a short-term improvement in the blink rate of non-dry eye computer users.
Ko et al., (2014) 27 participants	Laboratory	LCD	20-inch	Productivity, accuracy and working distance increased as font size on VDT increased. Adding reflective glare on the VDT reduced the working distance but had no effect on productivity or accuracy.
Moon et al., (2014) 288 participants	Office	Not specified	Not specified	Smartphone (VDT) use was an important dry eye risk factor in children.
Kochurova et al., (2015) 35 participants	Laboratory	LCD	14-inch	In young healthy participants, for sustained comfortable reading, the text size on VDT should be at least twice the individual's visual acuity.
Gajta et al., (2015) 95 participants	Laboratory	Not specified	Not specified	Using VDT for >8 hours per day was identified as a risk factor for dry eye.
Courtin et al., (2016) 11,365 participants	Systematic review and meta analysis	Not specified	Not specified	A higher prevalence of dry eye was observed amongst VDT users of >4 hours per day compared to VDT users of <4 hours per day.
Ranasinghe et al., (2016) 2210 participants	Office	Not specified	Not specified	Female gender, longer duration of occupation, higher daily computer usage, pre-existing eye disease, not using a VDT filter, use of contact lenses and higher ergonomics practices knowledge were all significantly associated with the presence of computer vision syndrome (CVS).
Kim et al., (2016) 715 participants	Office	Not specified	Not specified	Longer daily duration of smartphone use was associated with a higher likelihood of having multiple ocular symptoms.

Tauste et al., (2016) 426 participants	Office	Not specified	Not specified	Workers who wore contact lenses and were exposed to computer >6 hours per day were more likely to suffer CVS than non-lens wearers working at the computer for the same amount of time.
Moon et al., (2016) 916 participants	Office	Not specified	Not specified	Increased VDT use such as smartphones or computers in Korean children was found to be associated with the occurrence of ocular surface symptoms. Older-grade children (aged 10 to 12 years) in the urban group used smartphones for longer time periods than younger-grade children (aged 7 to 9 years) in rural areas.
Porcar et al., (2016) 116 participants	Office	LCD and LED	Not specified	Approximately 72% of VDT users experienced eye symptoms related to VDT use (tired eyes, sensitivity to bright light, dry eyes and blurred vision at distance).
Al-Rashidi & Alhumaidan, (2017) 634 participants	Office	Not specified	Not specified	Approximately 58.51% of the participants used computers for >8 hours per day. Eye strain and burning sensation were the most common symptoms reported.
Bogdănici et al., (2017) 60 participants	Office	Not specified	Not specified	Smartphone, television and laptops are the most commonly used VDT. Blurred vision, burning sensation, diplopia and foreign body sensation were the common complaints when using VDT.
Kim et al., (2017) 59 participants	Laboratory	LCD	9.7-inch	Using iPad Air (LCD) for 1 hour significantly increases mean total asthenopia score and caused a significant reduction in NIBUT.
Caterina et al., (2018) 194 participants	Office	Not specified	Not specified	Older participants spending >4 hours per day on VDT had a higher risk of developing dry eye. Participant's age and time spent on VDT per day were the main risk factors for dry eye in VDT workers.

Mowatt et al., (2018) 409 participants	Office	Not specified	Not specified	Neck pain, eye strain, shoulder pain and burning eyes were the most common symptoms associated with VDT use. Ocular symptoms and neck pain were less likely to manifest if the device was placed just below eye level.

¥ Visual Display Terminal is a term that is used to describe any forms of electronic display screen.

Table 1.1: Previous research on the effects of VDT use.

In view of the visual symptoms commonly encountered with VDT use, in the UK the Health and Safety Executive (Health and Safety Executive, 2003) provides guidelines on how best to work with Display Screen Equipment, DSE (for standardization purposes, DSE will be referred as VDT in this thesis). The guidelines (DSE 1992) include advice on how to avoid the health risks associated with screen- based work, including musculoskeletal disorders, visual fatigue and mental stress (Health and Safety Executive, 2003). Examples of recommendations from DSE 1992 includes adequate lighting, adjustable chair height, sufficient legroom and glare free screen (Health and Safety Executive, 2003). Although such guidelines have been invaluable for occupational use of VDTs, health and safety recommendations for smart devices are still poorly considered. Indeed, the lack of literature on the health effects of smart devices is likely to be a significant factor in this shortfall. However, when considering the similarity between VDTs and smart devices it may be safely foreseen that a closer working distance, associated with smart devices, will lead to greater accommodative and convergence demand which may lead to higher incidence of visual fatigue and discomfort (Rossignol et al., 1987; Moon et al., 2016). Furthermore in a questionnaire based study, smartphones were found to be associated with increased risk of dry eyes in children (Moon et al., 2014). Given the lack of literature on the effects of smartphones on visual function, there is a significant need for further investigation on the potential impact these devices have on basic clinical factors such as tear stability, blink rate, and ocular accommodation. The following sections provides a literature review on these key clinical parameters associated with VDT and smart device use.

1.2 The Tear Film

1.2.1 Physiology and Components of the Tear Film

The human tear film (Figure 1.1 and 1.2) is located anterior to the ocular surface covering both the cornea and the conjunctiva. The most anterior aspect of the tear film is provided by

the lipid layer, which is estimated to be approximately 0.1 µm thick (Holly & Lemp, 1977). The aqueous layer lies next to the lipid layer with a thickness of 10.4 µm (Creech et al., 1998). Posterior to the lipid layer and adjacent to the corneal epithelium, the mucus layer has a thickness of 0.02 to 0.04 µm (Rohit et al., 2013). The innermost layer of the tear film is made of glycocalyx that originates from the superficial layer of the ocular epithelia surface (Levin et al., 2011).

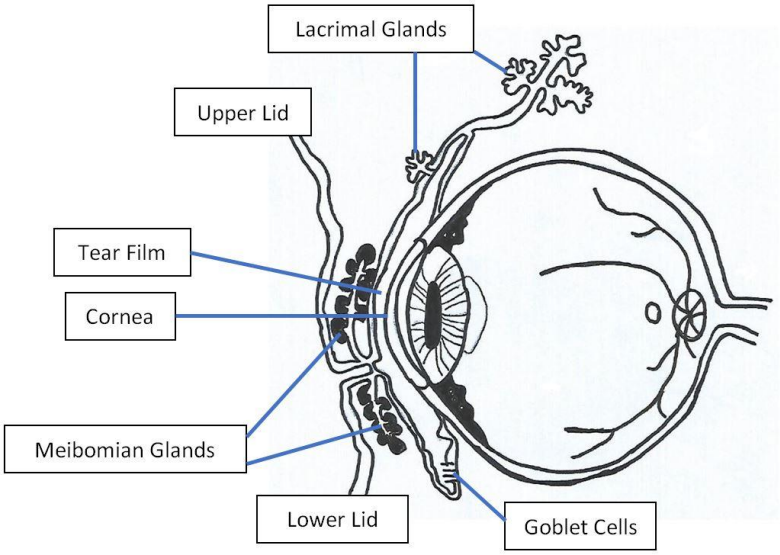


Figure 1.1: The cross section of the human tear components reproduced from Dartt, (2002).

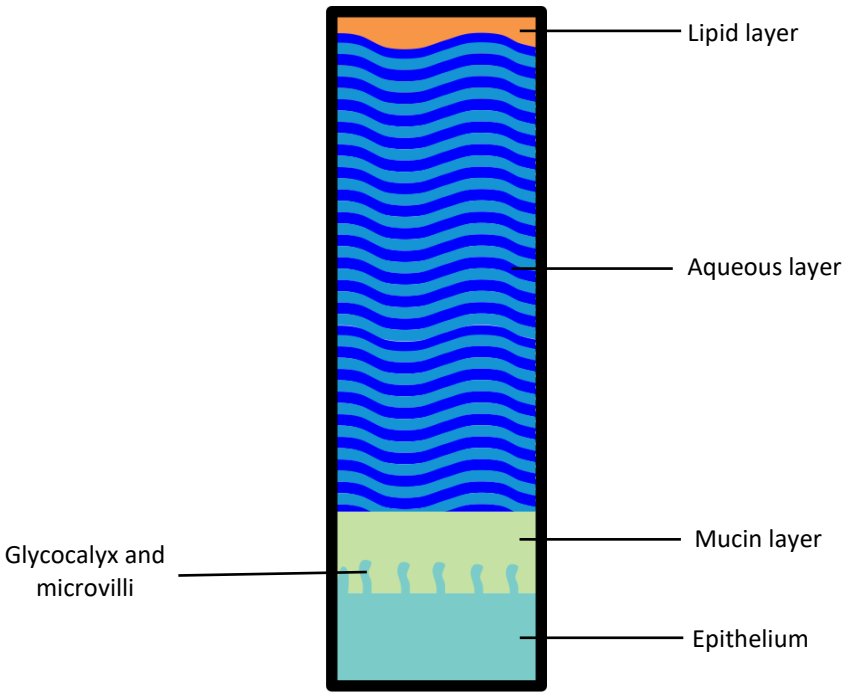


Figure 1.2: The tear film.

1.2.1.1.1 The Lipid Layer

The meibomian glands contribute to the bulk secretion of the lipid layer (Foulks, 2007). The openings of the glands are located along both the superior (30 to 40 glands) and inferior (20 to 30 glands) lid margins (Bron et al., 2004; Ong & Larke, 1990). The primary ducts of the meibomian glands are surrounded by the acinar clusters, identified as grape like structures. Each meibomian gland itself is a tubulo-acinar, holocrine (modified sebaceous) gland that discharges both polar and nonpolar lipid secretions (Bron & Tiffany, 2004; Bron et al., 2004). In regards to the distribution of the meibomian secretions, 300 mg of the lipids are retained in the marginal reservoir of the lid margin, while only 9 mg of the same secretions appear to be present in the tear film (Chew, Hykin, et al., 1993; Chew, Jansweijer, et al., 1993).

Although the exact content of the lipid layer varies (Isreb et al., 2003), it generally constitutes approximately 77% wax and sterol esters, 8% phospholipids, and 9% di- and triglycerides

(McCulley & Shine, 2003). The secretion of the meibomian glands is liquid at body temperature as it has a melting point between 19.5 and 32.9 ^{0}C (Bron et al., 2004).

1.2.1.2 The Aqueous Layer

The aqueous layer of the tear film is primarily produced by the lacrimal glands (Cerretani & Radke, 2014; Chiang et al., 2005; Stern et al., 2004). A secondary source of the aqueous layer originates from the surface epithelium of the conjunctiva, a small portion on the corneal epithelium and the accessory lacrimal glands (Bron, 1997; Dartt, 2002; Mishima et al., 1966). The lacrimal glands are made of a large orbital and a small palpebral portion, which are continuous with each other around the edge of the aponeurosis of the levator palpebrae superioris (Snell & Lemp, 2011). The gland itself is a tubular-acinar structure and the lobules separated from one another by loose connective tissue (Figure 1.1).

Originally, the lacrimal secretions are an isotonic mixture of water, salt and proteins (Murube, 2006). However, when passing through the cell lining of the ducts system, the lacrimal secretions are modified to contain lysozyme, lactoferrin (antibacterial enzyme), IgA (immunoglobulin) and beta-lysin (bactericidal protein), providing antimicrobial properties (Snell & Lemp, 2011; Levin et al., 2011). Growth factors that are unique to the lacrimal glands such as lacritin, have also been identified in the aqueous tear layer (McKown et al., 2009).

1.2.1.3 The Mucin Layer

The mucin layer is synthesized by the conjunctival goblet cells, as well as the conjunctival and corneal epithelial cells (Chao et al., 1980). The backbone for the mucin layer is the gel-forming mucus MUC5AC which is produced by the conjunctival goblet cells (Levin et al., 2011). Mucin MUC5AC and MUC4 (which is also produced by the conjunctiva) have been suggested to play an important role in forming the tear-film layer at the 'air and ocular surface'-epithelium

interface (Inatomi et al., 1996; Tei et al., 1999). At the apical surface of the corneal and conjunctival epithelium, the mucin-like glycoprotein (MUC1) is synthesize constituting the glycocalyx (Gipson & Inatomi, 1998).

The mucin layer also contains: ectodomains (domain of a membrane protein that extends into the extracellular space), remnants from membrane-spanning mucins, membrane-spanning mucins secreted by a soluble pathway, proteins synthesized and secreted by the goblet cells, electrolytes and water (Levin et al., 2011).

The actual thickness of the mucin layer is still unconfirmed; Prydal suggested that the mucin layer may be as thick as 30 μm (Prydal et al., 1992) but others have suggested a thinner layer of 0.02 to 0.04 μm (Holly, 1973).

1.2.1.4 The Glycocalyx Layer

The glycocalyx layer is a network of polysaccharides that expands from the cellular surfaces (Figure 1.2). Glycocalyx consists of mucopolysaccharides and glycoproteins which are located on the apical portion of the microvilli on both the corneal and conjunctival epithelia (Gipson & Argüeso, 2003). The major component of the glycocalyx layer is the membrane-associated mucins that are produced by the goblet cells in the conjunctiva and the stratified squamous epithelium covering the cornea and conjunctiva (Argüeso et al., 2003; Gipson & Argüeso, 2003; Inatomi et al., 1995; Pflugfelder et al., 2000).

1.2.2 Importance of Tear Film

A primary function of the tear film is to hydrate the cornea and the conjunctiva, whilst acting as an irrigation system to wash out ocular debris and foreign bodies. The tear film also provides protection from infections as it contains antibodies (Tiffany, 2008). With a refractive

index of 1.336 (Bennett & Barry, 2004), the tear film is the first layer of the refractive surface of the eye (Levin et al., 2011). The thickness of the tear film is in the order of 6 to 20 µm; a uniform reduction in the thickness of the tear film would result in an insignificant refractive change of 0.10 D (Montés-Micó, 2007). Due to this small refractive power, the presence of the tear film is commonly discarded from the calculation of the power of the eye, particularly when comparing it to the higher power of the cornea (approximately 45 dioptres) (Rolando & Zierhut, 2001).

1.2.2.1 Function of the Lipid Layer

The lipid layer functions as a hydrophobic barrier that prevents tear overflow onto the lids as well as preventing sebum from the skin entering the tear film (Nicolaides et al., 1981). The hydrophobicity is attributed to the presence of non-polar lipids, such as cholesteryl esters and triglycerides that are present in the lipid layer in the 'tear-air' interface (Greiner et al., 1996; Kulovesi et al., 2010; McCulley & Shine, 1997). This mucocutaneous junction acts to isolates the tear-wettable conjunctiva from the oil-wettable eyelid skin and therefore, preventing overflow in both direction (Norn, 1985). During extended periods of eyelid closure, such as during sleep, the lipid layer forms a water tight seal to prevent evaporation of the tear film (Foulks & Bron, 2003; McCulley & Shine, 2003). Notably, the lipid layer reduces the amount of tear evaporation during waking hours and provides lubrication for the eyelids upon blinking (Adler et al., 1987; Kawashima & Tsubota, 2013; Tomlinson et al., 2011). Furthermore, the lipid layer functions as a barrier to impede the passage of bacteria into the tear film and subsequently the cornea (Nicolaides et al., 1981). The function of the lipid layer secreted by the meibomian glands can also be further divided into the lipids that are located on the lid

margin reservoir and the lipids that are present in the tear film lipid layer as shown in Table 1.2 (Bron et al., 2004).

Lipid on the Lid Margin Reservoir
• prevent contamination with sebum. • prevent maceration of the lid skin by the tears. • ensure lid-skin hydrophobic state and prevent tears spillage.
Lipid in the Tear Film
• prevent evaporation. • act as a barrier to foreign body. • seal the lid margin during closure. • provide some anti-microbial properties. • ensure a smooth optical surface for the cornea. • spread over the aqueous sub-phase, lower free energy and impart stability to tear film.

Table 1.2: Functions of lipid layer from Bron et al., (2004).

1.2.2.2 Function of the Aqueous Layer

The aqueous layer has multiple functions that are important to maintain the health and integrity of the ocular surface. This layer is vital as it creates a suitable environment for the epithelial cells of the ocular surface, allowing cell movement over the ocular surface, transport of oxygen and supply of essential nutrients to the cornea (Rolando & Zierhut, 2001; Willcox et al., 2017). Furthermore, since the bulk of the tear layer consists of the aqueous layer, it also functions as an irrigation system to remove epithelial debris, foreign bodies and toxic elements (Levin et al., 2011). Growth factors that are present in this layer have been found to regulate the aqueous tear production (Sullivan et al., 2017; van Setten et al., 1992).

1.2.2.3 Function of the Mucin Layer

The mucin layer plays a role in spreading the tear film to ensure optimal ocular surface wetting; the whole ocular surface is hydrophilic because of the mucin layer covering it (Rolando & Zierhut, 2001) ensuring that the apical epithelial are well hydrated. The mucin layer also prevents adhesion of cells, foreign bodies or pathogen onto the ocular surface (Rolando & Zierhut, 2001). Moreover, the mucin layer also contributes to the maintenance of the dioptric integrity of the tear film in the inter-blink period and safeguards the ocular surface during blinking, minimizing the trauma to the surface (Dilly, 1985; Tiffany, 1994).

1.2.2.4 Function of the Glycocalyx Layer

A glycocalyx layer plays an important role in ocular surface lubrication by maintaining wettability and eliminating foreign particles and pathogens (Gipson & Argüeso, 2003; Nagyová & Tiffany, 1999; Tiffany, 2008). The membrane-spanning mucins in the glycocalyx are disadhesive, allowing the mucous layer to move over the ocular surface (Levin et al., 2011), which in turn makes the ocular surface hydrophilic.

1.2.3 Drainage of the Tears

The drainage of tears from the ocular surface is vital to allow a balance between the rate of inflow of tear fluid from the lacrimal glands and the accessory lacrimal tissue, as well as the permeation of water from the corneal epithelium through aquaporin controlled channels (Tiffany, 2008). Tear fluid is drained through the superior and inferior lacrimal punctum following each blink and also by evaporation from the eye, during the open eye phase (Figure 1.3). Upon lid closure, the superior and inferior lacrimal punctum press against each other and thus prevent outflow. As the lids open, there is a drop in canalicular pressure and tear fluid is drawn into the punctum from the medial lake (Lemp & Weiler, 1983). Furthermore,

there is also evidence showing absorption of tear fluids occurring when the tear fluid passes through the canaliculus (Paulsen et al., 2002).

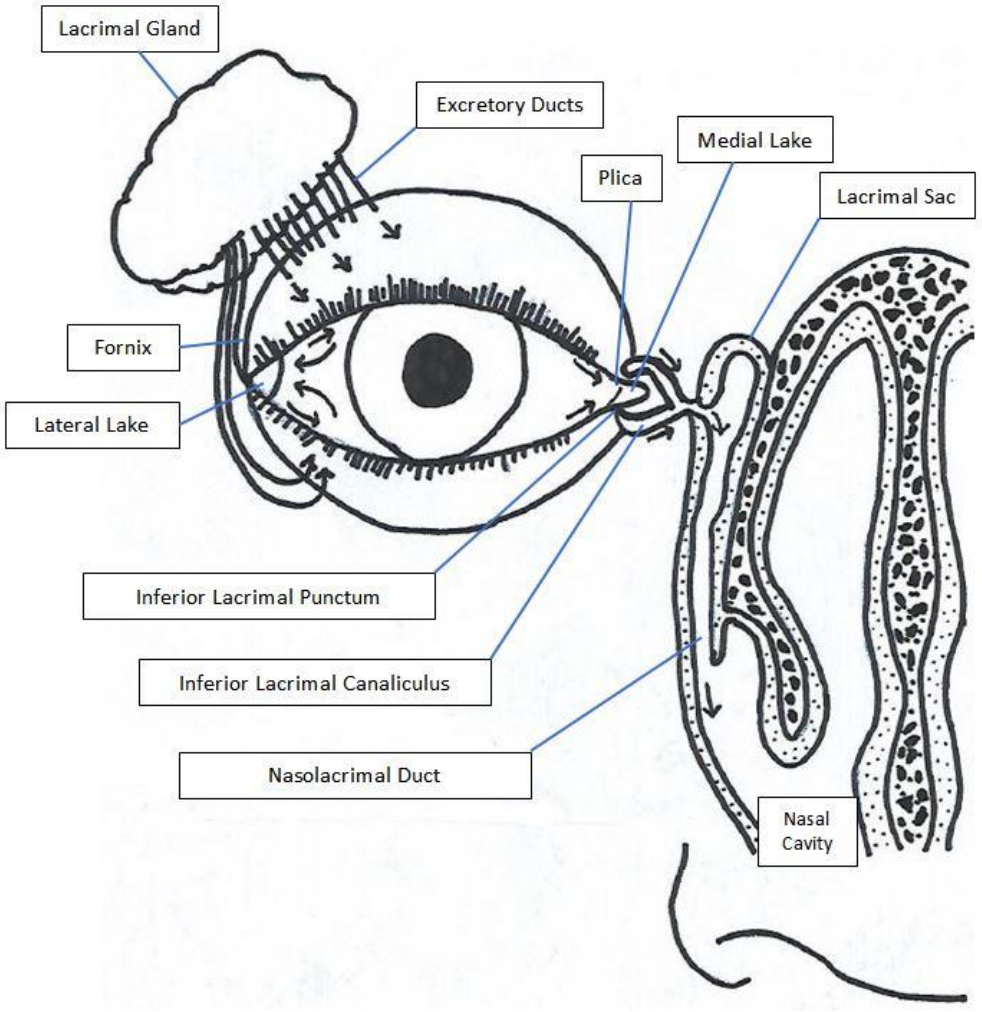


Figure 1.3: The tear drainage reproduced from Duane, (2005).

While sleeping, the lid margins are positioned side by side with each other and the lacrimal sac is closed. In this condition, the tear fluid is drained from the medial lake by the canaliculus. The punctum is positioned such that it is in contact with the medial lake or with the eyeball (when the eye rotates medially) due to the tonus from the orbicularis oculi muscle located in

the eyelids. The tear fluid enters the canaliculus via capillary forces. Contraction from the lacrimal part of the orbicularis oculi shortens and compresses the canaliculus and causes dilatation of the lacrimal sac. This in turn will cause the tear fluid to be drawn into the sac. This is referred to the pumping mechanism of the orbicularis oculi (Snell & Lemp, 2011). In the nasolacrimal duct, tear fluids move downwards due to gravitational forces. Movement of air during inspiration and expiration (breathing) assists evaporation of the tear fluids at the orifice located in the nasal cavity.

1.2.4 Types of Tear

1.2.4.1 Basal Tears

Basal tears, also known as normal tears, are necessary to maintain the state of hydration of the ocular surface. They are provided by continuous secretion from the accessory lacrimal glands scattered throughout the conjunctival sac (Snell & Lemp, 2011).

1.2.4.2 Reflex Tears

Reflex tearing is a condition whereby excessive tears are produced in instances where foreign bodies enter the eye or when crying. It is mainly influenced by reflex nervous stimulation of the main lacrimal glands. The afferent pathway of this reflex is through the trigeminal nerve and the parasympathetic pathway is through the facial nerve (Remington, 2012).

1.2.5 Measurable Tear Parameters

Several methods can be used to assess the characteristics of the tears and these are divided into assessment of (i) tear production (ii) tear stability and (iii) laboratory based tear composition tests. A summary of the measurable tear parameters can be seen in Figure 1.4 below.

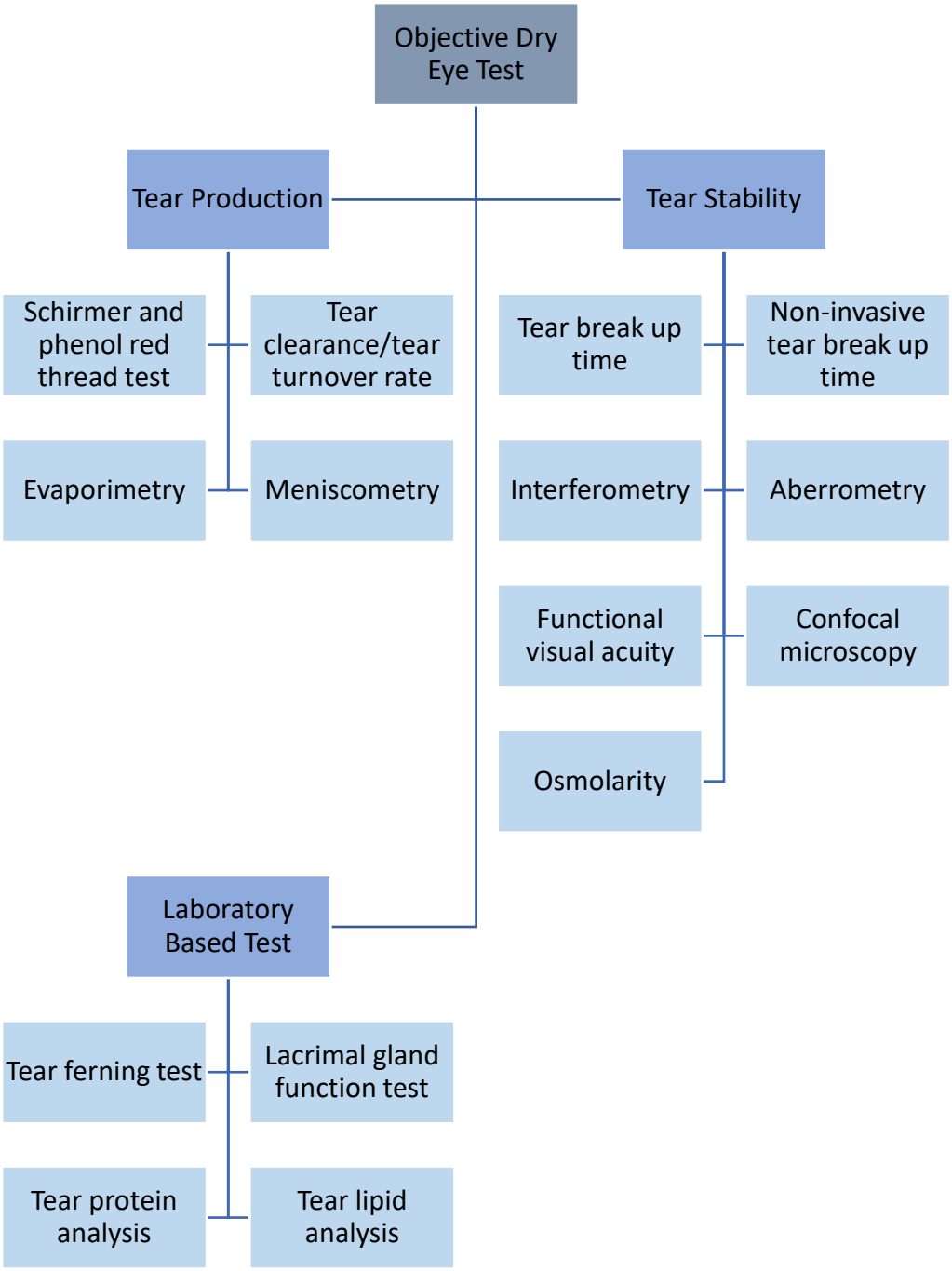


Figure 1.4: The available objective assessment for the evaluation of dry eye.

1.2.5.1 Tear Production

1.2.5.1.1 Schirmer Test and Phenol Red Thread (PRT) Test

The Schirmer and PRT tests are two separate invasive tests that provide a measure of the tear volume. Both methods utilize insertion of a wick (either paper or thread based) into the lower

conjunctival sac and measurement of the wetted length over a period of time (Masmali et al., 2014; Vashisht & Singh, 2011).

The Schirmer test was first introduced in 1903 and is one of the most commonly used methods of assessing the tear volume in the clinical settings (Jamaliah & Fathilah, 2002; Nichols et al., 2000; Schirmer, 1903). Schirmer test strips are composed of filter paper measuring 35 × 5 mm. The Schirmer test strip is usually placed in the lower conjunctival sac at the junction of the lateral and middle thirds of the lower eyelid while avoiding contact with the cornea. After 5 minutes, the length of the wetted portion of the Schirmer test strip is measured.

The Schirmer test can be further divided into two types. The first test is called 'Schirmer 1' which measures both the reflex and basal tear secretions (total tear secretion). The second test is called 'Schirmer 1 with anesthesia' and it uses topical anesthesia to allow an isolated assessment of the basal secretions without the presence of reflex tear secretion. For both Schirmer tests, a value of less than 5 mm is indicative of abnormal tear secretion, possibly a sign of dry eye (Bron et al., 2007). Similarly a value of less than 10 mm has been suggested to signify marginal dry eyes (Saleh et al., 2006; Vashisht & Singh, 2011).

Although Schirmer 1 with anaesthesia may provide a more accurate measurement of basal tear secretion the overall effectiveness of anaesthetic administration in conjunction with Schirmer 1 is controversial (Clinch et al., 1983; Loran et al., 1987; Jordan & Baum, 1980). Concerns regarding the degree of anaesthesia achieved and the efficiency of blotting residual fluid from the cul-de-sac after instillation have been thought to affect the accuracy of the tests (Senchyna & Wax, 2008). Furthermore, incomplete anaesthesia (sensation of the lower eyelids) and psychogenic variables often produce a certain level of reflex tearing after

aesthetic instillation possibly confounding measures of basal tear secretions (Jordan & Baum, 1980; Clinch et al., 1983; Loran et al., 1987; Afonso et al., 1999). Li et al., (2012) found that the Schirmer 1 test with topical anaesthesia (0.5% proparacaine hydrochloride eye drops) was more reliable in reflecting the status of dry eyes compared to Schirmer 1 without anaesthesia. In dry eye, Serin et al., (2007) advocated that the Schirmer test should be administered with the patient's eyes closed to reduce variability and improve repeatability. Variability concerning exact placement along the lid margin has been thought to affect the repeatability of the test, however Loran et al., (1987) reported that placement of the Schirmer strip along the medial and lateral aspects of the eye in up or down gaze had no effect on the test reliability.

Despite the obvious benefits offered by the various versions of the Schirmer tests, the literature is equivocal on its validity and sensitivity to differentiate between mild to moderate cases of dry eye (Sullivan et al., 2010). Factors relating to patient discomfort (testing without anaesthesia), potential risk of conjunctival and corneal injury and difficulty in performing the test in paediatric cases are known limitations of the test. Moreover uncertainty concerning the quantity of fluid absorbed by the paper strips being proportional to the wetted length, difficulty in evaluating the wetting length in cases where the leading edge of the wetted area is round or oblique, and the lack of control over reflex lacrimation may further affect the accuracy and reliability of the test (Cho & Yap, 1993a; Savini et al., 2008). To overcome some of these limitations, investigators have advocated changing the length of the test time from 5 minutes to 1 minute (Bawazeer & Hodge, 2003).

The PRT was developed to overcome the poor variability, repeatability and sensitivity of the Schrimer test. Made out of a fine cotton thread the PRT test also attempted to reduce the

conjunctival and lid irritation when inserted into the conjunctival sac (Kurihashi et al., 1977). The first version of the test was made of a fine white thread (0.25 mm in diameter, 70 mm in length) which was impregnated with fluorescein at one end (3 mm). The thread is inserted into the unanaesthetized temporal conjunctival sac for 30 seconds. As the tears are absorbed by the thread, the impregnated fluorescein dye is visible and denotes the length of the thread wetted by the tears. The work of Kurihashi et al. (1977) advocated a modification to the PRT such that the cotton thread was impregnated with phenol red dye instead of fluorescein and only inserted for 15 seconds (Hamano et al., 1983); the pH level of the tears alters the colour of the phenol red dye from yellow to red.

In comparison to the Schrimer test, the PRT significantly reduces reflex tear production due to a thinner design and shorter testing time (Hamano et al., 1983). As such, the test was considered to be a reliable indicator of basal tear secretion (Sakamoto et al., 1993). However, several investigators have failed to provide experimental evidence as to whether PRT actually measures tear production or whether it provides a quantification of the residual tears in the inferior conjunctival sac (Tomlinson et al., 2001). The literature also suggests that a combination of Schirmer 1 and PRT tests strongly improves the screening procedure to detect patients with ocular dryness related to Sjögren's syndrome (de Monchy et al., 2011).

It is generally agreed that a PRT test value of less than 10 mm indicates dry eye (Cho et al., 1996b; Hamano et al., 1983; Masmali et al., 2014; Saleh et al., 2006). In healthy eyes, the PRT test has been reported to demonstrate good repeatability (Masmali et al., 2014) and shows slightly lower values in closed eye conditions (Doughty et al., 2007). However, in a dry eye population, there is a good agreement between the results for PRT and Schirmer tests (Vashisht & Singh, 2011).

The relationship between the PRT results and the characteristics of the tear meniscus is unclear. Yokoi et al., (2000) reported that, in a sample of dry eye patients, the PRT test did not show a significant correlation with the tear meniscus radius compared to the Schirmer test. Other researchers observed no statistical relationship between PRT and tear meniscus height (Nichols et al., 2003; Tomlinson et al., 2001) whilst others have reported a significant positive correlation between the two metrics (Wee et al., 2012). Similarly, there is poor concordance between PRT measures and results from tests assessing tear secretion or volume (Tomlinson et al., 2001). In view of these conflicting results, the validity of the PRT measures are questionable; it is uncertain as to whether PRT measures tear volume or whether it provides an assessment of tears residing in the eye (reservoir) and stimulates a low degree of reflex tearing (Tomlinson et al., 2001).

1.2.5.1.2 Tear Clearance/Tear Turnover Rate

Tear clearance or tear turnover rate is another method for assessing tear production. Measures of tear clearance are important because delayed drainage has been shown to contribute to chronic ocular inflammation (Dursun et al., 2002; Pflugfelder et al., 1998). Previously, tear clearance has been evaluated by instillation of a diagnostic dye (fluorescein) and visually comparing the fluorescein that was collected using Schirmer strips (from the lateral lower lid margin) on photographic standards (Pflugfelder et al., 1998). However, with this method, despite using anaesthesia reflex tearing was observed to be a confounding variable (Pearce et al., 2001).

An alternative method of assessing fluorescein clearance is the fluorescence multiplate reader, CytoFluor II fluorometer (CytoFluor II; PerSeptive Biosystems, MA). The CytoFluor system works by quantifying solubles (tear film) associated fluorescence measured using a

photomultiplier tube in a light-proof detection chamber; the detected fluorescence data is displayed as arbitrary fluorescence units (AFU) (Afonso et al., 1999; AppliedBiosystems, 1997).

CytoFluor II had been shown to provide a greater predictive value for ocular irritation than the Schirmer 1 test and shows good correlation with age, meibomian gland dysfunction, and decreased corneal and conjunctival sensation (Afonso et al., 1999). However, due to the complexity of the test, the CytoFluor II equipment has been found to be unsuitable for daily clinical usage and therefore, a grading scale [Standardized Visual Scale Test (SVST)] has been introduced (Macri et al., 2000). The SVST provides a simple system for assessing tear clearance; following instillation of fluorescein, the colour of the tear meniscus across the lateral aspect of the lower lid is visually compared with one of the colours of the SVST (score ranging from 0 to 6); a score greater than 3 signifies delayed fluorescein clearance (Macri et al., 2000).

Tear clearance can also be assessed by monitoring trace molecules that are administered into the tear film. This method can be performed by using either radioisotope (gamma scintigraphy) or fluorescein (fluorophotometry) tracers. However, due to safety and financial implications fluorophotometry is the most preferred option. Fluorophotometry has also been shown to be have higher sensitivity and spatial resolution compared to gamma scintigraphy (Maurice & Srinivas, 1992) and as such it is labelled as the gold standard technique for measuring tear clearance (Pearce et al., 2001; McCann et al., 2010).

Using fluorophotometry, tear clearance was reported to be 42% lower in patients with keratoconjunctivitis sicca (KCS) when compared to healthy eyes (Nelson, 1995). In a meta-analysis, tear clearance in dry eyes was found to be significantly lower when compared to normal eyes (Tomlinson et al., 2009). The same analysis reported that evaporative dry eye

patients showed a reduction of 30% in tear clearance while aqueous deficient dry eye patients showed a 60% reduction (Tomlinson et al., 2009).

In an attempt to provide a numerical measure of tear production and drainage, the Tear Function Index is calculated by dividing tear secretion, measured via the Schirmer test with anaesthetic, by the measures of tear drainage via the fluorescein clearance test (Xu et al., 1995; Xu & Tsubota, 1995). According to the Tear Function Index, a value of $\geq$96 is indicative of normal eyes, while a value of $\leq$95 is suggestive of dry eyes (Xu et al., 1995). Tear Function Index values of 15 and below have been noted in Sjogren syndrome (Kaye et al., 2001). Tear Function Index has been found to show higher specificity (91.8%) and sensitivity (78.9%) in diagnosing dry eyes associated with Sjogren syndrome when compared to the Schirmer or tear clearance rate test alone (Xu et al., 1995).

1.2.5.1.3 Evaporimetry

Evaporimetry provides a useful clinical measure of the evaporative water loss from the aqueous layer of the tears. High levels of aqueous evaporation leads to increased tear salinity resulting in dry eyes symptoms (Savini et al., 2008). The evaporimetry procedure is non-invasive and involves patients wearing swimming goggles or chambers modified to allow measures of tear evaporation (Mathers, 1993; Rolando & Refojo, 1983; Tsubota & Yamada, 1992).

Currently, there are 3 methods of measuring evaporimetry: The first method acquires measures by using 2 humidity sensors placed at different heights relative to the ocular surface (Hamano et al., 1980). The second method uses a closed chamber system where measures of tear evaporation are derived from the velocity of the humidity increase at a given ambient humidity (Mathers, 1993; Rolando & Refojo, 1983; Tsubota & Yamada, 1992). The third

method involves the use of an eyecup to form a ventilated chamber that tightly covers the eye being measured, and air of known water content is then infused into and out of the cup (Goto et al., 2003). Using this method, evaporation rates were measured by calculating the difference between the water content of the air entering and exiting the cup (Goto et al., 2003).

Evaporimetry has been found to have the sensitivity to sub-classify dry eyes (Tsubota, 1991; Tsubota & Yamada, 1992) and identify patients with unstable tear film due to meibomian gland dysfunction (Goto et al., 2003). In a meta-analysis by Tomlinson et., 2009, the investigators reported that the evaporation rate was higher in patients with aqueous deficiency and evaporative dry eyes compared to non-dry eye sufferers (Tomlinson et al., 2009).

1.2.5.1.4 Meniscometry

Assessment of the tear meniscus relates to the reservoir of tears that lie along the inferior and superior lid margins from which the pre-ocular tear film is formed after a blink (Tiffany, 2006). Meniscometry is a non-invasive method of assessing the tear meniscus curvature. The measurement of tear meniscus height is an indicator of the total tear volume (Johnson & Murphy, 2005a; Yokoi et al., 2004). Measurement of tear meniscus height has been found to be important in the diagnosis of tear deficiency since 75% to 90% of the total tear volume is located along the tear meniscus (Holly, 1980; Port & Asaria, 1990).

There is significant ambiguity concerning the characteristics of the upper and lower tear meniscus. Whilst some investigators have reported no significant differences between the tear meniscus of the upper and lower eyelids (with regards to height, area and curvature of the tear meniscus) (Wang et al., 2006) others have identified differences in height and

curvature (Creech et al., 1998; Johnson & Murphy, 2006). However, most studies only focus on the lower tear meniscus because of the relative high mobility of the upper lids and obscuration caused by the eyelashes.

Tear meniscus is normally measured using a slit lamp with a calibrated variable slit beam height (Yokoi & Komuro, 2004). However, a more accurate measurement (up to 0.03 mm) can be obtained by equipping the slit lamp with a micrometre (Lamberts et al., 1979; Miller et al., 2004; Nichols et al., 2004; Nichols et al., 2004a). To aid in the visibility of the tear meniscus on the slit lamp instillation of fluorescein dye has been advocated (Oguz et al., 2000; García-Resúa et al., 2009).

Other non-invasive methods of assessing the tear meniscus include video recording (Doughty et al., 2001; Doughty et al., 2002; Glasson et al., 2003), photography (Mainstone et al., 1996; Santodomingo-Rubido et al., 2006), tear interference imaging using TearScope (Uchida et al., 2007), optical coherence tomography (Savini et al., 2006; Wang et al., 2006), reflective meniscometry (Oguz et al., 2000; Yokoi et al., 1999), optical pachymetry and strip meniscometry (Dogru, 2006; Johnson & Murphy, 2005a).

More recently, a new non-invasive, portable, slit-lamp mounted digital meniscometer (PDM) that is able to measure the tear meniscus radius and height was developed (Bandlitz et al., 2014). The PDM had been validated and shown to provide accurate and reliable measurements of human tear meniscus radius and is suitable for both research and clinical practice (Bandlitz et al., 2014).

Due to methodological variations, there is significant overlap in average measures of tear meniscus between normal and dry eyes restricting standardisation for screening purposes.

The literature suggests differing values of normal tear meniscus height: 0.2 to 0.3 mm (Kulkarni et al., 1997), 0.25 to 0.4 mm (Kugoeva & Sokolovskiĭ, 1996), 0.35 mm (Mainstone et al., 1996) and 0.5 mm (Marquardt, 1986); possibly suggesting that a value of <0.2 mm are indicative dry eye. However, Doughty et al., (2002) suggested a value of $\leqslant$0.1 mm to be a suitable lower cut-off value for tear meniscus height to indicate dry eye.

1.2.5.2 Tear Stability

Tear stability is assessed to determine the integrity of the tear film layer (Holly & Lemp, 1977; Sweeney et al., 2013) and can aid in the diagnosis of dry eyes and assessment of the efficacy of the treatment of dry eyes (Bron, 2001; Gary, 2007; Nichols et al., 2000). Tests assessing invasive tear break up time (TBUT) and non-invasive tear break up time (NIBUT) can be used to assess the tear stability.

1.2.5.2.1 Tear Break Up Time (TBUT)

TBUT is an invasive method that requires instillation of fluorescein into the tear layer. First proposed by Norn in the 1960s (Norn, 1969), to date, it is the most commonly used objective clinical test to evaluate tear film stability (Downie et al., 2013; Korb, 2000; Smith et al., 2008). After instillation of fluorescein into the tear layer (using a moistened strip or a pipette), the cornea is observed using a slit lamp with cobalt blue light. A Wratten 12 yellow barrier filter can be used to enhance the quality of the image being observed (Cho & Douthwaite, 1995). TBUT is the time interval between a complete blink and the appearance of the first break, identified as discontinuity or dry spots observed across the tear film (Savini et al., 2008). Several investigators have shown that the 'break-up areas' normally occurs along the inferior central aspects of the cornea and least frequently across the superior quadrant of the cornea (Cho et al., 1992; Cho et al., 1996a; Elliott et al., 1998; Jiang et al., 2014; Rengstorff, 1974).

TBUT has been shown to reduce with increasing age (Briggs, 1998; Cho & Yap, 1993b) and is known to differ with ethnicity (Briggs, 1998; Cho & Yap, 1993b; Patel et al., 1985).

An abnormal tear film has been found to have a TBUT of less than 10 seconds (Lee & Kee, 1988; Lemp & Hamill, 1973; Mengher et al., 1985). TBUT values from 5 to 10 seconds are considered marginal and values of less than 5 seconds are indicative of dry eye symptoms (Pflugfelder et al., 1998). However, patients with mild or moderate dry eyes have a wide range of TBUT values making screening and diagnosis challenging (Lemp et al., 2011; Sullivan et al., 2012). For the categorization of dry eye symptoms, TBUT shows a sensitivity of 75% and specificity of 60% (Goto et al., 2004). Despite its popularity, measures of TBUT are highly variable (Elliott et al., 1998) and showed poor repeatability (large standard deviation of up to 20 seconds) in normal participants that were followed up for eight separate visit over a one month period and were at different times of the day (Vanley et al., 1977). Reproducibility of TBUT has been found to vary too, with levels in the order of 65% amongst normal eyes and 95% in dry eye patients (Lee & Kee, 1988). On the contrary, reproducibility of TBUT has been found to be improved when measurements are taken at two different times by a single examiner (95% limits of agreement: -5.71 to 5.83 seconds, up to $\pm$8 seconds difference between visits) (Nichols et al., 2004). A more reliable value of TBUT can be obtained by taking the mean from multiple measurement of TBUT (Cho et al., 1998; Nichols et al., 2004). However, if fluorescein is instilled before each measurement, then the cumulative effect of the instillation is likely to influence the results (Cho et al., 1998). Using data from a study carried out by Cho et al., (1998), Papas, (1999) reported that the differences between the first and second measurement of TBUT were not clinically significant.

More recently, an automated TBUT measurement has been introduced and has been validated against measurements obtained by a trained observer (Cebreiro et al., 2011). TBUT has also been shown to be affected by factors such as clinician experience level, partial blinking, use of local anaesthetic as well as the type of illumination technique being used on the slit lamp (Cho et al., 1992; Lemp & Hamill, 1973). Variables relating to the fluorescein i.e. type (i.e. impregnated strips or solution) concentration, pH value, quantity instilled and the presence or absence of preservatives have also been found to affect TBUT measurements (Mengher et al., 1985).

Indeed the amount of fluorescein instilled into the tear film is likely to be the main source of variability in TBUT values (Savini et al., 2008), since large amounts of fluorescein have been shown to increase the TBUT (Johnson & Murphy, 2005b). Studies have shown that reliability of the test is increased when less than 2 µL of fluorescein is administered using a laboratory micropipette versus the conventional strip method (Holly et al., 1986; Foulks, 2003). Reproducibility was also improved when the conventional fluorescein strips were replaced with modified fluorescein strips (strips that deliver 5 times less fluorescein) (Korb et al., 2001). Similarly, a narrow fluorescein strip (1 mm) was able to increase repeatability of TBUT (Pult & Riede-Pult, 2012).

1.2.5.2.2 Non-Invasive Tear Break Up Time (NIBUT)

The use of fluorescein in the evaluation of TBUT had been reported to affect the tear layer by temporarily increasing the tear volume, which causes changes in the surface tension of the tear film (due to the presence of contaminants or preservatives) and subsequently disrupting the stability of the aqueous layer (Cho & Brown, 1993; Holly, 1987). Other studies have indicated that fluorescein destabilises the tear layer and reduces the TBUT (Mengher et al.,

1985; Patel et al., 1985). Given these limitation improved non-invasive measures of TBUT have been sought (Bron et al., 2007).

Non-invasive tear break up time (NIBUT) implies that no diagnostic dyes are instilled into the tear layer, blinking is not forced or suppressed, no contact occurs between the measuring instrument and the eye, and the methodology minimises any alterations to the ocular environment (such as increased temperature changes associated with illumination levels).

In contrast to TBUT, which is based on identifying the first tear break-up by observing the disturbances in the fluorescein layer, NIBUT requires observation of an illuminated grid pattern reflected from the anterior tear surface; commonly the mires of a keratometer are assessed (Patel et al., 1985). In a stable tear film, the regular image of the target will be reflected while in an unstable tear film, the target will be distorted or irregular. The time in seconds from the last blink to the appearance of the first distortion, irregularity, discontinuity or break in the reflected image is recorded as NIBUT (Bron, 1997; Guillon, 1998; Jones & Nischal, 2013; Lamberts & MacKeen, 1986; Mohidin et al., 2002).

Assessment of the literature suggests poor concordance between TBUT and NIBUT with TBUT frequently exhibiting lower values (Cho & Douthwaite, 1995; Cho et al., 1996a; Cox et al., 2015). Studies have shown that the mean values of NIBUT are approximately 16 seconds for healthy eyes and 7 seconds for dry eyes (Farrell et al., 1992; Little & Bruce, 1994). However, Mengher et al., (1986) measured NIBUT on healthy and keratoconjunctivitis sicca (KCS) participants and found that NIBUT had a sensitivity of 82% in the diagnosis of KCS. This finding lead to a cut of value of <10 seconds in diagnosing KCS using NIBUT (Mengher et al., 1986).

When performed on the same participants, TBUT was found to provide higher values compared to NIBUT (Patel et al., 1985). The same study also reported that when fluorescein was instilled and later the NIBUT re-measured, the results were reduced by an average of 3.6 seconds. These observations are evidence that instillation of fluorescein causes changes to the tear film.

Improvement to the measurement of NIBUT using a keratometer have been proposed by means of adding a circular grid pattern, which is called 'HIR-CAL Grid' (white grid on a black background) (Hirji et al., 1989). Using this methodology, it was suggested that a total of five measurements could be obtained and the mean calculated to represent the NIBUT (Hirji et al., 1989). It was also suggested that fine grid pattern would allow easier detection of the distortion compared to standard mires (Craig et al., 1995).

Modifications of the NIBUT methodology also include the evaluation of a larger area of the ocular surface by attaching a hemispherical bowl on a slit lamp biomicroscope (Mengher et al., 1985). Within the bowl, an illuminated rectangular grid pattern is fixed which is then projected onto the corneal surface. The projected rectangular grid pattern enables assessment of the NIBUT over the whole cornea as oppose to only examining the central cornea when performing the test with a keratometer (Mengher et al., 1985).

The HIR-CAL Grid and Mengher-Tonge xeroscope showed excellent repeatability for measures of NIBUT (Madden et al., 1994). However, the HIR-CAL Grid NIBUTs were shorter than the Mengher-Tonge xeroscope, possibly due to the elevated humidity inside the xeroscope. Moreover inter-examiner differences were thought to impact measurements with these devices (Madden et al., 1994).

The Tomey RT-7000 Auto Refractor-Keratometer (Tomey Corporation, Nagoya, Japan) and the Oculus Keratograph 5M (Oculus, Wetzlar, Germany) are also able to assess NIBUT (Abdelfattah et al., 2015; Gumus et al., 2011; Wolffsohn et al., 2017). However, when compared together, both instruments showed poor intra-class correlation coefficient of 0.187 (95% confidence interval -0.097 to 0.406) and poor correlation (Lee et al., 2016); suggesting poor interchangeability. Although assessing the Oculus Keratograph 5M in both dry eye and healthy participants in two separate studies, the repeatability and reproducibility of NIBUT measures were found to be good (Hong et al., 2013; Tian et al., 2016).

1.2.5.2.3 Interferometry

Interferometry can also be used to investigate tear stability by observing and measuring the superficial lipid layer of the tear film. An assessment is made of the colour fringes resulting from the interference between light reflected from the surface of the lipid layer and the aqueous layer of the tear film. Interferometry has been used to assess both NIBUT and tear lipid layer thickness (Doane & Lee, 1998; King-Smith et al., 2010; Nichols et al., 2002; Szczesna et al., 2006; Yokoi & Komuro, 2004).

The TearScope Plus (Keeler Ophthalmic Instruments) and the DR-1 interferometer (Kowa Co. Ltd., Tokyo, Japan) are examples of devices that can be used to assess the lipid layer. Images obtained from both equipment are classified accordingly to standardised grading scales (Guillon-Keeler Tear Film Grading System for the TearScope and the Yokoi severity grading system for the DR-1) (Ban et al., 2009; Yokoi et al., 1996). Generally, the thicker lipid layers (≥90 nm) display colour and wavy patterns while the thinner lipid layers (≤60 nm) are more homogeneous (Remeseiro et al., 2012). Using the Guillon-Keeler system, lipid layer thickness

can be classified according to 6 key criterion: (a) open meshwork, (b) closed meshwork, (c) wave, (d) amorphous, (e) colour fringes and (f) globular (Guillon, 1998).

In 2003, this scale was amended to a 10 level scale [0=no lipid layer, 1=open meshwork, 2=detailed meshwork, 3=closed meshwork, 4=meshwork-wave combination, 5=wave, 6=wave-amorphous combination, 7=amorphous, 8=amorphous-colour combination and 9=colour (very thick lipid layer)] (Isenberg et al., 2003). Using this new scale, it was shown that the lipid layer of the tear film is much thicker in the first 6 postnatal months compared to adults (Isenberg et al., 2003). It was initially reported that eyes with meibomian gland dysfunction could be differentiated from normal eyes, by identifying a change from horizontal to vertical patterns at grades 1 and 2 and a darker interference colour with no fringes (Goto & Tseng, 2003). However, investigators also noted that, aqueous deficient dry eyes were also able to produce this pattern (Goto, 2004).

Goto & Tseng, (2003) reported that patients with lipid tear deficiency dry eye showed slower 'lipid spread' upon blinking compared to healthy individuals. In addition, the pattern of lipid spread in lipid tear deficiency dry eye was vertically streaking while for healthy individuals, it was horizontally wavy (Goto & Tseng, 2003). Furthermore, in healthy individuals, the lipid film was uniform while for the lipid tear deficiency dry eye, it was non-uniform (Goto & Tseng, 2003).

Another method that can be used to classify the superficial lipid layer of the tear film is by using the Yokoi scale (Yokoi et al., 1996). The Yokoi scale is composed of 5 grades: (Grade 1) somewhat grey colour, uniform distribution, (Grade 2) somewhat grey colour, non-uniform distribution, (Grade 3) a few colours, non-uniform distribution, (Grade 4) many colours, non-uniform distribution and (Grade 5) corneal surface partially exposed with no lipid layer

interference (Yokoi et al., 1996; Yokoi & Komuro, 2004). Normal eyes consist of grade 1 and 2 while higher grades (and sometimes even including grade 2) are indicative of dry eyes (Yokoi & Komuro, 2004).

Possibly due to the difficulty of its use and subjectivity, the TearScope Plus is no longer commercially available, despite development of new software applications to objectively categorize the lipid layer pattern (García-Resúa et al., 2013).

1.2.5.2.4 Videokeratography

Another method that can be used to assess tear stability is called videokeratography. In a 2008 survey, videokeratography was identified to be the most favoured technique for initial evaluation of patients with Lasik-related dry eyes (Smith et al., 2008). By assessing the distortion of a ring pattern image on the corneal surface, videokeratography provides a measure of surface regularity index (SRI) and surface asymmetry index (SAI) (McGinnigle et al., 2012). Both SRI and SAI are able to adequately describe the smoothing properties of the tear film (Tutt et al., 2000; Montés-Micó, Alió, et al., 2004).

High speed videokeratography such as the Tear Stability Analysis System (TSAS) enables a quantitative assessment of the tear film dynamics and may have clinical value in the management of ocular surface disorders (Kojima et al., 2004; Németh et al., 2002).

1.2.5.2.5 Aberrometry

Since changes in the tear film thickness and stability induce aberrations aberrometry allows a non-invasive assessment of the reduced retinal image quality and blurry vision commonly encountered in dry-eye patients (Tutt et al., 2000).

Using a Hartmann-Shack aberrometer, it was found that dry eye patients showed greater higher order aberrations compared to normal eyes (Montés-Micó, Cáliz, et al., 2004; Denoyer et al., 2012). Similar observations were noted by Lin et al. who observed that disruption of the tear layer stability increases anterior corneal higher order aberrations in normal eyes and more rapidly in dry eyes (Lin et al., 2005). These increased aberrations were thought to be due to the presence of the non-uniform thinning of the tear layer and exposure of the rough epithelial surface of the cornea (Himebaugh et al., 2012).

Several studies have indicate that instillation of artificial tears reduces optical aberration and may help in the management of dry eyes (Montés-Micó, Cáliz, et al. 2004; Montés-Micó et al., 2010; Lekhanont et al., 2014). Furthermore, in dry eyes disease patients, long term use of artificial tears was proven to be able to improve contrast sensitivity and decrease optical aberration (Ridder et al., 2009).

In view of its non-invasive nature and its ability to assess the ocular surface and optical performance of the eye, Dieckow, (2011) advocated that aberrometry should be used as a method to detect, monitor and evaluate the efficacy of dry eyes treatment.

1.2.5.2.6 Functional Visual Acuity

Clear vision is only possible when the ocular surface is smooth and when the tear film is stable (Goto et al., 2002; Kaido et al., 2007). The tear film instability that occurs in patient with dry eyes causes ocular surface irregularity and subsequent symptoms of blurred vision, especially when driving, reading and using VDTs (Goto et al., 2002).

Functional visual acuity measurement (FVAM) system was developed to assess the reduction in visual acuity experienced by dry eye patients. FVAM is a measure of visual acuity (using

Landot C) during sustained eye opening without blinking (Goto, Yagi, et al., 2003). In an effort to reflect everyday vision more accurately, Kaido et al., (2006, 2007) proposed a metric termed as the visual maintenance ratio (ratio between the FVAM and the baseline visual acuity), (Kaido et al., 2006; Kaido et al., 2007) and found this to be significantly reduced in patients with dry eyes when compared to non dry eye participants (Kaido et al., 2014).

FVAM system is an effective tool in the assessment of dynamic visual acuity changes in patients with dry eyes and it also plays an important role in evaluating management strategies for dry eyes (Ishida et al., 2005; Kaido et al., 2008). When coupled with dry eye symptoms questionnaire, FVAM may prove to be an improved screening tool for dry eye in VDT users (Kaido et al., 2015).

1.2.5.2.7 Confocal Microscopy

Confocal microscopes focus the light source and objective lens onto the same small area of interest; the focal volume of which is defined by the numerical aperture, magnification, and working distance of the objective lens (Minsky, 1988). Confocal microscopy enables clear visualisation of the corneal epithelium as well as the external tear surfaces allowing thickness measurements of the full tear layer (Prydal et al., 1992; Prydal et al., 1993). Using this technique Prydal et al., (1992) found the thickness of the human tear film to be 41 to 46 µm (Prydal et al., 1992). The technique has been found to be valuable for detailed imaging of tear film properties due to its non-contact nature and excellent focusing characteristics (Mathers & Daley, 1994).

Although confocal microscopy is able to measure tear film thickness and evaluate the changes that occurs to the corneal cells due to dry eyes, its use in clinical setting is still limited due to

the equipment being relatively expensive and, requiring specialised operators (Bron et al., 2007; Zucker & Price, 2001).

1.2.5.2.8 Osmolarity

Osmolarity measures the molecular concentration of all osmotically active particles in a solution. Tear osmolarity has been shown to be the single best marker of dry eye severity (Sullivan et al., 2010; Suzuki et al., 2010) with a sensitivity and specificity of 90% and 95%, respectively (Farris, 1994).

There are 3 methods that can be used to measure tear osmolarity. The first method, known as the freezing point depression (FPD) is the gold standard test (Farris et al., 1983; Gilbard, 1985). This method (FPD) only requires a small tear samples of approximately 0.1 µl which is normally collected using micro capillary glass tube (Gilbard et al., 1978). Samples are subsequently frozen, thawed and then viewed under a stereo microscope. The point at which the last crystal (frozen tears) melts is noted as the freezing point (Tomlinson et al., 2010). The other two techniques involve vapour pressure (Miller et al., 2004; Pensyl & Benjamin, 1999) and electrical conductivity or impedance to assess osmolarity (Ogasawara, et al., 1996; Tomlinson et al., 2010). Both vapour pressure and electrical impedance require a slightly larger tear samples of approximately 0.8 µl (Pensyl & Benjamin, 1999).

Generally, dry eyes causes an increase in tear osmolarity (Farris, 1994). Increased tear osmolarity is also associated with androgen deficiency, vitamin A deficiency, decreased blink rate, lacrimal gland under secretion (Gary, 2007) and thyroid ophthalmopathy (Iskeleli et al., 2008). Patients with dry eyes suffer an imbalance between tear secretion, evaporation and clearance which leads to increased tear osmolarity.

Ocular changes (concentration of inflammatory cytokines, loss of glycocalyx and reduction in goblet cell) have been reported following increased tear osmolarity. An increased concentration of inflammatory cytokines in the conjunctival epithelium was observed in patients with Sjogren's syndrome keratoconjunctivitis sicca (Pflugfelder et al., 1999). It was also noted that in Sjogren syndrome, surface wettability and tear film stability are reduced, possibly due to the loss of glycocalyx and the reduction in goblet cell (Rivas et al., 1992).

The TearLab® Osmolarity System (TearLab Corp., San Diego, California, USA) provides an objective clinical test for assessing dry eyes and the effectiveness of dry eye treatment (Benelli et al., 2010). The device uses electrical conductivity (electrical impedance) of fluids to determine osmolarity (Versura et al., 2010; Versura & Campos, 2013). The technique requires a 0.05 µL tear sample and takes 30 seconds to obtain measures from both eyes.

Osmolarity can also be measured using the Tear Osmometer (Advanced Instruments Inc., Norwood, MA, USA). This equipment uses the FPD technique to measure osmolarity. However, this equipment requires a larger tear sample (0.5 µL) and is therefore considered to be unsuitable for measurement of eyes with severe dryness (Yildiz et al., 2009).

Following a large multicentre study, it was proposed that osmolarity values greater than 308 mOsm/L (using TearLab) were indicative of mild dry eyes (Lemp et al., 2011). The same study also reported that in moderate to severe cases of dry eye, detection was achieved when a cut off of 312 mOsm/L (sensitivity, 73%; specificity, 92%) was used (Lemp et al., 2011). In a recent study, it was shown that osmolarity underwent changes in both dry eye patients and healthy normal control subjects over the course of 8 hours (Li et al., 2012).

1.2.5.3 Laboratory Based Test

1.2.5.3.1 Tear Ferning Test

When mucus is allowed to dry on a glass slide, it will eventually form fern like crystalline structure (arborisation). This phenomenon is termed 'ferning'. Papanicolaou was the first to documented this phenomenon and used it to investigate vaginal smears (Papanicolaou, 1946). However, it was Rolando who recognised and classified the variations observed in tear ferning test and developed the Rolando Tear Ferning Scale which consist of grade 1 to 4 (Rolando, 1984). Tear ferning test requires 1 µl of tears to be collected using a micropipette from the lower meniscus. Once collected, the tear sample is dropped onto a microscope slide and allowed to dry at $20 \pm 3\ ^{0}C$ for 10 minutes. When left to dry, the mucus and electrolytes in the tears produce fern like structures and these are viewed though a light microscope (Norn, 1994; Rolando, 1984).

To diagnose dry eyes, these fern like structures are classified according to Rolando's proposed grading scale (Table 1.3). Based on this grading system, grade 3 and 4 signifies dry eyes (Rolando, 1984).

Classification	Description
Grade 1	Uniform arborisation in the entire field of observation without spaces between the ferns. Single ferns are big and closely branched.
Grade 2	Arborisation is abundant, but the single ferns are smaller and have a lower frequency of branching than grade 1. Empty spaces appear between the ferns.
Grade 3	Arborisation is only partially present. Single ferns are little and incompletely formed with rare or no branching. Large spaces without ferning appear.
Grade 4	No ferning present. Mucus appears in clusters and threads. Contaminated and degenerated mucus may be seen mixed with exfoliated cells.

Table 1.3: Rolando's Tear Ferning Classification (Rolando, 1984).

Rolando's grading scale was reported to show high intra- and inter-observer agreement and has been found to provide an easy and consistent method for the classification of tear ferning patterns (Pensyl & Dillehay, 1998). However, a more recent paper reported poor correlation between tear ferning and tear film stability and showed limited sensitivity and specificity for the prediction of ocular surface comfort in both contact lens and non-contact lens wearers (Evans et al., 2009). In postmenopausal women, it was reported that tear Ferning of Grade 1 and 2 were found in patients with dry eyes (Srinivasan et al., 2007); this is opposed to the grading scale where Grade 1 and 2 should only be present in non-dry eye patients (Rolando, 1984).

One major drawback of the Rolando scale is that it utilizes gross categorization of the ferning patterns and thus restricts sensitivity. Also, the variance around grade 1 and 2 are large and not all types of tear ferning are represented by the scale (Masmali, 2010). To overcome this limitation, a new grading system consisting of a five point scale was recently developed (Masmali et al., 2014), with grade ≥2 being classified as abnormal (Masmali, Al-Qhtani, et al.,

2015). This grading scale (Masmali Tear Ferning Scale) has shown good validity in describing the ferning patterns (Masmali, Al-Bahlal, et al., 2015; Masmali, Al-Qhtani, et al., 2015).

1.2.5.3.2 Lacrimal Gland Function Test

Lacrimal gland function test is conducted to assess the integrity of the lacrimal glands. It is well documented that proteins in the tear layer such as lactoferrin, lysozyme and lipocalin are produced in the acini of the lacrimal glands (Dartt, 1989; Yoshino et al., 1996). Investigators have also found that corneal and conjunctival epithelia produce lactoferrin (Santagati et al., 2005) whilst the meibomian glands are a source of lactoferrin and lipocalin (Tsai et al., 2006).

Lacrimal gland function test normally assesses the presence of lactoferrin in the tear layer. Lactoferrin functions as an antimicrobial agent (Chandler & Gillette, 1983; Flanagan & Willcox, 2009), modulating the inflammatory response (Baveye et al., 1999), offering protection from oxidative damage (Kijlstra, 1990) and ultra-violet (UV) (Shimmura et al., 1996). Concentration of lactoferrin (mg/ml) can be assessed in labs by using commercial test plates 'LactoPlate' or 'LactoCard', using tears obtained via filter paper discs or by enzyme-linked immunosorbent assay (ELISA) (Kijlstra et al., 1983; Boersma & van Bijsterveld, 1987; McCollum et al., 1994).

In general, lactoferrin concentration has a mean value of 2.2 mg/ml in the normal eyes (Kijlstra et al., 1983) and its concentration is reduced in dry eyes (Farris et al., 1983). Similarly, Ohashi et al., (2003) reported lower levels of lactoferrin in eyes with Sjogren syndrome when compared to normal eyes (Ohashi et al., 2003). Notably, measures of lactoferrin concentration show high specificity (95%) and sensitivity (72%) when, compared to the Schirmer I test (specificity 85% and sensitivity 64%) (Dalt et al., 1996) .

Lactoferrin concentrations are lower with increasing age (Jensen et al., 1986) and that there is a decrease in lactoferrin concentration in patients with hepatitis C (Abe et al., 1999) and with certain types of ocular diseases (Chen, 1989); patients with keratoconjunctivitis sicca show reduced concentration of lactoferrin (Boersma & van Bijsterveld, 1987; McCollum et al., 1994).

1.2.5.3.3 Tear Protein Analysis

There are more than 400 types of protein that can be found in the human tear film (Wu & Zhang, 2007). In healthy eyes, the total protein concentration of tears is about 10% of that of the plasma (Sariri & Ghafoori, 2008). Changes in the tear film protein expression levels are associated with both systemic and ocular diseases as well as environmental factors (Wu & Zhang, 2007). Dry eyes associated with Sjogren syndrome were associated with an altered proteomic profile (Li et al., 2014).

Research on the protein contents of human tear film has been limited due to challenges in obtaining adequate size of tear samples, the complexity of the tear component itself and the limitations in the currently available analytical technologies (Li et al., 2008). Much of the literature on tear protein analysis is based upon qualitative or quantitative techniques which include: high-performance liquid chromatography (HPLC) techniques, one and two-dimensional gel electrophoresis (2-DE), and most commonly, enzyme-linked immunosorbent assay (ELISA) (Wu & Zhang, 2007). Recently, with the introduction of the high speed TripleTOF 5600 mass spectrometer, a total of 1543 proteins in the tear film can be identified; representing the largest number of human tear proteins reported to date (Zhou et al., 2012).

The majority of work on tear film protein analysis has been focused on the dry eyes with the aim of investigating the inflammatory role of the T-cell, specifically the response from effector

T-cells (Stern et al., 2002). This is because T-cells (primarily the $CD4^+$ T-cells) are responsible for the ocular surface inflammation that is associated with dry eye (De Paiva et al., 2007; Annan et al., 2009).

Cytokines are a broad and loose category of small proteins (5 to 20 kDa) that are important in cell signalling. Cytokines aid in cell to cell communication during immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma. Tear cytokines levels have been found to correlates with the severity of symptoms and ocular surface signs in all forms of dry eyes (Lam et al., 2009). Studies have also shown that different tear proteins are present in dry eye disease with and without meibomian gland dysfunction (Lam et al., 2009; Enríquez-de-Salamanca et al., 2010).

MMP-9 is a proteolytic enzyme that is produced by the ocular surface, glandular epithelial cells and immune cells under stress. MMPs are zinc-dependent endopeptidases with the potential to degrade all types of extracellular matrix (Sakimoto & Sawa, 2012). Kaufmann highlighted the importance of measuring the levels of matrix metalloproteinase 9 (MMP-9) in dry eyes and ocular surface disease (Kaufman, 2012). Dry eye is associated with high levels of MMP-9 and this is associated with disruption of the corneal epithelial barrier function (Pflugfelder et al., 2005; Smith et al., 2001). The levels of MMP-9 has also been noted to be higher in conditions such as in conjunctivochalasis (Acera et al., 2011), dysfunctional tear syndrome (Chotikavanich et al., 2009), meibomian gland disease (Geerling et al., 2011) and Sjogren syndrome (Konttinen et al., 1998; Solomon et al., 2001).

1.2.5.3.4 Tear Lipid Analysis

Tear lipid analysis aids in differentiating between healthy eyes and eyes with meibomian gland dysfunction (Pucker & Nichols, 2012). A complex mixture of non-polar lipids, polar lipids

and proteins are secreted by the meibomian glands (Butovich et al., 2008). Tear lipid analysis has previously been performed using methods based on hydrolysis and derivatization, including thin layer chromatography, nuclear magnetic resonance spectroscopy, infrared and Raman spectroscopy, gas chromatography and gas chromatography mass spectrometry (Butovich et al., 2008; Green-Church et al., 2011; Butovich, 2011). Unfortunately, even with all these methods, it is still challenging to obtain uncontaminated samples in sufficient quantity to be analysed. This is mainly because tear lipid analysis is prone to contaminants that originate from plasticizers or skin cell contamination (Butovich, 2013). Tear lipid analysis also shows low sensitivity and there is a risk of sample degradation due to prolonged analysis time (Butovich et al., 2008).

With the advent of improved analysis techniques, it is now possible to assess small quantities of meibomian secretion and tear film lipids. More recently, researchers have suggested that a combination of infrared spectra and Principal Component Analysis (PCA) may be used to characterize MGD and age-related changes in human meibum (Borchman et al., 2010). Using this method, researchers are able to discriminate between healthy eyes and eyes with meibomian gland dysfunction with 93% accuracy (Borchman et al., 2010). It is anticipated that differences between healthy eyes and those with Meibomian gland dysfunction may be related to changes in the amount of lipid saturation governing lipid-lipid strength (Borchman et al., 2011).

The composition of meibomian fatty acids has also been found to be different in meibomian gland dysfunction (Joffre et al., 2008) showing higher levels of branched-chain fatty acids and lower levels of saturated fatty acids (Joffre et al., 2008).

1.3 Blinking

1.3.1 Definition

Blinking is defined as either:

- a twitch blink consisting of a small movement (flutter) of the upper lids.
- an incomplete blink in which the descending upper lids covers less than two thirds of the cornea.
- a complete blink where the descending upper lids covers more than two third of the cornea (Abelson & Holly, 1977).

More recently, blinking has also been defined as a fast eyelid movement that closes and opens the palpebral fissure (Cruz et al., 2011).

The speed of the eyelid movement during a blink and the number of blinks per minute shows significant inter-subject variability (Bacher & Smotherman, 2004a; Doughty, 2002; Karson et al., 1984). The average blink speed is approximately 17 to 20 cm/s, with a maximum speed approximately 40 cm/s (Doane, 1980). Studies have suggested that the normal blink rate is 12 blinks/min (King & Michels, 1957) but, a higher rate of 24.8 blinks/min has also been reported (Collins et al., 1989).

1.3.2 Components of Blinking

Movement of the upper eyelids occurs when there is activity in the two reciprocal acting muscles: the levator palpebrae superioris (LPS) and the orbicularis oculi (OOC) (Oyster, 1999; Pult et al., 2015). The LPS muscle is innervated by the oculomotor (III) nerve while the OOC is innervated by the facial (VII) nerve (Levin et al., 2011). Blinking is caused by the antagonistic actions of the LPS and the OOC muscle (Bour et al., 2002; Evinger et al., 1991). The closing stage of a blink is caused by the phasic contraction of the OOC associated with a momentary pause in the tonic activity of the LPS (Sforza et al., 2008). When a blink occurs, LPS motor

neurons stop firing momentarily and at the same time, OOC's motor neurons activate the OOC producing a rapid lowering of the upper lids (Aramideh & Ongerboer de Visser, 2002). Shortly after the blink, the OOC motor neurons will deactivate and the LPS muscle will return to its original tonicity triggering the opening phase of the blink (Bour et al., 2002; Sibony, 1991). Several investigations have indicated that the medial frontal gyrus of the brain and the visual cortex is responsible for spontaneous eye blinking, whereas pre-central activation appears to be related to blink inhibition (Fink et al., 1997; Kato & Miyauchi, 2003; Hyo et al., 2005).

1.3.3 Importance of Blinking

Blinking functions as a protective mechanism for both the conjunctiva and the cornea (Oyster, 1999). Blinking also facilitates lubrication of the ocular surface (Nakamori et al., 1997). In contact lens wearers, blinking helps to moisten and clean the anterior surface of the contact lens. A complete blink will ensure that debris on the tear film will be swept to the inferior marginal tear strip and later, when the lids move upwards, a clean tear film is distributed (Benedetto et al., 1984; Maurice, 1973; Palakuru et al., 2007).

While complete blinking is able to maximize the extent of mucin distribution on the ocular surface, deliberate, forceful blinking was found to significantly increase the lipid layer thickness of the tear film (Korb et al., 1994). These two components provide the base for a functional tear film to allow a clear image to be formed on the fovea. A full blink is desirable and optimal and, incomplete blinking has been found to cause tear film instability (Hirota et al., 2013) and lead to conditions such as exposure keratopathy, lid wiper (portion of the central, posterior eyelid in apposition to the ocular surface) epitheliopathy, dry eye and contact lens intolerance (McMonnies, 2007). Although blinking is critical in maintaining a

smooth optical surface, in the absence of an adequate tear film, the mechanical forces involved in blinking might damage the lid wiper and the ocular surface (Cher, 2003; Berry et al., 2008).

Blinking has also been reported to be involved in visual information processing (Esteban et al., 2004). Within 100ms prior to a blink, the attenuation of visual input occurs (Wibbenmeyer et al., 1983; Manning et al., 1983). During blinking, vision is occluded for approximately 200 ms due to eyelid closure (Lawson, 1948). These 'blackout' periods would interfere significantly with our daily task. However, humans scarcely notice their blinks and the subjective visual world remains continuous and stable. Several studies have confirmed the presence of a suppression mechanism that fills in the blackout periods during blinking that would otherwise be perceived (Riggs et al., 1981; Barinaga, 2002).

1.3.4 Types of Blinking

There are three types of blinks: (i) spontaneous blink, (ii) reflex blink and (iii) voluntary blink.

1.3.4.1 Spontaneous Blink

Spontaneous blinking is the most common form of blinking (Levin et al., 2011) and is defined as a continuous, symmetrical and almost periodic movement of closing and opening of the eyelids. It occurs without the need for any external stimulus or internal effort (Esteban et al., 2004). Spontaneous blinks have a shorter duration and a lower amplitude when compared to voluntary blinks (Bour et al., 2000).

Several studies have reported that spontaneous blinks appear to be triggered by various aspects of information processing such as cognitive load (Marquart et al., 2015; Omori &

Tatsuhira, 2010) and fatigue (Stern et al., 1994) and that blink latency can be used to evaluate the complexity of an assigned task (Fogarty & Stern, 1989; Goldstein et al., 1992).

1.3.4.2 Reflex Blink

Reflex blinking (corneal reflex) occurs as a response to a certain event or stimulation to the globe and adnexa and acts as a protective mechanism (Levin et al., 2011). It can be elicited by rapidly moving objects, loud noise or bright flashes of light that stimulates the auditory and/or optic nerve (Rimpel et al., 1982). Reflex blinks are faster and have a higher velocity in comparison to spontaneous or voluntary blinks (Evinger et al., 1991).

During reflex blinking, the upper eyelid shows an early component of electrical signalling before the closing phase of the blink that opens the upper eyelid to a greater degree (Bour et al., 2000). Studies have shown that during reflex blinking, except for the superior oblique, the activity of all extra ocular muscles increases (Evinger & Manning, 1993).

1.3.4.3 Voluntary Blink

Voluntary blinking occurs consciously and deliberately (Kirkwood, 2006). The closing of the eyelid during voluntary blinks results from the actions of the palpebral and orbital portions of the OOC muscle. Using electromyogram (EMG), Kaneko and Sakamoto, (1999) found that the mean amplitude value for the voluntary blinks was significantly larger than those for spontaneous and reflex blinks (Kaneko & Sakamoto, 1999). Moreover it has been suggested that a complete, more rapid eyelid closure in voluntary blink might be caused by the spatial and/or temporal summation (Bour et al., 2000). Indeed, in a study utilising functional magnetic resonance imaging (fMRI), voluntary blinks have been found to be associated with the activation of middle part of the frontal gyrus and posterior parietal cortex (Bodis-Wollner

et al., 1999). The amplitude and peak velocity of the closing phases of voluntary blink were found to be reduced with increasing age (Sun et al., 1997).

During voluntary blinks, Bell's phenomenon, another protective mechanism of the eye manifests. Bell's phenomenon causes a strong conjugate upwards movement of the eye when resistance is applied against forceful opening of the eye (Bour et al., 2000). Winking can also be considered another form of voluntary blinking and is defined as one eye being closed while the other one is opened. Winking is a learned activity and is performed as part of a complex facial expression (Tasman & Jaeger, 1998).

1.3.5 Methods of Assessment

The blink rate can be challenging to measure due to the rapid speed of this physiological phenomenon. Using high speed cameras, voluntary blinks were reported to be completed in 572±25 ms (Kwon et al., 2013). Previously, the blink rate has been assessed with the use of a mechanical system which included a mirror and a small, polished steel ball-bearing attached to the upper eyelid that would be used to register the lid motion (Gordon, 1951) or using an oscilloscope (Carpenter, 1948). Other approaches have included photosensitive position detector (Evinger et al., 1984), potentiometer (Kennard & Glaser, 1964), or a writing pen attached to a kymograph drum (Vandermeer & Amsel, 1952). More recently the blink rate has been measured using (i) magnetic search coil method (MSC), (ii) infrared light emitting diode (IR-LED), (iii) electrooculography (EOG), (iv) electromyography (EMG) and (v) imaging/video techniques.

1.3.5.1 Magnetic Search Coil (MSC)

Magnetic search coil method (MSC) enables the measurement of the blink rate and movement of the eye (Garcia et al., 2011; Guitton et al., 1991; Robinson, 1963). MSC is based

on Faraday's law of electro-magnetic induction where a voltage is induced in a moving electric conductor that is oriented perpendicular to a magnetic field (Robinson, 1963). MSC enables low drift, linearity, high resolution and low noise level compared to other recording methods such as electrooculography or infrared light reflected from parts of the eye (Remmel, 1984).

This method requires the adhesion of a small coil of wire (Helmholtz coils) to the upper eyelid, near the eyelid margin and above the pupil (Eggert, 2007). At the same time, participants are placed inside an oscillating magnetic field produced by a cubic frame (Eggert, 2007). The magnetic field alternates with a high frequency between 50 to 100 kHz and induces an electrical voltage in the small search coil during each horizontal or vertical eye movement (Heide et al., 1999). Blinking is determined when there is a change in the electrical current when the eyelids slide over the curved surface of the eye (Garcia et al., 2011).

1.3.5.2 Infrared Light Emitting Diode (IR-LED)

The infrared reflectance method utilises infrared light emitting diodes (IR-LED) to detect eyelid movement and blinks (Anderson et al., 2013; Michael et al., 2008; Ryan et al., 2006). This method relies on the principle that the white sclera reflects more light than the pupil and the iris (Heide et al., 1999). Using this method, the ocular surface (cornea and sclera in particular) is illuminated with an infrared light source (IR-LED). Another device (either a photodiode or phototransistor) is then used to detect the infrared light reflected back from the eye (Johns et al., 2007). Most commonly, the IR-LED and the photodiode are attached to a spectacle frame allowing free head movement but alternatively, a table mounted device is also available (Katz et al., 1987).

Using IR-LED, blink is defined as the difference between the light emitted and the light reflected from eyelid and the eyeball (Caffier et al., 2003). The processing of data is conducted

by a microcomputer that is equipped with an analogue-to-digital converter (Thompson et al., 1994; Orłowska-Majdak et al., 2001).

1.3.5.3 Electrooculography (EOG)

Electrooculography (EOG) is based on the differences in electrical potential between the positive potential of the cornea and the negative potential of the retina which is maintained via an active ion transport within its pigmented layer (Heide et al., 1999). It can be used to diagnose changes in the retinal pigment epithelium as well as measure eye movement (saccades, fixations and blinks) (Bulling et al., 2011).

Blinking is detected when there is a change in the electrical potential (voltage) of the eye. During a blink, the eyelids acts as a sliding resistor that alters the potential between the cornea and retina. Specifically, the electrical potential becomes more positive when the eyelid covers the cornea and more negative during eyelid retraction (Stern et al., 1984).

For the measurement of blinks, silver chloride or lead electrodes are placed vertically above the eyebrows and on the malar prominence in line with the pupil (Denney & Denney, 1984). Using this method, blinking is not observed or visually recorded but instead defined as a minimal voltage change during a certain period of time (Barbato et al., 2007; Colzato et al., 2008; Mackert et al., 1990).

1.3.5.4 Electromyography (EMG)

Electromyography (EMG) is a technique used to evaluate and record the electrical activity produced by the skeletal muscle. It is used to investigate the relationship between OOC and LPS muscle, particularly during blinking (Aramideh et al., 1995; Kaneko & Sakamoto, 1999; Van Allen & Blodi, 1962). Evaluation of the OOC muscle activity is conducted by taping two

miniature silver electrodes (<2 mm diameter) to the medial and lateral aspect of the upper lid, near its lower margin (Evinger et al., 1991; Sibony, 1991). For the LPS muscle, activity is measured by inserting a needle electrode (0.3 mm diameter) through the preseptal skin in the middle portion of the upper eyelid and directed towards the levator palpebral superioris (Aramideh et al., 1994). Blink rate is determined from the EMG potentials that are recorded from the lower OOC by customizing an algorithm in MATLAB such that it can filter and count the blinks from the EMG output traces (Gowrisankaran et al., 2012). EMG can also be combined with other blink analysis techniques such as MSC or EOG to enable the assessment of eyelid positional changes (Evinger et al., 1991; Kaneko & Sakamoto, 1999).

1.3.5.5 Imaging/Video Techniques

Blink rate can be measured using imaging/video recording technique (Abe et al., 2009; Corthout et al., 2011; Ohzeki & Ryo, 2006). The first imaging technique used to investigate the eyelid movement was conducted by using a moving photographic paper that records the light reflected from a small, polished steel ball-bearing attached to the upper eyelids (Gordon, 1951).

High–speed video cameras are able to overcome this issue by improving the precision in the detection of eyelid movement (Doane, 1980; Kwon et al., 2013). Such cameras provide a high volume of data and image analysis software and line image cameras (Choi et al., 2003; Gittins et al., 1995) have been found to be of significant value (Somia et al., 2000; Frueh et al., 2005; Sforza et al., 2008; Malbouisson et al., 2010).

The eyelid movement can also be assessed automatically (via image analysis software) using video camera and an infrared LED that calculates the differences in brightness of the palpebral

fissure between the closing and opening phase of a blink (Tsubota, 1996) or using videonystagmography (Casse et al., 2007).

1.3.6 Variations in Blink Rate

The blink rate is known to vary with different tasks (Table 1.4). Studies have shown that the average blink rate is between 10 to 22 blinks/min (Doughty, 2001). In a controlled experiment involving 20 participants watching an educational film, it was found that the blink rate varied from 6 to 30 blinks/min (Carney & Hill, 1982). This difference occurs because blink rate is dependent on several factors including (i) age, (ii) ocular surface status, (iii) level of mental activity and (iv) presence of neurologic and psychiatric disease.

Measured During	Blink Rate (blinks/min) Mean±SD	References
Reading	13±8	Karson et al., (1985)
Reading	9.4±11.1	Cho et al., (2000)
VDU	3.6±1.8	Patel et al., (1991)
VDU	7.6±6.7	Tsubota, (1998)
Primary gaze in silence	12.1±4.4	Carney & Hill, (1984)
Primary gaze in silence	10.3±3.6	Zaman & Doughty, (1997)
Conversation	24±15	Karson et al., (1984)
Conversation	26.1±9.6	Al-Abdulmunem & Briggs, (1999)
Interview	23±15	Karson, (1983)
Interview	14.0±1.0	Adamson, (1995)

Table 1.4: Mean±SD of blink rate reported in literature.

1.3.6.1 Age

With regards to age, the first blink movements in fetuses have been detected at 33 and 43 weeks of gestational age with a rate of 0.10 blink/min, corresponding to 6.2 blinks per hour

(Petrikovsky et al., 2003). It was later reported that during the neonatal period, blink rate increases to 1.6 blink/min (Mantelli et al., 2007). In a mixed group of neonates and infants of up to 8 weeks of age, blink rate was found to be 0.714 blink/min (Zametkin et al., 1979). Infants up to 10 to 12 weeks of age have a higher blink rate of 2.7 blink/min (Bacher & Smotherman, 2004). In the same study, the investigators observed that blink rate increased during feeding and after the appearance of new visual stimuli (Bacher & Smotherman, 2004). The blink rate increases rapidly throughout childhood and adolescence, stabilizes in adulthood with a mean value of 10 to 20 blinks/min (Cruz et al., 2011) and does not change significantly from adulthood to old age (over 60 years old) (Bentivoglio et al., 1997; Sun et al., 1997; Zaman et al., 1998).

1.3.6.2 Ocular Surface Status

It is well established that blinking is triggered by corneal sensation (Levin et al., 2011) and therefore, it is logical to assume that if the ocular surface was to be anaesthetized, blinking may not be present. However, research has shown that topical anaesthesia was only able to reduce blink rate, but not totally abolish it (Borges et al., 2010; Collins et al., 1989; Naase et al., 2005; Nakamori et al., 1997).

TBUT provides an indication of the ocular surface status however studies examining the relationship between TBUT and blink rate have been equivocal. Al-Abdulmunem found a positive correlation between TBUT and blink rate (r=0.74) (Al-Abdulmunem, 1999) while Collins and associates observed no such significant correlation (Collins et al., 1989). A significant negative correlation between TBUT and blink rate has also been reported (Yap, 1991). Using digitized video recording, it was found that for both normal and dry eye patients, tear break-up on the corneal surface is not a prerequisite for a blink (Himebaugh et al., 2009).

Dry eyes also cause changes to the blink rate. It was reported that patients with dry eye showed a much higher blink rate compared to normal eyes (Nakamori et al., 1997; Tsubota, 1998). The amount of time that dry eye patients can keep their eyes open was also shorter compared to normal (Tsubota, 1996). A number of studies have shown that after blinking, the optical quality of the eye starts to degrade. About 4 to 5 seconds post-blink, higher order aberrations increase (Koh et al., 2006, 2008), contrast sensitivity decreases (Tutt et al., 2000; Thai et al., 2002), retinal vessel contrast decreases (Tutt et al., 2000) and corneal topography changes occur (Németh et al., 2001; Buehren et al., 2001). Medical conditions that involves ocular manifestation such as Graves' disease also showed a reduced blink rate (Garcia et al., 2010). Contact lens wear has also been found to affect the blink rate (York et al., 1971; Hill & Carney, 1984); both soft (Pointer, 1988) and hard contact lens wear (Hill & Carney, 1984) are known to significantly increase blink rate.

1.3.6.3 Cognitive Load

The blink rate is affected by cortical control and is strongly influenced by external activity-related factors as well as psychological and physiological influences (Stern et al., 1984). High levels of cognitive activities have been shown to reduce the blink rate (Holland & Tarlow, 1972, 1975; Stern et al., 1984; Wong et al., 2002). Holland & Tarlow, (1972) compared the blink rate of 23 participants aged 18 to 21 years old by asking them to (i) visualize and then verbally report the number that was played from an audio tape recorder; and (ii) mentally add and then verbally report the numbers that were played from an audio tape recorder. Results showed that for both tasks, blink rate was reduced as the cognitive demand escalated (Holland & Tarlow, 1972). In a further study, blink rate was measured while the activity of operational memory (cognitive system with a limited capacity that is responsible for

temporarily holding information available for processing) was manipulated while mental load was kept constant (Holland & Tarlow, 1975). Results showed that blink rate was significantly reduced when the cognitive operation of internal counting was being performed (Holland & Tarlow, 1975). The authors concluded that blink rate was reduced as an attempt to decrease the blackout periods caused during blinking, so that the cognitive activities during operational memory and the mental load would not be disrupted (Holland & Tarlow, 1975). Similarly, several studies have also shown that the blink rate is reduced when reading (Cho et al., 2000; Doughty, 2001; Karson et al., 1981) and when viewing text on VDT (Freudenthaler et al., 2003; Kazuo & Nakamori, 1993; Schlote et al., 2004; Tsubota, 1998).

As task difficulty increased (from watching film, to reading, to counting number of times the letter 'a' appears in reading material), blink rate also reduced (York et al., 1971). Similarly, Himebaugh and colleagues observed a reduction in blink rate when participant's task was changed from looking straight ahead, to watching a movie, to identifying rapidly changing letters and to playing a computer game (Himebaugh et al., 2009). Interestingly, blink rate has also been found to be linked to emotions, with reduced blink rates being observed when a participant lies since lying requires a significant level of cognitive demand (Leal & Vrij, 2008).

In contrast, blink rate was found to be increased in conditions such as visual fatigue (Kaneko & Sakamoto, 2001; Stern et al., 1994), driving (Lal & Craig, 2002), flying an aeroplane (Morris & Miller, 1996) and when experiencing panic or anxiety (Kojima et al., 2002). Blink rate also increases with sleep deprivation (Barbato et al., 1995; Barbato et al., 2000, 2007; Crevits et al., 2003), and when performing tasks that require speaking (Karson et al., 1981; Bentivoglio et al., 1997; Doughty, 2001; Mori et al., 2008) and memory recall (Karson et al., 1981).

1.3.6.4 Presence of Neurologic and Psychiatric Disease

Dopamine is a neurotransmitter that is involved in both motor and cognitive functioning (Roberts et al., 2005). An imbalance in the dopaminergic activity will lead to basal ganglia motor syndrome (Esteban et al., 2004). It has been observed that the blink rate can be used as a clinical marker for central dopaminergic activity (Karson, 1983; Taylor et al., 1999) since a high blink rate is associated with increased dopamine levels (Karson et al., 1981; Taylor et al., 1999).

The positive correlation between blink rate and dopamine level have also been noted in a variety of clinical studies that involve dopamine dysfunction. This is particularly true as low blink rates have been observed in low levels of dopamine, such as in mental retardation (Bodfish et al., 1995), repetitive behaviour disorder (Goldberg et al., 1987), alcohol abuse (Misawa et al., 1983), cocaine abuse (Colzato et al., 2008), Parkinson's disease (Sandyk, 1990; Biousse et al., 2004; Korosec et al., 2006; Agostino et al., 2008; Fitzpatrick et al., 2012), progressive supranuclear palsy (Esteban et al., 2004; Bologna et al., 2009) and in children with attention-deficit/hyperactivity disorder (ADHD) (Konrad et al., 2003).

Conversely, higher blink rates have been noted in conditions associated with high hyperdominergic activity such as in focal dystonia (Karson et al., 1984), schizophrenia (Chan & Chen, 2004; Karson, 1983; Mackert et al., 1991; Mackert et al., 1990; Mackintosh et al., 1983), Huntington disease (Karson et al., 1984). High blink rates have also been identified in neurodevelopmental conditions such as depression (Mackintosh et al., 1983), panic disorder (Kojima et al., 2002), psychosis (Karson et al., 1986; Lovestone, 1992), autism (Goldberg et al., 1987), Prader-Willi syndrome (Holsen & Thompson, 2004) and fragile X syndrome (Roberts et al., 2005).

1.4 Dry Eye

1.4.1 Introduction

Dry eye (DE) is 'a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyper-osmolarity, ocular surface inflammation and damage, and neuro-sensory abnormalities play etiological roles' (Craig et al., 2017).

Symptoms of dry eye includes itching, foreign body sensation, ocular discomfort, tearing and photophobia (Vashisht & Singh, 2011). Patients with dry eye experience discomfort that consequently lead to a negative impact on the quality of life (Mertzanis et al., 2005). Dry eye has the potential to be a high economic burden to patients due to the need for regular ocular lubricants (Reddy et al., 2004).

Worldwide, the prevalence of dry eye varies from as low as 5% in Australia (McCarty et al., 1998) to as high as 34% in a Taiwanese population (Lin et al., 2003). The prevalence of dry eye was 11% in a Spanish population (Viso et al., 2009) while it was reported to be 14.5% in Malaysia (Jamaliah & Fathilah, 2002). Other factors that influence the prevalence of dry eye include progressing age (Gayton, 2009; Moss et al., 2008), VDT use (Uchino et al., 2008) and gender, with females showing a high preponderance for dry eye (Uchino et al., 2011).

1.4.2 Types of Dry Eye

Based on its aetiology, dry eyes can be classified as either aqueous deficient or evaporative; these categories are then further classified into various sub-types (Figure 1.5).

Aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE) both manifest with reduced tear film stability as well as an increased tear osmolarity (Benelli et al., 2010; Lin & Yiu, 2014; Suzuki et al., 2010; Utine et al., 2011). ADDE refers to a failure in the lacrimal secretion while

EDE results from excessive water loss from evaporation of the exposed ocular surface, in the presence of normal lacrimal secretory function (Lin & Yiu, 2014).

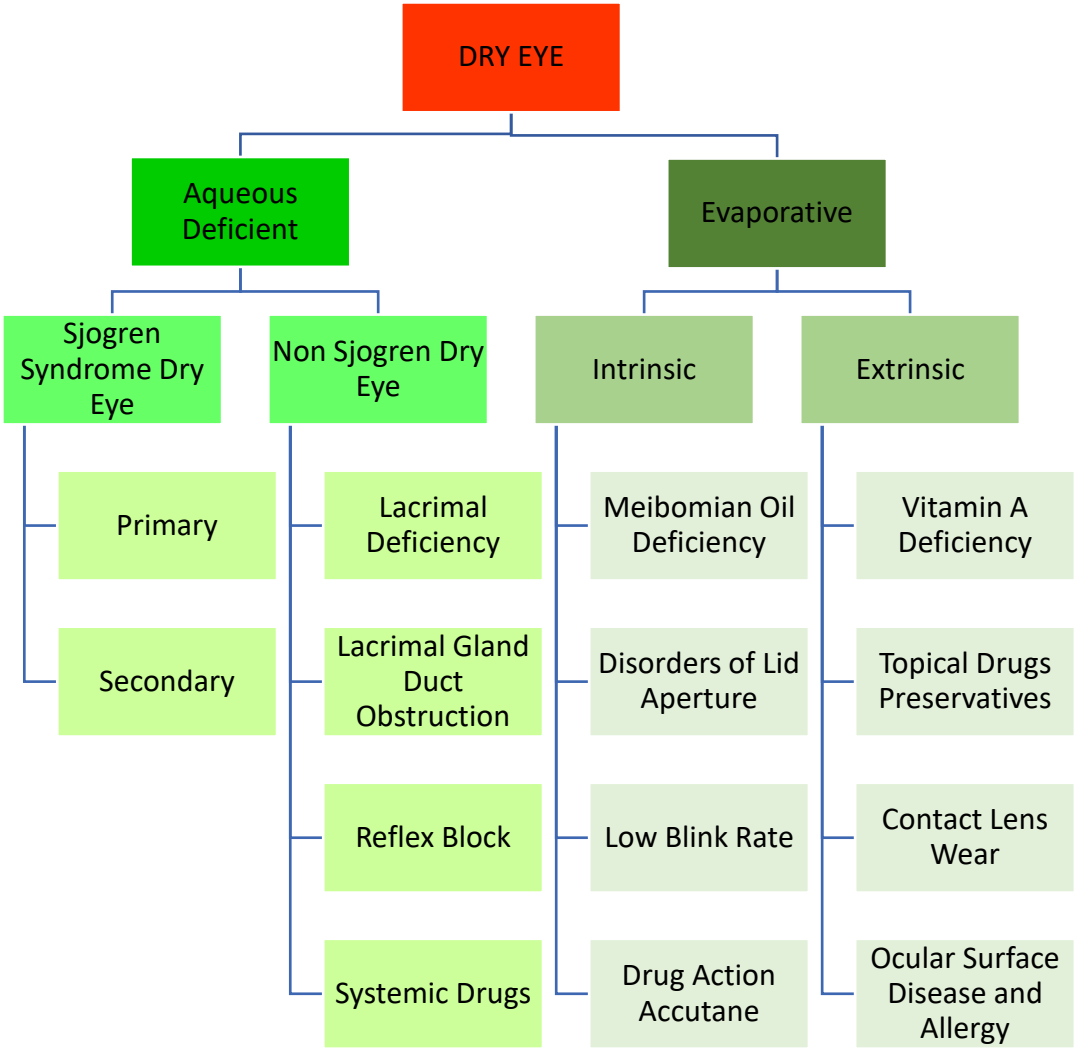


Figure 1.5: Classifications of dry eye according to aetiology from Gary, (2007).

ADDE can be divided into Sjogren Syndrome Dry Eye (SSDE) and Non Sjogren Syndrome Dry Eye (Non-SSDE). SSDE is a type of exocrinopathy (autoimmune disease of the exocrine system), which causes the salivary and the lacrimal glands to be affected by autoimmune disease. Primary Sjogren Syndrome is where the syndrome develops by itself (with no presence of any other autoimmune disease or secondary to any other conditions). Secondary Sjogren

Syndrome is when the syndrome develops in combination with another autoimmune disorder, commonly rheumatoid arthritis. Non-SSDE occurs when there is dry eye but with no presence of Sjogren Syndrome. Non-SSDE could be due to lacrimal deficiency (age related dry eye), lacrimal gland obstruction (cicatrizing conjunctivitis), reflex hyposecretion due to sensory motor block and systemic drug use (beta-blockers, antihistamines, diuretics and antispasmodics).

EDE is caused by either intrinsic or extrinsic factors. Intrinsic EDE occurs when the regulation of the tear evaporation is directly affected. This occurs in conditions such as meibomian oil deficiency, disorders of the eyelids, low blink rate and the effect of drugs such as systemic retinoids. In contrast, extrinsic EDE is due to conditions that indirectly increase the evaporation of the tear film. This includes vitamin A deficiency, effects of topical drug preservatives such as benzalkonium chloride, contact lens wear, ocular surface disease as well as ocular allergy.

1.4.2.1 Methods of Assessment

1.4.2.1.1 Objective Assessment

There are several objective diagnostic tests that can be used to assess dry eye (Figure 1.4) and none are deemed as the 'gold standard' test in assessing dry eye. These tests can be divided into invasive or non-invasive tests. In general, invasive test are ill-favoured as they tend to modify the parameter which they are designed to measure (Yokoi & Komuro, 2004).

In a retrospective study involving dry eye patients, symptom assessment (82.8%), fluorescein staining (55.5%), and tear break-up time (40.7%) were the most frequently used tests in the diagnosis of dry eye (Nichols et al., 2000). A more recent study showed that the most

commonly performed objective dry eye test was the tear break up time (93%), corneal staining (85%), tear film assessment (76%), conjunctival staining (74%) and the Schirmer test (54%) (Smith et al., 2008).

1.4.2.1.2 Subjective Assessment

Dry eye can also be assessed subjectively by asking about patient's history and symptoms or through the use of validated questionnaires (Bhatnagar et al., 2015; McGinnigle et al., 2012; Pflugfelder et al., 1998; Simpson et al., 2008).

1.4.2.1.3 Patient's History and Symptoms

Characteristic symptoms reported by dry eye patients includes grittiness, soreness, dryness, photophobia, redness and ocular fatigue (McGinnigle et al., 2012). With dry eye, numerous studies have indicated poor correlation between the signs of dry eye and the severity of patient's symptoms (Begley et al., 2003; Bhatnagar et al., 2015; Hay et al., 1998; Nichols et al., 2004a; Vitale et al. , 2004).

In the initial stages of dry eye, patients are known to exhibit moderate to severe symptoms, even when there is only mild ocular surface changes (Adatia et al., 2004; Johnson, 2009). However, once dry eye progresses to a more advanced stage, the symptoms tend to decrease which has been attributed to a loss in corneal sensitivity (Begley et al., 2003; Bourcier et al., 2005; Situ et al., 2008; Xu et al., 1996).

1.4.2.1.4 Validated Questionnaires

Questionnaires provide a scale for assessing the subjective symptoms associated with a patient's dry eye. These questionnaires consist of a series of questions with numerical values attributed to the answers: a sum of score can be calculated from the patient's responses

(Chalmers et al., 2010; Sakane et al., 2013). The Dry Eye Workshop 2007 identified a total of 14 questionnaires (Table 1.5) that were deemed suitable for the assessment of dry eye (Gary, 2007).

Number	Validated Questionnaires
1	McMonnies Dry Eye History Questionnaire
2	Canada Dry Eye Epidemiology Study (CANDEES)
3	Ocular Surface Disease Index (OSDI)
4	Salisbury Eye Evaluation
5	Dry Eye Epidemiology Projects (DEEP)
6	Women's Health Study questionnaire
7	National Eye Institute-Visual Function Questionnaire (NEI-VFQ)
8	Dry Eye Questionnaire (DEQ)
9	Contact Lens DEQ
10	Melbourne Visual Impairment Project
11	NEI-Refractive Error questionnaire
12	Sicca Symptoms Inventory
13	Bjerrum questionnaire
14	Japanese dry eye awareness questionnaire

Table 1.5: Fourteen validated questionnaires that were endorsed by the Dry Eye Workshop 2007 (Gary, 2007).

Although there are 14 endorsed validated questionnaires, only the McMonnies Dry Eye Index and the Ocular Surface Disease Index (OSDI) are commonly used in ophthalmic research involving dry eye (Gary, 2007; Wolffsohn et al., 2017). McMonnies questionnaire functions as a screening test for dry eye and it utilizes dichotomous (yes/no) responses and considers epidemiologic risk factors, frequency of symptoms and sensitivity to environmental factors (McMonnies, 1986).

In contrast, the OSDI was developed to assess the severity of symptoms related to dry eye disease and their effect on vision (Dougherty et al., 2011). Unlike the McMonnies

questionnaire, the OSDI does not use dichotomous response but instead uses 12-item Likert scale, with higher scores representing greater disability. The OSDI was reported to have good to excellent reliability, validity, sensitivity and specificity (Schiffman et al., 2000). When comparing the McMonnies and OSDI questionnaires, the OSDI was found to be more reliable (Nichols et al., 2004b; Schiffman et al., 2000).

1.4.3 Treatment of Dry Eye

In general, the goals for the treatment of dry eye aim: to relieve the symptoms, improve visual acuity and quality of life, restore the ocular surface and tear film to the normal homeostatic state, whilst managing the underlying defect (Alves et al., 2013; Behrens et al., 2006; Gary, 2007; Jackson, 2009; Jones et al., 2017).

Tear supplementation using artificial tears (lubricants) is the primary mode of treatment for dry eye (Gary, 2007). However, artificial tears only provide palliative relief to ocular irritation in patients with aqueous tear deficiency, but do not prevent the underlying inflammation or reverse conjunctival squamous metaplasia in chronic dry eye (Lin & Yiu, 2014).

Tear retention is also another viable treatment option. Implants called punctal plugs are used to either permanently or temporarily occlude the lacrimal puncta (Rabensteiner et al., 2013; Brissette et al., 2015; Marcet et al., 2015). Tear retention could also be achieved using moisture chamber spectacles which are able to slow the evaporation of the tears from the ocular surface (Gresset et al., 1984; Hart et al., 1994). In severe cases of dry eye, contact lenses can be used to protect and hydrate the ocular surface. Such therapeutic contact lens are available as silicone rubber lenses and gas permeable scleral- bearing hard contact lenses with or without fenestration (Bacon et al., 1994; Pullum et al., 2005; Romero-Rangel et al.,

2000; Rosenthal et al., 2000). In certain cases, the contact lenses are made out of high oxygen permeability to enable overnight lens wear (Tappin et al., 2001).

Dry eye can also be treated with pharmacological agents (Gayton, 2009; Bhavsar et al., 2011) by controlling the inflammation on the ocular surface or through the restoration of aqueous and mucin secretions (secretogogues). Inflammation control can be achieved by using cyclosporine-A (CsA) (Tatlipinar & Akpek, 2005; Kymionis et al., 2008), corticosteroids (Avunduk et al., 2003; Pflugfelder et al., 2004; Yang et al., 2006) and tetracycline (Krakauer & Buckley, 2003; Voils et al., 2005; Aronowicz et al., 2006; Javadi & Feizi, 2011). The restoration or stimulation of aqueous and/or mucin secretion can be achieved by using diquafosol (Mundasad et al., 2001; Murakami et al., 2004; Tauber et al., 2004).

Non-pharmaceutical agents, such as the naturally occurring biological components (serum and saliva) can also be used as a valid treatment for dry eye (Geerling et al., 2001). Being of autologous origin, serum and saliva lack antigenicity and contain numerous growth factors, neurotrophins, vitamins, immunoglobulins and extracellular matrix proteins, that are involved in ocular surface maintenance. These are invaluable as they assist in the proliferation of primary human corneal epithelial cells, which are normally damaged in dry eye. Studies have shown that isotonic saliva and serum offer greater therapeutic potential for severely ADDE compared to pharmaceutical based tear substitutes (Geerling et al., 2001; Noble et al., 2004). However, because of the preparation itself is labour intensive, concerns with sterility and in certain cases the need for surgical procedures (salivary submandibular gland transplantation), this method of dry eye treatment is reserved for extremely severe stages of dry eye (Geerling et al., 2000; Kojima et al., 2005).

Essential fatty acids also play a role in dry eye management (Rand & Asbell, 2011). Omega-3 fatty acid have been found to be associated with improved TBUT and Schirmer's results (Liu & Ji, 2014; Macrì et al., 2003). In a prospective placebo-controlled clinical trial, linoleic acid and gamma-linoleic acid administered orally, twice a day led to significant improvement in ocular irritation symptoms, and a reduction in ocular surface lissamine green staining (Barabino et al., 2003). More recently, in a study involving 256 young and middle aged (28.96±4.2 years old) VDT users, it was shown that consumption of omega-3 fatty acid (2400 mg/day) significantly improved dry eye symptoms, tear stability and conjunctival cytology staining (Bhargava et al., 2016).

Dry eye can also be controlled by incorporating changes to the patient's environment. Common methods include the introduction of humidifiers in an attempt to reduce tear evaporation (Norbäck et al., 2006) or by wearing swim goggles to increase the periocular humidity that will reduce symptoms of dry eye (Korb et al., 1996; Korb & Blackie, 2013). Furthermore, VDTs or any electronic displays should be placed below eye level to decrease the vertical palpebral aperture size, and patients should be encouraged to take periodic breaks by closing their eyes when reading or working on computers (Blehm et al., 2005; Rosenfield, 2011). Consumption of systemic anticholinergic medications (antihistamines and antidepressants) should be minimized or eliminated as these are known to reduce tear secretion and cause dry eye (Fraunfelder et al., 2012; Koçer et al., 2015; Ousler et al., 2004).

In occupations requiring extensive periods of VDT work, several investigators have noted the benefits of using animation software (Institute of Optometry, FHNW, CH-Olten) (Nosch et al., 2015) or Wink glass (WG, Masunaga Group, America) (Ang et al., 2014) to remind participants to blink whilst they are engaged in a VDT related tasks. Other options include the use of

spectacles that offer 50% blue light blocking capabilities which have been shown to ameliorate visual impairment associated with tear film instability in dry eye patients (Kaido et al., 2016).

Although there are many options for the treatment of dry eye, the Delphi study advocated that the management strategy for dry eye should be based upon patient's signs and symptoms (Behrens et al., 2006). More recently, a dry eye management algorithm was derived; it presents a step-wise approach in implementing the various management and therapeutic options according to dry eye severity (Jones et al., 2017). Thus, careful consideration should be made before prescribing treatment regimens for dry eye patients.

1.5 Ocular Protection Index (OPI)

The relationship between the interblink interval (IBI) and the tear film break up time can be assessed by calculating the Ocular Protection Index (OPI) (Bron et al., 2014). This is achieved by dividing the tear film break up time by the IBI, (Ousler et al., 2008), as show below (Equation 1.1).

$$OPI = \frac{Tear\ film\ break\ up\ time\ (TBUT)}{Interblink\ interval\ (IBI)} \qquad \text{Equation 1.1}$$

The OPI describes the ocular surface protection and it enables eye care practitioners to assess the risk of ocular surface damage in relation to dry eye. An OPI value of <1.0 indicates that the tear film break up occurred within the IBI, suggesting ocular surface exposure which may lead to dryness and worsening of dry eye signs and symptoms (Ousler et al., 2008). In contrast,

an OPI value of ≥1.0 indicates that the tear film break up did not occur within the IBI period, thus, the eye is protected from desiccation throughout the blink cycle (Ousler et al., 2008).

As further development of the OPI metric, the Ocular Protection Index (OPI) 2.0 System utilizes a fully automated software algorithm which provides a real-time measurement of corneal exposure (breakup area) for each IBI during a 1 minute video (Abelson et al., 2012). The OPI 2.0 System has been shown to be valid and able to accurately distinguish between a group of predefined dry eye and normal participants (Abelson et al., 2012).

Although there a limited number of studies that have examined the clinical value of OPI, several studies had demonstrated that OPI could be a valuable indicator as a risk detector for dry eye. In a Korean study, one hour of computer VDT work was proven to significantly reduced the OPI (Suh et al., 2010). In a study involving adolescence participants and usage of computer for playing games and viewing internet lectures; it was found that the OPI was significantly lower during computer games compared to the internet lectures (Kim et al., 2007). In a study involving 329 dry eye patients, it was reported that patients with low OPI (<1.00) had significantly higher OSDI scores compared to patients with high OPI (≥1.00) (Badian et al., 2014). The OPI had also been used as an indicator to assess the performance of ocular lubricants for dry eye management (Ousler et al., 2007).

1.6 Dry Eye and VDT

In the last 20 years there has been a significant increase in the use of VDT (personal computer and laptops) and smart devices (tablets, smartphones and other portable smart devices) (Uchino et al., 2014). However, researchers often group VDT and smart device together and fail to distinguish them according to their design specifications. The growth of smart device use is unprecedented and it is estimated that almost 84% of the world's population will be

using smartphone technology by 2018 (Parihar et al., 2016). Both VDTs and smart devices emit relatively high energy blue light in the wavelength range of 450 to 495 nm (Kaido et al., 2016); close to that of the ultra-violet spectrum (Kitchel, 2000). The proliferation of smart device use has been accompanied by a dramatic increase in the extent of blue light exposure and associated health risks (Kaido et al., 2016; Tosini et al., 2016). Several studies have shown that blue light increases alertness (Lockley & Gooley, 2006; Rahman et al., 2014; Najjar et al., 2014), stimulates cognitive function (Daneault et al., 2014; Vandewalle et al., 2007) as well negatively affect sleep and circadian timing (Chang et al., 2015). Since blue light is considered a high energy light (compared to the normal visible spectrum), overexposure may pose risks relating to development of age-related macular degeneration (Algvere et al., 2006; Liu et al., 1989; Taylor et al., 1990) and cataracts (Lerman, 1988; Liu et al., 1989).

The relationship between VDT use and dry eye had been well established (Amada & Inoshita, 2017; Hikichi et al., 1995; Rosenfield, 2011, 2016; Rosenfield et al., 2012; Wu et al., 2014). The literature shows that dry eye is associated with lower work productivity and impaired work performance amongst VDT users (Uchino et al., 2014). Interestingly the prevalence of dry eye in VDT users differs between gender (Uchino et al., 2008, 2011, 2013; Uchino et al., 2014; Yokoi et al., 2015). In a recent systematic review and meta-analysis, it was revealed that (i) the prevalence of dry eye in VDT workers were 49.5%, (ii) dry eye was more common in female VDT users compared to male and (iii) the prevalence of dry eye increases with increasing age (Courtin et al., 2016).

Much of the evidence associating VDT use and dry eye in humans is founded upon the use of dry eye symptom questionnaires (Hayes et al., 2007; Kawashima et al., 2015; Uchino et al., 2008, 2011, 2013). Using animal models, researchers have attempted to objectively assess

ocular changes associated with VDT use; Nakamura et al., (2010) used an evaporative environment to elucidate the effects of blink rate changes and corneal exposure on rats. Morphological examination of the rats showed a chronic reduction of tear secretion accompanied with lacrimal gland disfunction. Thus, suggesting that lacrimal gland hypofunction is associated with VDT use and may be a critical mechanism for VDT associated dry eye (Nakamura et al., 2010).

In humans, extended use of VDT causes a reduction in blink rate (Schlote et al., 2004; Blehm et al., 2005) and thus, increases the ocular surface dryness (Yokoi et al., 2015). The change in blink rate with VDT use is thought to be cortically driven and is related to the cognitive demand of the task (Acosta et al., 1999; Himebaugh et al., 2009; Patel et al., 1991; Schlote et al., 2004). Excessive tear evaporation from the ocular surface occurs during VDT use because the tear film break up time (TBUT) is shorter than the IBI (Yaginuma et al., 1990; Tsubota & Nakamori, 1995; Acosta et al., 1999). Uchino et al., (2008) observed that more than 4 hours of VDT use was associated with an increased risk of dry eye symptoms.

Although there are numerous studies that investigated dry eye and VDT use, these have not been replicated with smart devices (Shrestha et al., 2011; Uchino et al., 2014; Wu et al., 2014). The two main studies of note were conducted by Moon et al., (2014,2016). In their 2014 study the investigators evaluated the risk factors of dry eye in school children using smart devices (Moon et al., 2014). Following on from their initial study, in 2016 the same investigators assessed the risk and protective factors associated with paediatric dry eye in relation to smart device usage, according to region and age (Moon et al., 2016). Results from both studies suggested that smart device use in children was strongly associated with paediatric dry eye (Moon et al., 2016; Moon et al., 2014). However, both of Moon's studies assessed

smartphone use via retrospective questionnaires, and not by actual experimental procedures that exposes participants to smartphone use (Moon et al., 2016).

1.7 Accommodation Response

Accommodation is defined as the refractive power change of the crystalline lens that occurs when changing focus from far to near (Maddock et al., 1981). To achieve the vergence change, the crystalline lens becomes thicker, more curved and moves anteriorly (Choi et al., 2015). The intricacies of the human accommodative mechanism are still debated, however Helmholtz's theory of accommodation is the most widely accepted model (Helmholtz, 1855). Helmholtz and more recently *in vivo* studies examining the anterior segment during accommodation (Sheppard & Davies, 2010b; Lewis et al., 2012; Strenk et al., 2010) suggest that when viewing a distance object, the ciliary muscle is in its relaxed state and the diameter of the ciliary body collar is at its widest. This increased diameter results in zonular fibre tension which holds the crystalline lens in its flattest form. During accommodation, the ciliary muscle contracts reducing the collar diameter and relaxes the tension on the zonules; consequently the lens assumes its natural more spherical shape (Helmholtz, 1855; Glasser, 2006).

The use of computer and electronic devices for work and non-work related activities have become more prevalent in the modern society (Bababekova et al., 2011). It has been estimated that in 2000, up to 75% of all workers used VDT at their workplaces (Hayes et al., 2007). Research has shown that 90% of people that use VDT for more than 2 hours per day experience vision related symptoms (Salibello & Nilsen, 1995). Those who spend more than 4 hours per day on VDT show a higher incidence, severity and duration of computer-related symptoms (Rossignol et al., 1987). These symptoms may be related to the altered

accommodation status of the eye when exposed to VDT use (Lovasik & Kergoat, 1988; Collins et al., 1994; Scheiman, 1996).

With the advent of modern technology, reading is no longer restricted to printed materials such as books, or a desktop computer. Portable devices such as smartphones, tablets and e-readers (referred to as smart devices for the purpose of this thesis) have facilitated this move from printed media (Bababekova et al., 2011; Hue et al., 2014). The smartphone is no longer just a communication device but is the most common platform for accessing the internet.

The relatively small screen size on smartphone relative to a VDT means that smartphone requires a closer working distance and hence a greater accommodative demand (Bababekova et al., 2011). Therefore, it could be assumed that the prolonged use of smartphone in close working distances may result in the development of asthenopic symptoms (Thomson, 1998). Indeed, it was recently reported that eyestrain symptoms were greater after reading from a smartphone for 60 minutes (Long et al., 2017). Despite the increase in accommodative load with smart device use, at present there is an absence of literature assessing accommodative dynamics when using these devices.

1.7.1 Measurement of Accommodation

In a clinical setting, accommodation can be measured using one of 5 methods (Table 1.6) (Goss, 1992). However, none of these methods are suitable for the study of accommodative dynamics given their low temporal resolution (<0.1 seconds) (Heron & Winn, 1989; Wolffsohn et al., 2002).

Accommodation Test Type	Clinical Setting Example
Amplitude of accommodation	Push-up method
Relative accommodation range	Negative relative accommodation (NRA) Positive relative accommodation (PRA)
Accommodative facility or speed	Lens power changes Viewing distance changes
Lag of accommodation	Monocular estimate method (MEM) Nott retinoscopy
Determination of dioptric accommodative stimulus at which accommodative stimulus and accommodative response are equal	Low neutral dynamic retinoscopy Binocular cross cylinder test

Table 1.6: Types of clinical test and examples.

To investigate the dynamics of accommodation, researchers can either use an open field auto-refractor (Sheppard & Davies, 2010b; Laughton et al., 2015), photorefractor (Seidemann & Schaeffel, 2003; Horwood et al., 2015) or abberometer (Bernal-Molina et al., 2017; Win-Hall & Glasser, 2009) which can assess refractive error continuously, while participants are fixating binocularly on a stimulae. Furthermore, these devices provide an objective measure of the dioptric change in the power of the eye and exclude subjective factors such as depth of focus of the eye (Win-Hall et al., 2007).

1.7.1.1 Canon Autoref R-1

The first objective open field binocular auto refractor was the Canon Autoref R-1 (Tokyo, Japan) (McBrien & Millidot, 1985). The Canon Autoref R-1 utilizes infrared light and the grating principle to obtain its measurements providing an assessment of refraction in 0.2 seconds (McBrien & Millidot, 1985). The proprietary device only allows a single static measurement, however, following modification it can record accommodation continuously (Pugh & Winn, 1988; Pugh & Winn, 1989; Davis et al., 1993).

1.7.1.2 Shin Nippon SRW-5000

The Shin-Nippon SRW-5000 (Ryusyo Industrial Co. Ltd, Osaka, Japan), is an objective open view auto refractor that superseded the Canon Autoref R-1 in the mid-1990s (Mallen et al., 2015). The device calculates refractive error in 2 stages (Mallen et al., 2001); first, an infrared ring target is imaged after being reflected from the retina. A lens within the machine is then moved to bring the ring into focus; secondly, this image is then analysed digitally in multiple meridians to produce the refractive error. The Shin-Nippon SRW-5000 has shown excellent validity, repeatability and utility in clinical and research settings (Chat & Edwards, 2001; Mallen et al., 2015; Wolffsohn et al., 2001) and is able to measure accommodative changes dynamically (Wolffsohn et al., 2001).

1.7.1.3 Grand Seiko WR-5100K

The Grand Seiko WR-5100K measures refractive error by analysing the diameter and shape of a ring of infrared light projected onto the retina, similar to the Shin-Nippon SRW-5000 (Mallen et al., 2001). A myopic change in the eye increases the ring diameter and astigmatism distorts the ring elliptically (Win-Hall et al., 2007).

1.7.1.4 Grand Seiko WAM-5500

The Grand Seiko WAM-5500 is a binocular open field auto refractor and keratometer that enables dynamic recording of refraction and pupil size via a computer interface that uses the WAM communication system (WCS-1) software (Sheppard & Davies, 2010a). As with the Shin-Nippon SRW-5000, the refractive error is calculated in 2 stages (Mallen et al., 2001). Pupil size is measured by automatic detection of the iris boundary and subsequent superimposition of a best-fit circle on both static and dynamic modes (Sheppard & Davies, 2010a). Keratometry

is obtained by image analysis of an infrared ring that is reflected on the cornea, the diameter of which is measured in 3 meridians separated by 60^0.

A 5.6-inch colour monitor is incorporated into the Grand Seiko WAM-5500 allowing visualisation of the participant's pupil thus enabling optimal alignment with the participant's visual axis. In the high-speed mode, mean spherical equivalent refractive error (spherical component + cylindrical power/2) and pupil diameter can be recorded at a rate of 5 Hz; providing an objective measurement of the participant's dynamic accommodative response to a visual stimulus (Sheppard & Davies, 2010a).

1.7.1.5 Open Field Aberrometer

Aberrometers allow assessment of the monochromatic aberrations of the human eye (Liang et al., 1994; Salmon et al., 1998; Marcos, 2006). In clinical practice, aberrometers are routinely used to diagnose optical defects of the eye and in the evaluation of clinical treatments, such as cataract surgery (Yamaguchi et al., 2009; Bellucci & Morselli, 2007), refractive laser surgery (Marcos et al., 2001; Chalita et al., 2004), contact lenses (Bakaraju et al., 2015; Cheng et al., 2016; Choi et al., 2007) and dry eyes (Montés-Micó et al., 2004).

In addition, aberrometery can measure accommodation objectively (Win-Hall & Glasser, 2009; Bernal-Molina et al., 2017). A binocular open-view Hartmann-Shack wavefront sensor has been developed that enables the real-time measurement of refraction and pupil size (Bhatt et al., 2013) however, such devices are not commercially available at present.

1.7.1.6 Open Field Photorefraction

Photorefraction analyses the vergence of light reflected from the fundus to provide a measure of refraction (Howland & Howland, 1974). Specifically, photorefraction works by projecting

light into the eye from an array of infrared light-emitting diodes (LED) positioned eccentrically from the camera aperture. The slope of reflected light formed across the pupil indicates the polarity (myopic or hyperopic) and magnitude of the eye's defocus (Schaeffel et al., 1993). Photorefraction has been used to investigate dynamic measurement of accommodation (Schaeffel et al., 1993; Ukai & Kato, 2002). However, calibration of this device according to each subject's luminance profile is vital for obtaining accurate refractive power estimates and thus, can be prone to erroneous results (Blade & Candy, 2006; Schaeffel et al., 1993).

1.7.2 The Accommodative Stimulus-Response Curve

The accommodative stimulus–response curve (ASRC) describes the accommodative response as a function of the accommodative stimulus (Chen et al., 2017). The ASRC provides crucial information on the dynamics of accommodation such as the slope of the accommodation response (Abbott et al., 1998; Gwiazda et al., 1993; McBrien & Millodot, 1986; Yeo et al., 2006), accommodative lag (Tosha et al., 2009; Gambra et al., 2009), accommodative error index (Lin & Jiang, 2013; Chauhan & Charman, 1995) and accommodative error area (Lin & Jiang, 2013). These parameters provide insight into potential relationships between accommodation and ocular anomalies, such as amblyopia (Ciuffreda et al., 1984) and myopia (Abbott et al., 1998; McBrien & Millodot, 1987; Millodot, 2015; Schmid & Strang, 2015; Yeo et al., 2006).

There are 4 main methods that can be employed to measure the ASRC; (i) decreasing distance series, (ii) positive lens series (iii) negative lens series and (iv) Badal optical stimulator (Table 1.7). The literature shows that these methods generated different outcomes, whereby higher accommodative responses were obtained with the positive lens compared to the negative lens method (Abbott et al., 1998; Gwiazda et al., 1993; Yeo et al., 2006).

Method	Description
Decreasing distance series (DDS)	Targets were viewed at 5 decreasing distance (4 m, 1 m, 0.50 m, 0.33 m and 0.25 m). The angular size was kept constant on all distance by physically changing the size of the target (Abbott et al., 1998).
Positive lens series (PLS)	Target at 0.25 m were viewed through positive lenses decreasing in power (from +4 D to 0 D) (Abbott et al., 1998; Gwiazda et al., 1993).
Negative lens series (NLS)	Target at 4 m were viewed through negative lens of increasing power (from 0 D to +4 D) (Hazel et al., 2003; Gwiazda et al., 1993; Abbott et al., 1998).
Badal optical stimulator (BOS)	A compact device (consisting of lenses and target) that is commonly attached to an auto refractor. It presents targets at different stimulus vergence (Gallagher & Citek, 1995; Schor et al., 1986).

Table 1.7: Description of methods to obtain ASRC.

When utilizing DDS, PLS and NLS to stimulate accommodation, the target size is not adjusted for lens-induced magnification and minification, or changes in angular size due to changes in the fixation distance (Chen et al., 2017). In comparison, BOS allows presentation of targets at varying stimulus vergences without altering the retinal image size and therefore, minimizes cues to proximity (Aldabaet al., 2017; Ciuffreda et al., 1984; Lin & Jiang, 2013; McBrien & Millodot, 1987; Seidel et al., 2003; Subbaram & Bullimore, 2002). Due to such differences, the accommodative response measured with the various methods would yield disparate results. The entire ASRC can be characterise by the slope of accommodative response. Yeo et al., (2006) and Abbott et al., (1998) evaluated accommodative response curves using DDS, PLS and NLS. Results showed that the gradient of the curves were significantly different between the 3 methods. The differences reported in these studies may be attributed to numerous factors such as contrast (Charman & Heron, 2015; Ciuffreda & Rumpf, 1985; Ward, 1987a), spatial frequency (Ciuffreda & Hokoda, 1983; Ward, 1987b; Xu et al., 2015) and target luminance (Gray et al., 1993; Johnson, 1976; Ward, 1987a). Gwiazda et al., (1993) proposed

that NLS may induce more accommodative response error and that proximal factors play a large role; they concluded that BOS might prove to be a better choice for future accommodative studies as it can eliminate the proximal cue of the accommodative stimulus.

1.7.3 Factors affecting Accommodation Response

1.7.3.1 Spatial Frequency

It is well established that accommodation response (AR) increases with higher spatial frequency (SF) (Charman & Tucker, 1977, 1978; Tucker & Charman, 1987; Tucker et al., 1986). Furthermore sinusoidal targets with mid-spatial frequency (commonly defined as 3 to 5 cycles per degree) have been found to be the most effective stimulus for accommodation, either because they induced the most accurate AR (Mathews & Kruger, 1994; Owens & Wolfe, 1985) or because they produced the smallest variations (Bour, 1981; Ciuffreda & Rumpf, 1985; Day et al., 2009; Owens, 1980).

1.7.3.2 Target Luminance

Using Snellen letters and other targets of wide spatial bandwidth, AR has been found to progressively reduce in accuracy as luminance is reduced from photopic to scotopic levels (Campbell, 1954; Johnson, 1976; Nadell & Knoll, 1956a, 1956b). However, this effect is dependent on the SF spectrum of the stimulus target. Campbell, (1954) observed that AR was negatively correlated to luminance. In contrast, Nadell & Knoll, (1956b) found that AR was higher in photopic and scotopic conditions when compared to mesopic conditions. These findings suggest that luminance is a vital component of the accommodative response (Bour, 1981; Charman & Tucker, 1977; Ciuffreda & Hokoda, 1985; Ciuffreda & Hokoda, 1983; Owens, 1980; Raymond et al., 1984).

1.7.3.3 Pupil Size

Hennessy et al., (1976) showed that smaller artificial pupil size reduces the accommodative amplitude. A reduction in pupil size increases the depth of focus, enabling the eye to see clearly with a greater accommodative lag (Ripps et al., 1962).

1.7.3.4 Stimulus Contrast

The relationship between stimulus contrast and AR is ambiguous (Bour, 1981; Charman & Tucker, 1978; Ciuffreda & Hokoda, 1985; Ciuffreda et al., 1990; Heath, 1956). A reduction in stimulus contrast within a certain range has no effect on AR (i.e. increased the accommodative lag) (Schmid et al., 2005; Tucker & Charman, 1986; Ward, 1987c). However, if contrast is reduced to the minimum threshold levels then accommodative inaccuracy has been shown to increase (Charman & Heron, 2015; Ciuffreda & Rumpf, 1985; Raymond et al., 1984; Ward, 1987c).

1.7.3.5 Other Factors

The literature also suggests that cognitive demand affects accommodation. Kruger, (1980) found that an increase in accommodation response was evident with increased cognitive demand. The researchers attributed this findings to the attempts made by the participants to view the stimulus target which were initiated by changes in cognitive sensory rather than retinal image quality (Kruger, 1980).

In conclusion, there are numerous factors that influences the AR. These factors should be carefully considered when designing accommodative studies to optimise accuracy and reliability.

1.7.4 Accommodative Response and VDT

Collier & Rosenfield, (2011) examined accommodation and vergence during sustained VDT fixation to determine whether the magnitude of or changes in accommodation and/or vergence were related to discomfort during VDT use. Participants were asked to read text aloud from a laptop computer at a viewing distance of 50 cm for a sustained 30-minute period. At every 2 minute interval, the AR to the VDT was measured objectively using a Grand Seiko WAM-5500. The vergence response was assessed by measuring the associated phoria (AP) using a customized fixation disparity target that appeared on the laptop screen and the degree of difficulty of the reading task was rated by participants on a scale from 1 to 10. Results showed no significant changes in AR or AP during the 30 minute VDT task. However, the researchers found that participants who converged accurately on the screen were more likely to be symptomatic compared to those exhibiting Exo fixation disparity (Collier & Rosenfield, 2011). These findings suggest that symptoms associated with VDT use may be related to an increased vergence response during VDT operation but are unlikely to result from a change in the AR.

Hue et al., (2014) investigating the symptoms associated with reading on two smart devices [Amazon Kindle (Amazon Inc., Seattle, Washington) and Apple iPod (Apple Inc., Cupertino, California)] and a printed hard copy. During the reading task, the AR was measured objectively at 1 min intervals using a Grand SeikoWAM-5500. The subjective assessment of their symptoms were assessed post reading task using the OSDI questionnaire. There was a larger lag of accommodation when reading from the iPod relative to the hardcopy and the reading rate was slower with the iPod. However, symptom scores were similar for the two formats, whereas subjects perceived more symptoms with the Kindle relative to the hard copy despite

the lack of differences in the AR and reading speed. In another study, Moulakaki et al., (2017) assessed AR following reading on a iPad mini, (Apple Inc., California, USA) and a iPhone 4S, (Apple Inc., California, USA). In comparison to Collier & Rosenfield, (2011) and Hue et al., (2014), Moulakaki et al., (2017) showed no significant differences in the AR between the two devices.

Harb et al., (2006) assessed the accommodative behaviour of emmetropes and myopes whilst participants read a novel from a computer screen for 10 minutes at various distances (66.6, 40 and 28.6 cm). The mean lag of accommodation for all participants significantly increased with closer reading distance. It was evident that myopes had significantly greater variability in their accommodation responses compared to emmetropes and had larger accommodative lags at further reading distances (Harb et al., 2006). Long et al., (2017) examined the effect of viewing distance on eyestrain symptoms when reading from a smartphone and found that the subjective perception of eyestrain was associated with a closer working distance.

Much of the literature surrounding accommodative response and VDT or smart devices, utilise traditional targets such as text or Maltese cross. More recently, a study was conducted to evaluate the effect of detailed and non-detailed emoji symbols used in messaging applications frequently found in smart devices (Montés-Micó et al., 2017). The study itself did not utilize smart devices, instead the emoji were projected on an internal microdisplay. The detailed emoji consisted of 'happy and sad smileys' and non-detailed emoji consisted of 'heart and star' emoji targets. Results showed that there were no differences in accommodation between the various emojis (Montés-Micó et al., 2017).

Despite the widespread use of smart devices there is currently a paucity of literature assessing their impact on ocular accommodation. The few studies that have attempted to address this

question have been limited to the evaluation of accommodative lag or pre- and post-subjective symptoms. As such, a more detailed investigation of smart devices and their impact on accommodative dynamics is warranted.

1.8 Characterising Smartphone Usage Habits

Currently, there are numerous methods that can be employed to acquire smartphone usage habits of participants. One such method manual extraction of the data from the smartphone operating system; the process is complex and can be considered an invasion of personal privacy as the researcher has access to all data contained on the device (Soikkeli et al., 2011). An alternative method involves asking participants to download certain apps that can aid in monitoring their smartphone usage (Li et al., 2015). Although there are technical limitations relating to software compatibility between the apps and smartphone's operating system and the requirement for sufficient memory for installation of the apps, this method is preferable as the participant can use the app to report their smartphone usage habits to the researchers without revealing the specifics of their smartphone activities. However, the most common methods to assess smartphone usage habit are questionnaire based, in which participants are required to report their smartphone usage habits using an ordinal based Likert scale (Alfawareh & Jusoh, 2014; Moon et al., 2014; van Deursen et al., 2015; Aljomaa et al., 2016; Moont et al., 2016; Parasuraman et al., 2017). Such questionnaires are widely utilized as they are simple to administer, require no complicated manual extraction from smartphone's operating system and the participant's privacy is assured. Although, due to the subjective nature of the questionnaires, the results are likely to be affected by inaccuracies from poor recall and report of smartphone usage history (Pecoraro et al., 1979; Bush et al., 1989; Heliovaara et al., 1993; Paganini-Hill & Chao, 1993).

The literature indicates that smartphone usage habits are considerably diverse (Soikkeli et al., 2011; Aljomaa et al., 2016; Parasuraman et al., 2017). For instance, the average number of session per day (how many times smartphone are used per day) ranged from 3 to 46 sessions, with the shortest session being 50 seconds long and the longest session lasting 30 minutes (Soikkeli et al., 2011). Parasuraman et al., (2017) reported that 36.7% of participants checked their phone about 30 times per day and that 64.3% of participants used their smartphone for <1 hour on a daily basis. In other studies, users were reported to be engaged with their smartphones for approximately 2 hours on a daily basis (Moon et al., 2014; Sadagopan et al., 2017).

Few studies have investigated the relationship between smartphone usage habits and the impact on the visual system. In fact, the little evidence that is available is based upon questionnaire based studies conducted on Korean children (Moon et al., 2014). In an experimental setting, Park et al., (2014) demonstrated that playing games and watching videos on a smartphone for 61 minutes caused a significant reduction in the frequency of blinks and increased symptoms of dry eye and epiphora. In another study, smartphone use was suggested to be an important risk factor for dry eyes in children (Moon et al., 2014). Although these studies provide some indication of a significant association between smartphones and dry eyes, their applicability to other population groups is restricted. Furthermore, the limitations of being questionnaire based studies also needs to be considered.

1.9 Research Rationale

A significant body of literature implicates prolonged VDT use to symptoms of asthenopia and dry eyes. Whereas much of this research has extended our understanding of the visual impact

of VDT, there is a dearth of literature concerning these effects during smart device usage. Historically, VDTs have been used as a surrogate for smart devices despite the significant differences in their design and utility. Importantly, much of the evidence on the ocular and symptomatic effects of VDT use have been restricted to evaluation of pre- and post-device usage, failing to capture the changes that occur during usage. In regard to engagement in the task on the VDT, most studies fail to discriminate whether the clinical changes observed differ with the type of task being performed. As tear film stability and blink rates are co-dependent, variation in cognitive load from different tasks is likely to affect the blink rate and hence the tear film. Furthermore, much of this literature concerns examination of each eye individually failing to consider the habitual binocular status under which these devices are commonly used. The lack of literature on real-time changes to key clinical outcome measures such as the tear film stability, reflects the lack of suitable and accessible techniques for assessing these metrics. Therefore, the principle objective of the thesis was to address this deficit in the literature and to design and develop a device for assessing binocular real-time tear film changes during smart device use. As a comparative test, the thesis reports on the design, development and validation of a novel Open Field Tear Film Analyser (OFTA). The novel application of the binocular OFTA during engagement in different tasks provides a unique method of examining the *in vivo*, binocular, real-time assessment of tear film stability and blink rates.

The thesis also aims to assess existing and novel *in vivo* methods for assessing the tear film characteristics during smart device use. Tear osmolarity measured with the TearLab has been widely used an objective clinical measure of tear quality and an important marker for dry eyes (Foulks et al., 2015). The thesis evaluates the utility of the TearLab to measure pre- and post-

tear osmolarity changes after performing two different tasks on a smart device. The effect of repeated measurement on tear osmolarity were also investigated to ascertain the variability of the tear osmolarity values.

Visual fatigue is commonly associated with VDT use. However, a real-time assessment of the accommodative response to the smaller screens and texts of smart devices at a relatively close working distance has yet to be assessed. The thesis also aims to examine the dynamic accommodative response to smart device with differing visual targets.

With 84% of the global population using smart devices (Parihar et al., 2016), characterisation of habitual smart device use is essential. As such, a novel questionnaire pertaining to smart device usage and two validated ocular comfort questionnaires were carried out. The thesis also investigates the utility of objective smartphone apps to capture usage habits over an extended period of time. Differences in global trends for smart device use have been widely reported in literature. The thesis examines two distinct population groups from the UK and Malaysia to ascertain variation in smart device usage habits and the ocular comfort.

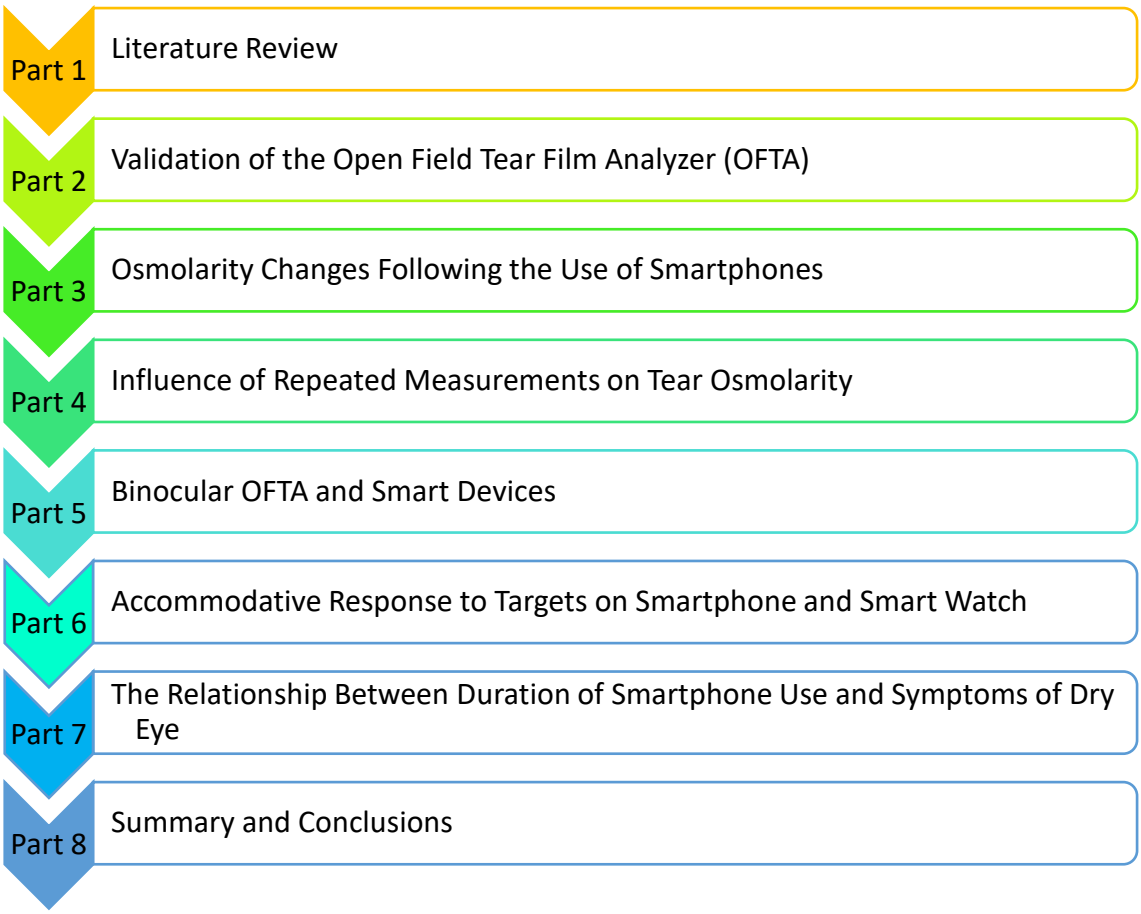


Figure 1.6: Flow chart depicting the order and progression of the various chapters presented in the thesis.

Chapter 2: Validation of the Open Field Tear Film Analyzer (OFTA)

2.1 Introduction

There are many methods, both subjective and objective, that can be used to assess dry eye. A recent survey identified that in the United Kingdom and Australia evaluation of patient symptoms, fluorescein tear break-up time, meibomian gland assessment, and corneal fluorescein staining were the most commonly used techniques to diagnose dry eye (Downie et al., 2016). Although fluorescein break-up time is widely used to assess dry eye, it is considered an invasive procedure because it involves instillation of fluorescein into the tear film, which is known to cause a reduction in tear film stability (Mengher et al., 1985).

Fluorescein sodium is available in liquid form and can be instilled into the eye via an eye dropper but due to the possible risk of pseudomonas corneal infection this modality of drug application is rarely used (Vaughn, 1955). In turn, sterile, single-use fluorescein impregnated paper strips are the most popular method of delivering fluorescein dye into the eye. When using these paper strips, the most common technique for instillation requires a small drop of sterile unpreserved saline to be applied to the tip of the strip which is then gently applied to the bulbar conjunctiva (Cho et al., 1998; Maudgil et al., 1989). Despite the popularity of fluorescein paper strips, there is no standardized procedure for moistening and applying the strip to the eye which is known to cause variability in the clinical test results (Johnson & Murphy, 2005). Specifically, there is no agreement as to whether the moistened strip should be shaken before instillation (Lemp & Hamill, 1973; Lowther, 1997; Nelson, 1994) or whether the strip should be applied to the tear meniscus (Nelson, 1994) or to the superior (Lowther, 1997), inferior (Lemp & Hamill, 1973; Vanley et al., 1977), temporal (Holly et al., 1986) or inferior temporal bulbar conjunctiva (Pflugfelder et al., 1998). Therefore, when assessing the tear film break-up time, non-invasive techniques are advocated due to the potential

variability in test results that originate from assessing the fluorescein break-up time. Indeed, non-invasive break-up time (NIBUT) has been shown to have high sensitivity and specificity for dry eye detection (Gary, 2007). NIBUT can be assessed using instruments such as the Keeler TearScope Plus (Windsor, Berks, United Kingdom) (Guillon, 1998; Nichols et al., 2002; Raig et al., 2016), mires on a keratometer (Hirji et al., 1989) or using placido discs such as the Medmont E300 Corneal Topographer (Medmont International Pty Ltd, Vermont, Victoria, Australia) (Downie, 2015) and the Oculus K5M (Abdelfattah et al., 2015; Mousavi et al., 2018).

Yap, (1991) suggested that there was a relationship between the tear film stability and blink rate; and that blinking was initiated to reconstitute a compromised tear film. However, the Yap (1991) study was limited by the methods involving continuous measurement of blink rate whereas tear film stability was only assessed at a single time point using fluorescein; therefore, an actual conclusion on whether the tear film stability was directly associated with the blinking rate could not be established. Numerous investigations have shown that the blink rate decreases by approximately 40-60% with prolonged VDT use (Doughty, 2001; Freudenthaler et al., 2003; Kazuo & Nakamori, 1993; Schlote et al., 2004; Tsubota, 1998). In fact it is generally observed that the blink rate reduces whilst performing concentrated tasks such as, watching a movie, identifying rapidly changing letters and playing computer games (Carney & Hill, 1982; Carpenter, 1948; Himebaugh et al., 2009; Karson et al., 1981; Ziemssen et al., 2005). Indeed, Stern et al., (1984) suggested that blink rate is under cortical control and is strongly affected by external factors, including physiologic and psychologic influences, as well as task-related factors. Cortically driven blink rate inhibition that occurs during VDT related tasks has been shown to result in a lower blink rate, and a further reduction was observed during engagement with tasks requiring increased cognitive demand (Acosta et al.,

1999; Himebaugh et al., 2009; Patel et al., 1991; Schlote et al., 2004). Consequently, lower blink rates are likely to result in an increased rate of tear film evaporation and symptoms of dry eyes (Kazuo & Nakamori, 1993; Wolkoff et al., 2005).

A number of studies have shown that the occurrence of dry eye is associated with VDT use (Blehm et al., 2005; Uchino et al., 2008, 2013; Yan et al., 2008; Thorud et al., 2012). Such evidence is based upon studies that have assessed the tear film before and after VDT use, demonstrating that the tear film stability reduces after engaging in VDT tasks. A significant limitation of all such evidence relates to the absence of an open field device that can assess the tear film in real-time. Traditionally, VDT devices have been used for occupational purposes (Smith et al., 1984) and as such dry eye symptoms associated with VDT use affected a relatively small proportion of the population (National Research Council, 1983). Smartphones can be considered to be analogous to VDT screens but have both occupational and lifestyle applications. Indeed smartphone ownership is widespread, and users are reported to spend approximately 2 hours on their phone on a daily basis (Moon et al., 2014; Sadagopan et al., 2017). In a recent study, smartphone use was suggested to be an important risk factor for dry eye in children (Moon et al., 2014; Moon et al., 2016); although these reports need further confirmation as the investigation was solely based upon subjective questionnaires. With the growing popularity of smartphone use amongst all age groups, it is essential that clinicians are able to identify and assess the effect of such devices on the eyes.

All commercially available devices for measuring NIBUT utilise fixed internal targets requiring patients to fixate on them under close viewing environments. Such set ups are limited to sampling the characteristics of the tear film in a short period of time under artificial viewing conditions. Therefore, these devices fail to represent the real-world binocular viewing

environment. To attain an accurate assessment of the tear film under normal viewing conditions the most appropriate method for assessing NIBUT should permit binocular viewing of an external fixation target whilst continuingly assessing the tear film and blink characteristics. Moreover, the facility to assess tear film characteristics in real-time is also essential to provide an accurate assessment of the clinical changes that are likely to occur with time whilst individuals are engaged in a given task.

2.2 Objective

The lack of an open field device for measuring tear film has meant that our understanding of how the human tear film changes when performing specific tasks is limited. The purpose of this study was to develop and validate a non-invasive open field instrument that is able to assess real-time changes of the tear film. The intra- and inter-observer repeatability of this custom designed device is assessed and compared to commercially available closed field instrumentation.

2.3 The Open Field Tear Film Analyzer (OFTA)

2.3.1 Ideas and Conceptual Design

The OFTA was designed to enable simultaneous observation and investigation of the tear film stability whilst participants are engaged in their visual task (Figure 2.1). The developmental phase of the OFTA consisted of the light source selection, as well as the cone and mire development.

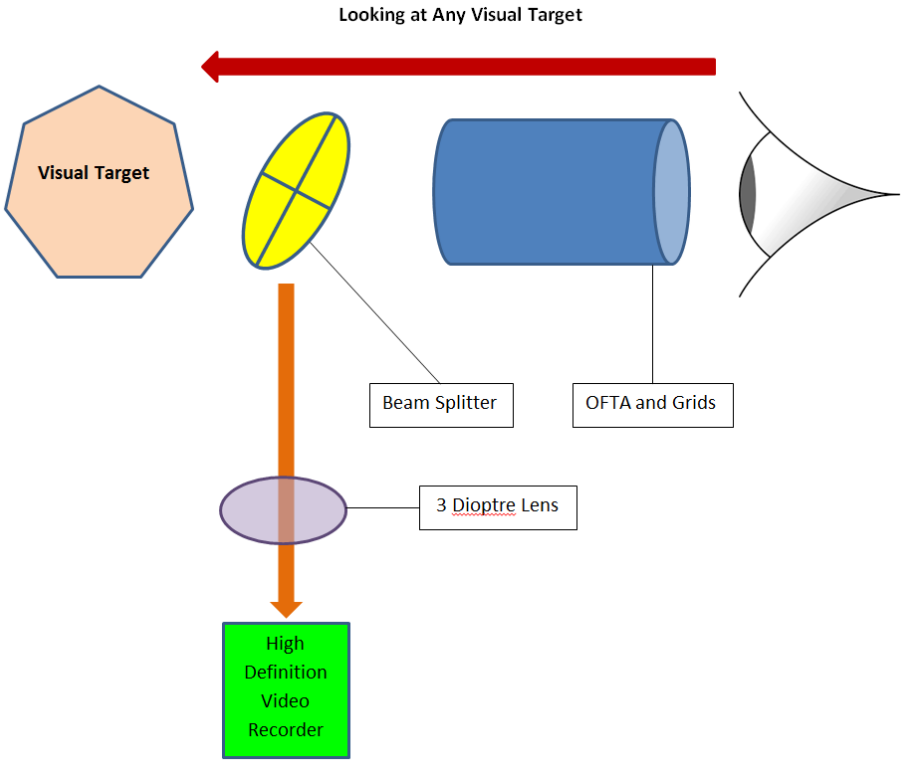


Figure 2.1: The conceptual design of the OFTA.

2.3.2 The OFTA Light Source Selection

The OFTA measures tear film stability using a non-invasive procedure analogous to assessing the NIBUT with a keratometer. The device requires a mire to be projected onto the tear film surface allowing the break up time to be determined by identifying ruptures, breaks or distortions in the mires images. To ensure sufficient illumination to create these mire images, a suitable light source needed to be identified. Key requirements and considerations when identifying the most appropriate light source include:

1. Sufficient illumination to create the mire images: diffuse illumination that will ensure adequate coverage of the OFTA mires compared to light-emitting diode (LED).
2. Temperature: this is particularly important as increased ocular surface temperature has been associated with reduced tear film stability (Purslow & Wolffsohn, 2007; Wolkoff, 2008).

3. Wrap around – a flexible light source was required to allow the light to be wrapped around the inside of the cone that was going to house the OFTA.

Light Tape (LT) [Electro-Luminx Corp., Virginia, America] provides a uniform emittance of light, which propagates in multidirections from the illuminated surface of the tape. The LT employed for the OFTA is composed of a new generation of flexible light sources utilizing electroluminescence technology (Figure 2.2); this type of lighting is based upon excitation of light emitting phosphors that generate the light by applying a current through two electrically conductive plates either side of the phosphors. The LT is a 500 microns thick plastic tape that emits light from its surface [within the visible spectrum with a peak wavelength of 470 nm and an absolute peak radiance of 0.004 watt per steradian per square metre (W. sr. m−2)]. The intensity of the light emitted enables clear visualisation of the tear film. The light is non-coherent and uncollimated and there are no safety issues associated with its use. Being a cold light source, it does not cause a rise in temperature and thus it was anticipated that this would minimize changes to the ocular surface temperature (in comparison to using conventional light bulbs that emit heat). The LT was also chosen as it provides diffuse illumination that would ensure adequate coverage of the OFTA mires. LED strip lights considered during the development stages, failed to provide uniform illumination across the strip length and required the use of diffusers to achieve the homogenous light distribution needed for the study. Moreover, the LT was the only diffuse light source that could be successfully wrapped onto the external surface of the OFTA cones.

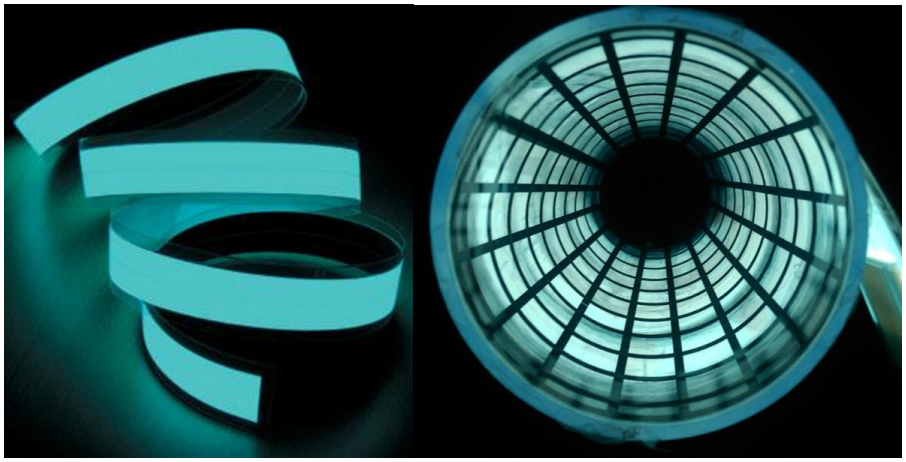
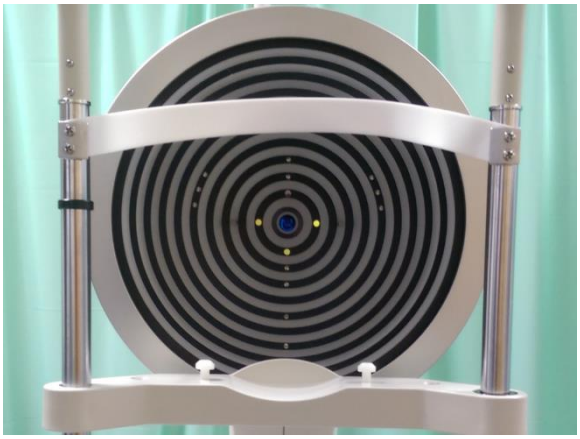


Figure 2.2: The Light Tape (LT) as a light source for the OFTA.

2.3.3 Determination of the Optimal OFTA Cone

To determine the optimal configuration of the OFTA cone, commercially available devices for assessing NIBUT and corneal topography were considered. These included the Oculus K5M (Oculus Optikgerate GmbH, Wetzlar, Germany) and Medmont E300 Corneal Topographer (Medmont International Pty Ltd, Vermont, Victoria, Australia); both of these devices provide measures of NIBUT. Although the corneal topographers Tomey TMS-5 (Tomey, Nagoya, Japan) and Nidek OPD-III (Nidek, Gamagori, Japan) do not provide measures of NIBUT, their design specifications were also considered. A simplified illustration of the 'examination head' of these 4 instruments can be seen in Figure 2.3 to Figure 2.6.

(a) Frontal view.



(b) Schematic view.

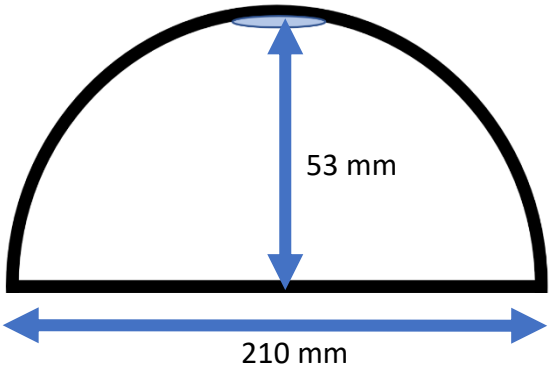


Figure 2.3: Illustration of the ‘examination head’ for Oculus K5M.

(a) Frontal view.

(b) Schematic illustration.

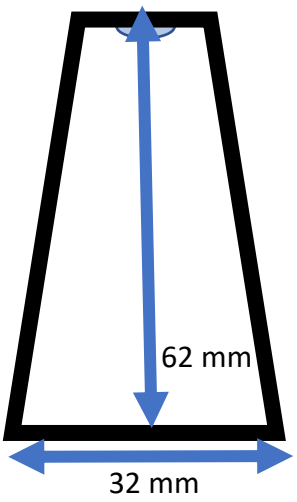
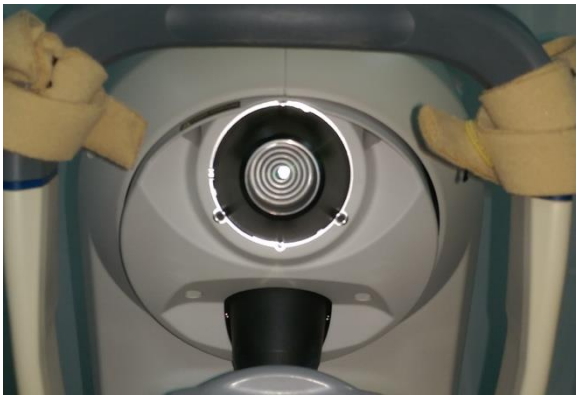


Figure 2.4: Illustration of the ‘examination head’ for Medmont E300.

(a) Frontal view.



(b) Schematic illustration.

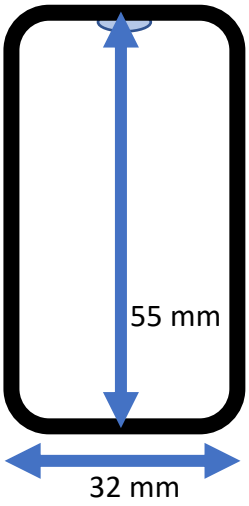
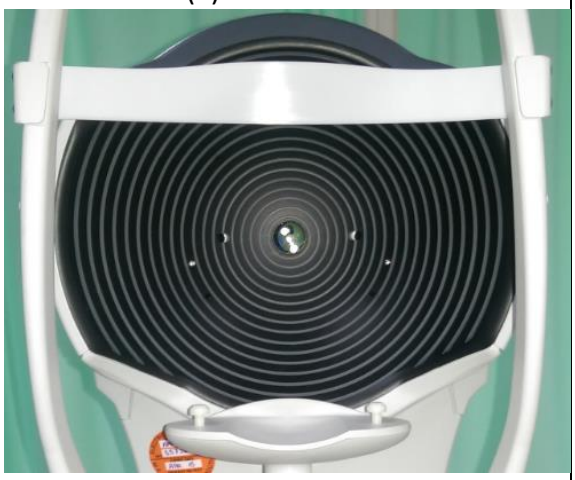


Figure 2.5: Illustration of the ‘examination head’ for Tomey TMS-5.

(a) Frontal view.



(b) Schematic illustration.

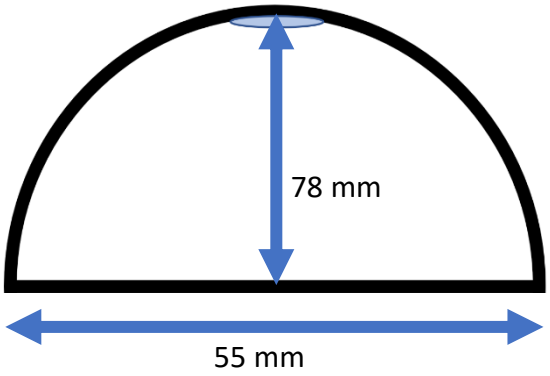


Figure 2.6: Illustration of the ‘examination head’ for Nidek OPD-III.

	Oculus K5M	Medmont E300	Tomey TMS-5	Nidek OPD-III
Shape	Spherical	Conic	Cylindrical	Spherical
Number of mires	22 V 22 H	32 H 29 V	31	33 V 39 H
Mire thickness	Constant 5.5 mm from internal to external	Decreases from 10 mm (internal) to 0.5 mm (external)	Decreases from 4 mm (internal) to 0.25 mm (external)	Increases from 4.5 mm (internal) to 7 mm (external)
Depth	53 mm	62 mm	55 mm	78 mm
Width (diameter)	210 mm	32 mm	32 mm	223 mm
Vertex distance (measured from outermost mire to corneal apex)	18 mm	-3 mm	2 mm	2 mm
Camera opening	10 mm	3 mm	5 mm	24 mm

Table 2.1: Characteristics of the placido based instruments. A Draper 52380 Vernier Calliper (Draper Tools, Hampshire, UK) was used to measure the parameters displayed.

The Oculus K5M has 22 placido rings and a large diameter (width) of 210 mm (Oculus, 2018) while the Medmont E300 has 32 rings with a significantly smaller diameter (width) size of 32 mm (Medmont, 2015). Interestingly, the diameter (width) size of Tomey TMS-5 is 32 mm which is similar to that of Medmont E300 (Table 2.1). In addition, the diameter (width) of the Nidek OPD-III is 223 mm, which is akin to that of the Oculus K5M.

One of the principal objectives of this work was to assess the real-time changes to the tear film and blink rate of both eyes simultaneously whilst participants are engaged with a task on a VDT under habitual viewing conditions (Chapter 5). The feasible of achieving this aim with a shape based upon one of these 4 commercially available devices was initially considered. As such, the diameter of the Oculus K5M and OPD-III heads were found to be too large to allow simultaneous binocular assessment of the tear film. In comparison, the size of the Medmont

E300 and Tomey TMS-5 was deemed to be suitable to enable simultaneous binocular measurement of NIBUT, however the field of view was considered too small to allow viewing of a visual task through the aperture.

Hamer et al., (2016) assessed the repeatability of keratometry measurements using the OPD-III, Medmont E300 and Tomey TMS-5 and found poorest repeatability and disparity of agreement with the Tomey TMS-5; the only instrument with a cylindrical shaped topography cone. As no commercially available instrument would satisfy the research objectives, the OFTA was designed and developed. When considering the shape of the 4 devices, it was evident that the conical design allowed for a larger corneal area to be examined whilst still providing a sufficient field of view for the participant to perform a VDT based task. In addition, the OFTA was designed to be an open field system to address the current lack of a non-invasive binocular open field instruments that can measure NIBUT.

During the design stages of the OFTA, numerous cone prototypes were designed using the Computer Aided Design (CAD) software, SolidWorks (SolidWorks Corp., Waltham, America). These were then manufactured using the 3D printer at Plymouth University. The first OFTA prototype (Figure 2.7) was found to have several limitations as the viewing aperture was too small and thus narrowing the field of view for the participants. Furthermore, the lack of a detachable holder made it harder to attach the device to a stand to assess the tear film (Figure 2.7).

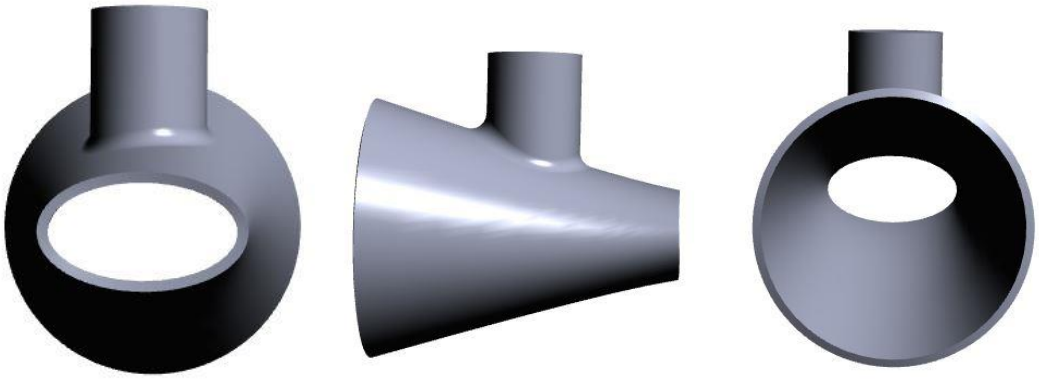


Figure 2.7: The OFTA Prototype 1.

With these limitations in mind, Prototype 2 was designed with a larger viewing aperture with an elliptical conformation and a detachable holder to allow easy attachment to a stand (Figure 2.8). A limitation of this prototype was the difficulty in attaching the mires to the inside surface of the cone due its elliptical shape. Subsequently Prototype 3 was designed with a circular shape (Figure 2.9) and provided a suitable housing for the mires; however, it was not possible to attach the LT securely.

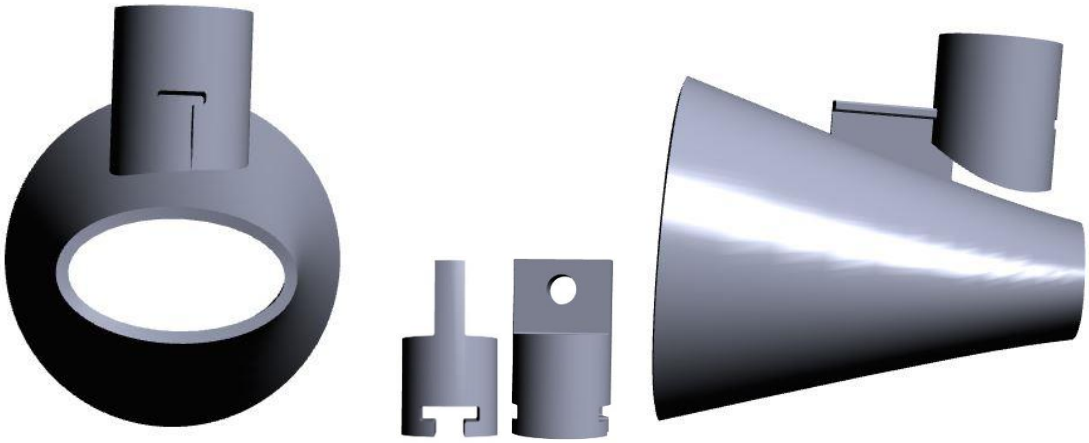


Figure 2.8: The OFTA Prototype 2.

Figure 2.9: The OFTA Prototype 3.

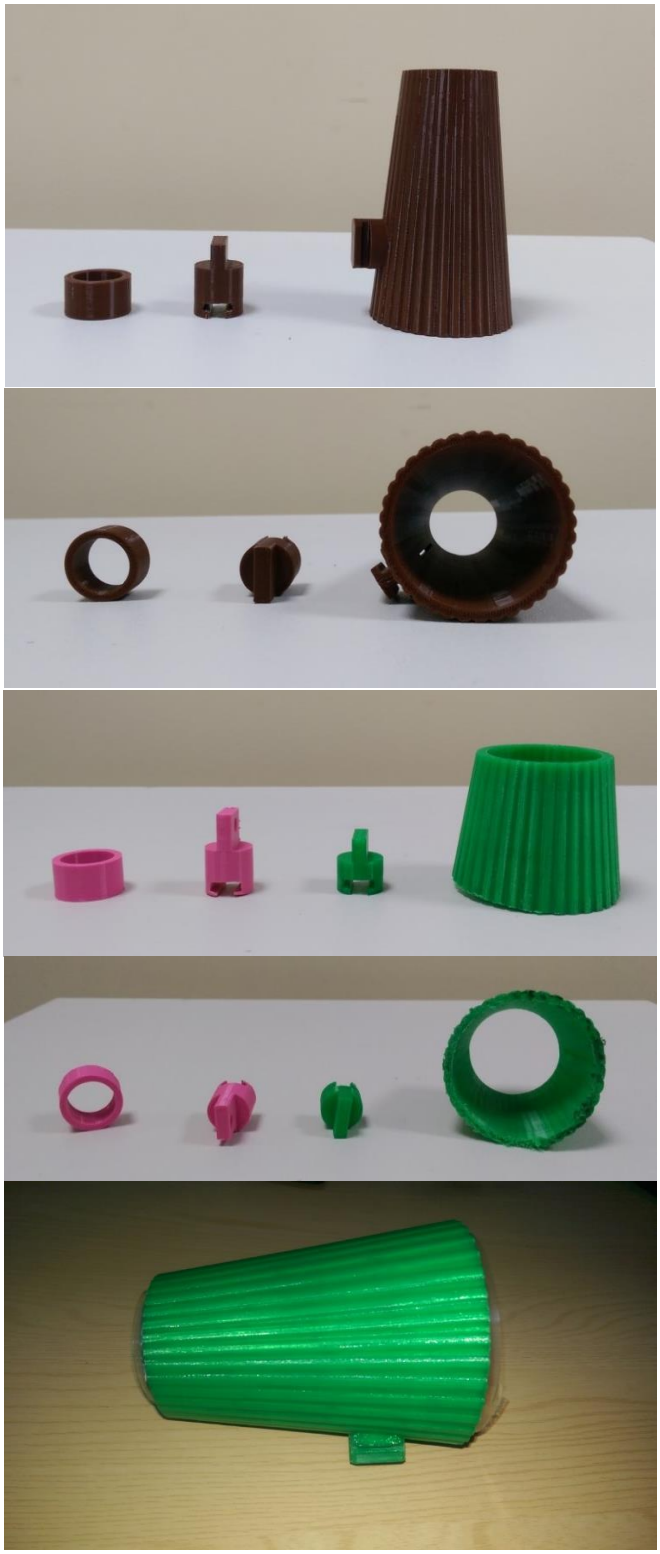


Figure 2.10: Various OFTA cones and holders prototype.

Photographs of the 3D printed OFTA prototype cones are shown in Figure 2.10. These prototypes were not chosen as the final version, as they were either too small to allow sufficient observation or appropriate fitting of the mires.

The final design (prototype 4) incorporated 2 components; (i) OFTA cone and (ii) OFTA cone holder. The device has a circular viewing aperture, detachable handle and enabled the LT and OFTA mire to be securely attached (Figure 2.11). The larger end of the OFTA acts as the observation aperture (10 cm diameter) and is where the participant's eye is positioned. The opposing side of the cone has a smaller aperture (5 cm), allowing participants to view a target of regard or perform a visual task, whilst also enabling the examiners to visualise and record the tear film stability (Figure 2.11). The OFTA prototype cone, together with the LT and the OFTA mire were held firmly by the OFTA prototype 4 cone holder (Figure 2.12).

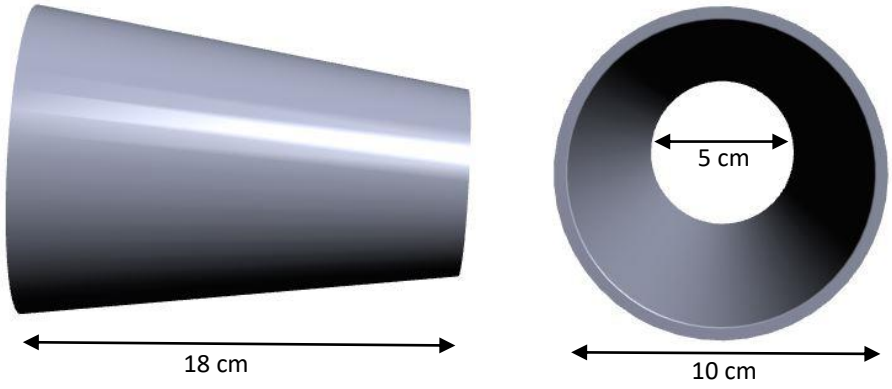


Figure 2.11: The OFTA Prototype 4 Cone.

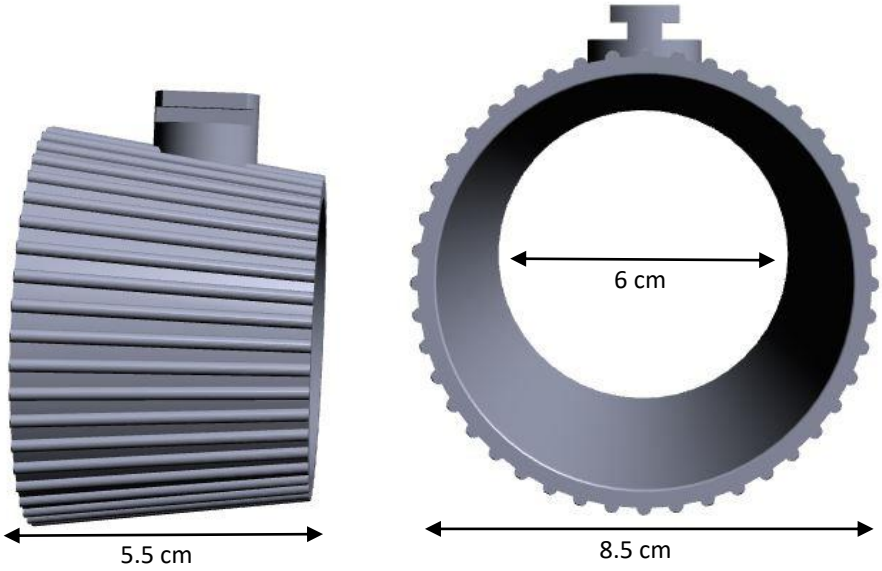


Figure 2.12: The OFTA Prototype Cone Holder.

2.3.4 Determination of Optimal OFTA Mire

The next phase of the development sought to design and develop the mires for the OFTA cone. Placido based mires of different configuration are used by instruments such as the Oculus K5M, Medmont E300, Tomey TMS-5 and Nidek OPD-III (see Table 2.1 earlier). The size of the mires in the commercial instruments differed and no one design provided an obvious advantage for NIBUT evaluation. Hence, a trial and error approach was used to determine the optimal mire design for the OFTA.

As the Oculus K5M and Medmont E300, the OFTA would determine the NIBUT by allowing visualisation of the mires reflected from the tear film. During the design stages of the mire grid, numerous schematics were produced in Adobe Illustrator (Adobe System, San Jose, America). The OFTA mires were printed onto a clear transparent plastic sheet that provided the flexibility to shape the print into a cone (Figure 2.13); the mire sheet was then inserted into the cone and adhered to the inside surface.

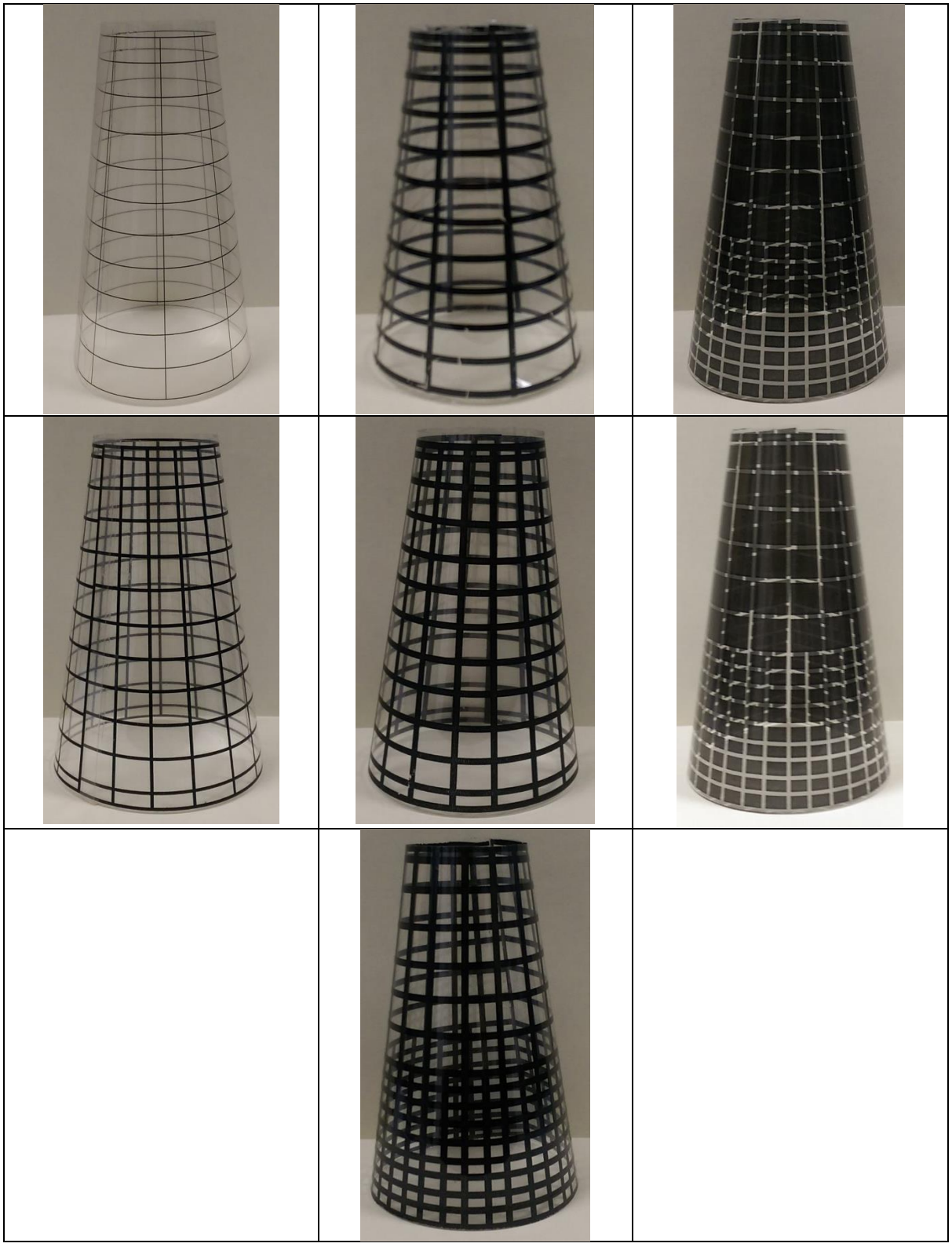


Figure 2.13: Various OFTA cones mires that were printed onto a clear transparent plastic sheet.

For each OFTA mire design, there were 2 versions: one with 1 mm mire thickness and the other with 2 mm mire thickness (Figure 2.14, Figure 2.16, Figure 2.18 and Figure 2.20). These measurements were chosen to evaluate the effect of mire grid line thickness on the visualisation of the mires. A reversed contrast version of the mire grid similar to that of the Oculus K5M and OPD-III was also trialled. The OFTA mire 1, 2, 3 and 4 were first tested on a smooth steel ball (Figure 2.15, Figure 2.17, Figure 2.19 and Figure 2.21) to determine the mire's clarity and later, on real participant's eyes to ascertain if the mires could be used to assess the tear film stability.

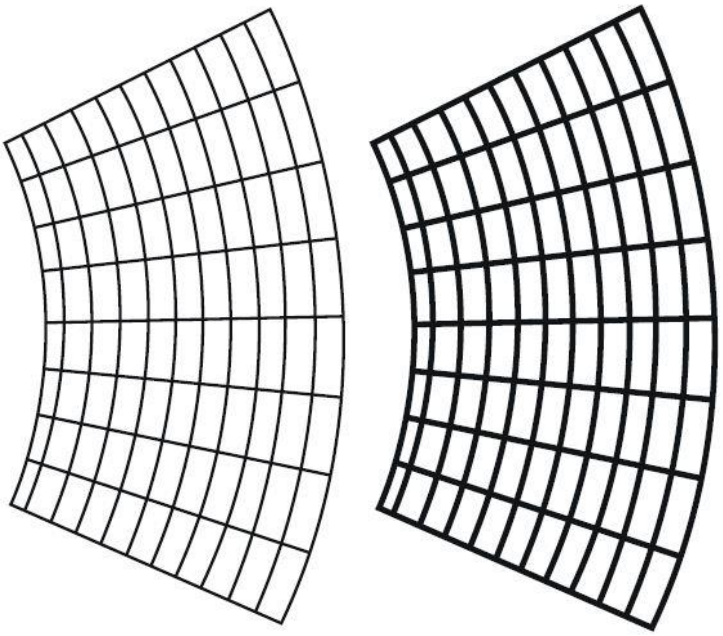


Figure 2.14: OFTA mire 1 [1 mm (thin lines) and 2 mm (thicker lines) mire thickness].

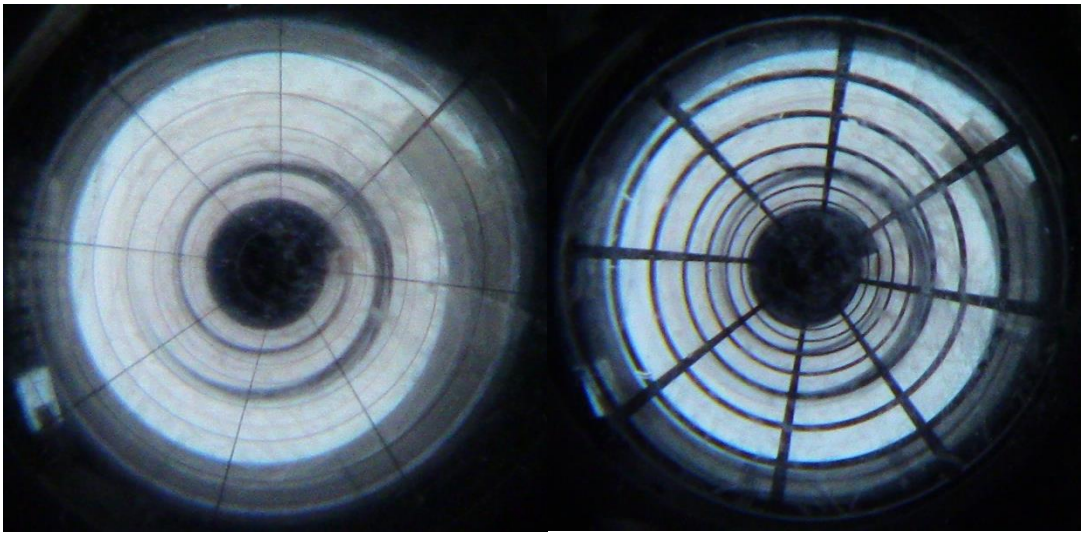


Figure 2.15: The appearance of OFTA mire 1 [1 mm (thin lines) and 2 mm (thicker lines) mire thickness] seen on steel ball.

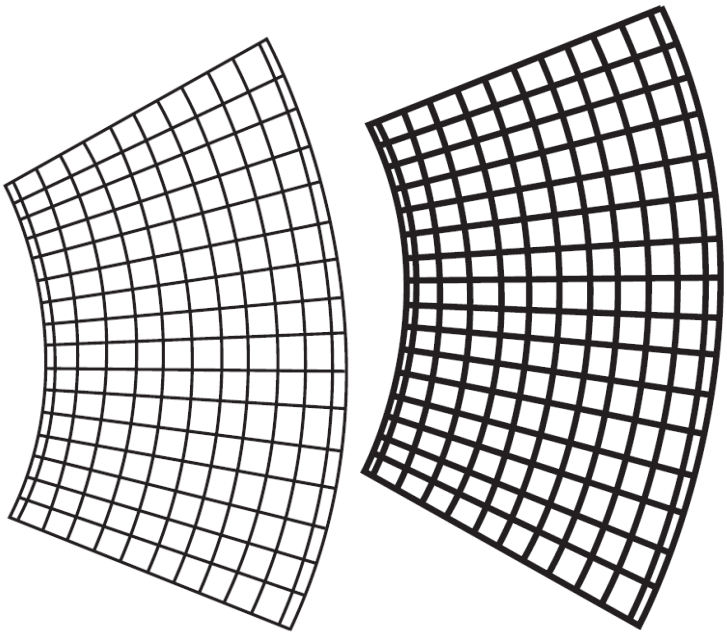


Figure 2.16: OFTA mire 2 [1 mm (thin lines) and 2 mm (thicker lines) mire thickness].

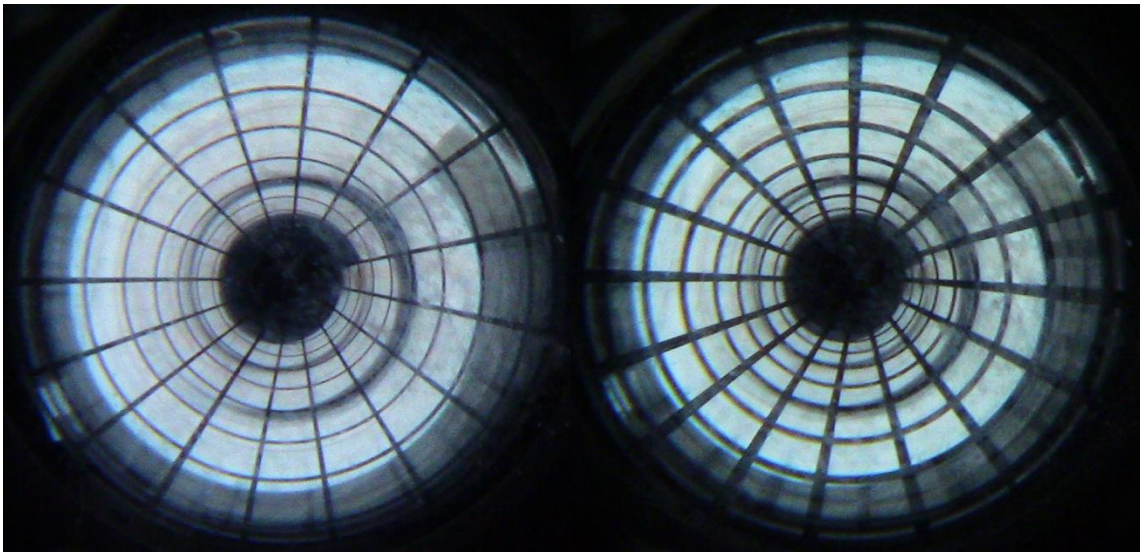


Figure 2.17: The appearance of OFTA mire 2 [1 mm (thin lines) and 2 mm (thicker lines) mire thickness] seen on steel ball.

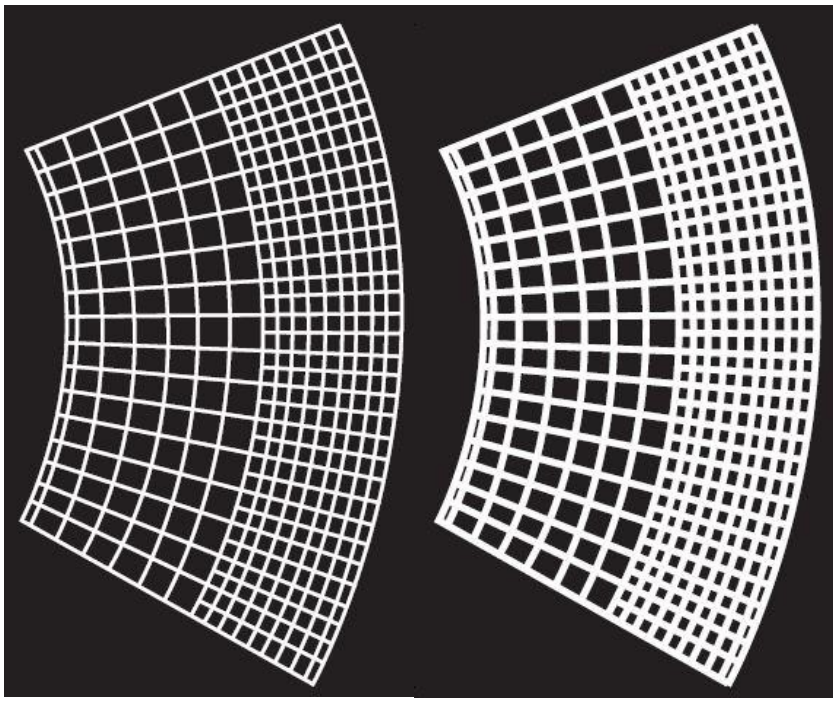


Figure 2.18: OFTA mire 3, reverse contrast [1 mm (thin lines) and 2 mm (thicker lines) mire thickness].

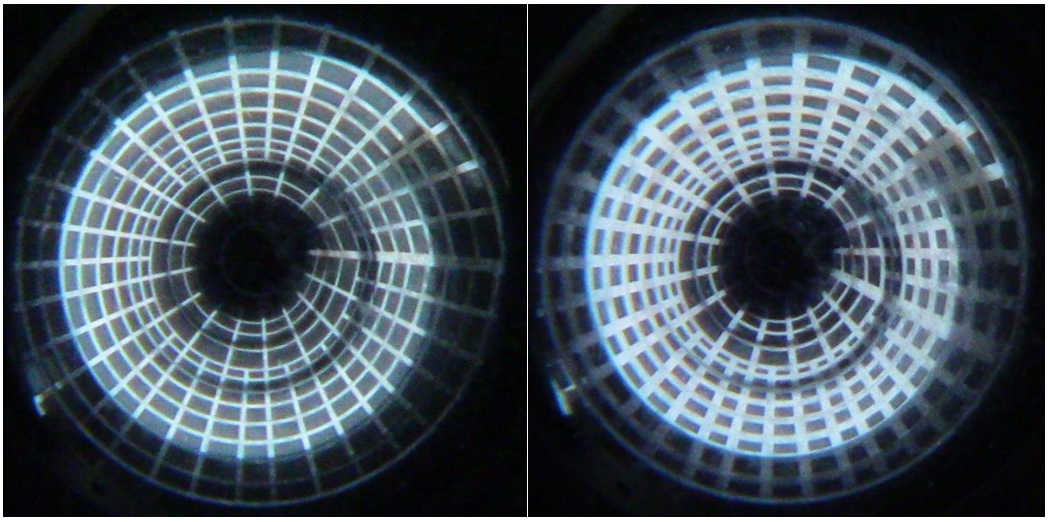


Figure 2.19: The appearance of OFTA mire 3, reverse contrast [1 mm (thin lines) and 2 mm (thicker lines) mire thickness] seen on steel ball.

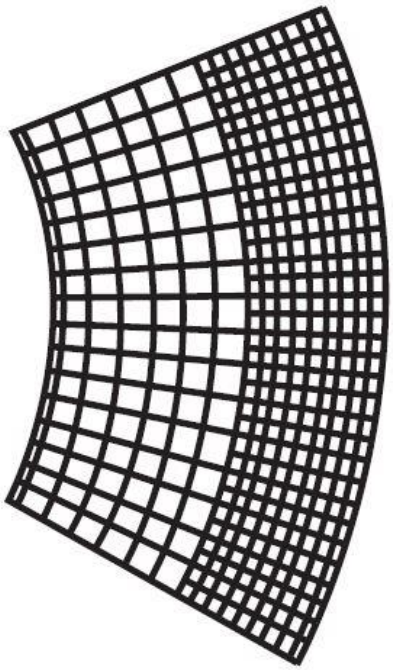


Figure 2.20: OFTA mire 4 (2 mm mire thickness).

Figure 2.21: The appearance of OFTA mire 4 (2 mm mire thickness) seen on steel ball.

Following preliminary testing, the 2 mm OFTA mire thickness was found to offer optimal visualization of the tear film stability compared to the 1 mm version. The reverse contrast OFTA mire design (Figure 2.18 and Figure 2.19) was found to offer poor visualization of the tear film. Through visual inspection, it was determined that the design that offered the clearest mires was version 4 (Figure 2.20 and Figure 2.21). In this design (version 4); the size of the smaller square in OFTA mire 4 was 3 × 5 mm and the larger square was 8 × 7 mm (Figure 2.20).

2.3.5 The Final Product (The OFTA)

The OFTA Prototype 4 Cone was fabricated using a stereolithography 3D printer by the company i.materialise (Belgium). The cone is composed of a transparent resin; an additive manufacturing process that employs a tank of liquid ultraviolet curable photopolymer resin and an ultraviolet laser to build parts of a model one layer at a time. Making the cone transparent allowed maximal illumination from the LT to reach the participant's tear film layer to enable optimal visualization of the mires. The LT was coiled around the outer part of the

transparent OFTA cone, which was then inserted into the OFTA cone Holder. The non-transparent holder was fabricated by using a Plymouth University 3D printer.

When the power source (240 V) for the LT was switched on, the mire pattern was projected onto the participant's tear film layer. A HD video camera (Panasonic HC-V250) was used to record the tear film stability. The video camera has an optical image stabilizer, enabling HD recording to a resolution of 1080 pixels at ×50 optical zoom. A 3.33 dioptre plano-convex lens, LA1256, N-BK7 (Thorlabs Ltd., Ely, United Kingdom) with 300 mm focal length and 50.8 mm lens diameter allowed magnification of the mire images. The 3.33 D lens was positioned between the HD video camera and the 70/30 Reflection/Transmission ratio beam splitter. The 70/30 ratio was chosen for the beam splitter as it provided improved clarity of the image.

Dovetail rails were used to secure the HD video camera, OFTA and the beam splitter together (Figure 2.22). The entire OFTA system was secured onto an adjustable tripod that could be set for a participant's head height whilst seated (Figure 2.23).

Figure 2.22: The completed OFTA system.

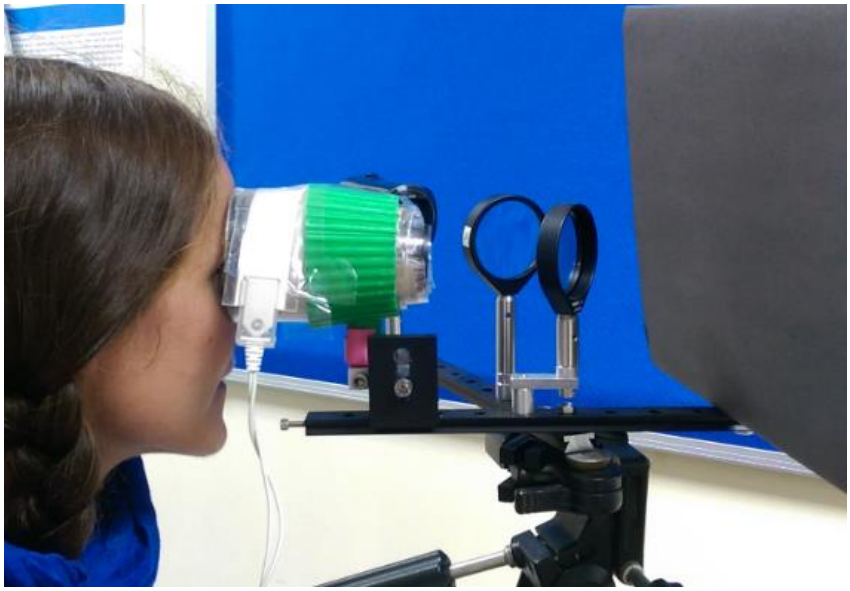


Figure 2.23: Positioning of participant on the OFTA system.

2.4 Methodology

2.4.1 The Open Field Tear Film Analyser (OFTA)

The two primary objectives of this study were:

- To assess the validity of the OFTA for assessing non-invasive tear break up time (NIBUT) against commercially available devices [Bausch and Lomb (B&L) Keratometer (Bausch & Lomb, Rochester, NY) and Oculus K5M (Oculus Optikgerate GmbH, Wetzlar, Germany)].
- To determine the repeatability and reproducibility of the OFTA for assessing NIBUT.

2.4.2 Ethical Approval

Ethical approval was obtained from the Research Ethics Committee, Faculty of Health & Human Sciences and Peninsula School of Medicine & Dentistry, Plymouth University. The letter of approval can be seen in the Appendix A (reference number 14/15-330). This study adheres to the tenants of the Declaration of Helsinki, International Conference of Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and the Plymouth University's Principles for Research Involving Human Participants.

2.4.3 Sample Size

The sample size was calculated using the software G*Power, version 3.1.9.2 (Faul et al., 2007, 2009; Prajapati et al., 2010). Sample size calculations for this study were based upon a correlation model with a moderate effect size of 0.3 (Cohen, 1988, 1992), significance level of $p<0.05$ and with a power of 80% was used for this calculation. According to the G*Power calculations, a total sample size of 82 participants were required for this study.

2.4.4 Inclusion and Exclusion Criteria

Participants were recruited via convenient sampling method, from the staff and student population of the School of Health Professions [Peninsula Allied Health Centre (PAHC), Plymouth University]. The inclusion and exclusion criteria of the study were listed below.

2.4.4.1 Inclusion Criteria

- Completed a comprehensive eye examination within the last 12 months.
- Aged 18 - 40 years old.
- Contact lens wearers were asked to cease contact lens wear for a minimum of 2 days if wearing soft contact lenses and 1 week if wearing rigid gas permeable lenses (Liesegang, 2002; Marfurt et al., 2010; DelMonte & Kim, 2011).

2.4.4.2 Exclusion Criteria

- Pregnant or breast-feeding.
- Application of any eye drops within the last 48 hours before examination.
- Use of medication within the last 30 days which influences the body water regulation system (e.g. antidepressants, diuretics, corticosteroids, histamine-receptor antagonist, immune-modulators).
- Change of ocular therapy within the last 30 days.
- Permanent application of eye drops or ocular medication.
- On-going ocular treatment.
- Any kind of ocular pathology or history of refractive surgery.

- Any kind of systemic disease which affect the body water regulation system (Marfan syndrome, osteogenesis imperfect, pseudozanthoma elasticum, Ehlers-Danlos, diabetes, rosacea, acne, cardiovascular disease, thyroid disease) (Baudouin, 2001; Gudmundsen et al., 1992; Stankiewicz & Mikita, 1998; Stern et al., 1998).
- Participation in a pharmacological studies occurring concurrently.
- Presence of nystagmus.
- History of or currently experiencing dry eye disease.

2.4.5 Visit Schedule

The study was comprised of 3 separate visits, which were at least 24 hours apart. Visit 1 (V1) and visit 2 (V2) were conducted by the principle investigator of the study (AS), whilst visit 3 (V3) was conducted by a second co-investigator (PB). Data from V1 and V2 were used for the reliability analysis, whilst results from V3 were used to determine the reproducibility of the test.

2.4.6 Procedure

All procedures were performed on both eyes for all participants.

2.4.6.1 Non-Invasive Tear Stability

At all study visits, the NIBUT was measured using the B&L Keratometer, Oculus K5M and OFTA in a randomized order. Participants were asked to blink twice before being asked to keep their eyes open for as long as possible. The instructions were kept consistent between instrument, participants and investigators. Measurements were taken on both eyes and calibration was verified every morning before assessing participants.

2.4.6.1.1 Bausch and Lomb One Position Keratometer

In this study, the Bausch and Lomb one position keratometer (B&L Keratometer) was used to measure NIBUT (Elliott, 2013). Throughout the measurement, the contralateral eye was

occluded. Participants were required to blink twice and then look straight ahead for as long as possible. After opening the eyes from the second full blink, NIBUT was assessed subjectively using a stopwatch (Fastime O, Fastime) by noting the time taken for the mire images to distort/break/rupture (Little & Bruce, 1994). A total of 3 measurements were taken on each eye and these measurements were later averaged for analysis purposes.

2.4.6.1.2 Oculus Keratograph 5M

The Oculus K5M has multiple features that allows analysis of the ocular surface, including tear meniscus height (TMH), NIBUT, meibography, and conjunctival hyperaemia assessment (Sarezky et al., 2016). The device is a non-invasive, placido-disc corneal topographer that measures NIBUT objectively using an infrared (IR) light source that is invisible to the human eye; thus, avoiding glare and reflex tearing during the examination and improving its accuracy (Sedaghat et al., 2017).

The repeatability and reproducibility of the Oculus K5M has been evaluated and shown to be acceptable (Best et al., 2012; Hong et al., 2013; Tian et al., 2016). Due to this, it has been used in numerous studies involving tear film stability, TMH, contact lenses and dry eyes (Abdelfattah et al., 2015; Koh et al., 2015; Mousavi et al., 2017; Raig et al., 2016; Wolffsohn et al., 2017).

Throughout the NIBUT measurement, the contralateral eye was occluded. Participants were required to make 2 full blinks and then look straight ahead for as long as possible. NIBUT was measured as the time in seconds between the last complete blink and the first perturbation of a grid projected onto the surface of the cornea which the device automatically detects using the integrated software (Koh et al., 2015). The Oculus K5M records the tear film for a period of 24 seconds, from which it objectively generates 2 measures of NIBUT using image

analysis. The first metric denotes the time taken to the first distortion of the placido disc mires (NIBUT-first), the second metric averages the time point for all break up incidents that occur in the 24 seconds (NIBUT-average) (Tian et al., 2016). In the current study, only 'NIBUT-first' was assessed as the objective was to identify when the first tear break up occurred. A total of 3 measurements were taken on each eye and were later averaged for analysis purposes.

2.4.6.1.3 Open Field Tear Film Analyser (OFTA)

Participants were required to look straight ahead (after 2 full blinks) while the tear stability was recorded using the OFTA system. Throughout the measurement, the contralateral eye was occluded. The video recordings obtained from the OFTA were saved to an external hard disk drive and were later examined by investigators who subjectively determined the NIBUT endpoint. The OFTA video files were viewed on a 21.5" LED monitor screen with a resolution of 1920 x 1080 pixels (Brilliance LED monitor, 221P3LPYES, Philips), using an open source software VideoLAN Client (Version 2.2.2 Weatherwax, VLC media player). Using a stopwatch (Fastime O, Fastime) NIBUT was defined as the time taken for the mires to exhibit their 'first change' after a blink. The criterion for determining these changes included: distortions, break-ups or ruptures of the OFTA mires. A total of 3 NIBUT measurements were recorded and later averaged for data analysis.

2.4.7 Data Analysis

Validity refers to whether an instrument measures what it was designed to measure (Field, 2005); in this study, it refers to the ability of the OFTA to provide valid NIBUT measurement. The software SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, New York) was used for data analysis. Initial data inspection using visual method (histogram), the Sharpiro-Wilks tests as well as Z-score for skewness and Z-score for Kurtosis revealed that the data was

not distributed normally. Therefore, the Friedman test (χ), was performed to assess if there were any significant differences in measures of NIBUT between the 3 instruments. An alpha level of $p<0.05$ was adopted to signify statistical significance and Bonferroni correction was applied to *post-hoc* testing, to reduce type 1 error, where applicable. For the pair-wise comparison, the *p*-value adjustment was done automatically by SPSS (Adjusted Significance, p_{adj}) and remained at $p_{adj}<0.05$ as suggested by IBM Corporation, (2012) and Lund & Lund, (2014). In addition, Spearman's correlation between measures of NIBUT from the 3 instruments were evaluated to assess their associations. Furthermore, Bland and Altman plots between NIBUT and the 3 instruments during Visit 1 were created with Sigma plot (SYSTAT Software Inc., San Jose, California, USA) and were also used to determine the validity and therefore potential inter-changeability of the instruments. Reliability is the ability of a measure to produce consistent results when the same entities are measured under different conditions (Field, 2005; Bartlett & Frost, 2008); in this case, it refers to the ability of OFTA to produce consistent NIBUT results when it is measured under different conditions such as different visit or by different examiner. The reliability of the instruments was assessed by assessing the Intraclass Correlation Coefficient (intra-observer ICC) while the reproducibility of the instruments was determined using Interclass Correlation Coefficient (inter-observer ICC) (Bartko, 1966; Shrout & Fleiss, 1979; Patton et al., 2006; Koo & Li, 2016). Both intra- and inter-ICC were calculated using SPSS using 'two mixed mode' model and 'absolute agreement' analysis. Reliability was analysed by comparing the NIBUT measurement between V1 and V2 (same investigator) and this was represented by the intra-observer ICC. Reproducibility was assessed by comparing the NIBUT measurement between V1 and V3 (different investigators) and this was represented by the inter-observer ICC. In addition, Bland and Altman plots for the OFTA NIBUT during V1, V2 and V3 was also produced to investigate the reproducibility of

the OFTA. A log transformation (base=10) was conducted for each Bland and Altman plot that demonstrated heteroscedasticity (Bland & Altman, 2010; Cox et al., 2015). Due to the maximum NIBUT with the Oculus K5M being limited to 24 seconds, all data analysis were divided into (i) analysis based on all NIBUT values and (ii) analysis based on NIBUT $\leq$24 seconds; this was carried out to compensate for the ceiling effect of the Oculus K5M and since these results would be more clinically relevant.

2.5 Results

2.5.1 Descriptive

Eighty-four participants (32 males and 52 females) with a mean$\pm$SD age of 23.73$\pm$4.77 years old were recruited for this study. No air draft was present in the examination room as it has been reported that exposure to high air velocity (1.0 m/s) for 30 minutes would cause a significant decrease in tear stability (Wyon & Wyon, 1987). The environmental conditions in the examination room were controlled throughout the study with a mean temperature of 21.40$\pm$0.62 ^{0}C and mean relative humidity (RH) of 41.95$\pm$1.19%. Both temperature and RH were controlled as elevated temperature has been observed to make the tear film less stable (Purslow & Wolffsohn, 2007; Wolkoff, 2008) whilst a reduction in RH from 40% to 5% produced an immediate reduction in NIBUT (Abusharha & Pearce, 2012). There was no significant difference in the results between eyes and thus only data from the RE were analysed to avoid statistical bias (Best et al., 2012).

2.5.2 Results from all NIBUT data from Oculus K5M, B&L Keratometer and OFTA

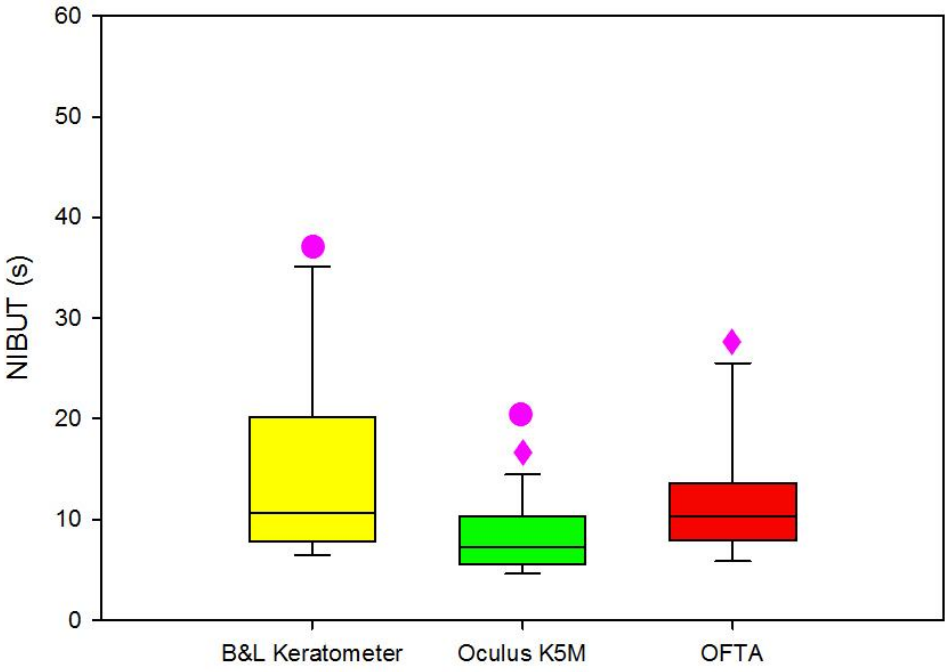
The mean$\pm$SD for V1, V2 and V3 for all NIBUT values obtained with the B&L Keratometer, Oculus K5M and OFTA are shown in Table 2.2.

Instrument	NIBUT (s), Mean±SD		
	Visit 1 (n=84)	Visit 2 (n=66)	Visit 3 (n=20)
B&L Keratometer	15.10±12.04	13.34±12.01	14.73±14.94
Oculus K5M	8.63±4.34	9.50±5.03	11.45±5.33
OFTA	13.06±8.49	13.25±6.85	18.87±14.24

Table 2.2: All NIBUT values during V1, V2 and V3 obtained using the 3 instruments.

2.5.3 Validity Based on all NIBUT data from Oculus K5M, B&L Keratometer and OFTA

Figure 2.24 shows the boxplot for all NIBUT values obtained for all 3 instruments during V1. For all boxplots, the top whisker represents the 90^{th} percentile and the lowest whisker represents the 10^{th} percentile.



Legends:

B&L Keratometer.
Oculus K5M.
OFTA.
Significant differences between Oculus K5M – B&L Keratometer.
Significant differences between Oculus K5M – OFTA.

Figure 2.24: Box plot representing median and interquartile range for NIBUT on all 3 instruments during the first visit (V1) (all NIBUT values).

A significant difference in median NIBUT between the 3 instruments was found [$\chi^2(2) = 41.1670$, $p<0.0005$]. *Post-hoc* analysis revealed that NIBUT obtained with the Oculus K5M was significantly lower when compared to the B&L Keratometer (Z=6.095, $p_{adj}<0.0005$) and the OFTA (Z=-4.783, $p_{adj}<0.0005$). However, the median NIBUT obtained using the OFTA and B&L Keratometer were not significantly different (Z=1.312, $p_{adj}=0.569$).

The measures of NIBUT from all 3 devices were significantly correlated ($p<0.05$) (Figure 2.25), however, the correlation between each instrument were either weak or moderate (below r=0.5) (Field, 2005) (Figure 2.25).

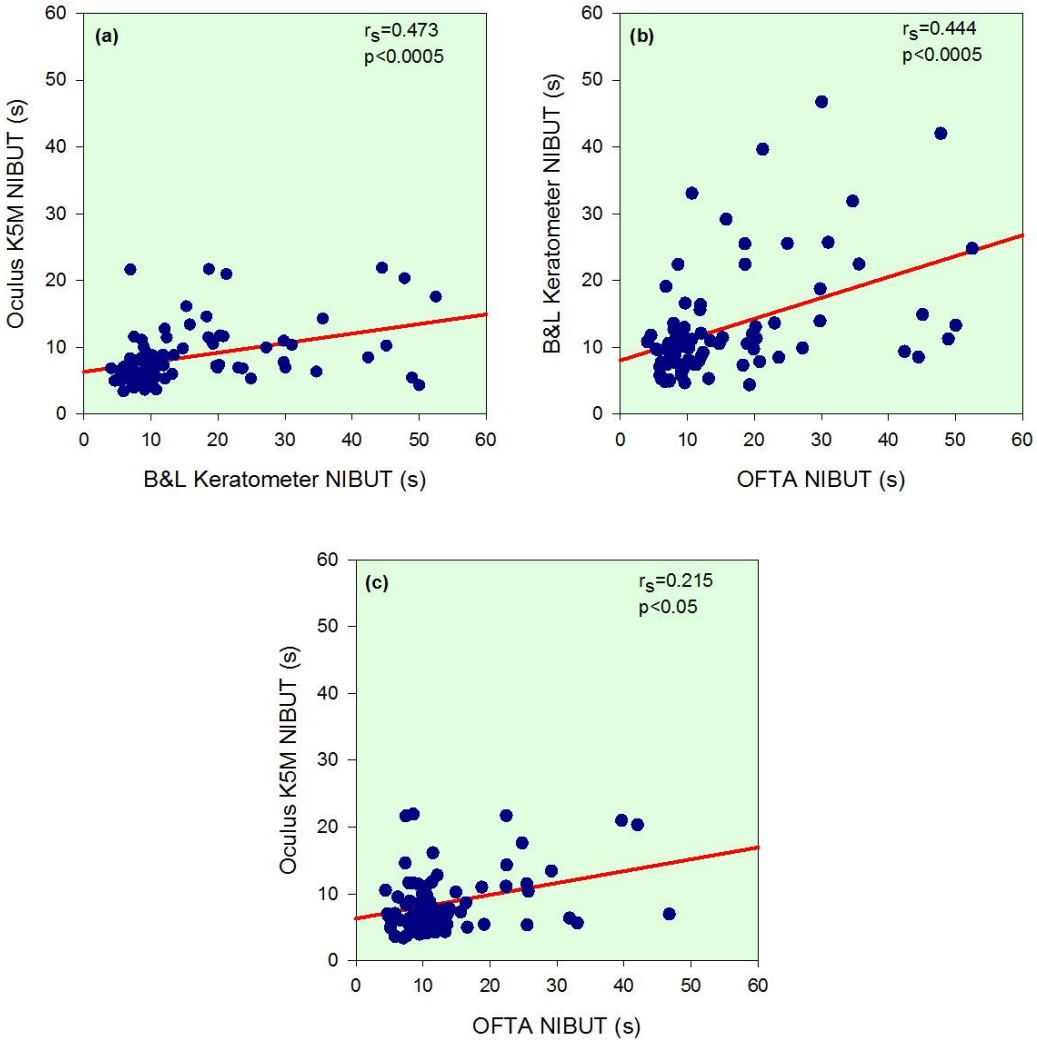


Figure 2.25: Spearman's correlation between (a) Oculus K5M and B&L Keratometer, (b) B&L Keratometer and OFTA, (c) Oculus K5M and OFTA.

When including all NIBUT data (including those >24 seconds), Bland and Altman plots comparing B&L Keratometer and Oculus K5M, showed a mean difference of 7.36 seconds, with Limits of Agreement (LoA) of -14.31 to 29.03 seconds (Figure 2.26). The mean difference between the B&L Keratometer vs. OFTA was 2.94 seconds with LoA of -19.11 to 24.98 seconds. Whilst the mean difference between the Oculus K5M and OFTA was 4.43 seconds with a LoA of -11.41 to 20.26 seconds. A proportional bias was present; as the mean NIBUT values increase, the mean differences between the instruments became more apparent.

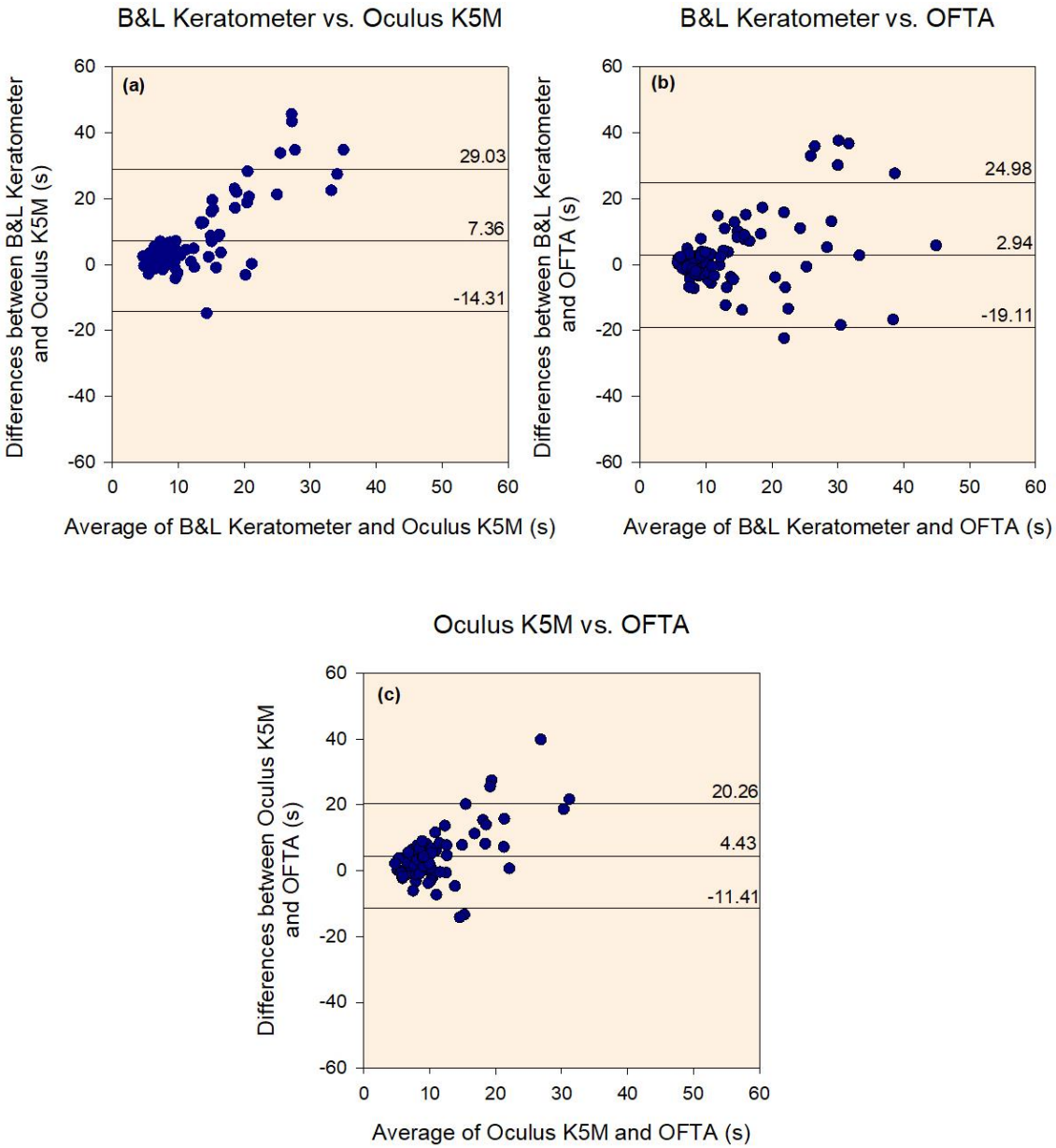


Figure 2.26: Bland and Altman plots of NIBUT (non-transformed data, all NIBUT values) between (a) B&L Keratometer and Oculus K5M, (b) B&L Keratometer and OFTA, (c) Oculus K5M and OFTA.

The NIBUT Bland and Altman plots in Figure 2.26 demonstrate a heteroscedastic pattern, this is comparable to other studies that investigated the differences between NIBUT and TBUT (Cho & Douthwaite, 1995; Nichols et al., 2002; Best et al., 2012; Lan et al., 2014; Cox et al., 2015).

In this study, the presence of heteroscedasticity was confirmed by both visual inspection of the Bland and Altman plots and by using mathematical calculations proposed by Brehm et al., (2012). The mathematical method involves calculation of Kendall's tau (τ) correlation between the absolute differences and the corresponding means; when a positive $\tau>0.1$ was found, the data were denoted heteroscedastic. When $\tau<0.1$ or negative, the data were considered homoscedastic (Brehm et al., 2012). If the data was heteroscedastic, the data was transformed by logarithms to the base 10. Thereafter, the Kendall's τ correlation was calculated again. If τ decreased, reliability analysis and Bland and Altman plots were re-assessed on the log-transformed data. If the transformed τ increased, analysis was done on the non-transformed (original) data. For this study, the Kendall's tau results can be seen in Table 2.3 below.

Parameter	Kendall's τ (Original Data)	Heteroscedastic (Yes or No)	Kendall's τ (Log Data)
V1 (B&L Keratometer vs Oculus K5M)	0.442	Yes	0.245
V1 (B&L Keratometer vs OFTA)	0.440	Yes	0.144
V1 (Oculus K5M vs OFTA)	0.292	Yes	-0.078

Table 2.3: Kendall's τ for original data (all NIBUT values) and subsequent Kendall's τ after log transformation on the original data.

Based on the results on Table 2.3 and the visual inspection of the data, Bland and Altman plots for V1 (B&L Keratometer, Oculus K5M and OFTA) were plotted based on the log transformed data (Figure 2.27) (for all NIBUT values).

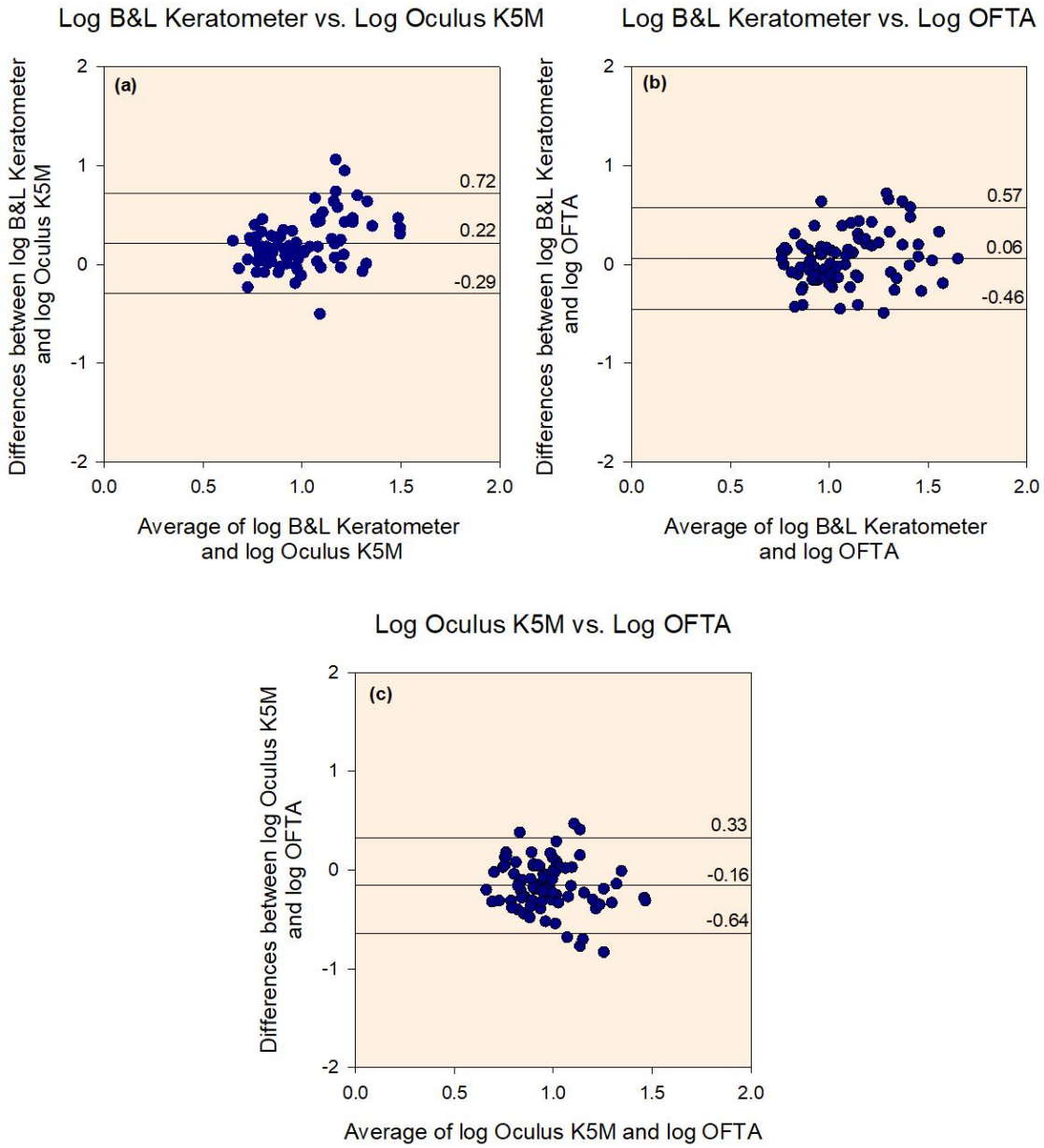


Figure 2.27: Bland and Altman plots of NIBUT (log transformed data, all NIBUT values) between (a) B&L Keratometer and Oculus K5M, (b) B&L Keratometer and OFTA, (c) Oculus K5M and OFTA.

Based on Figure 2.27, the Bland and Altman plots of the log transformed data (all NIBUT values) comparing log B&L Keratometer and log Oculus K5M showed a mean difference of 0.22 (back transformed 1.66), with Limits of Agreement (LoA) of -0.29 to 0.72 (back transformed 0.51 to 5.25). The mean difference between log B&L Keratometer and log OFTA was 0.06 (back transformed 1.15) with LoA of -0.46 to 0.57 (back transformed 0.35 to 3.72). Whilst the mean

difference between log Oculus K5M and log OFTA was -0.16 (back transformed 0.69) with a LoA of -0.64 to 0.33 (back transformed 0.23 to 2.14). Visually, heteroscedasticity was less evident in the transformed dataset, however, proportional bias was still present in the log transformed Bland and Altman plots assessing the B&L Keratometer and Oculus K5M (r_s=0.368, p=0.001). Using the calculated LoA, the range of possible expected NIBUT values can be seen in Table 2.4.

To enable the clinically relevant interpretation of these Bland and Altman plots, Table 2.4 was created (Cox et al., 2015). The measures listed under 'Oculus K5M Value' and 'OFTA Value' are values that could be obtained as NIBUT measurements. For each of these selected values, a corresponding column labelled 'Possible Range of B&L Keratometer Values' (Table 2.4a and Table 2.4b) and 'Possible Range of Oculus K5M Values' (Table 2.4c) provide a high and a low value based on the 95% LoA. For example (see Table 2.4a), a NIBUT value of 4 seconds at 'Oculus K5M Value' could produce a NIBUT of 2.04 to 21.00 seconds on the B&L Keratometer. Whereas a NIBUT value of 4 seconds at 'OFTA Value' (Table 2.4c) could produce a NIBUT of 0.92 to 8.56 seconds on the Oculus K5M.

(a) NIBUT (s)		
Oculus K5M Value	**Possible Range of B&L Keratometer Values**	
1	0.51	5.25
4	2.04	21.00
7	3.57	36.75
10	5.10	52.50
13	6.63	68.25
16	8.16	84.00
19	9.69	99.75
22	11.22	115.50
24	12.24	126.00

(b) NIBUT (s)		
OFTA Value	**Possible Range of B&L Keratometer Values**	
1	0.35	3.72
4	1.40	14.88
7	2.45	26.04
10	3.50	37.20
13	4.55	48.36
16	5.60	59.52
19	6.65	70.68
22	7.70	81.84
24	8.40	89.28

(c) NIBUT (s)		
OFTA Value	**Possible Range of Oculus K5M Values**	
1	0.23	2.14
4	0.92	8.56
7	1.61	14.98
10	2.30	21.40
13	2.99	27.82
16	3.68	34.24
19	4.37	40.66
22	5.06	47.08
24	5.52	51.36

Table 2.4: Range of NIBUT values when comparing (a) Oculus K5M and B&L Keratometer, (b) OFTA and B&L Keratometer, and (c) OFTA and Oculus K5M (all NIBUT values).

2.5.4 Results from only NIBUT data ≤24 seconds from Oculus K5M, B&L Keratometer and OFTA

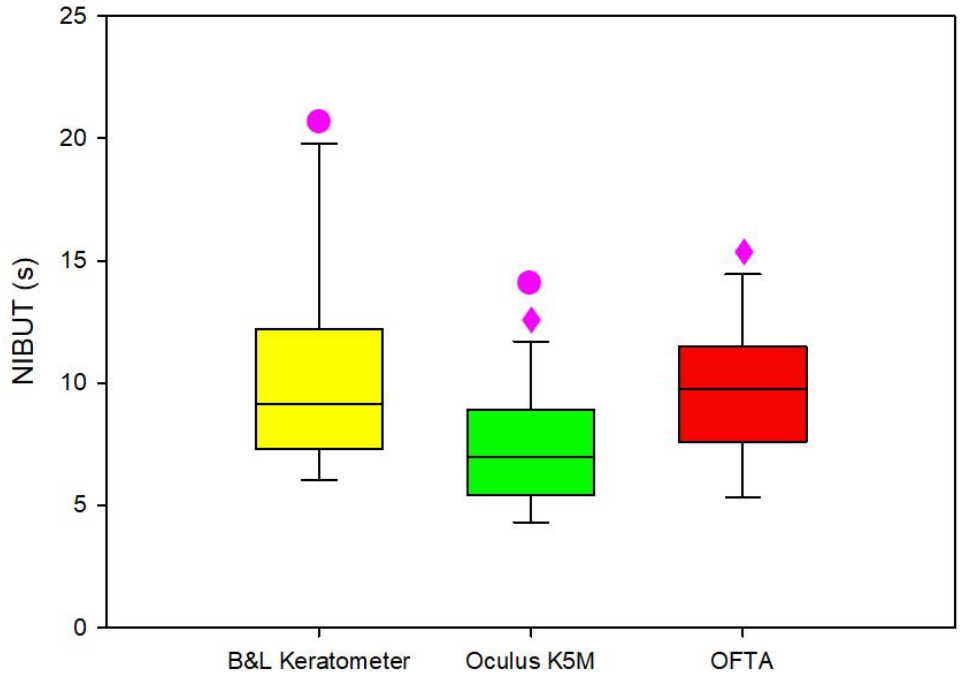
To account for the ceiling effect of the Oculus K5M potentially effecting the results observed the analysis was also conducted with NIBUT ≤24 seconds (Table 2.5). To account for the ceiling effect of the Oculus K5M potentially effecting the results observed, the analysis was also conducted with NIBUT ≤24 seconds (a subset of participants whose NIBUT values were greater than 24 seconds were excluded) (Table 2.5).

Instrument	**NIBUT (s), Mean±SD**		
	Visit 1 (n=65)	**Visit 2 (n=58)**	**Visit 3 (n=15)**
B&L Keratometer	10.82±4.91	9.83±4.15	9.72±5.26
Oculus K5M	7.89±3.63	8.69±4.37	9.90±4.57
OFTA	10.01±3.76	11.68±4.51	12.07±5.10

Table 2.5: NIBUT values ≤24 seconds during V1, V2 and V3 obtained using the 3 instruments.

2.5.5 Validity based on NIBUT data ≤24 seconds from Oculus K5M, B&L Keratometer and OFTA

When considering only NIBUT ≤24 seconds, a significant difference in median NIBUT between the 3 instruments was found [$\chi^2(2) = 21.262$, $p<0.0005$]. *Post-hoc* analysis revealed that NIBUT obtained with the Oculus K5M was significantly lower when compared to the B&L Keratometer (Z=0.754, $p_{adj}<0.0005$) and the OFTA (Z=-0.631, $p_{adj}=0.001$). However, the median NIBUT obtained using the OFTA and B&L Keratometer were not significantly different (Z=0.123, $p_{adj}=1.000$) (Figure 2.28).



Legends:

- B&L Keratometer.
- Oculus K5M.
- OFTA.
- Significant differences between Oculus K5M – B&L Keratometer.
- Significant differences between Oculus K5M – OFTA.

Figure 2.28: Box plot representing median and interquartile range for NIBUT on all 3 instruments during the first visit (V1) (only NIBUT ≤24 seconds).

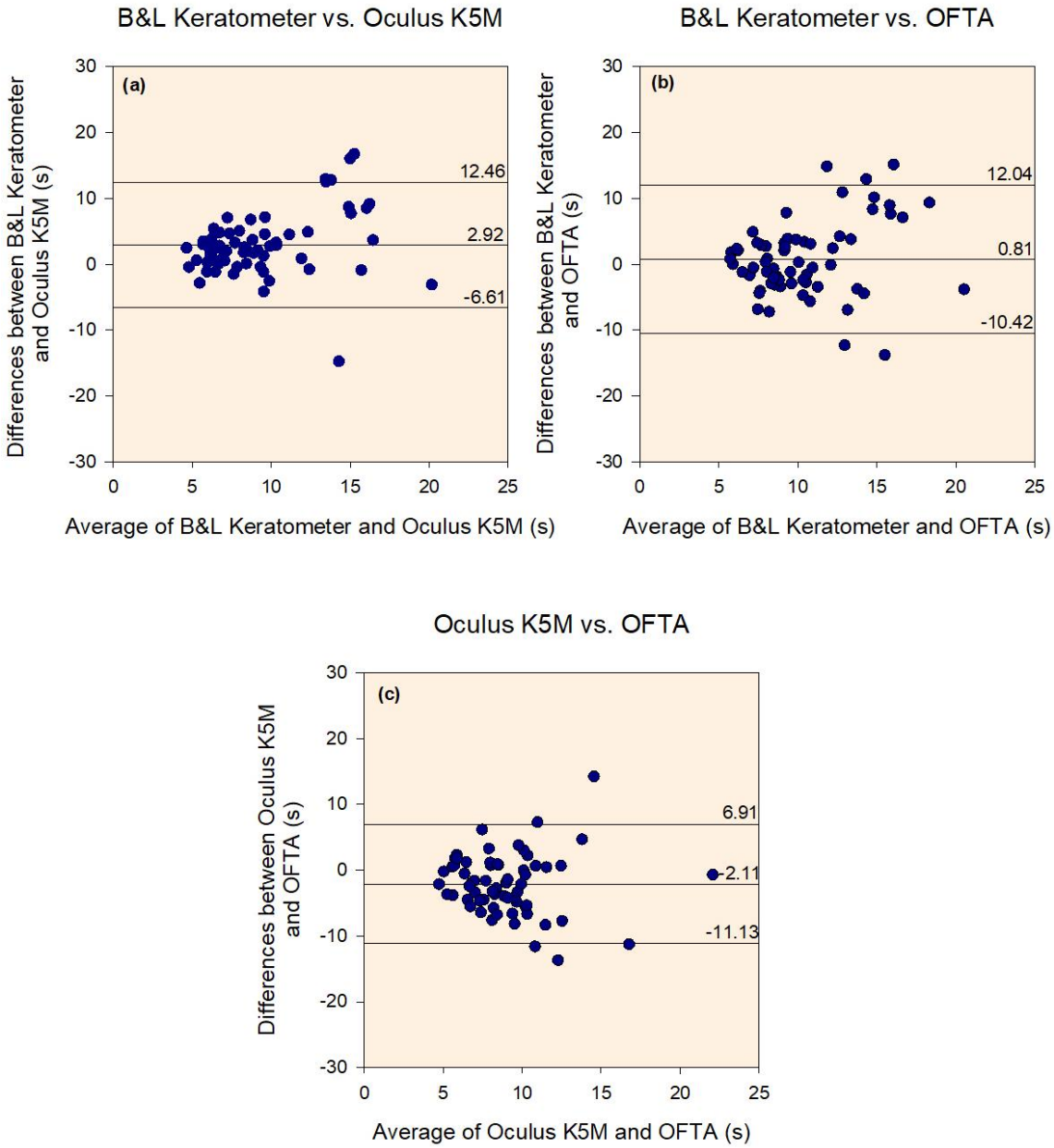


Figure 2.29: Bland and Altman plots of NIBUT (non-transformed data, only NIBUT ≤24 seconds) between (a) B&L Keratometer and Oculus K5M, (b) B&L Keratometer and OFTA, (c) Oculus K5M and OFTA.

Bland and Altman plots were replotted with NIBUT data ≤24 seconds (Fig 2.29). The graphs comparing B&L Keratometer and Oculus K5M showed a mean difference of 2.92 seconds, with Limits of Agreement (LoA) of -6.61 to 12.46 seconds (Figure 2.29). The mean difference between the B&L Keratometer vs. OFTA was 0.81 seconds with LoA of -10.42 to 12.04 seconds.

Whilst the mean difference between the Oculus K5M and OFTA was -2.11 seconds with a LoA of -11.13 to 6.91 seconds. The heteroscedasticity was still evident according to visual inspection, Kendall's τ showed a heteroscedasticity spread of the data on all but the Oculus K5M and OFTA plot (Table 2.6).

Parameter	Kendall's τ (Original Data)	Heteroscedastic (Yes or No)	Kendall's τ (Log Data)
V1 (B&L Keratometer vs Oculus K5M)	0.220	Yes	0.044
V1 (B&L Keratometer vs OFTA)	0.120	Yes	0.103
V1 (Oculus K5M vs OFTA)	-0.091	No	0.063

Table 2.6: Kendall's τ for original data (only NIBUT $\leq$24 seconds) and subsequent Kendall's τ after log transformation on the original data.

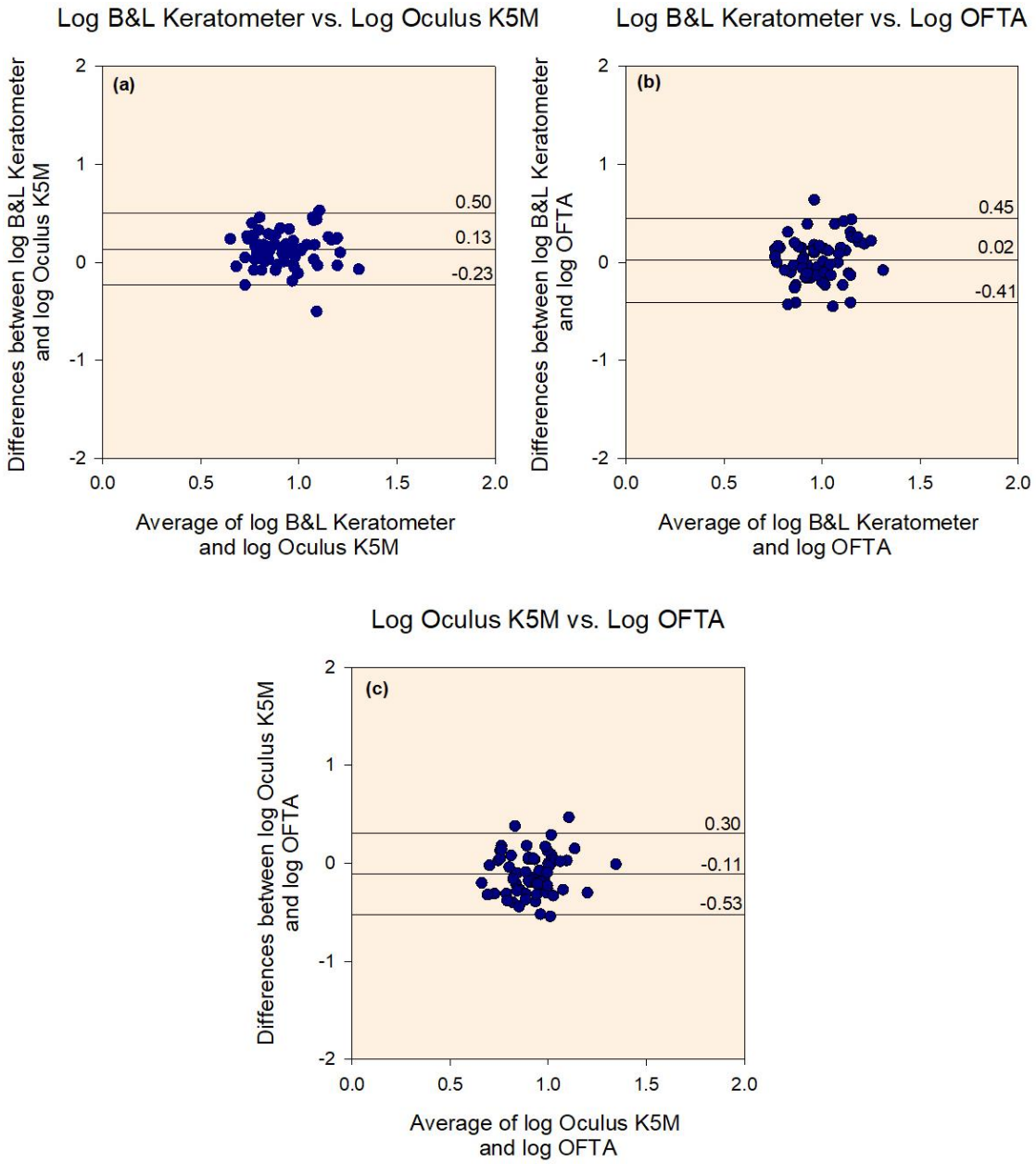


Figure 2.30: Bland and Altman plots of NIBUT (log transformed data, only NIBUT ≤24 seconds) between (a) B&L Keratometer and Oculus K5M, (b) B&L Keratometer and OFTA, (c) Oculus K5M and OFTA.

Based on Figure 2.30, the Bland and Altman plots of the log transformed data (NIBUT ≤24 seconds) comparing log B&L Keratometer and log Oculus K5M showed a mean difference of 0.13 (back transformed 1.35), with Limits of Agreement (LoA) of -0.23 to 0.50 (back transformed 0.59 to 3.16). The mean difference between log B&L Keratometer and log OFTA was 0.02 (back transformed 1.05) with LoA of -0.41 to 0.45 (back transformed 0.39 to 2.82).

Whilst the mean difference between log Oculus K5M and log OFTA was -0.11 (back transformed 0.78) with a LoA of -0.53 to 0.30 (back transformed 0.30 to 2.00). Using the calculated LoA, the range of possible expected NIBUT values can be seen in Table 2.7.

(a) NIBUT (s)		
Oculus K5M Value	**Range of B&L Keratometer Values**	
1	0.59	3.16
4	2.36	12.64
7	4.13	22.12
10	5.90	31.60
13	7.67	41.08
16	9.44	50.56
19	11.21	60.04
22	12.98	69.52
24	14.16	75.84

(b) NIBUT (s)		
OFTA Value	**Range of B&L Keratometer Values**	
1	0.39	2.82
4	1.56	11.28
7	2.73	19.74
10	3.90	28.20
13	5.07	36.66
16	6.24	45.12
19	7.41	53.58
22	8.58	62.04
24	9.36	67.68

(c) NIBUT (s)		
OFTA Value	**Range of Oculus K5M Values**	
1	0.30	2.00
4	1.20	8.00
7	2.10	14.00
10	3.00	20.00
13	3.90	26.00
16	4.80	32.00
19	5.70	38.00
22	6.60	44.00
24	7.20	48.00

Table 2.7: Range of NIBUT values when comparing (a) Oculus K5M and B&L Keratometer, (b) OFTA and B&L Keratometer and (c) OFTA and Oculus K5M (NIBUT values $\leq$24 seconds).

2.5.6 Reliability

The reliability (intra-observer ICC) for the 3 instruments (for all NIBUT values) are shown in Table 2.8. The OFTA demonstrated the highest intra-observer ICC values while the Oculus K5M was found to have the least intra-observer ICC values.

Instruments	ICC Value	Confidence Intervals
B&L Keratometer	0.365	-0.593 to 0.748
Oculus K5M	0.270	-0.569 to 0.517
OFTA	0.566	-0.120 to 0.830

Table 2.8: Intra-observer ICC values for all instruments assessed.

In addition, the reliability of the B&L Keratometer, Oculus K5M and OFTA NIBUT was assessed using Bland and Altman plots (Appendix I). Heteroscedasticity was confirmed based on Kendall's tau calculations (Appendix I) and the visual inspection of the Bland and Altman plots, log transformed Bland and Altman reliability plots were plotted for 'all NIBUT values' (Figure 2.31) and 'only NIBUT ≤24 seconds' (Figure 2.32).

2.5.6.1 Reliability all NIBUT Values

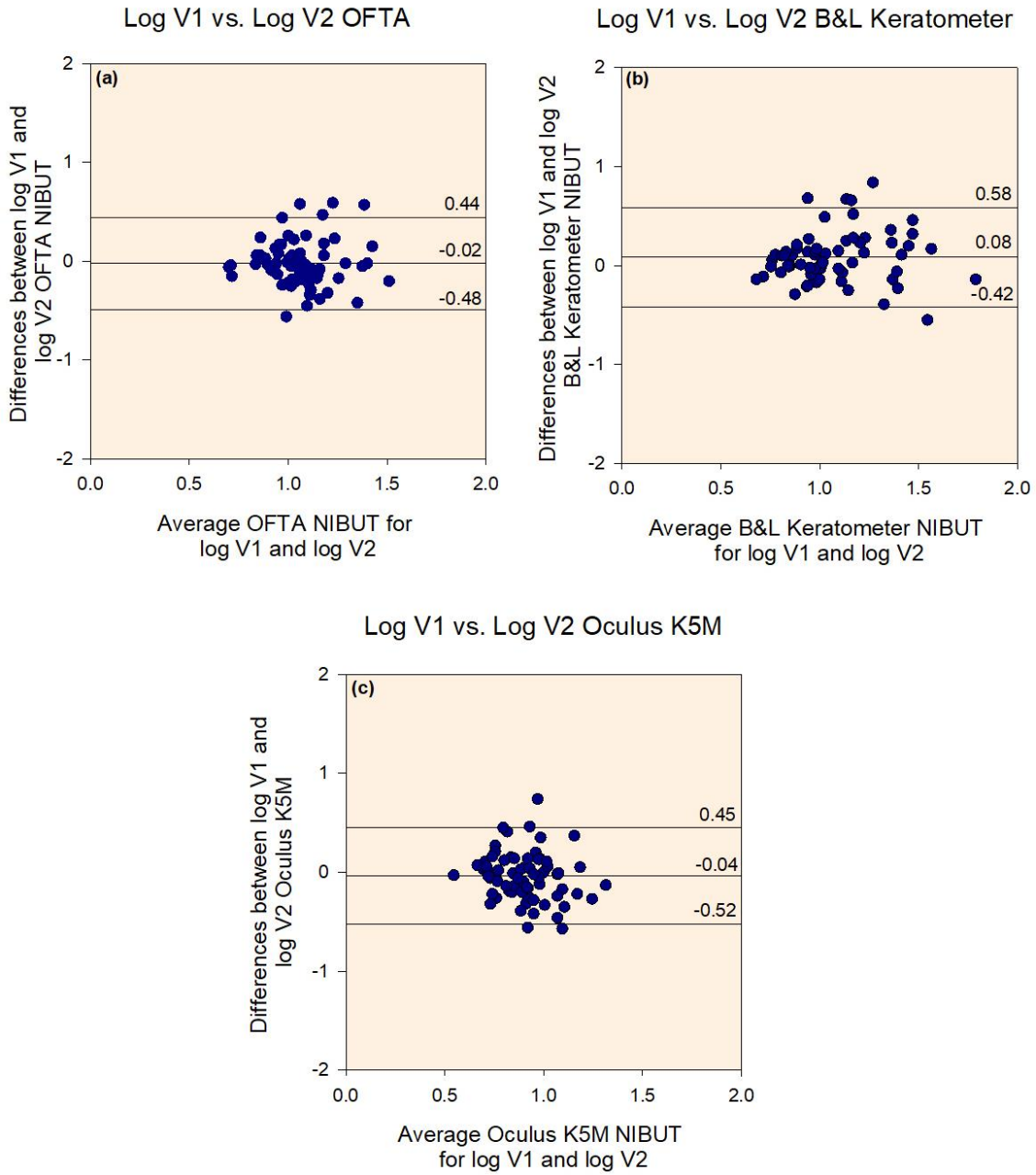


Figure 2.31: Bland and Altman reliability plots of NIBUT (log transformed data, all NIBUT values) between V1 and V2 for (a) OFTA, (b) B&L Keratometer, (c) Oculus K5M.

Bland and Altman plots of the log transformed OFTA (Figure 2.31) had a mean difference of -0.02 (back transformed 0.95), with LoA of 0.44 to -0.48 (back transformed 0.33 to 2.74). The mean difference for B&L Keratometer (all NIBUT values) during V1 and V2 was 0.08 (back transformed 1.21), with LoA of 0.58 to -0.42 (back transformed 0.38 to 3.83). The mean difference for Oculus K5M (all NIBUT values) during V1 and V2 was -0.04 (back transformed 0.92), with LoA between 0.45 to –0.52 (back transformed 0.30 to 2.81). Using the calculated LoA, the range of possible expected NIBUT values can be seen in Table 2.9. The measures listed under 'Visit 1 Values' are values that could be obtained as NIBUT measurements using the OFTA, B&L Keratometer and Oculus K5M during Visit 1. For each of these selected values, a corresponding column labelled 'Possible Range of Values at Visit 2' provides a high value and a low value that is based on the 95% LoA. For example (Table 2.9a), an OFTA NIBUT value of 4 seconds during Visit 1 could produce an OFTA NIBUT of 1.32 to 10.96 seconds during Visit 2; (Table 2.9c) an Oculus K5M NIBUT value of 4 seconds at Visit 1 could produce an Oculus K5M NIBUT of 1.20 to 11.24 seconds during Visit 2.

(a) OFTA NIBUT (s)		
Visit 1 Values	**Possible Range of Values at Visit 2**	
1	0.33	2.74
4	1.32	10.96
7	2.31	19.18
10	3.30	27.40
13	4.29	35.62
16	5.28	43.84
19	6.27	52.06
22	7.26	60.28
24	7.92	65.76

(b) B&L Keratometer NIBUT (s)		
Visit 1 Values	**Possible Range of Values at Visit 2**	
1	0.38	3.83
4	1.52	15.32
7	2.66	26.81
10	3.80	38.30
13	4.94	49.79
16	6.08	61.28
19	7.22	72.77
22	8.36	84.26
24	9.12	91.92

(c) Oculus K5M NIBUT (s)		
Visit 1 Values	**Possible Range of Values at Visit 2**	
1	0.30	2.81
4	1.20	11.24
7	2.10	19.67
10	3.00	28.10
13	3.90	36.53
16	4.80	44.96
19	5.70	53.39
22	6.60	61.82
24	7.20	67.44

Table 2.9: NIBUT values at Visit 1 and possible expected NIBUT values at Visit 2 for (a) OFTA, (b) B&L Keratometer and (c) Oculus K5M (all NIBUT values).

2.5.6.2 Reliability NIBUT Values ≤24 seconds

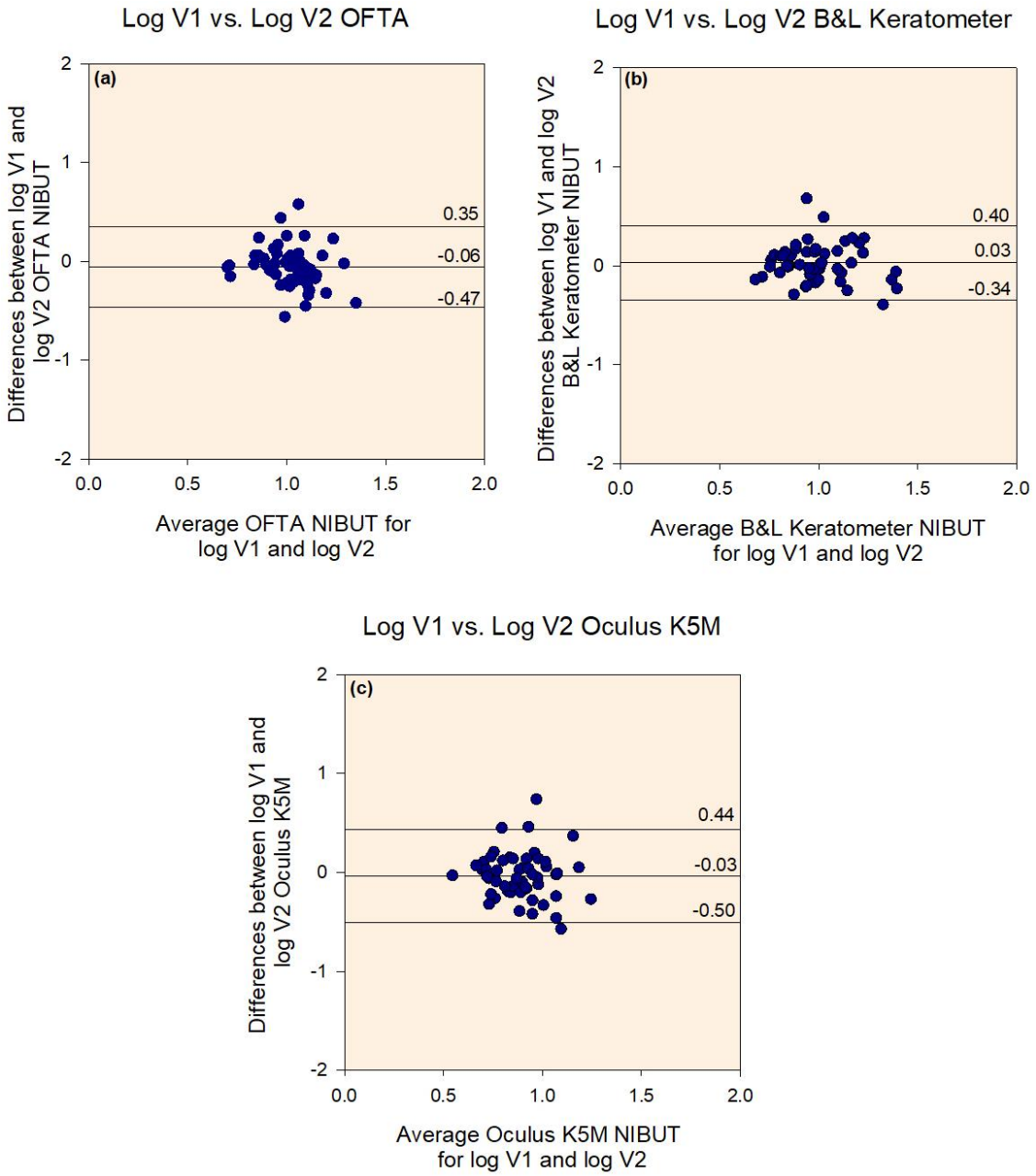


Figure 2.32: Bland and Altman reliability plots of NIBUT (log transformed data, only NIBUT ≤24 seconds) between V1 and V2 for (a) OFTA, (b) B&L Keratometer, (c) Oculus K5M.

Bland and Altman plots for the reliability data were replotted with NIBUT data ≤24 seconds (Fig 2.32). For the OFTA (Fig 2.32a) the mean difference for V1 and V2 was -0.06 (back transformed 0.88), with LoA of 0.35 to -0.47 (back transformed 0.34 to 2.25). The mean difference for the B&L Keratometer (Fig 2.32b) during V1 and V2 was 0.03 (back transformed

1.07), with LoA of 0.40 to -0.34 (back transformed 0.45 to 2.54). Whilst the mean difference for Oculus K5M (Fig 2.32c) during V1 and V2 was -0.03 (back transformed 0.93), with LoA between 0.44 to -0.50 (back transformed 0.31 to 2.75). Using the calculated LoA, the range of possible expected NIBUT values can be seen in Table 2.10.

(a) OFTA NIBUT (s)		
Visit 1 Values	**Possible Range of Values at Visit 2**	
1	0.34	2.25
4	1.36	9.00
7	2.38	15.75
10	3.40	22.50
13	4.42	29.25
16	5.44	36.00
19	6.46	42.75
22	7.48	49.50
24	8.16	54.00

(b) B&L Keratometer NIBUT (s)		
Visit 1 Values	**Possible Range of Values at Visit 2**	
1	0.45	2.54
4	1.80	10.16
7	3.15	17.78
10	4.50	25.40
13	5.85	33.02
16	7.20	40.64
19	8.55	48.26
22	9.90	55.88
24	10.80	60.96

(c) Oculus K5M NIBUT (s)		
Visit 1 Values	**Possible Range of Values at Visit 2**	
1	0.31	2.75
4	1.24	11.00
7	2.17	19.25
10	3.10	27.5
13	4.03	35.75
16	4.96	44.00
19	5.89	52.25
22	6.82	60.50
24	7.44	66.00

Table 2.10: NIBUT values at Visit 1 and possible expected NIBUT values at Visit 2 for the (a) OFTA, (b) B&L Keratometer and (c) Oculus K5M (NIBUT $\leq$24 seconds).

2.5.7 Reproducibility

The reproducibility (inter-observer ICC) for the 3 instruments (for all NIBUT values) were shown in Table 2.11. The OFTA demonstrated the highest inter-observer ICC values while the Oculus K5M was found to have the least inter-observer ICC values.

Instruments	ICC Value	Confidence Intervals
B&L Keratometer	0.494	-0.330 to 0.803
Oculus K5M	0.298	-0.490 to 0.700
OFTA	0.559	-0.052 to 0.821

Table 2.11: Inter-observer ICC values for all instruments.

In addition, the reproducibility of the B&L Keratometer, Oculus K5M and OFTA NIBUT during V1 and V3 was assessed using Bland and Altman plots (Appendix I). Kendall's tau (τ) was calculated for each plot, which suggested a homoscedastic pattern. However, visual inspection of the data revealed a heteroscedastic distribution (Appendix I). Bland and Altman plots, log transformed Bland and Altman reliability plots were plotted for 'all NIBUT values' (Figure 2.33) and 'NIBUT $\leq$24 seconds' (Figure 2.34).

2.5.7.1 Reproducibility all NIBUT Values

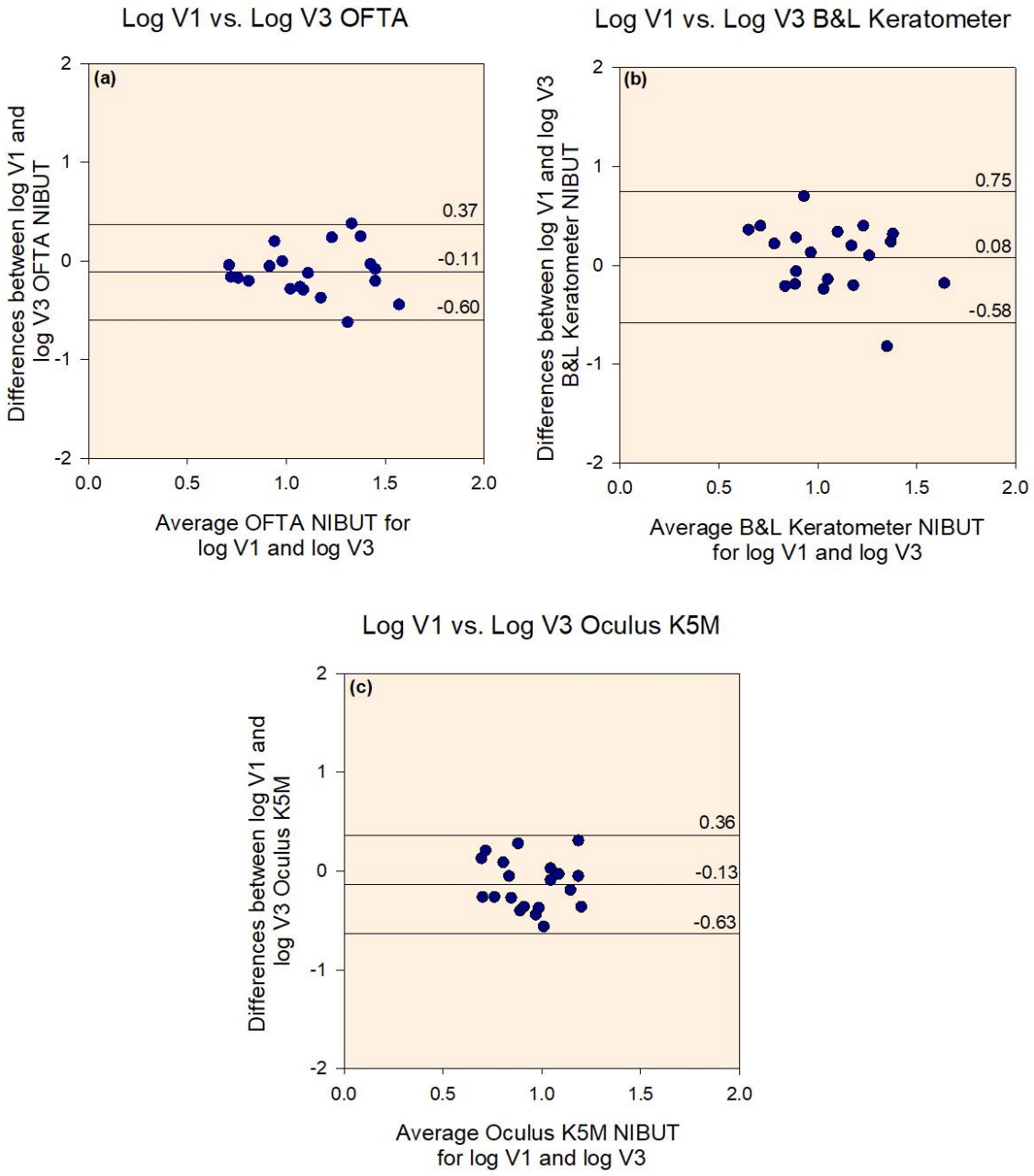


Figure 2.33: Bland and Altman reproducibility plots of NIBUT (log transformed data, all NIBUT values) between V1 and V3 for (a) OFTA, (b) B&L Keratometer, (c) Oculus K5M.

Based on all NIBUT vales, Figure 2.33 shows the reproducibility of the log transformed OFTA had a mean difference of -0.11 (back transformed 0.77), with LoA of 0.37 to -0.60 (back transformed 0.25 to 2.36). The mean difference for B&L Keratometer during V1 and V3 was 0.08 (back transformed 1.21), with LoA of 0.75 to -0.58 (back transformed 0.26 to 5.57). The

mean difference for Oculus K5M during V1 and V3 was -0.13 (back transformed 0.74), with LoA between 0.36 to –0.63 (back transformed 0.24 to 2.31). Using the calculated LoA, the range of possible expected NIBUT values can be seen in Table 2.12.

(a) OFTA NIBUT (s)		
Visit 1 Values	**Possible Range of Values at Visit 3**	
1	0.25	2.36
4	1.00	9.44
7	1.75	16.52
10	2.50	23.60
13	3.25	30.68
16	4.00	37.76
19	4.75	44.84
22	5.50	51.92
24	6.00	56.64

(b) B&L Keratometer NIBUT (s)		
Visit 1 Values	**Possible Range of Values at Visit 3**	
1	0.75	5.57
4	3.00	22.28
7	5.25	38.99
10	7.50	55.70
13	9.75	72.41
16	12.00	89.12
19	14.25	105.83
22	16.50	122.54
24	18.00	133.68

(c) Oculus K5M NIBUT (s)		
Visit 1 Values	**Possible Range of Values at Visit 3**	
1	0.24	2.31
4	0.96	9.24
7	1.68	16.17
10	2.40	23.10
13	3.12	30.03
16	3.84	36.96
19	4.56	43.89
22	5.28	50.82
24	5.76	55.44

Table 2.12: NIBUT values at Visit 1 and possible expected NIBUT values at Visit 3 for the (a) OFTA, (b) B&L Keratometer and (c) Oculus K5M (all NIBUT values).

2.5.7.2 Reproducibility NIBUT Values ≤24 seconds

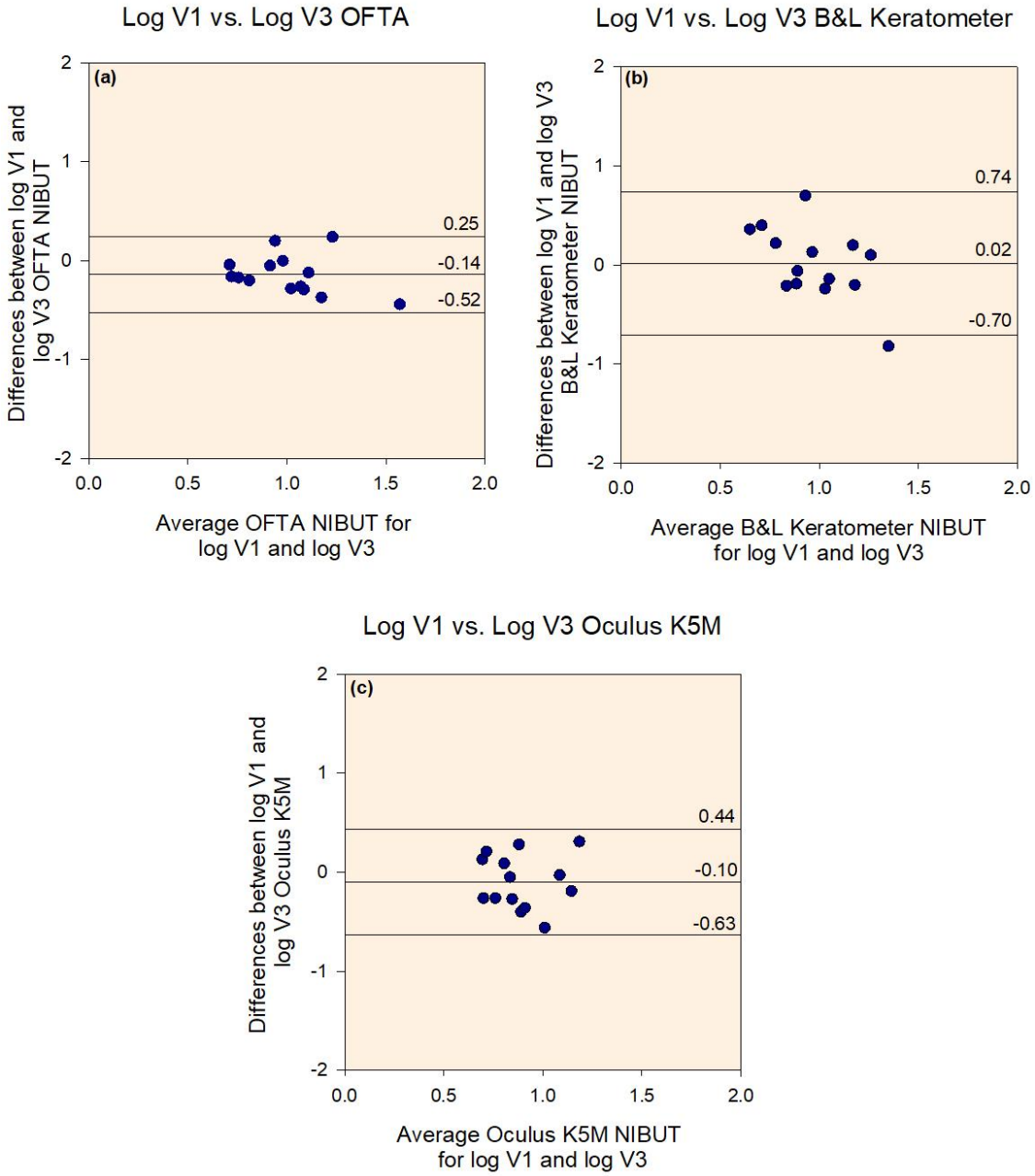


Figure 2.34: Bland and Altman reproducibility plots of NIBUT (log transformed data, only NIBUT ≤24 seconds) between V1 and V3 for (a) OFTA, (b) B&L Keratometer, (c) Oculus K5M.

Based on the NIBUT values ≤24 seconds, (Figure 2.34) Bland and Altman plots of the log transformed OFTA had a mean difference of -0.14 (back transformed 0.73), with LoA of 0.25 to -0.52 (back transformed 0.30 to 1.76). The mean difference for B&L Keratometer during V1 and V3 was 0.02 (back transformed 1.04), with LoA of 0.74 to -0.70 (back transformed 0.20 to

5.49). The mean difference for Oculus K5M during V1 and V3 was -0.10 (back transformed 0.80), with LoA between 0.44 to –0.63 (back transformed 0.23 to 2.73). Using the calculated LoA, the range of possible expected NIBUT values can be seen in Table 2.13.

(a) OFTA NIBUT (s)		
Visit 1 Values	**Possible Range of Values at Visit 3**	
1	0.30	1.76
4	1.20	7.04
7	2.10	12.32
10	3.00	17.60
13	3.90	22.88
16	4.80	28.16
19	5.70	33.44
22	6.60	38.72
24	7.20	42.24

(b) B&L Keratometer NIBUT (s)		
Visit 1 Values	**Possible Range of Values at Visit 3**	
1	0.20	5.49
4	0.80	21.96
7	1.40	38.43
10	2.00	54.90
13	2.60	71.37
16	3.20	87.84
19	3.80	104.31
22	4.40	120.78
24	4.48	131.76

(c) Oculus K5M NIBUT (s)		
Visit 1 Values	**Possible Range of Values at Visit 3**	
1	0.23	2.73
4	0.92	10.92
7	1.61	19.11
10	2.30	27.30
13	2.99	35.49
16	3.68	43.68
19	4.37	51.87
22	5.06	60.06
24	5.52	65.52

Table 2.13: NIBUT values at Visit 1 and possible expected NIBUT values at Visit 3 for the (a) OFTA, (b) B&L Keratometer and (c) Oculus K5M (NIBUT $\leq$24 seconds).

2.6 Discussion

2.6.1 Introduction

The working principles of the three devices (B&L Keratometer, Oculus K5M and OFTA) used to assess the NIBUT are very similar; all are based upon projection of a light source onto the cornea and imaging the Purkinje image/grids/mires reflected from the tear film. In contrast, the method by which the NIBUT is determined differs; the B&L Keratometer and OFTA measures are based upon subjective endpoints whilst the Oculus K5M utilizes image analysis to detect an objective endpoint.

2.6.2 Validity

The longest NIBUT values were obtained with the B&L Keratometer. Discrepancies in NIBUT measures between devices may be partly explained by considering the area of cornea that is observed with each instrument. Both the OFTA and Oculus K5M project the mires across both the central and peripheral cornea. However, the B&L keratometer only observes the central area of the cornea and hence, is unable to detect tear break-up that occurs across the peripheral cornea. In comparison, the Oculus K5M provided the shortest NIBUT values which may be explained when considering both the hardware and software of the system. This was the only objective system for determining the endpoint and it is possible that the Oculus K5M software may be interpreting interferences in the image captured as breaks in the tears (Best et al., 2012). In addition, the image quality attained by the camera of the Oculus K5M is superior to that of the OFTA, which is likely to have increased the sensitivity of tear break-up time detection. Furthermore, the shorter NIBUT values obtained with the Oculus K5M can also be attributed to the maximum time limit of 24 seconds, thus, creating a ceiling effect that reduced the overall median NIBUT time.

The NIBUT Bland and Altman plots comparing the results from each device showed significant heteroscedasticity. Hence the data was log transformed in accordance with Cox et al., (2015) and Best et al., (2012) who also found heteroscedasticity with NIBUT measurements. Table 2.11 provides an overview of the limits of agreement across a range of NIBUT values. This provides a reference point to determine the clinical significance of the transformed Bland and Altman results. The table reveals the gross variability between the results from the Oculus K5M and from NIBUT values obtained using the B&L Keratometer. For example, if a NIBUT value of 10 seconds is attained from the Oculus K5M, then the range of possible values

attained using the B&L Keratometer, according to the limits of agreement, could vary between 5.10 and 52.50 seconds (Table 2.4). In comparison, the range of possible values of the Oculus K5M are between 2.30 and 21.40 seconds when a value of 10 seconds is found with the OFTA (Table 2.4).

Significant proportional bias was observed between the 'B&L Keratometer and Oculus K5M' (Figure 2.26a) and the 'OFTA and Oculus K5M' (Figure 2.26c). This is still evident (Figure 2.27a) following the transformation of data when examining the B&L Keratometer and the Oculus K5M (r_S=0.368, p=0.001). As the mean NIBUT value increased, the mean differences in NIBUT values increases with the results from the B&L Keratometer increasing greater than that of the Oculus K5M (Figure 2.26). We hypothesize that this proportional bias was partly caused by the 'ceiling effect' of the Oculus K5M, whereby the instrument stops measuring the NIBUT if the eye was opened for longer than 24 seconds, with no tear break-up occurring within that period of time. Thus, a separate set of Bland and Altman plots were created with all values breaching this 24-second ceiling being excluded. This removed the proportional bias however, heteroscedasticity still prevailed (Figure 2.29) and hence the data was log transformed. This reduced data set (Table 2.5) revealed the same trends as the data when those values above 24 seconds were included: the Oculus K5M and OFTA had the most similar results, followed by those from the B&L Keratometer and OFTA, with the Oculus K5M and B&L Keratometer showing the most discrepancy. However, the disparity of the limits of agreement between the Oculus K5M and B&L Keratometer were closer (5.90 to 31.60 seconds for a 10 second Oculus K5M value) (Table 2.7). Furthermore, heteroscedasticity was present in the plot comparing the results from the OFTA and B&L Keratometer. The results suggest that the variability of NIBUT results increases with higher NIBUT values.

Based on Table 2.4 and Table 2.6, the possible range of NIBUT values obtained from the B&L Keratometer was larger compared to possible range of NIBUT values obtained using the Oculus K5M. The results suggest that the OFTA provides a better NIBUT measurement as the 95% limits of agreement are much narrower compared to the other 2 instruments.

The unacceptably wide limits of agreement, along with the fact that there was a significant difference in NIBUT observed in the Friedman's test, indicate that the results from the Oculus K5M are not interchangeable with those of the B&L Keratometer and OFTA. The NIBUT values obtained from the OFTA and Oculus K5M are the most comparable but still demonstrate discrepancy when considering higher NIBUT values.

2.6.3 Reliability and Reproducibility

All ICC values obtained in this study were far from the acceptable minimum of 0.75 for a good agreement (Landis & Koch, 1977; Rankin & Stokes, 1998; Field, 2005; Koo & Li, 2016). The highest intra- and inter-observer ICC values were observed with the OFTA (Table 2.8 and Table 2.11). The Bland and Altman plots for reliability (Figure 2.31) revealed similar limits of agreement for the OFTA (3.30 to 27.40 seconds for a Visit 2 NIBUT value of 10 seconds) and Oculus K5M (3.00 to 28.10 seconds for a Visit 1 NIBUT value of 10 seconds), whereas the limits of agreement when using the B&L Keratometer showed a greater spread (3.80 to 38.30 seconds for a Visit 1 value of 10 seconds) (Table 2.9). Interestingly, the Intra-observer ICC values were greater for the OFTA than both the B&L Keratometer and the Oculus K5M (Table 2.8).

When examining the reproducibility of the three devices and comparing the NIBUT values at Visit 1 and the possible range of NIBUT values at Visit 3, the OFTA NIBUT and Oculus K5M NIBUT showed similar 95% LoA whereas the B&L Keratometer NIBUT 95% LoAs were

unacceptably wide (Table 2.12). When those values above 24 seconds were excluded (Table 2.13), the OFTA demonstrated the narrowest 95% LoAs suggesting that within this range, the OFTA has better repeatability and reproducibility compared to the other 2 instruments. In addition, the inter-observer ICC values for the OFTA were greater than that of the Oculus K5M (Table 2.11). It is well known that measures of NIBUT show significant variability and while every care was taken to ensure that the NIBUT being measured was stable, normal day to day variation in the tear film may have affected our analysis.

2.7 Conclusion

This study concluded that:

- The OFTA demonstrated higher levels of inter- and intra-observer repeatability relative to those found with the Oculus K5M and the B&L Keratometer.
- The B&L Keratometer demonstrated the greatest disparity of NIBUT values when compared to the OFTA and Oculus K5M.
- There was a significant difference in NIBUT results between the Oculus K5M and both the B&L Keratometer and OFTA.

Chapter 3: Osmolarity Changes Following the Use of Smartphones

3.1 Introduction

Dry eye was recently defined as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the cornea and conjunctiva (Craig et al., 2017). In addition, the condition was also associated with increased osmolarity of the tear film as well as inflammation of the ocular surface (Gary, 2007). Neurosensory abnormalities have also been observed to contribute to the aetiology of dry eye since a reduction in tear secretion causes inflammation and peripheral nerve damage (Belmonte et al., 2017). Consequently this inflammation causes sensitization of polymodal and mechano-nociceptor nerve endings which leads to a sensation of dryness and pain (Belmonte et al., 2017).

The prevalence of dry eye varies widely across the world ranging from 0.39% to 50%, depending on the study population (Chia et al., 2003; Doughty et al., 1997; Jamaliah & Fathilah 2002; Lin et al., 2003; Moss et al., 2000; Stapleton et al., 2017; Schaumberg et al., 2003). Notably, the occurrences of dry eye has increased concurrently with the growing use of VDT (Kawashima et al., 2014; Kojima et al., 2011; Nakamura et al., 2010; Uchino et al., 2008, 2014; Uchino et al., 2014), and has become a significant health issue affecting the quality of life in industrialized countries (Miljanović et al., 2007; World Health Organization, 1987). In an epidemiologic study involving Japanese office workers using VDT, the prevalence of clinically diagnosed dry eye was 10.1% in males and 21.5% in females; severe symptoms of dry eye were observed amongst 26.9% males and 18.7% females (Uchino et al., 2008). Length of VDT usage contributes to dry eye; <2 hours of VDT use had a lower prevalence of dry eye (31.1%) compared to >4 hour of VDT use (41.1%) (Uchino et al., 2008).

The tear film stability is influenced indirectly by the types of visual task performed. Several studies have demonstrated that visual tasks that require higher level of cognitive demand are accompanied by a longer inter blink interval (IBI) (Himebaugh et al., 2009; Holland & Tarlow, 1972; Stern et al., 1984). Consequently, a longer IBI leads to greater periods of ocular surface exposure which is associated with higher levels of evaporation causing symptoms of dry eye (Willcox et al., 2017; Wolkoff et al., 2005).

Various methods can be employed to screen for the presence of dry eye. These methods include; subjective questionnaires such as the McMonnies (Gothwal et al., 2010; Nichols et al., 2004b), Ocular Surface Disease Index (OSDI) (Schiffman et al., 2000; Dougherty et al., 2011) and Ocular Comfort Index (OCI) (Johnson & Murphy, 2007). Other methods of detecting dry eyes include fluorescein tear break up time (Pult & Riede-Pult, 2012), non-invasive tear break up time (Wang et al., 2017), Schirmer test (Li et al., 2012), tear ferning (Masmali et al., 2014) and tear osmolarity (Wong et al., 2017). It is generally accepted that the clinical assessment of dry eye is confounded by the inherent variability of the tear film (Mohidin et al., 2002; Briggs, 1998; Brown & Cho, 1994), the influence of environmental factors (Abusharha & Pearce, 2016; González-García et al., 2007; Paschides et al., 1998; Purslow & Wolffsohn, 2007) as well as the subjective nature of the clinical measurements (Cho & Douthwaite, 1995; Mengher et al., 1985). Tear osmolarity is the only objective method of investigating the balance between tear production, evaporation, drainage and absorption (Tomlinson & Khanal, 2005). It has been shown to be a reliable method for diagnosing and grading dry eye and can also be used to monitor the effectiveness of therapeutic interventions (Foulks & Pflugfelder, 2014). Furthermore, tear osmolarity measurements demonstrate higher repeatability and validity when compared to subjective questionnaires for the assessment of dry eye (Fenga et

al., 2014). Specifically, a condition called hyper osmolarity (high tear osmolarity value) is considered to be indicative of dry eye (Craig et al., 2017) and is considered to be the single best marker for dry eye disease (Farris, 1994; Tomlinson et al., 2010). Despite its diagnostic value the test does not provide a real-time and continuous assessment of the tear film and only provides a single sample at a given time.

In regards to dry eye associated with VDT use, one study observed that engaging in VDT use for more than 3 hours was associated with significantly higher tear osmolarity (Julio et al., 2012). Similarly, Chu et al., (2013) reported that prolonged daily computer use of more than 6.55 hours caused a significant increase in tear osmolarity. Smart devices i.e. smartphones, tablets, watches, can be considered to be analogous to VDT screens and with their growing vocational and non-vocational use, it may be postulated that the prevalence of dry eye will also increase. As discussed in Chapter 1, there is a significant lack of literature investigating the effects of smart devices on the anterior ocular surface. In view of the continuing popularity of smart devices amongst all age groups, it is of significant clinical interest to evaluate the potential impact these devices may have on the eye.

3.2 Objective

The study presented in this chapter is a prospective, repeated measures study design that aims to evaluate tear osmolarity following smart device use. The primary objectives of the investigation was to determine the influence of various electronic display platforms (Apple iPhone 6, Apple iPhone 6S, Samsung Galaxy S6, paper, Nokia 5210 and Apple Smart Watch) on tear osmolarity following engagement with a reading and game task. The platforms were chosen as they represent the different sizes and display characteristics of smart devices (see Appendix F).

In regards to the choice of the task being performed on the smart devices, consideration was given to differences in cognitive load of different tasks as it has been shown to affect the blink rate (Holland & Tarlow, 1972, 1975; Wong et al., 2002). It is unclear if such differences in cognitive demand translate into clinical differences in the tear film quality as a consequence of the altered blink rate. Game playing is associated with problem solving and reasoning which is associated with conscious cognitive processes involving the participant's working memory (Kalyuga & Plass, 2008). Furthermore the task requires physical engagement with the device and differences in the nature of the game from being competitive, immersive and the strong emotional impact they may have, all contribute to the participant's cognition (Kalyuga & Plass, 2008; Bavelier et al., 2011; Granic et al., 2014; Lee & Heeter, 2017). In contrast, reading may be considered to be a more passive activity which although requires cognitive and memory processing, does not require physical engagement from the participant and thus, is expected to require lesser cognitive load compared to game playing. Reading is an activity for which intensive practice is generally recognised as beneficial for academic performance (Cunningham & Stanovich, 1991). In comparison to gaming, the more important mechanism that governs reading is the breadth of vocabulary (Cunningham & Stanovich, 1991). Since reading and gaming tasks are the most common activities performed on smartphones (Cloud, 2014; Haug et al., 2015; Li et al., 2015; Liu et al., 2016; Deloitte, 2017; Ofcom, 2017; Lopez-Fernandez et al., 2018) these were assessed in this study.

3.3 Methods

3.3.1 Ethical Approval

Ethical approval was obtained from Research Ethics Committee, Faculty of Health & Human Sciences and Peninsula School of Medicine & Dentistry, Plymouth University (Appendix B, reference number 15/16-468). Prior to the start of data collection, participants were fully

informed of the experiment and all relevant questions were answered accordingly. Written consent was obtained before the start of data collection.

3.3.2 Sample Size

The sample size was calculated using the software G*Power, version 3.1.9.2 (Prajapati et al., 2010; Faul et al., 2007). Previous studies examining osmolarity have used variable sample sizes (ranging from 10 to 52 participants) (Utine et al., 2011; Gokhale et al., 2013; Koktekir et al., 2014; Öncel et al., 2012b). Sample size calculations for this study were based upon a repeated measures ANOVA model with a moderate effect size of 0.25 (Cohen, 1992; Cohen, 1988), a significance level of $p<0.05$ with a power of 80%. According to the G*Power calculations, a total sample size of 30 participants were required for this experiment.

3.3.3 Inclusion and Exclusion Criteria

Participants were recruited from the staff and student population of Plymouth University using convenience sampling. The inclusion and exclusion criteria of the study are listed below.

3.3.3.1 Inclusion Criteria

- Completed a comprehensive eye examination within the last 12 months.
- Rigid gas permeable contact lens wear ceased for a minimum of 1 week.
- Aged between 18 and 35 years old.
- Soft contact lens wear ceased for a minimum of 2 days.
- Able to see decimal 0.50 at 30 cm (Snellen 6/12).
- A minimum of 6.50 D accommodation.
    - The target was displayed at a distance of 30 cm corresponding to 3.33 D.
    - Previous studies have suggested that for sustained reading either 50% (Millodot & Millodot, 1989), 66% (Vilupuru et al., 2005) or 80% (Wolffsohn et al., 2011); 80% of the total amplitude of accommodation is required to be kept in reserve for sustained viewing of a near target. When viewing a target at 30 cm this

corresponds to either 6.66D, 5.05D or 4.16D, respectively (Millodot & Millodot, 1989; Vilupuru et al., 2005; Wolffsohn et al., 2011). Considering the study required multiple near vision tasks, a liberal minimum amplitude of accommodation of 6.50 D was required.

- Willing to participate in the study.

3.3.3.2 Exclusion Criteria

- History of any form of ocular surgery including LASIK.
- Participation in a pharmacological studies occurring concurrently.
- Suffering any form of ocular or systemic diseases.
- Pregnant or breast feeding.
- Taking medications.

3.3.4 Measurement of Tear Osmolarity

Tear osmolarity is measured in milliosmoles per litre (mOsm/L) and values between 275 and 308 mOsm/L are considered to be normal (Lemp et al., 2011). In this study, measurements of tear osmolarity were obtained using the TearLab® osmometer (OcuSense Inc., San Diego, CA) (Figure 3.1); a non-invasive instrument that utilizes the principle of electrical impedance to assess the tear osmolarity (Sollanek et al., 2012). The TearLab allows rapid determination of osmolarity from micro samples with an *in vitro* error margin of 1-2% (Lemp et al., 2011).

Measurements from the TearLab have been found to correlate well with the Clifton osmometer (Clifton Technical Physics, Hartford, NY): A gold standard osmometer that utilizes freezing point depression to measure tear osmolarity (Tomlinson et al., 2010). The TearLab demonstrates good repeatability and validity even when solutions of high salt content are measured (Yoon et al., 2014). Recently, Rocha et al., (2017) demonstrated that the TearLab showed improved accuracy and precision in measuring osmolarity of contrived tear solutions

of known target values when compared to the i-Pen Osmometer (i-Med Pharma, Dollard-des-Ormeaux, Quebec, Canada).

Figure 3.1: The TearLab® (OcuSense Inc., San Diego, CA).

The TearLab was calibrated using the check cards before each measurement. Once calibrated, approximately 50 nL of tear sample was collected from the temporal aspect of participant's lower tear meniscus (Benelli et al., 2010). To achieve this the tip of the TearLab test card was placed in contact with the surface of the lateral inferior tear meniscus (Li et al., 2012).

3.3.4.1 Length of Time for Performing Reading and Gaming Task

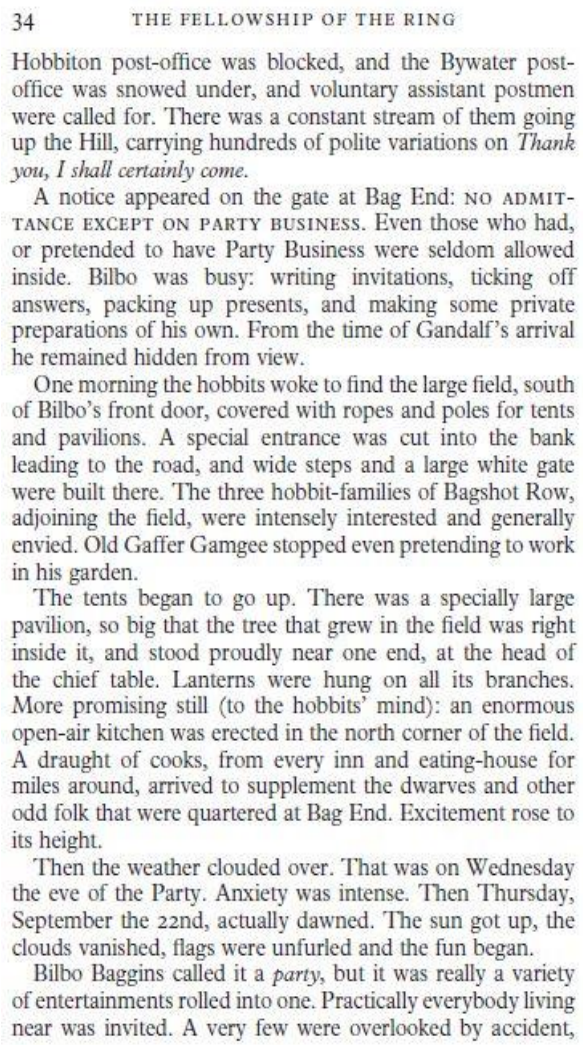
To the best of the author's knowledge, there is only one study that has investigated the reading time on smartphones (West & Chew, 2014). However, the investigators only assessed the total time spent reading for the whole month in reference to gender; the study reported that females spent longer reading on smartphones compared to males (207 minutes vs. 33 minutes per month) (West & Chew, 2014). If assuming that there are 30 days per month,

these figures would equate to 6.9 minutes and 1.1 minutes of smartphone based reading per day for females and males, respectively. In regards to gaming tasks, Verto, (2016) reported that the average time spent playing games on smartphones, per session, was 5 minutes 35 seconds. Hence, to standardise the task duration for both the reading and gaming tasks, participants were required to perform each task for 5 minutes .

3.3.4.2 Reading Task

The reading task involved reading a passage of text on 4 smart devices (Apple iPhone 6, Apple iPhone 6S, Samsung Galaxy S6 and paper) at a fixed distance of 30 cm at their own pace. Participants were required to read for 5 minutes on each platform, after which, tear osmolarity was measured on both eyes (BE). Participants were required to rest for 5 minutes between tasks (Occhipinti et al., 1988). The order of the platforms being introduced was randomized.

A PDF version of JRR Tolkien's novel, The Fellowship of the Ring was selected as the reading material. The text was displayed in a Helvetica letter height size 1.0205 mm. Using the conversion methods outlined by Rabbetts & Bennett, (2007), this was equivalent to a letter size of 0.43 decimals or 6/14 on the smart devices. In addition, a paper copy of the text was produced to the same specifications as those presented electronically Figure 3.2.



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Hobbiton post-office was blocked, and the Bywater post-office was snowed under, and voluntary assistant postmen were called for. There was a constant stream of them going up the Hill, carrying hundreds of polite variations on *Thank you, I shall certainly come.*

A notice appeared on the gate at Bag End: NO ADMITTANCE EXCEPT ON PARTY BUSINESS. Even those who had, or pretended to have Party Business were seldom allowed inside. Bilbo was busy: writing invitations, ticking off answers, packing up presents, and making some private preparations of his own. From the time of Gandalf's arrival he remained hidden from view.

One morning the hobbits woke to find the large field, south of Bilbo's front door, covered with ropes and poles for tents and pavilions. A special entrance was cut into the bank leading to the road, and wide steps and a large white gate were built there. The three hobbit-families of Bagshot Row, adjoining the field, were intensely interested and generally envied. Old Gaffer Gamgee stopped even pretending to work in his garden.

The tents began to go up. There was a specially large pavilion, so big that the tree that grew in the field was right inside it, and stood proudly near one end, at the head of the chief table. Lanterns were hung on all its branches. More promising still (to the hobbits' mind): an enormous open-air kitchen was erected in the north corner of the field. A draught of cooks, from every inn and eating-house for miles around, arrived to supplement the dwarves and other odd folk that were quartered at Bag End. Excitement rose to its height.

Then the weather clouded over. That was on Wednesday the eve of the Party. Anxiety was intense. Then Thursday, September the 22nd, actually dawned. The sun got up, the clouds vanished, flags were unfurled and the fun began.

Bilbo Baggins called it a *party*, but it was really a variety of entertainments rolled into one. Practically everybody living near was invited. A very few were overlooked by accident,

Figure 3.2: An example of the text used for the reading task.

The passage of text was varied between devices to ensure that a memorisation effect did not occur. Due to technical limitations, it was not possible to display the text on the smartwatch and Nokia 5210 phone and thus, the influence of reading on these devices was not assessed.

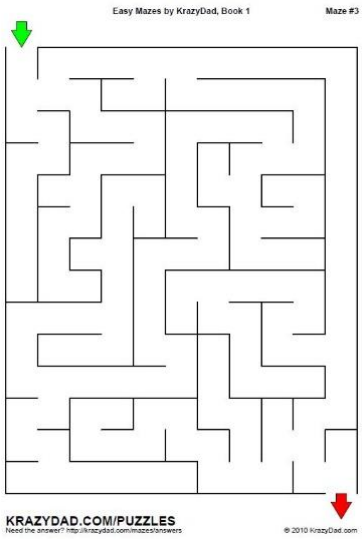
3.3.4.3 Gaming Task

The gaming task involved engaging with a maze game on 6 platforms (Apple iPhone 6, Apple iPhone 6S, Samsung Galaxy S6, paper, Nokia 5210 & Apple Smart Watch) for 5 minutes, following which the tear osmolarity of both eyes were assessed. Participants were required

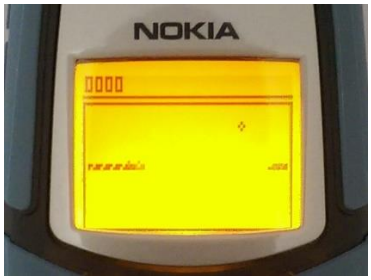
to rest for 5 minutes between tasks and the order of the platforms being introduced was randomized.

Innate differences between the operating systems of the various platforms precluded the same game being used on all devices; hence 4 different types of maze games were utilised for this task (Figure 3.3). Specifically, Maze King from Mobirix was chosen for Apple iPhone 6, Apple iPhone 6S and Samsung Galaxy S6 while Snake II was chosen for Nokia 5210. For the paper platform, a maze game from https://krazydad.com/mazes/ was printed on a white piece of paper measuring 16 cm in length and 7.5 cm wide (matching the iPhone 6). For the Apple Smart Watch, the default maze game offered by the device was used.

Maze King
(Apple iPhone 6, Apple iPhone 6S and Samsung Galaxy S6)



Printed maze game
(Paper)



Snake II
(Nokia 5210)

Default maze
(Apple Smart Watch)

Figure 3.3: Game task being used on all platforms.

3.3.4.4 Lighting, Glare and Contrast

For both tasks, where possible, luminance, illuminance and contrast (Table 3.1) were best matched and these were in accordance with the recommended minimum level of 35 cd/m^2 display luminance for VDTs (North, 1993). Although the brightness for each platform was adjusted, it was challenging to standardize the luminance between the platforms for both tasks (Table 3.1 and Table 3.2) but particularly the gaming task (Table 3.2). In fact, due to technical restrictions during the gaming task, it was not possible to increase the luminance of

the Apple Smart Watch and Nokia 5210 platforms to match the level of the smartphones and paper.

Room lights were switched off during the entire study duration for both tasks. Lighting was provided by the smart device's own screen lighting and for the paper platform, an LED was used instead (Table 3.1). For the paper platform, the illuminating light (LED) was positioned such that the luminance matched that of smartphones. No glare sources were present and the LED lighting were equal throughout the study. For the reading task, the contrast of each target was calculated using Weber's contrast formula (Equation 3.1).

$$\textit{Weber's contrast} = \frac{I - I_b}{I_b} \qquad \text{Equation 3.1}$$

I: Text luminance, cd/m^2

I_b: Background luminance, cd/m^2

Reading Task – Platform	Luminance* (cd/m^2)	Illuminance^ (lux)	Contrast (Weber)
Apple iPhone 6	39.9	107	0.8674
Apple iPhone 6S	45.2	107	0.8674
Samsung Galaxy S6	42.0	101	0.8831
Paper	59.7	106	0.8762

* Measured using Konica Minolta Luminance Meter LS-150.
^ Measured using CHY 230 Light Meter.

Table 3.1: Luminance, illuminance and contrast of the reading material on all platforms.

Gaming Task – Platform	Luminance* (cd/m²)
Apple iPhone 6	34.4
Apple iPhone 6S	37.1
Samsung Galaxy S6	38.4
Paper	44.1
Nokia 5210	3.4
Apple Smart Watch	3.1

* Measured using Konica Minolta Luminance Meter LS-150.

Table 3.2: Luminance for the gaming task.

3.3.4.5 Baseline Measurements

A baseline measurement of osmolarity was taken at the start of the participant visit. The measurement was attained with the participant in primary position of gaze and viewing a 15 × 15 cm Maltese cross target located 2m in front of their line of sight (Figure 3.4).

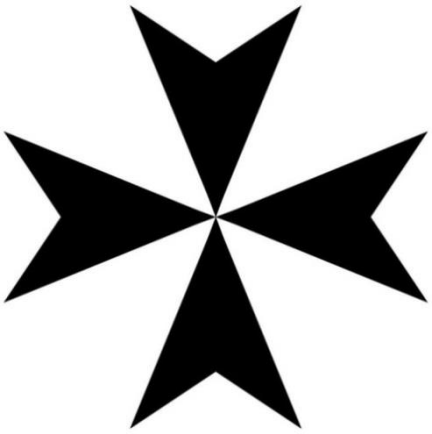


Figure 3.4: Maltese cross used as a fixation target for baseline measurement.

In addition, two validated questionnaires, the Ocular Surface Disease Index (OSDI) and the McMonnies Dry Eye Questionnaire, were used to evaluate the participant's subjective perception of ocular comfort at the start of the study.

3.3.5 Data Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, New York). Initial data inspection was through a visual method (histogram) followed by assessment of the Sharpiro-Wilks test and Z-scores for skewness and Kurtosis; the tests confirmed the data to show a non-normal distribution. Friedman tests (χ) were used to determine if there were any significant differences in osmolarity between the platforms following the reading or gaming task. Where applicable, *post-hoc* testing using Wilcoxon signed-rank tests (Z) was conducted to determine significant pair-wise comparisons. A Bonferroni correction was applied to reduce Type 1 error. For the pair-wise comparison, the *p*-value adjustment was done automatically by SPSS (Adjusted Significance, p_{adj}) and remained at $p_{adj}<0.05$ as suggested by IBM Corporation, (2012) and Lund & Lund, (2014). A Spearman's rank correlation coefficient was used to examine the relationship between the OSDI score, McMonnies Dry Eye Questionnaire scores and the baseline tear osmolarity results. The right eye (RE) was used for data analysis; however, analysis on the left eye data (LE) revealed similar trends (Appendix G).

3.4 Results

Thirty-three participants (14 males and 19 females) with a mean age of 26.52$\pm$4.17 years were assessed. Room temperature (mean=21.39$\pm$0.92 ^{0}C) (Purslow & Wolffsohn, 2007; Wolkoff, 2008) and humidity (mean=42.47$\pm$1.24%) (Abusharha & Pearce, 2012) are known to affect the tear film and were controlled in this study. No air draft was present in the examination room as it has been reported that exposure to high air velocity (1.0 m/s) for 30 minutes would cause a significant decrease in tear stability (Wyon & Wyon, 1987).

3.4.1 Tear Osmolarity Following the Reading Task

The mean and standard deviations (±SD) tear osmolarity values following the reading task are displayed in Table 3.3 and Figure 3.5. For the reading task, there was no significant difference in osmolarity values between the 4 platforms [$\chi^2(3) = 1.495$, p=0.683]. The O

Task & Platform	Tear Osmolarity (mOsm/L) (Mean±SD)
Reading-Apple iPhone 6	293.91±11.05
Reading-Apple iPhone 6S	292.70±9.00
Reading-Samsung Galaxy S6	294.45±9.56
Reading-Paper	293.58±10.20

Table 3.3: Descriptive statistics for tear osmolarity (reading task).

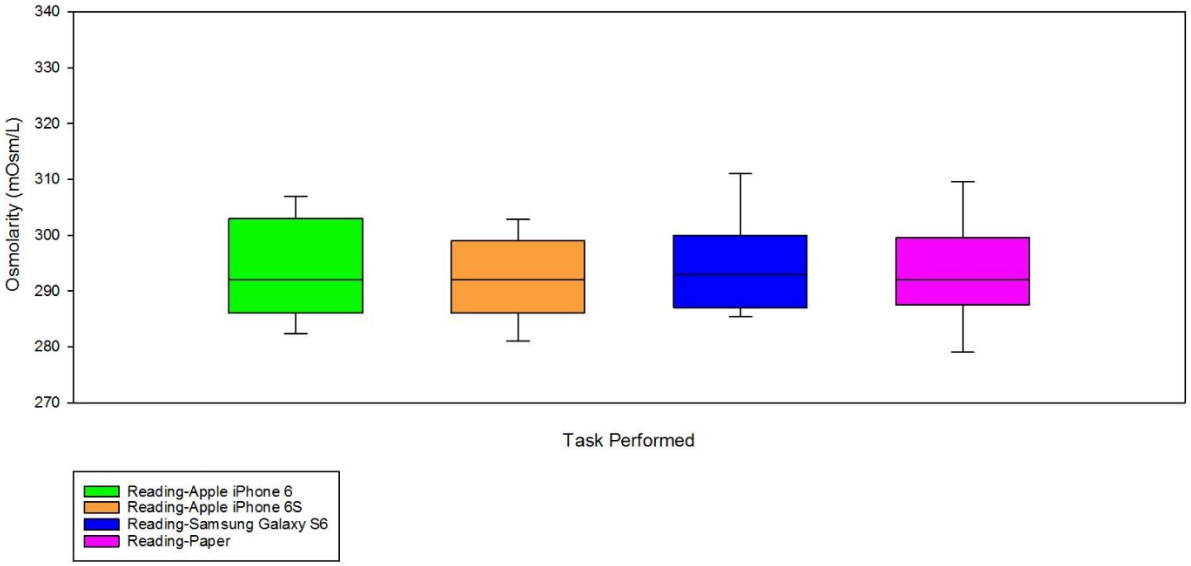


Figure 3.5: Box plot representing median and interquartile range for tear osmolarity values following the reading task.

3.4.2 Tear Osmolarity Following the Gaming Task

The tear osmolarity values following the gaming task are shown in Table 3.4 and Figure 3.6. A significant difference in osmolarity values was found between the 6 platforms [$\chi^2(5) = 22.337$, $p<0.0005$]. *Post-hoc* analysis using Wilcoxon signed-rank tests (Z) revealed that the osmolarity level following completion of the maze game on paper were significantly higher than those obtained after engaging with the maze game on the Apple Smart Watch ($p_{adj}<0.0005$) and the Snake II game on the Nokia 5210 ($p_{adj}=0.015$) (Table 3.5).

Task & Platform	Tear Osmolarity (mOsm/L) (Mean±SD)
Gaming-Apple iPhone 6	289.39±7.76
Gaming-Apple iPhone 6S	289.67±7.14
Gaming-Samsung Galaxy S6	291.15±11.45
Gaming-Paper	292.85±8.42
Gaming-Nokia 5210	287.45±5.69
Gaming-Apple Smart Watch	282.88±7.24

Table 3.4: Descriptive statistics for tear osmolarity (gaming task).

Pairwise Comparison (Task & Platform)	Adjusted P Value for Pairwise Comparison
Gaming-Apple Smart Watch vs. Gaming-Nokia 5210	1.000
Gaming-Smart Watch vs. Gaming-Apple iPhone 6	0.293
Gaming-Smart Watch vs. Gaming-Samsung Galaxy S6	0.224
Gaming-Smart Watch vs. Gaming-Apple iPhone 6S	0.095
Gaming-Smart Watch vs. Gaming-Paper	<0.0005*
Gaming-Nokia 5210 vs. Gaming-Apple iPhone 6	1.000
Gaming-Nokia 5210 vs. Gaming-Samsung Galaxy S6	1.000
Gaming-Nokia 5210 vs. Gaming-Apple iPhone 6S	1.000
Gaming-Nokia 5210 vs. Gaming-Paper	0.015*
Gaming-Apple iPhone 6 vs. Gaming-Samsung Galaxy S6	1.000
Gaming-Apple iPhone 6 vs. Gaming-Apple iPhone 6S	1.000
Gaming-Apple iPhone 6 vs. Gaming-Paper	0.912
Gaming-Samsung Galaxy S6 vs. Gaming-Apple iPhone 6S	1.000
Gaming-Samsung Galaxy S6 vs. Gaming-Paper	1.000
Gaming-Apple iPhone 6S vs. Gaming-Paper	1.000

*Statistically significant.

Table 3.5: *Post-hoc* pairwise comparison for the gaming task.

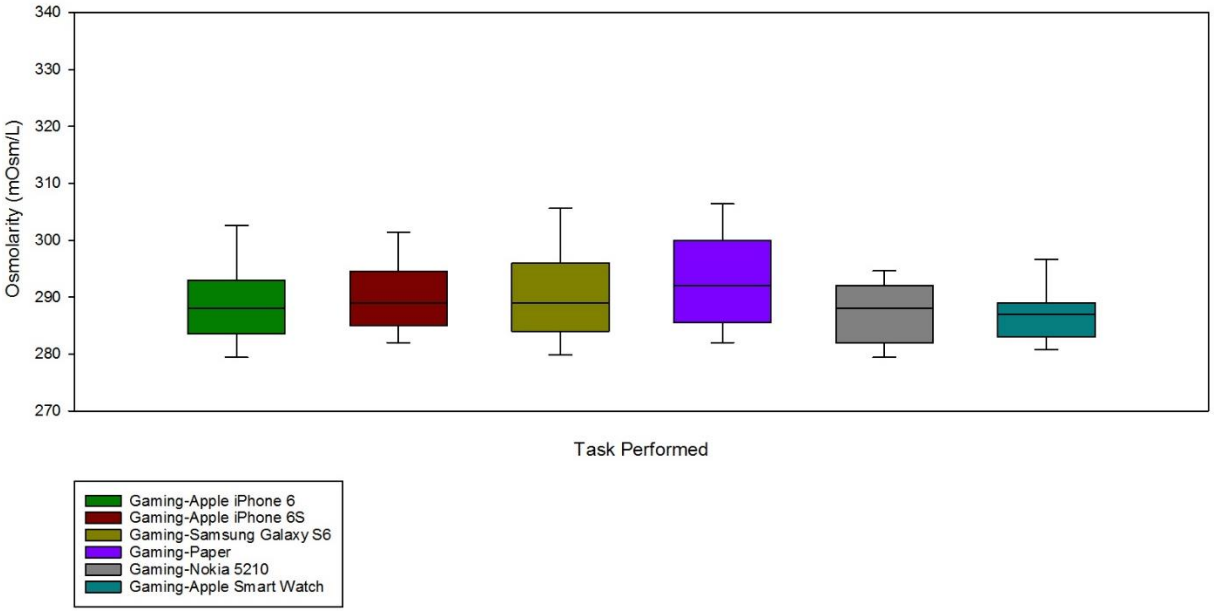


Figure 3.6: Box plot representing median and interquartile range for tear osmolarity values following the gaming tasks.

3.4.3 Comparison of Osmolarity Values at Baseline and Following both Reading and Gaming Tasks on the Various Platforms

The mean tear osmolarity value at baseline was 295.82±8.49 mOsm/L. A significant interaction was observed between baseline osmolarity and choice of task [χ^2 (10) = 68.444, p<0.0005]. The results from the *post-hoc* analysis can be seen in Table 3.6 below.

		Baseline	Reading				Gaming				
			iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	Apple Smart Watch
Reading	iPhone 6	1.000									
	iPhone 6S	0.371	1.000								
	Samsung Galaxy S6	1.000	1.000	1.000							
	Paper	1.000	1.000	1.000	1.000						
Gaming	iPhone 6	0.002*	1.000	1.000	0.673	1.000					
	iPhone 6S	0.004*	1.000	1.000	1.000	1.000	1.000				
	Samsung Galaxy S6	0.004*	1.000	1.000	1.000	1.000	1.000	1.000			
	Paper	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000		
	Apple Smart Watch	<0.0005*	0.002*	0.019*	<0.0005*	0.001*	1.000	1.000	1.000	0.004*	
	Nokia 5210	<0.0005*	0.025*	0.197	0.004*	0.022*	1.000	1.000	1.000	0.049*	1.000

The p values presented in this table had been adjusted (p_{adj}) and the symbol * denote statistical significance.

Table 3.6: *Post-hoc* pairwise comparison for osmolarity values at baseline and both reading and gaming tasks on the various platforms.

Post-hoc analysis revealed that the osmolarity values were significantly higher at baseline than after the gaming tasks for 5 of the 6 platforms (Apple iPhone 6: p_{adj}=0.002, Apple iPhone 6S: p_{adj}=0.004, Samsung Galaxy S6: p_{adj}=0.004, Nokia 5210: p_{adj}<0.0005, Apple Smart Watch: p_{adj}<0.0005, Paper: p_{adj}=1.00). In contrast, measures of osmolarity following the reading tasks for all platforms were not significantly different compared to baseline values (p_{adj}>0.05). It was also revealed that osmolarity values were significantly lower when game playing on Apple Smart Watch compared to: reading on Apple iPhone 6S (p_{adj}=0.019), game playing on paper (p_{adj}=0.004), reading on paper (p_{adj}=0.001), reading on Samsung Galaxy S6 (p_{adj}<0.0005) and reading on Apple iPhone 6 (p_{adj}=0.002). Additionally, game playing on Nokia 5210 produced a significantly lower osmolarity values compared to playing games on paper (p_{adj}=0.049), reading on paper (p_{adj}=0.022), reading on Apple iPhone 6 (p_{adj}=0.025) and reading on Samsung Galaxy S6 (p_{adj}=0.004).

3.4.4 Tear Osmolarity Changes with Regards to Baseline

The changes in tear osmolarity values (compared to baseline) during each of the reading and gaming task can be seen in Table 3.7 below.

Task-Platform	Mean Average Changes in Tear Osmolarity (mOsm/L)
Reading-Apple iPhone 6	1.91±9.62
Reading-Apple iPhone 6S	3.12±10.84
Reading-Samsung Galaxy S6	1.36±10.04
Reading-Paper	2.24±9.86
Gaming-Apple iPhone 6	6.42±10.78
Gaming-Apple iPhone 6S	6.15±9.22
Gaming-Samsung Galaxy S6	4.67±12.16
Gaming-Paper	2.97±8.18
Gaming-Nokia 5210	8.36±8.29
Gaming-Apple Smart Watch	8.76±9.10

Table 3.7: The mean average changes in tear osmolarity between baseline and all tasks.

According to Lemp et al., (2011), a value of ≥308 mOsm/L are indicative of dry eye. Table 3.8 examines the number of participants with osmolarity values greater than this diagnostic value.

Task	Number of Participants		
	Osmolarity 308 mOsm/L or higher	Osmolarity <308 mOsm/L	Total
Baseline	3	30	33
Reading-Apple iPhone 6	2	31	33
Reading-Apple iPhone 6S	2	31	33
Reading-Samsung Galaxy S6	3	30	33
Reading-Paper	4	29	33
Gaming-Apple iPhone 6	1	32	33
Gaming-Apple iPhone 6S	1	32	33
Gaming-Samsung Galaxy S6	2	31	33
Gaming-Paper	3	30	33
Gaming-Nokia 5210	0	33	33
Gaming-Smart Watch	0	33	33

Table 3.8: A breakdown in tear osmolarity values observed in this study.

3.4.5 Correlation Between the Baseline Osmolarity Values and the Subjective Assessment of Dry Eye

The OSDI demonstrated a mean score of 5.17±2.91 while the McMonnies mean score was 3.70±2.05. Normal values for OSDI and McMonnies are considered to be <12 (Schiffman et al., 2000; Miller et al., 2010) and <15 respectively (Nichols et al., 2004; McMonnies et al., 1998; Guo et al., 2016; Tang et al., 2016). Based on this criterion, the participants examined in the present study were unlikely to have dry eye. No significant correlation was found between the baseline osmolarity values and both McMonnies and OSDI scores (Figure 3.7).

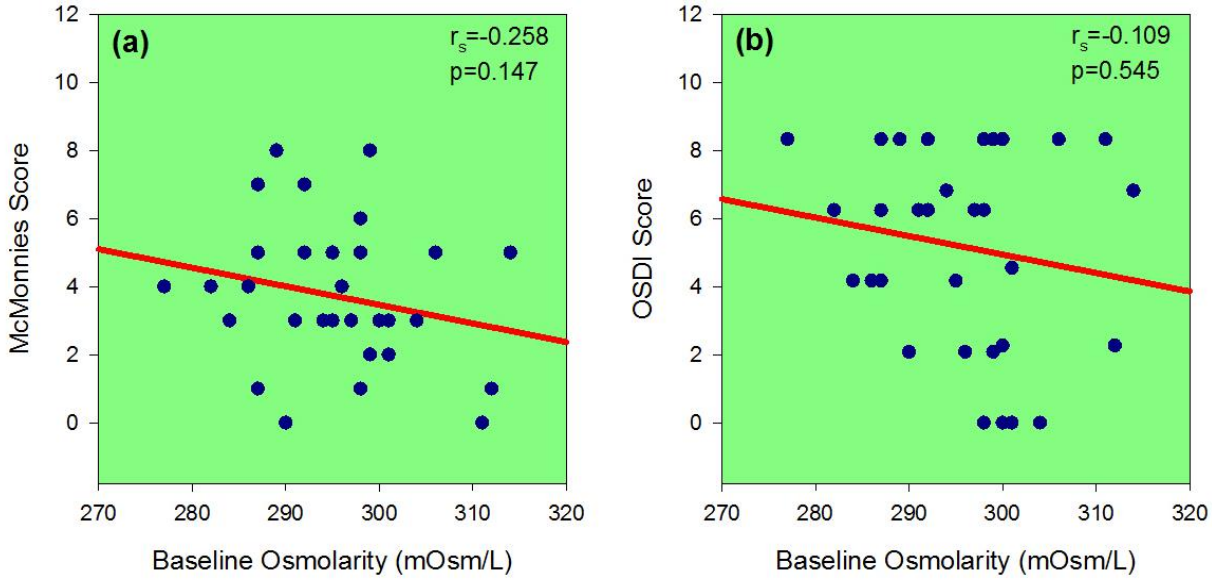


Figure 3.7: Spearman's correlation between (a) McMonnies Score and Baseline Osmolarity, (b) OSDI Score and Baseline Osmolarity.

3.5 Discussion

3.5.1 Introduction

Dry eye associated with long periods of VDT use have been well documented (Kawashima et al., 2015; Uchino et al., 2008) but the clinical changes that bring about these aetiological

alterations are poorly understood. In view of the growing popularity of smart devices in everyday life (Rainie & Perrin, 2017; Rideout et al., 2010), it is important that clinicians are able to assess the impact these devices may have on the ocular surface layers. The absence of repeatable and objective methods for quantifying and categorising the tear film characteristics partly explain the ambiguity in the literature. Tear osmolarity has been purported to be a useful diagnostic marker in dry eyes (Lemp et al., 2011; Versura & Campos, 2013; Willcox et al., 2017) and the present study sought to investigate changes in osmolarity that occur as a consequence of engaging in tasks of varying cognitive demand on paper and smart devices.

3.5.2 Clinical Significance of the Tear Osmolarity Changes with Platform and Task

A significant difference was found between the baseline osmolarity values and the results post gaming on all platforms with the exception of the paper platform. However, when assessing the average change in osmolarity values, it is apparent that these changes although statistically significant, were not of clinical relevance (Table 3.7). Indeed, the average change from baseline in these statistically significant osmolarity values ranged between 8.76$\pm$9.10 mOsm/L (Apple Smart Watch) and 6.42$\pm$10.78 mOsm/L (Apple iPhone 6). Eperjesi et al., (2012) reported that when the same operator is taking repeated TearLab tear osmolarity readings over time, only increases or decreases of more than 33 mOsm/L can be classified as clinically relevant. Furthermore, Table 3.8, examined the number of participants whose osmolarity values were greater than 308 mOsm/L, a value regarded as a diagnostic threshold for dry eye. Only three participants changed in classification when comparing baseline with each task. Therefore, based on these observations, it can be concluded that these results fail to have any clinical significance but warrant further investigation.

3.5.3 Effect of Gaming Task on Osmolarity

Unexpectedly, the results of the study showed that osmolarity reduced significantly more when participants were engaged in the gaming task on the Nokia 5210 and Apple Smart Watch when compared to the maze game on paper. As such, these counterintuitive findings would suggest that there was an increased risk of dry eye when playing a game on paper as opposed to when using a Nokia 5210 phone or Apple Smart Watch.

There are several factors that may explain these observations. Firstly, differences in luminance levels between the platforms may partly explain these results. The higher luminance of the paper may have triggered the natural reflex to narrow the palpebral aperture, possibly lengthening the IBI times and thus, affecting the osmolarity of the tears. In a review, Wolkoff et al., (2005) discuss that an increased in IBI times would cause an increase in tear evaporation subsequently leading to higher osmolarity values. Another possible factor may be that the crowding effect from the smaller Apple Smart Watch and Nokia 5210 screen had a psychological effect that influences the participants blink rate which may, yet again change the osmolarity values. For each of these theories, it is assumed that blink rate plays a vital role in maintaining tear osmolarity however, there is a paucity of evidence that examines the role of the blink rate on tear osmolarity.

3.5.4 Effect of Reading Task on Osmolarity

No difference in osmolarity values were found between the platforms following the reading task. Luminance and the cognitive difficulty of each reading task between the platforms were similar and controlled to a greater extent in comparison to the gaming task. Therefore, the findings support the assertion above that the difference in osmolarity with the gaming tasks is likely to be due to the variable luminance and screen size.

3.5.5 Changes in Osmolarity Throughout the Study

The literature provides compelling evidence for an association between increased levels of ocular discomfort with long periods of VDT use (Bergqvist & Knave, 1994; Nakazawa et al., 2002; Ranasinghe et al., 2016). It is anticipated that a reduced blink rate during VDT use (Patel et al., 1991; Bentivoglio et al., 1997; Nakamori et al., 1997; Blehm et al., 2005; Rosenfield, 2011), increases the rate of tear evaporation (Bron & Tiffany, 2004; Sweeney et al., 2013) resulting in tear hyper osmolarity leading to symptoms of discomfort and damage to the ocular surface (Murube, 2006; Foulks, 2007; Chu et al., 2013). Furthermore, the reduced blink rate also contributes to a poor tear film quality, which initiates localised areas of corneal dessication, subsequently leading to dry eye (Blehm et al., 2005). In addition, Lui and colleagues reported that tear hyper osmolarity was linked to tear film instability and thus, resulting in ocular discomfort, burning and stinging (Liu et al., 2009).

Significant increase in tear osmolarity values caused by the reduced blinking rates and higher evaporation rate associated with VDT use have been reported by previous researchers (Fenga et al., 2014; Yazici et al., 2015). However, contradicting results had been reported by other researchers; in a different study involving 2 hours of watching television in a controlled environment (temperature of 23 ^{o}C, 5% relative humidity (RH) and localized air flow with a mean velocity of 0.43 meters/second), it was found that tear osmolarity was not significantly different before and after performing the task (López-Miguel et al., 2014).

In this current study, contradicting results were found. Instead of observing an increase in tear osmolarity following the reading and gaming task, it was found that tear osmolarity results actually reduced following the gaming task on each of the platforms, when compared to baseline levels. A significant reduction in tear osmolarity during gaming task could be

translated into a lesser occurrence of dry eye when performing this task, since hyper osmolarity does not occur and hence damage to the ocular surfaces is prevented.

Methodological factors are likely to explain these unexpected observations. In the present investigation, tear osmolarity was only measured once following exposure to each platform and task. In view of the fact that consecutive measures of tear osmolarity with the TearLab can show variability of up to 35 mOsm/L (Khanal & Millar, 2012), it may be surmised that one reading was not sufficient to provide an accurate measure. Indeed, (Szczesna-Iskander, 2016) advocate that at least 3 consecutive measurements are needed to provide clinically reliable tear osmolarity readings.

Another factor that may have impacted the current results is the number of tear osmolarity measurements that were conducted on each participant's eye. Each participant underwent 11 tear osmolarity measurements at the same visit. A single measurement was performed at baseline and 4 and 6 readings were captured during the reading and gaming tasks, respectively. It is possible that the number of measurements conducted in the study reduced the tear osmolarity as 50 nL of tears were collected for each sample. It may be hypothesised that; multiple episodes of tear collection would affect the concentration of salts in the tear film and inadvertently reduce the tear osmolarity. However, this phenomenon has yet to be reported in the literature and thus, cannot be confirmed.

3.5.6 Correlation Between McMonnies and OSDI Questionnaires and the Baseline Osmolarity Values

The McMonnies (Guo et al., 2016; Nichols et al., 2004b) and OSDI (Schiffman et al., 2000) questionnaires have been confirmed to be valid tools for effectively discriminating between normal, mild to moderate, and severe dry eye. In this study, the correlation between tear

osmolarity, McMonnies and OSDI were not significant. These findings are suggestive of the multifactorial nature of dry eyes symptoms and the difficulty in associating subjective outcomes with a single objective clinical measure.

3.5.7 The Limitations of a Non-Continuous Measurement of Osmolarity

Tear osmolarity is a dynamic property of the human tear film. It's current assessment by sampling its characteristics at a given point in time is unlikely to provide a comprehensive assessment of how osmolarity changes during the day or when performing a task. The tear film is known to be affected by the blink rate (Holly, 1985; Tsubota & Nakamori, 1995), which is subsequently influenced by environmental and psychological factors (Holland & Tarlow, 1972; Martin & Carvalho, 2015; Stern et al., 1984). In view of this association, it is essential that the tear characteristics are evaluated in reference to the blink rate and that continuous measurements are assessed to improve characterisation of the tear film.

3.6 Conclusion

This study concluded that:

- Tear osmolarity values reduced following the gaming task on each of the platforms relative to baseline levels however, these results were not of clinical significance.
- Osmolarity reduced when participants were engaged in the gaming task on the Nokia 5210 and Apple Smart Watch when compared to the maze game on paper.
- There was no difference in osmolarity values between the platforms following the reading task.
- No significant correlation was found between the baseline osmolarity values and both McMonnies and OSDI scores.

Chapter 4: Influence of Repeated Measurements on Tear Osmolarity

4.1 Introduction

Tear osmolarity plays an important role in the mechanism of dry eye (Mathews et al., 2017; Yi et al., 2018) and it has been suggested to be a valuable indicator of the interaction between tear production, evaporation, drainage and absorption (Lemp, 1995; Sullivan et al., 2012). High levels of tear osmolarity (hyperosmolarity) are believed to initiate an inflammatory response that causes ocular surface damage (Messmer et al., 2010; Chao et al., 2016; Bron et al., 2017; Willcox et al., 2017; Wolffsohn et al., 2017). Tomlinson et al., (2006) reported that the mean tear osmolarity in non-dry eye adults is 302±9.7 mOsm/L; this assertion was based on a meta-analysis of studies examining tear osmolarity using either freezing point depression or a vapour pressure osmometer. Interestingly, Jacobi et al., (2011) and Sullivan et al., (2010) found comparable values when measuring tear osmolarity in non-dry eye adults using an electrical impedance based osmometer (TearLab) with a median of 301 mOsm/L (range 298 to 304 mOsm/L) and mean of 302.2±8.3 mOsm/L respectively. Lemp et al., (2011) concluded that the most sensitive threshold between normal and mild/moderate dry eye was 308 mOsm/L, whilst the most specific cut off was 315 mOsm/L and values higher than this being indicative of hyperosmolarity.

It is unclear if tear osmolarity remains constant throughout the day and indeed, there is much ambiguity surrounding the diurnal variation of tear osmolarity. Using freezing point depression, Terry & Hill, (1978) observed that osmolarity values were lower upon waking in comparison to the rest of the day; these observations were confirmed by a study that employed the TearLab to assess diurnal variation of tear osmolarity (Niimi et al., 2013). In other studies employing the TearLab, Li et al., (2012) noted hypo-osmotic values at noon

relative to the morning whilst Khanal & Millar, (2012) and Öncel et al., (2012a) observed no differences in osmolarity throughout the day. In a small case study using freezing point depression, Gilbard et al., (1978) monitored a non-dry eye participant for several weeks (exact duration not mentioned) and observed tear osmolarity to fluctuate between 295 and 309 mOsm/L; these observations have been suggestive of the normal variation in tear osmolarity. The contradicting findings of diurnal changes in tear osmolarity within the literature may stem from the different methods (freezing point depression or electrical impedance) utilized to measure the osmolarity itself as well as the repeatability of the tests. When considering the TearLab in isolation, Khanal & Millar, (2012) demonstrated that measures of tear osmolarity showed variability of up to 35 mOsm/L. In concordance Bunya et al., (2015), Schmidl et al., (2015) and Szczesna-Iskander, (2016) all noted the high variability observed with the TearLab whilst, Szalai et al., (2012) reported an overlap in values between healthy and dry eye groups. These observations are suggestive of the innate variability of both tear osmolarity and the TearLab test itself and highlight the need to assess the normal fluctuations in osmolarity, particularly when consecutive repeated measurements are collected on a single day.

In Chapter 3, osmolarity values were examined following reading and gaming tasks. During this study, a baseline measurement was collected, followed by a measurement after each reading and gaming task, respectively. The results from the study indicated that the baseline values were greater than the results following the reading task, whilst measurements after the gaming task were lower than the reading task. When considering these results in view of the study design, it is possible that an order effect confounded the results thus limiting direct comparison between the different tasks as well as the baseline values. As such, it was postulated that the change in osmolarity values may be due to the repeated measures and

that multiple episodes of tear collection affected the concentration of salts in the tear film causing a reduction in osmolarity. To validate these observations, the present study examines whether tear osmolarity reduces as a consequence of multiple measurements.

4.2 Objective

This is a prospective repeated measure study design with the primary aim to determine if consecutive measures of tear osmolarity results in a change in readings. Furthermore, the study also examined the intraobserver variability of the osmolarity measurements.

4.3 Methods

4.3.1 Ethical Approval

Ethical approval was obtained from Research Ethics Committee, Faculty of Health & Human Sciences and Peninsula School of Medicine & Dentistry, Plymouth University (Appendix B, reference number 17/18-902). Prior to the start of data collection, participants were fully informed of the experiment and all relevant questions were answered accordingly. Written consent was obtained before the start of data collection.

4.3.2 Inclusion and Exclusion Criteria

Participants were recruited from the staff and student population of Plymouth University using purposive sampling. Potential participants were age and gender matched to the population of Chapter 3. The inclusion and exclusion criteria of the study are as follows:

4.3.2.1 Inclusion Criteria

- Completed a comprehensive eye examination within the last 12 months.
- Rigid Gas Permeable contact lens wear ceased for a minimum of 1 week.
- Aged between 18 and 35 years old.
- Soft contact lens wear ceased for a minimum of 2 days.

- Willing to participate in the study.

4.3.2.2 Exclusion Criteria

- History of any form of ocular surgery including LASIK.
- Participation in a pharmacological studies occurring concurrently.
- Suffering any form of ocular or systemic diseases.
- Pregnant or breast feeding.
- Taking medications effecting the tear film.

4.3.3 Measurement of Tear Osmolarity

The methodology for acquisition of tear osmolarity measurements with the TearLab followed the protocol adopted in Chapter 3.

4.3.3.1 Repeated Measurement of Tear Osmolarity

On each participant, a single measurement of tear osmolarity was collected 11 times with 15-minute intervals using the TearLab® osmometer (OcuSense Inc., San Diego, CA); this interval time ensured a complete tear turnover rate (Occhipinti et al., 1988). As room humidity (Abusharha & Pearce, 2012) and temperature (Purslow & Wolffsohn, 2007; Wolkoff, 2008) are known to affect the tear film, a humidifier was used to achieve humidity levels between 40% to 45% and the room temperature was controlled between 20 ^{0}C and 25 ^{0}C. Mesopic lighting conditions (approximately 100 lux) were maintained in the room to ensure similar conditions to Chapter 3. Additionally, participants were instructed not to conduct any visual task throughout the three hours including viewing any digital devices or reading material.

4.3.4 Data Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, New York). Initial data inspection was through a visual method (histogram) followed by assessment of the Sharpiro-Wilks test and Z-scores for skewness and kurtosis; the tests

confirmed the data to show a non-normal distribution. To examine the applicability of the present study (now referred as Osmolarity Study 2) to those of Chapter 3 (now referred as Osmolarity Study 1), appropriate statistical tests were conducted on the age (unpaired t test), gender (frequency) and tear osmolarity levels (Mann Whitney) of the participants. Friedman tests (χ) were used to determine if there were any significant differences between the repeated measures of tear osmolarity. In addition, Spearman's correlation was also assessed to examine the correlation between tear osmolarity and number of measurements (Norman, 2010; Schober et al., 2018). To assess the intraobserver variability in measurements, the coefficient of variance (CoV) was calculated; CoV of <10% is generally considered to represent good repeatability (Fleiss, 1981).

4.4 Results

Thirty-three participants (15 males and 18 females) with a mean($\pm$SD) age of 24.45$\pm$5.96 years were assessed. Participants had a mean($\pm$SD) OSDI and McMonnies score of 8.59$\pm$7.97 and 4.09$\pm$3.01, respectively. Room temperature (mean$\pm$SD 21.73$\pm$0.48 ^{0}C) (Purslow & Wolffsohn, 2007; Wolkoff, 2008) and humidity (mean$\pm$SD 42.07$\pm$0.55%) (Abusharha & Pearce, 2012) were controlled in the study.

4.4.1 Age, Gender and Osmolarity Differences between Osmolarity Study 1 (Chapter 3) and Osmolarity Study 2 (Current Chapter)

The mean($\pm$SD) or percentage (where applicable) for age, gender and osmolarity values can be seen in Table 4.1.

Parameters	Osmolarity Study 1 Mean±SD	Osmolarity Study 2 Mean±SD
Age (Years)	26.52±4.17	24.45±5.96
Gender	Male=14 (42.4%) Female=19 (57.6%)	Male=15 (45.5%) Female=18 (54.5%)
Tear Osmolarity (mOsm/L)	295.82±8.49	295.25±10.35

Table 4.1: Comparisons of age, gender and tear osmolarity between both experiments.

Participant's age, gender and tear osmolarity values were not significantly different between the two studies (p>0.05).

4.4.2 Effect of Repeated Measures on Tear Osmolarity

Table 4.2 and Figure 4.1 show the mean±SD of tear osmolarity measured in the present study. No significant difference was observed between repeated measures of tear osmolarity [$\chi^2(10) = 12.797$, p=0.235]. The O

Measurement Number	Tear Osmolarity (mOsm/L) Mean±SD
Measurement 1	294.58±12.39
Measurement 2	290.88±16.71
Measurement 3	295.61±13.19
Measurement 4	300.03±13.74
Measurement 5	297.09±14.59
Measurement 6	294.27±9.36
Measurement 7	295.15±11.82
Measurement 8	294.94±17.77
Measurement 9	293.09±14.62
Measurement 10	295.85±18.57
Measurement 11	296.27±14.69

Table 4.2: Descriptive statistics (Mean±SD) for each measurement of tear osmolarity.

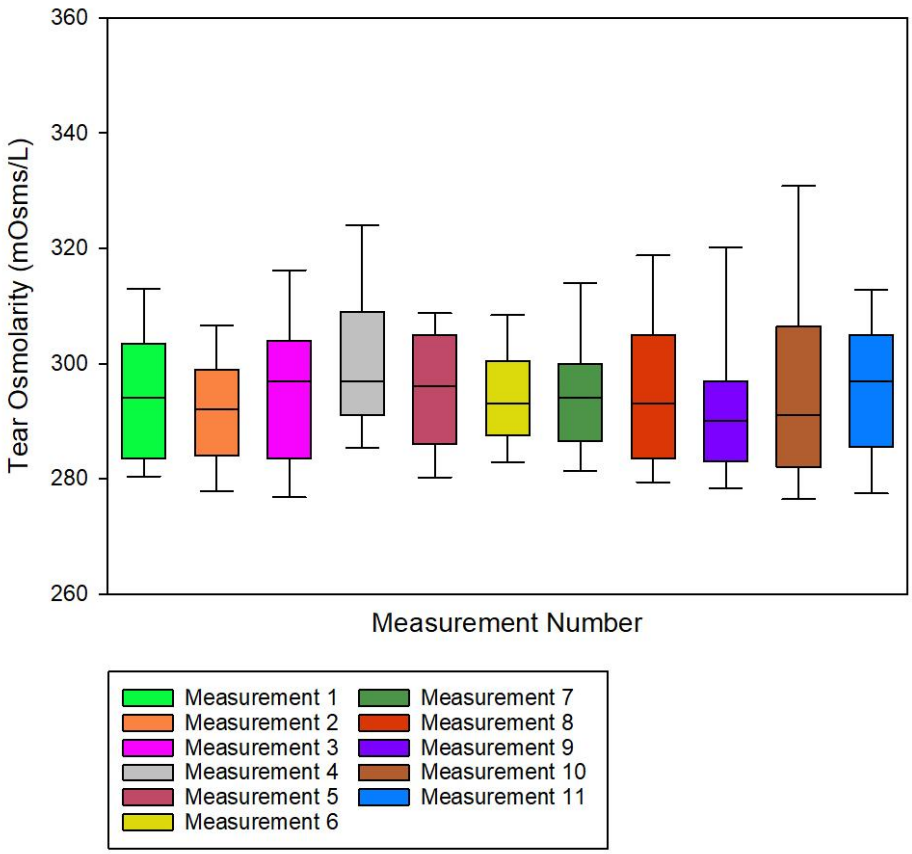


Figure 4.1: Box plot representing median and interquartile range of multiple tear osmolarity measurements.

As shown in Figure 4.2, the Spearman's correlation was found to be non-significant (r_s=-0.027, *p*=0.603,). Mean CoV for 11 TearLab measures of tear osmolarity was 3.1±1.7% (range 2.0% to 10%), suggesting high levels of repeatability.

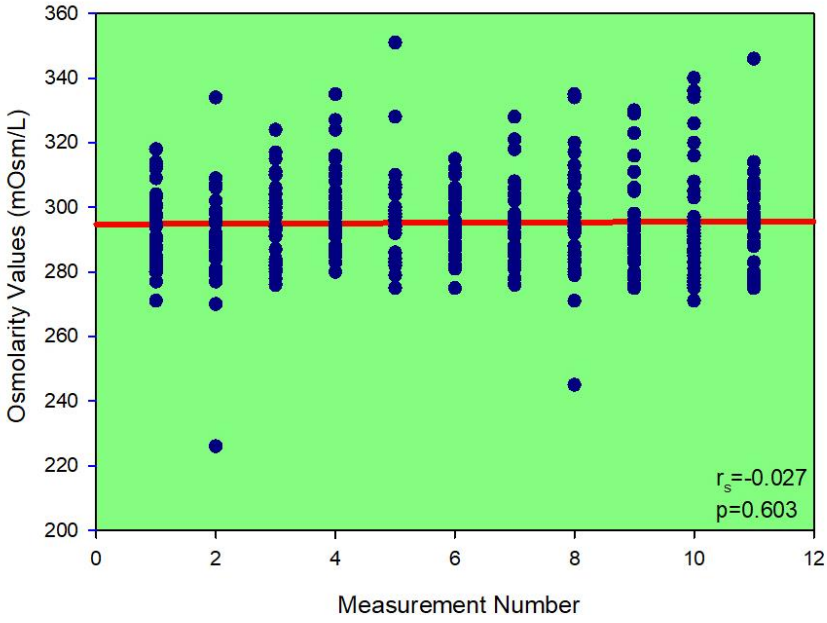


Figure 4.2: Spearman's correlation plots for number of measurement versus tear osmolarity.

4.5 Discussion

The objective of Chapter 3 was to determine if tear osmolarity was affected by the visual task being performed. Surprisingly, the results suggested that baseline values were greater than the results following the reading task and furthermore, measurements after the gaming tasks were lower than the reading task. It was hypothesised that these unexpected results were a consequence of the multiple episodes of tear collection affecting the concentration of salts in the tear film and inadvertently reducing tear osmolarity values. However, the observations of the present study do not support this supposition: Across the 11 measurements, no significant difference was identified, and no correlation was noted between the number of measurements and osmolarity values. Thus, these results support the hypothesis that exposure to the task itself may have caused the reduction in tear osmolarity, however, other possible factors that may have caused this effect must be considered.

4.5.1 Environmental Factors

Several studies have investigated the effects of environmental factors such as humidity (Abusharha & Pearce, 2012; Tesón et al., 2013), temperature (Abusharha & Pearce, 2015) and altitude (Jha, 2009; Willmann et al., 2014) on tear film stability, however, comparatively few have assessed the specific impact of these factors on tear osmolarity. Wyon & Wyon, (1987) demonstrated that tear film stability decreased following exposure to high air velocity. Others have shown humidity to affect the tear film stability (Korb et al., 1996; Maruyama et al., 2004; Uchiyama et al., 2007) with higher humidity levels causing increased lipid layer thickness (Korb et al., 1996). Temperature is also a factor and chronic exposure to low temperatures have been shown to cause tear film instability (Abusharha & Pearce, 2015).

More recently, Fagehi, (2018) investigated the effect of environmental changes on tear stability in an external environment and after 30 minutes of being in a clinical environment with constant temperature and humidity. The investigators found a significant difference in TBUT, Schirmer test and tear prism height between the two conditions and concluded that tear film stability was highly influenced by a change in environmental conditions (Fagehi, 2018). Similarly, López-Miguel et al., (2014) conducted clinical and laboratory based assessments of the tear film before and after 2 hours of exposure to a desiccating environment (5% humidity). They found that exposure to the experiment's environmental conditions reduced both corneal epithelial integrity and tear stability in participants with and without mild-to-moderate dry eye (López-Miguel et al., 2014). Such evidence is indicative of the environmental effects on tear film stability, but both Fagehi, (2018) and López-Miguel et al., (2014) failed to assess the time taken for the tear film to adapt to the new environment. Moreover, no consideration was given to the effects of the invasive measurements on future

tear film measurements. It is important to note that the environmental studies mentioned above consider its effect on tear stability as opposed to tear osmolarity. The DEWS II report suggests that patients with compromised tear stability will experience higher osmolarity values (Willcox et al., 2017; Wolffsohn et al., 2017). However, the research shows a lack of consensus in the relationship between tear osmolarity and tear break up time (Aragona et al., 2002; Wolkoff et al., 2005; Liu et al., 2009; Messmer et al., 2010; Versura et al., 2010; Sullivan et al., 2012; Szalai et al., 2012).

Indeed, the only studies known to the author that have examined the effects of the environment on tear osmolarity have found contrasting results. Abusharha & Pearce, (2012) found that a decrease in humidity did not alter osmolarity values whilst Willmann et al., (2014) observed hyperosmolarity values with high altitude environment. Tesón et al., (2013) found a statistical difference in osmolarity values between two groups of participants who were exposed to separate controlled environments of differing humidity and barometric pressure. However, they did not observe a difference between the pre-exposure values and those collected following two hours of exposure to this environment.

Whilst the internal ambient temperature and humidity were controlled and matched between Chapter 3 and the present study, the external environmental conditions were not evaluated. Both studies were not conducted concurrently and hence it is conceivable that the external environmental conditions may have adversely influenced the results of one of these studies and not the other. Given that the mean tear turnover rate is 30% per minute (Occhipinti et al., 1988), it was deemed appropriate to allow a 10-minute adaptation time to the room environment before the first tear osmolarity measurement was taken in both

Chapter 3 and 5. In view of the lack of evidence in the literature, it is unclear if 10-minutes was a sufficient adaption time and further studies are required to address this uncertainty.

4.5.2 Variability of Tear Osmolarity Measurements

In the present study, intraobserver repeatability of the TearLab measurements was found to be high suggesting that the test is repeatable. Although the TearLab has been shown to provide an accurate, repeatable and reproducible tear osmolarity measurement (Tomlinson et al., 2010; Versura et al., 2010; Gillan, 2013; Yoon et al., 2014), several investigators have also questioned the high variability observed with the device (Eperjesi et al., 2012; Khanal & Millar, 2012; Szalai et al., 2012; Bunya et al., 2015; Schmidl et al., 2015; Szczesna-Iskander, 2016). Indeed, Eperjesi et al., (2012) assessed the variability of osmolarity and found that changes of less than 33 mOsm/L should not be considered an actual osmolarity variation and can be attributed to the TearLab device measurement noise. Szczesna-Iskander, (2016) conducted an analogous study where tear osmolarity was collected multiple times within a controlled environment. In their study, they assessed osmolarity 10 times at shorter intervals of 1 minute and showed that across the 10 measurements, randomly occurring outlying values frequently occurred (Szczesna-Iskander, 2016). Of particular relevance is their observation that the left eye osmolarity values showed higher variability for first 5 measurements relative to the later 5 and the mean osmolarity values for the first 3 measurements were significantly higher than the subsequent values (Szczesna-Iskander, 2016). Conversely, Keech et al., (2013) found a gradual increase in osmolarity values when taking multiple measurements, however this observation was found on a dry eye population.

Other factors such as the length of time taken to collect the tear sample (Khanal & Millar, 2012; Szczesna-Iskander, 2016) and the angle at which the TearLab chip is positioned and the

location of the sampling site have also been found to affect the variability of the osmolarity readings (Lemp, 1995; Wunderlich et al., 2011; Li et al., 2012).

4.5.3 Anxiety and Familiarity with the Procedure

Patient anxiety is an inhibitive factor within a healthcare setting and can encumber a practitioner's ability to carry out their routine practice (Corah et al., 1985; Doerr et al., 1998; Margrain & Anderson, 2003). Within an eye care setting, anxiety is known to influence measures of IOP (Shily, 1987; Kaluza et al., 1996; Brody et al., 1999) and increase the complication rate in surgical procedures (Nijkamp et al., 2004; Mavros et al., 2011; Kim et al., 2012; Britteon et al., 2017). Researchers examining anxiety in dental practice found that patient familiarly with a practice and its procedures is known to improve stress levels (Armfield et al., 2007). It is therefore conceivable that the participants may have felt anxiety with initial measures of tear osmolarity but less with later measurements. However, given that both studies evaluated tear osmolarity on 11 occasions, it is unlikely that this factor would have influenced one study and not the other.

The study in Chapter 3 was designed to investigate the effect of smartphone use on tear osmolarity, however, due to flaws in the study design the order effect caused by multiple measurements could not be dismissed. The results from this study suggest that the multiple readings of tear osmolarity do not cause a reduction of osmolarity values. However, given that the reduction in tear osmolarity found in Chapter 3 was small and not clinically significant it is likely that the inherent variability of the tear film device may have been a factor in the results. What is apparent is that more studies are required to examine the effects of task performance on smart devices and tear osmolarity.

4.5.4 Limitations and Future Work

The main limitation of this investigation is that of the participant sample. The study was designed to match that of Chapter 3. However, both studies were not conducted concurrently and as such, participants were not randomized between the two groups (those performing the tasks and those not). Despite the best efforts to stratify participants according to their ages, the effect of cohort sampling cannot be overlooked. In addition, the studies were conducted on different days and hence, external environmental factors may have affected the results. Furthermore, future work should seek to confirm the length of time required for the tear film to adapt to a new environment.

4.6 Conclusion

This study concluded that:

- Repeated measures of tear osmolarity with the TearLab had no significant effect on measures of osmolarity.
- High levels of intraobserver repeatability were observed for osmolarity measurements with the TearLab.
- Further studies are required to determine if the osmolarity changes found in Chapter 3 are related to the variability of the measurement itself or due to the influence of the tasks being performed by the participants.

Chapter 5: Binocular OFTA and Smart Devices

5.1 Introduction

With 1.75 billion users, smartphones have become an essential component of everyday life (EMarketer, 2014) for both vocational and non-vocational purposes (Rosenfield et al., 2012). In a recent review, 92% of adults aged 18 to 29 years were found to own a smartphone (Rainie & Perrin, 2017), with the average individual spending approximately 2 hours per day using these devices (Moon et al., 2014; Sadagopan et al., 2017).

Despite the growing popularity of smartphones, there is little known about the potential impact of these devices on the ocular surface and visual system. On evaluation of the literature it is evident that the terms visual display terminal (VDT), visual display unit (VDU) and display screen equipment (DSE) are used interchangeably with no specific mention of smartphones. When applying the criterion provided by the Health and Safety Executive, United Kingdom, smartphones are considered a form of VDT, however, for the purposes of the present investigation, these devices need to be considered as a separate entity. Therefore, the term VDT will be used to describe conventional display screens and laptops, whereas the term smart device encompasses the emerging technologies such as smartphones and smartwatches.

Historically, much of visual ergonomics research has been focused on computer based VDT. The term computer vision syndrome (CVS) has been used to define the combination of eye and vision problems associated with the use of computers (Blehm et al., 2005; Rosenfield, 2011) which include visual fatigue (Mocci et al., 2001), dry eye, musculoskeletal symptoms (Parihar et al., 2016) and headaches (Collins et al., 1990; Dillon & Emurian, 1996; Nakaishi &

Yamada, 1999; Rossignol et al., 1987; Shin & Zhu, 2011; Shrestha et al., 2011; Wolkoff et al., 2005).

In regards to the impact of VDT use on the anterior ocular surface (Kojima et al., 2011), blink rate (Cardona et al., 2014; Schlote et al., 2004) and tear film stability (Hirayama et al., 2013; Yokoi et al., 2015) have been investigated. These, previous studies have reported an increased prevalence of dry eye amongst VDT users by up to 60% (Kawashima et al., 2015; Uchino et al., 2008, 2013) but do not assess the real-time changes in ocular surface properties whilst using these devices. Furthermore, these investigations fail to consider the impact of both the visual task and the type of VDT being investigated; these factors are known to influence ocular discomfort independently (Chu & Rosenfield, 2011; Himebaugh et al., 2009; Skotte et al., 2007; Ziefle, 1998). On review of the literature, robust investigations that control for the type of VDT and visual task whist objectively assessing the anterior ocular surface, using metrics such as blink rate and tear film stability are required.

5.1.1 Blinking

Blinking is essential for stimulating tear production, aiding tear distribution, (Tsubota & Nakamori, 1995; Nakamori et al., 1997; Montés-Micó, 2007) and preventing ocular dryness (Doane, 1981; Perez et al., 2011). It is commonly assessed by examining either the blink rate (BR), spontaneous eyeblink rate (SEBR) or the interblink interval (IBI). BR or SEBR corresponds to the number of blinks per minute while IBI represents the duration in seconds between 2 blinks (Cruz et al., 2011). Since the blink rate is affected by psychological and physiological factors (Holland & Tarlow, 1975; Stern et al., 1984), it is important to identify if the changes in blink behaviour are in reference to the task being performed whilst also considering the platform being used to perform the task.

Nakamori et al., (1997) reported that blink rate reduces and maximum IBI increases during VDT use in healthy participants. In support of these findings Schlote et al., (2004) also found a significant reduction in blink rate after using the VDT for 30 minutes in dry eye participants.

Chu et al., (2014) conducted a study to examine the blink rate of participants using VDT and hard copy. In this well-designed investigation, blink rate was not significantly different between both methods of reading; however, there was a significant increase in incomplete blinks associated with VDT use (7.02%) when compared to hard copy (4.33%). As the visual task was consistent between the two platforms the importance of the display independent of the task was highlighted. Argiles et al., (2015) also showed similar results, with the blink rate reducing when reading from 3 VDT platforms (1 tablet and 2 PC) in comparison to 3 paper copies. Notably the investigators also observed that there were significantly more incomplete blinks during VDT reading when compared to reading from hard copy. These observations are important as an increased number of incomplete blinks during VDT has been found to be associated with ocular discomfort (Chu et al., 2014; Hirota et al., 2013). Patel et al., (1991) found that conducting a gaming task on a VDT increased the IBI but failed to examine the effects of different tasks on IBI. Despite the evidence that blink characteristics are modulated by cognitive load, there is a paucity of literature assessing changes in the blink rate with tasks of differing engagement levels on VDTs.

5.1.2 Non-Invasive Tear Break Up Time (NIBUT)

NIBUT is a gold standard measure for evaluating the tear film stability using non-invasive techniques and is important in diagnosing dry eye (Bron et al., 2014; Golding et al., 1997; Lin & Yiu, 2014; Wolffsohn et al., 2017). The effect of VDT use on tear film stability and subsequently dry eye had been well documented (Blehm et al., 2005; Portello, 2012;

Rosenfield, 2011; Tsubota et al., 1996). In a large scale epidemiological study involving 672 Japanese VDT workers, there was a high prevalence of dry eye in relatively young VDT users (76.5% in females and 60.2% in males), with the majority of participants having short TBUT without abnormal tear secretion or obvious ocular surface staining (Uchino et al., 2013). Moreover, in a study involving 3549 VDT users, the investigators found that more than 4 hours of VDT use was associated with an increased risk of dry eye (Uchino et al., 2008). Additionally, Nakamura et al., (2010) reported that lacrimal gland hypofunction was associated with VDT use suggesting that it may be involved in the mechanism for VDT associated dry eye.

5.1.3 Blinking and Tear Film

The relationship between blinking and the tear film are intertwined; blinking helps in re-surfacing the ocular surface with the tear film and therefore plays a crucial role in tear stability (Himebaugh et al., 2009; Owens & Phillips, 2001). As such, researchers often investigate blinking and tear stability concurrently. Himebaugh et al., (2009), attempted to assess changes in blinking and tear stability in real-time during 4 visual tasks (looking straight ahead, watching a movie, identifying rapidly changing letters, and playing a computer games). The study examined the participants' one eye on a video-slit lamp assessing invasive NaFl break up time and blinking simultaneously; the contralateral eye was used to view the four visual tasks. When participants were divided into dry eye and normal groups, the results showed that the blink rate reduced significantly in both groups during the game and letter tasks. Furthermore, fluorescein break-up area in the normal group was typically located in the inferior corneal region; whereas dry eye group showed a greater tear break-up area inferiorly, centrally and superiorly (Himebaugh et al., 2009). In support of these observations, in a non-invasive study consisting of 2 hours of sustained VDT work, it was shown that there was a

significant reduction in NIBUT between pre and post VDT task (Teoh et al., 2012). The same study also showed a non-statistically significant reduction in blink rate during the VDT task (Teoh et al., 2012).

Since cognitive load and level of task engagement are known to affect the blink rate, it is unsurprising that the tear film stability also varies with these factors. Indeed, in a study assessing the influence of fast and slow-paced computer games, Cardona et al., (2011) observed a real-time decrease in blink rate with both games, however the fast-paced game showed a significantly lower blink rate. When the investigators assessed fluorescein break up time and NIBUT, pre- and post-task, the fast paced games showed a larger effect on the tear film (Cardona et al., 2011).

5.1.4 Ocular Protection Index (OPI)

Given the concomitant relationship between blinking and tear film stability, the OPI metric was developed to quantify the relationship between the tear film break up time and the IBI. The OPI is calculated by dividing the NIBUT by the IBI (Gary, 2007). An OPI value of <1.00 is suggestive of an exposed ocular surface, increasing the risk of dry eye; whilst an OPI score >1.00 is indicative of an ocular surface that is protected by the tear film and is hence less likely to result in dry eye (Ousler et al., 2008). Much of the of the literature on OPI stems from observational studies on dry eye and clinical trials for ocular lubricants (Abelson et al., 2011; Ousler et al., 2002; Rolando et al., 2009; Simmons & Vehige, 2007). On review of the literature, it is evident that VDT use significantly affects blinking and NIBUT. Although no studies have investigated changes in OPI during VDT use, it could be safely assumed that changes in OPI will manifest since this metric is derived from TBUT and IBI. The same

assumptions cannot be made for smart devices given that little is known about blink and tear film behaviour when using these devices.

5.1.5 Ocular Surface and Smart Devices

At present, there is a significant lack of literature on the effects of smart devices on the tear film. Moon et al., (2014) evaluated the risk factors of dry eye in school children and found that smart device use was strongly associated with dry eye in children.

In a further study, Moon et al., (2016) reported that in the paediatric population, the mean daily duration of smart device use was linked to dry eye. When the researchers ceased smartphone use for 4 weeks, both subjective symptoms and objective signs of dry eye had improved suggesting that smartphone use in children was strongly associated with paediatric dry eye (Moon et al., 2016).

5.2 Objective

Smart devices mimic the actual function of VDTs but are more portable and offer many lifestyle and occupations uses. Furthermore, the ergonomics of use are vastly different with users typically holding the devices at a closer working distance and different angle of gaze. Smart devices also vary considerably in size and design. Therefore, the ocular surface consequences of using these devices are difficult to predict.

Controlling for the visual task and type of display in studies investigating dry eye on smart device use is paramount. Blink rate (Portello et al., 2013) and tear film stability needs to be investigated (Willcox et al., 2017) as these contribute to the development of dry eye.

The study presented in this chapter is a prospective, repeated measures study design that aims to evaluate NIBUT and blink rate in real-time during smart device use. The primary

objectives of the study was to determine the influence of various display platforms (Apple iPhone 6, Apple iPhone 6S, Samsung Galaxy S6, paper, Nokia 5210 and Apple Smart Watch) on NIBUT and blink rate when engaging with a reading and gaming task.

5.3 Methodology

5.3.1 Ethical Approval

Ethical approval was obtained from Research Ethics Committee, Faculty of Health & Human Sciences and Peninsula School of Medicine & Dentistry, Plymouth University (Appendix B, reference number 15/16-468). Prior to the start of data collection, participants were fully informed of the experiment and all relevant questions were answered accordingly. Written consent was obtained before the start of data collection.

5.3.2 Sample Size

In a study by Himebaugh, (2009), real-time invasive fluorescein tear break up time was assessed in 32 participants whilst they were engaged in a given task. Our sample size calculations using the software G*Power, version 3.1.9.2 (Faul et al., 2007; Prajapati et al., 2010) corroborated this sample size. The calculations for this study were based upon a repeated measures ANOVA model with a moderate effect size of 0.25 (Cohen, 1988, 1992), a significance level of $p<0.05$ with a power of 80%. According to the G*Power calculations, a total sample size of 30 participants was required for this experiment.

5.3.3 Inclusion and Exclusion Criteria

Participants were recruited from the staff and student population of Plymouth University using convenience sampling. The inclusion and exclusion criteria of the study are listed below:

5.3.3.1 Inclusion Criteria

- Aged between 18 and 35 years old.
- Completed a comprehensive eye examination within the last 12 months.
- RGP lens wear ceased for a minimum of 1 week.
- Soft contact lens wear ceased for a minimum of 2 days.
- Willing to participate in the study.
- Able to see decimal 0.50 at 30 cm (Snellen 6/12).
- A minimum of 6.50 D accommodation.

5.3.3.2 Exclusion Criteria

- History of any form of ocular surgery including LASIK.
- Participation in a pharmacological studies occurring concurrently.
- Suffering any form of ocular or systemic diseases.
- Pregnant or breast feeding.
- Taking medications.

5.3.4 The Binocular OFTA

Visual tasks such as reading and playing games on smart devices are normally performed under binocular viewing conditions. With regards to the tear film, all commercially available devices only assess the eye monocularly and fail to provide an assessment of the ocular characteristics in the natural binocular setting. For the purposes of this study, the Binocular OFTA was developed from the monocular device described in Chapter 2; and the components and working principles of the Binocular OFTA were based upon the monocular OFTA that was described previously in Chapter 2. The schematic of the Binocular OFTA system can be seen in Figure 5.1 below.

The device was designed to mimic a habitual viewing angle and posture that is normally conformed when reading or playing games on a smartphone. Furthermore, the device allows both eyes to fixate upon the target minimising fatigue. Most studies that have assessed the

NIBUT pre-and post-task performance of a task, fail to identify real-time changes that occur to the tear film. To address this limitation the binocular OFTA provides the means to evaluate the blink characteristics and NIBUT simultaneously, while participants are carrying out a given activity.

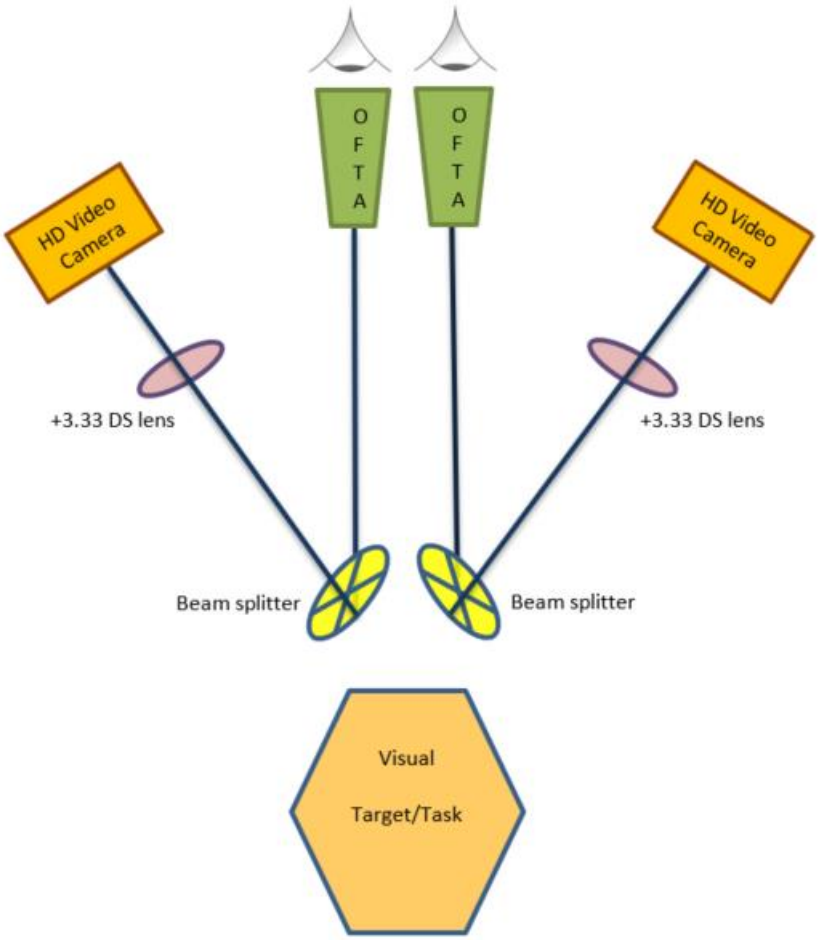


Figure 5.1: Schematic of the Binocular OFTA system.

The Binocular OFTA system consists of 2 monocular OFTA that will be operating side by side so that binocular measurements can be made at the same time while participants were exposed to visual task (Figure 5.1 and Figure 5.2).

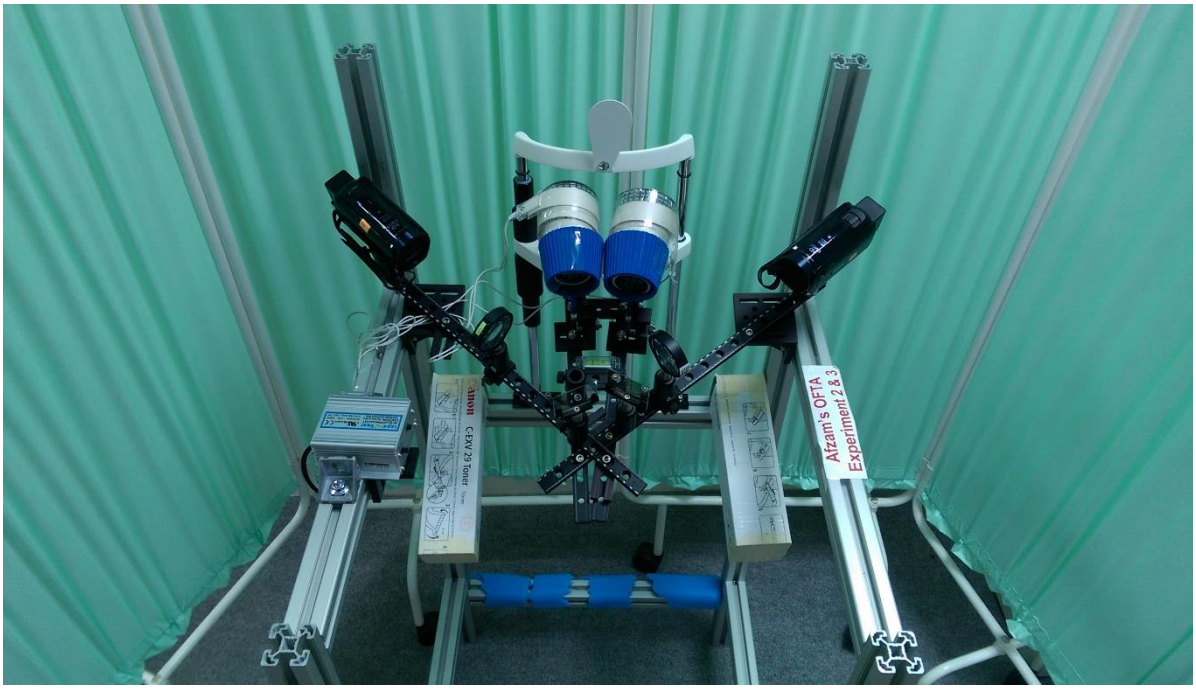


Figure 5.2: The mounted Binocular OFTA System.

Dovetail rails were used to secure each monocular OFTA unit to develop the binocular system (Figure 5.2). The binocular OFTA was then attached to a bespoke stand constructed from 12 Aluminium Alloy Struts with a 40 x 40 mm profile (RS Components, Corby, UK) (Figure 5.3 and 5.4). The viewing angle of the system was set to 35^0 inferior to mimic actual near task conditions (Lee et al., 2015). A forehead and chin rest was also attached to ensure that the head position was controlled throughout the tests.

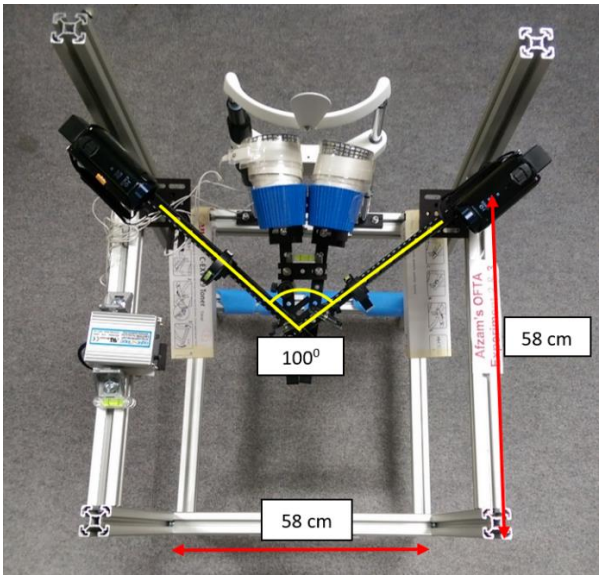


Figure 5.3: Base and angle dimensions for the Binocular OFTA System.

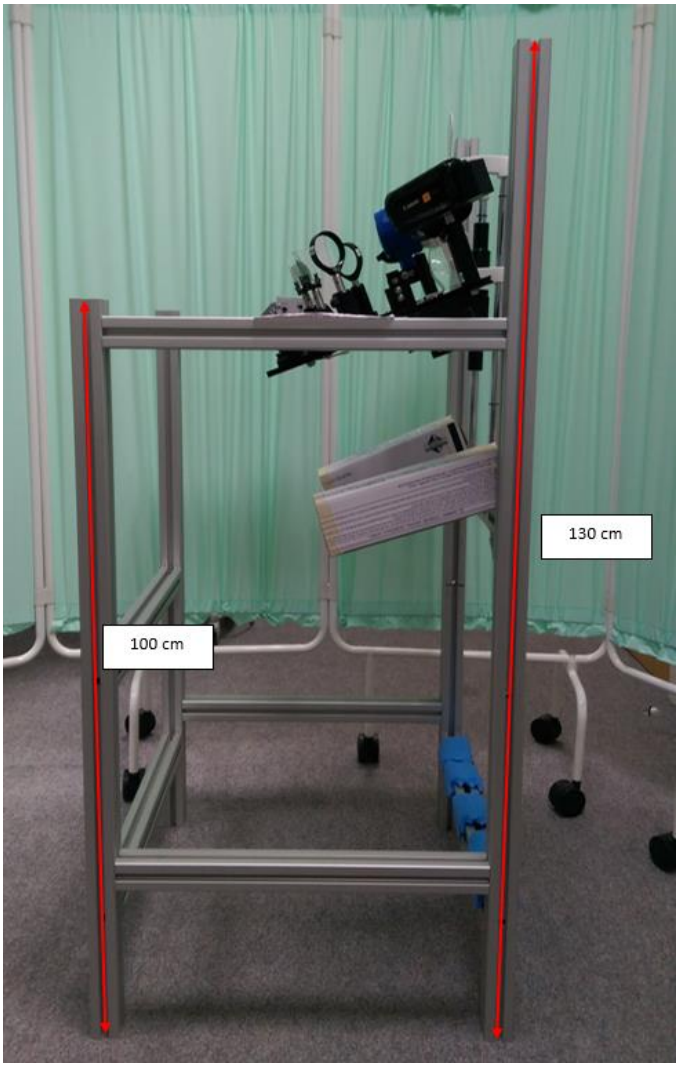


Figure 5.4: Height dimensions for the Binocular OFTA System.

The completed assembled Binocular OFTA System seen from various angle, can be seen in Figure 5.5 below.

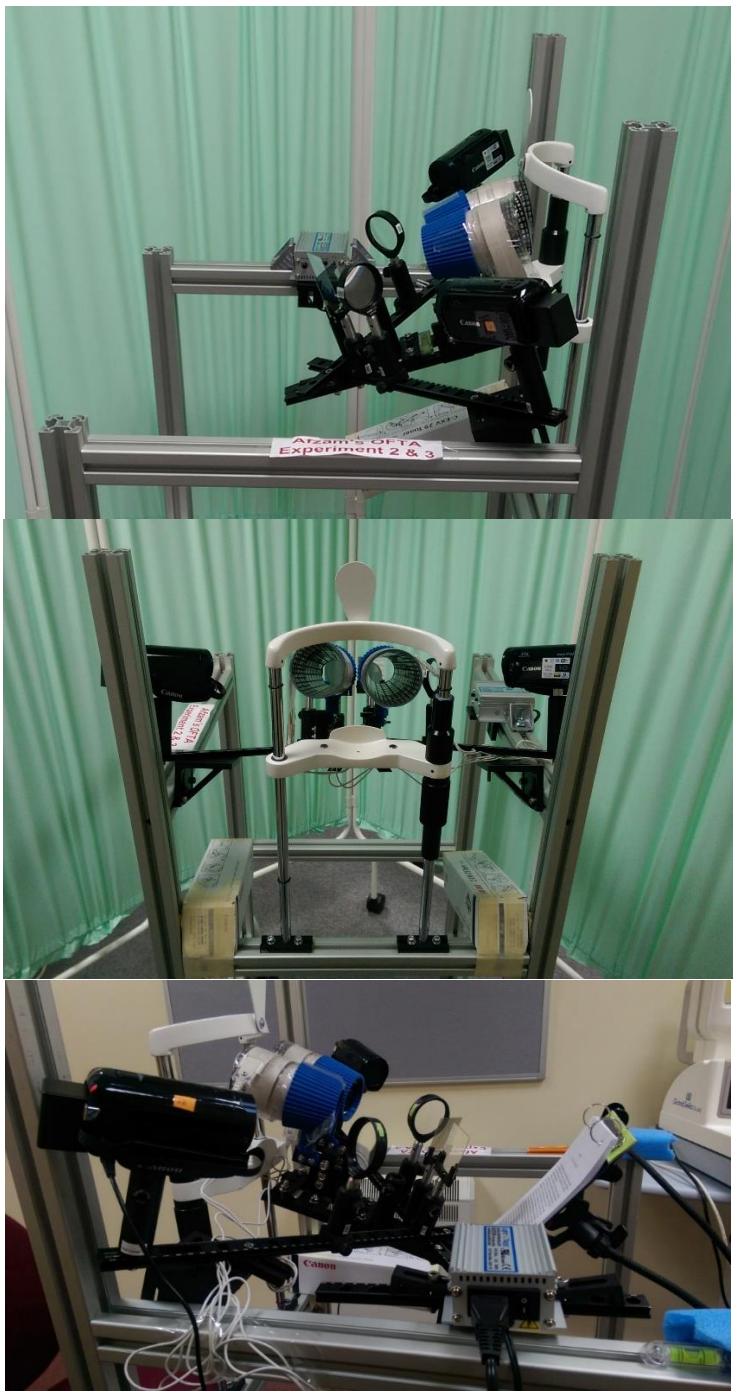


Figure 5.5: The Binocular OFTA System (from various angle).

Data was collected via video recordings which were stored on an external hard drive WD My Book, (Western Digital, San Jose, California, USA). Manual image analysis was later performed to determine the blink characteristics, NIBUT and OPI.

5.3.4.1 Blink and Tear Film Characteristics

Using the binocular OFTA, six parameters were investigated while participants were engaged in the reading and gaming tasks on the various platforms (see Table 5.1 below). For the purposes of this study, blinks were only counted when the upper eyelid covered at least half of the pupil. A custom designed reticule overlay was printed on a transparent film to consistently identifying a blink (Figure 5.6). The overlay was placed on top of a 21.5" LED monitor screen with a resolution of 1920 x 1080 pixels (Brilliance LED monitor, 221P3LPYES, Philips). The placement of the overlay was adjusted for each participant such that it was centred with the pupil. The pupil was aligned horizontally and vertically, using the appropriate red circle that best matched the pupil diameter (Figure 5.7). Video recordings of the Binocular OFTA were viewed on the monitor and blinks were manually counted when the upper eyelids moved past the horizontal blue line on the reticule (covers half the pupil). Various measures relating to the IBI were assessed to improve its validity and reliability (Carney & Hill, 1982; Cruz et al., 2011) (Table 5.1).

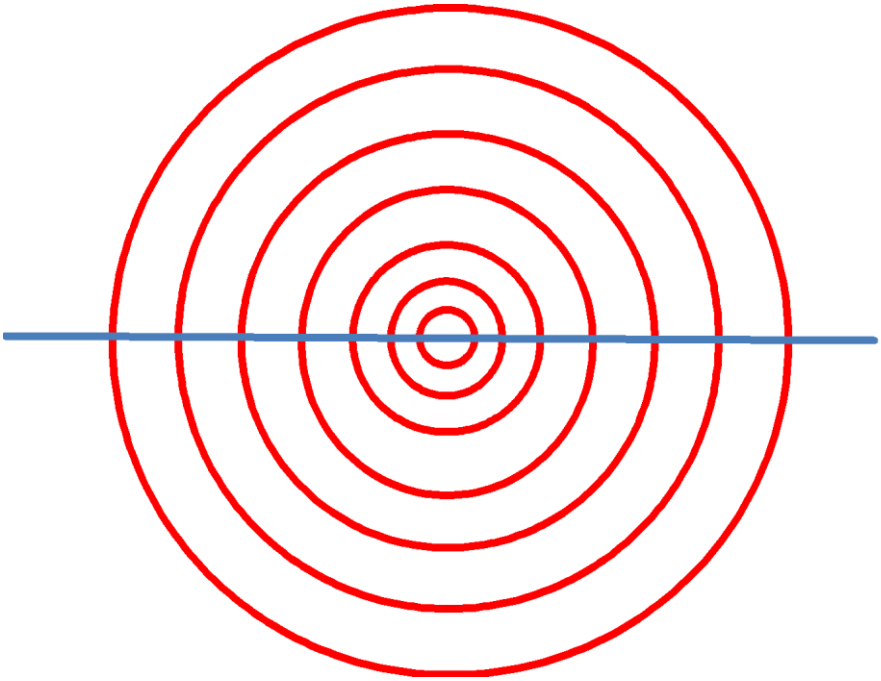


Figure 5.6: Reticule created for determining and counting blinks in this study.

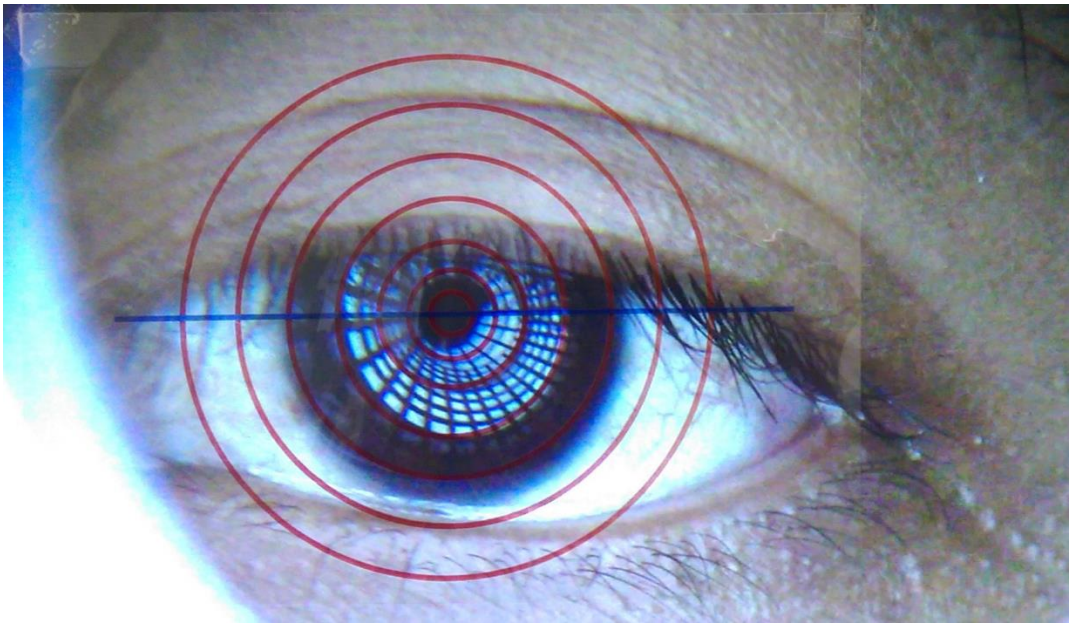


Figure 5.7: Reticule was properly aligned to participant's pupil.

To ensure that the natural blink characteristics were captured during the study, the participants were not informed of the exact outcome measures being assessed to avoid any confounding effects from artificial control of the blink response (Doane, 1980).

To determine NIBUT, VideoLAN Client (Version 2.2.2 Weatherwax, VLC media player) was used to assess the video recording on the same LED screen used to monitor the blinking. A stopwatch (Fastime O, Fastime) was used to assess the NIBUT that occurred on the videos. Measures of NIBUT were recorded and later averaged for data analysis. Table 5.1 summarises the outcome measures assessed.

Parameters Assessed	Definition
Blinks	A fast eyelid movement that closes and opens the palpebral fissure. Total number of blinks for 5 minutes was assessed.
Minimum IBI	The minimum (shortest) time in seconds between blinks.
Maximum IBI	The maximum (longest) time in seconds between blinks.
Average IBI	The average IBI time in seconds between blinks.
NIBUT	The time (seconds) between the last blink and the first appearance of distortion/rupture or break-up of the OFTA rings/mires.
OPI	Calculated by dividing the NIBUT value to the interblink interval (Average IBI).

Table 5.1: Definition of investigated parameters.

As tear film stability shows minimal diurnal variation (Patel et al., 1988; Pena-Verdeal et al., 2016), the length of the study session was unlikely to introduce an additional variability.

The image analysis described above was a manual process. For each given task/conditions, there were 3 videos of 5 minutes duration each (15 minutes of video duration in total per task/conditions). The analysis time for a single 5 minutes video recording would be approximately 20 minutes given that repeated viewings were required to acquire both the

total number of blinks (blink rates) and NIBUT from the videos. This means that for a single task/conditions, the 3 videos would take 60 minutes for manual image analysis. Therefore, for a single participant, the video analysis of 11 task/conditions (amounting to 33 videos) took 660 minutes. In this study, there were 33 participants (1089 videos in total for all the 11 task/conditions). Thus, the total analysis time for this study was approximately 21 780 minutes or 363 hours. During the video analysis process, the principal investigator would spend approximately 10 hours a day analysing images. Thus, variability in results may have been caused by fatigue of the examiner throughout the analysis process.

To examine the effect of this fatigue, a small study was conducted to assess the reproducibility of the analysis process. The primary investigator was tasked with evaluating 110 randomly selected videos 3 times each resulting in a total of 330 videos. These were assessed over 10 days with an expected analysis time of 10 hours per day (33 videos a day). A second investigator selected the videos and coded all videos from 1-330 in a random order. The primary investigator was blinded to this order and undertook the analysis chronologically according to the code. Thus, the Coefficient of Variation (CoV) was calculated for each of the original 110 videos using the values from the repeated measures. The mean (CoV) can be seen in Table 5.2 below. Given that CoV values are low, it can be concluded that the analysis process was minimal despite the long hours of data analysis.

Parameters Assessed	Coefficient of Variation (CoV) Mean±SD
Blink Rate	0.000±0.000
Minimum IBI	0.049±0.052
Maximum IBI	0.003±0.005
Average IBI	0.006±0.006
NIBUT	0.012±0.013
OPI	0.012±0.009

Table 5.2: The calculated CoV for each outcome measure.

5.3.4.2 Reading Task

The protocol for the reading task was the same as that used in Chapter 3. In summary, participants were required to read the text for 5 minutes on each platform during which time the binocular OFTA system recorded the tear film mires for both eyes (Figure 5.8). Participants were then asked to rest for 5 minutes between tasks (Occhipinti et al., 1988). The order of the platforms being introduced was randomized. The platforms were on the OFTA system at a distance of 30 cm and at a viewing angle of 35^0 (Lee et al., 2015).

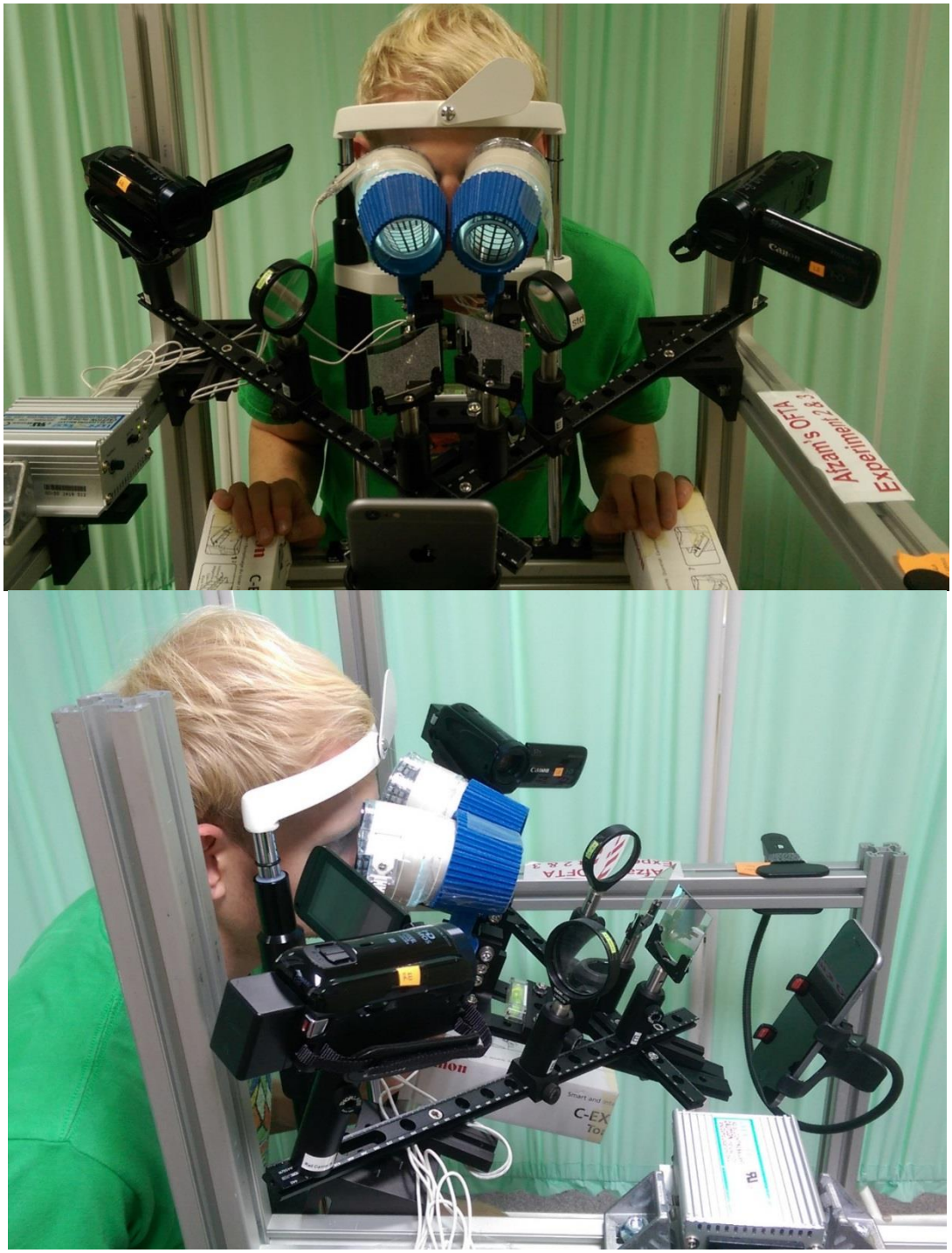


Figure 5.8: Participant's position for the reading task measurement. Note the reading material was being held by a holder.

5.3.4.3 Gaming Task

The protocol for the gaming task was the same as that used in Chapter 3. In summary, participants were required to engage with a maze based game for 5 minutes on each platform

during which time the binocular OFTA system recorded the tear film mires for both eyes. Participants were then asked to rest for 5 minutes between tasks (Occhipinti et al., 1988). The order of the platforms being introduced was randomized. The platforms were on the OFTA system at a distance of 30 cm and a viewing angle of 35^0 (Lee et al., 2015).

5.3.4.4 Baseline Measurement

The OFTA system was used to capture baseline recordings of the tear film and blink at the start of the participant's visit (Figure 5.9). The measurement was attained with the participant looking through the OFTA cones and fixating upon a 15 × 15 cm Maltese cross target located 2 m in front of their line of sight to ensure steady fixation (Figure 5.10). Participants were instructed to look at the target for 5 minutes while the video recording of their eyes was acquired.

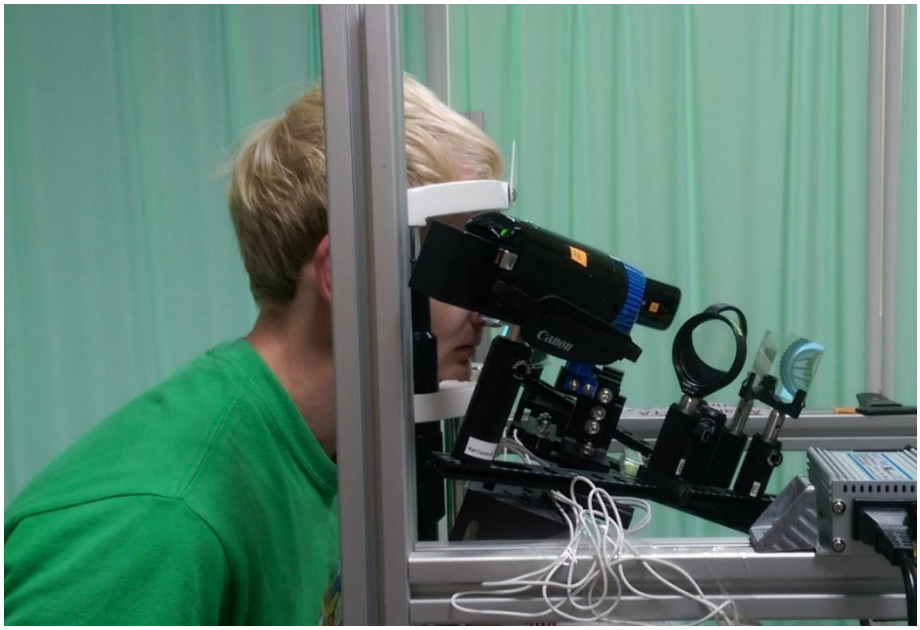


Figure 5.9: Participant's positioning on the Binocular OFTA.

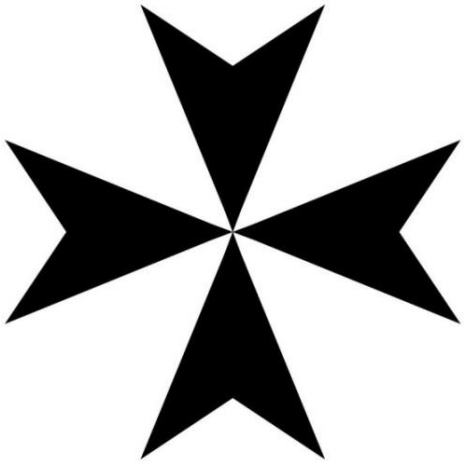


Figure 5.10: Maltese cross used as a fixation target for baseline measurement.

5.3.5 Data Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, New York). Initial data inspection was through a visual method (histogram) followed by assessment of the Sharpiro-Wilks test and Z-scores for skewness and Kurtosis; the tests confirmed the data to show a non-normal distribution. Friedman tests (χ) were used to determine if there were any significant differences between the parameters assessed when using the different platforms for reading and playing games. Where applicable, *post-hoc* testing using Wilcoxon signed-rank tests (Z) was conducted to determine the significant pairwise comparison and a Bonferroni correction applied to reduce Type 1 error (IBM Corporation, 2012; Lund & Lund, 2014). Where a Bonferroni correction was applied, the adjusted significance values (p_{adj}) were displayed. In addition, the changes from baseline value during the reading and gaming task were also calculated for each of the parameters investigated. A Spearman's rank correlation coefficient was used to examine the relationship between the OSDI scores, McMonnies Dry Eye Questionnaire scores and the baseline tear film and blink characteristic metrics.

5.4 Results

Thirty-three participants (14 males and 19 females) with a mean age of 26.52±4.17 years were assessed. Room temperature (mean=21.39±0.92 ^{0}C) (Purslow & Wolffsohn, 2007; Wolkoff, 2008) and humidity (mean=42.47±1.24%) (Abusharha & Pearce, 2012) are known to affect the tear film and were controlled in this study. No air draft was present in the examination room as it has been reported that exposure to high air velocity (1.0 m/s) for 30 minutes would cause a significant decrease in tear stability (Wyon & Wyon, 1987). The results showed no significant difference between eyes and thus only data from the right eye (RE) was further analysed to avoid statistical bias (Best et al., 2012).

5.4.1 Blink and Tear Film Characteristics During the Reading Task

5.4.1.1 Blink Rate During the Reading Task

Table 5.3 display the mean and standard deviations (±SD) for the blink rate for each platform. When considering the reading task, there was a significant difference in the blink rate between the 4 platforms [$\chi^2(3) = 18.528$ $p<0.0005$] Table 5.4 and Figure 5.11. *Post-hoc* analysis revealed that participants had a higher blink rate when reading on paper compared to reading on Samsung Galaxy S6 ($p_{adj}<0.0005$), Apple iPhone 6 ($p_{adj}=0.019$) and Apple iPhone 6S ($p_{adj}=0.019$) (Table 5.4).

Task & Platform	Blink Rate (Blink/minute) (Mean±SD)
Reading-Apple iPhone 6	13.35±11.48
Reading-Apple iPhone 6S	13.86±11.74
Reading-Samsung Galaxy S6	13.30±10.49
Reading-Paper	16.73±13.59

Table 5.3: Descriptive statistics for blink rate during the reading task.

Pairwise Comparison (Task & Platform)	Adjusted P Value for Pairwise Comparison
Reading-Samsung Galaxy S6 vs. Reading-Paper	<0.0005*
Reading-Apple iPhone 6 vs. Reading-Paper	0.019*
Reading-Apple iPhone 6S vs. Reading-Paper	0.019*
Reading-Samsung Galaxy S6 vs. Reading-Apple iPhone 6	1.000
Reading-Samsung Galaxy S6 vs. Reading-Apple iPhone 6S	1.000
Reading-Apple iPhone 6 vs. Reading-Apple iPhone 6S	1.000

*Statistically significant.

Table 5.4: Pairwise comparisons for blink rate during the reading task.

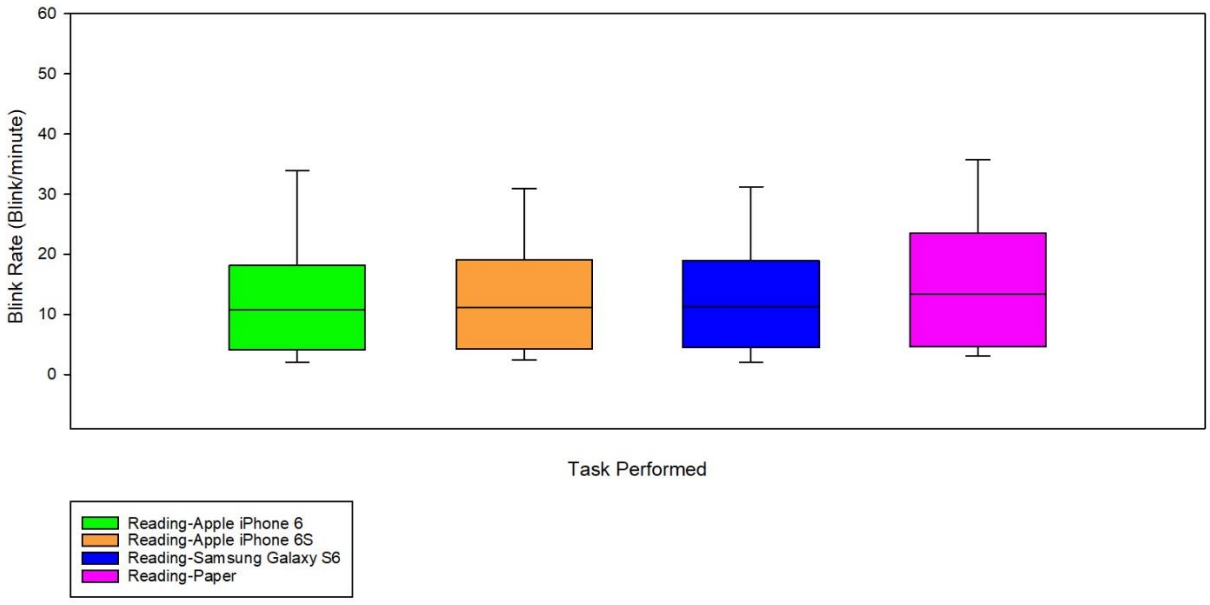


Figure 5.11: Box representing median and interquartile range for blink rate during the reading task.

5.4.1.2 Minimum, Maximum and Average IBI During the Reading Task

The results for the Minimum, Maximum and Average IBI were displayed in Table 5.5 and Figure 5.12.

IBI Metric	Task & Platform	IBI (seconds) (Mean±SD)
Minimum IBI	Reading-Apple iPhone 6	1.68±4.49
	Reading-Apple iPhone 6S	1.93±4.47
	Reading-Samsung Galaxy S6	3.76±15.14
	Reading-Paper	1.47±4.49
Maximum IBI	Reading-Apple iPhone 6	31.18±29.57
	Reading-Apple iPhone 6S	25.54±20.60
	Reading-Samsung Galaxy S6	33.90±34.81
	Reading-Paper	28.54±25.90
Average IBI	Reading-Apple iPhone 6	11.36±15.17
	Reading-Apple iPhone 6S	11.37±15.34
	Reading-Samsung Galaxy S6	13.27±22.00
	Reading-Paper	9.79±14.83

Table 5.5: Descriptive statistics for Minimum, Maximum and Average IBI during the reading task.

Pairwise Comparison (Task & Platform)	Adjusted P Value for Pairwise Comparison
Maximum IBI **Reading-Samsung Galaxy S6 vs. Reading-Apple iPhone 6S**	0.034*
Average IBI **Reading-Apple iPhone 6 vs. Reading-Paper**	0.007*
Average IBI **Reading-Apple iPhone 6S vs. Reading-Paper**	0.029*
Average IBI **Reading-Samsung Galaxy S6 vs. Reading-Paper**	<0.0005*
Maximum IBI **Reading-Apple iPhone 6S vs. Reading-Paper**	1.000
Maximum IBI **Reading-Apple iPhone 6S vs. Reading-Apple iPhone 6**	0.242
Maximum IBI **Reading-Paper vs. Reading-Apple iPhone 6**	1.000
Maximum IBI **Reading-Paper vs. Reading-Samsung Galaxy S6**	0.242
Maximum IBI **Reading-Apple iPhone 6 vs. Reading-Samsung Galaxy S6**	1.000
Average IBI **Reading-Apple iPhone 6S vs. Reading-Apple iPhone 6**	1.000
Average IBI **Reading-Apple iPhone 6S vs. Reading-Samsung Galaxy S6**	0.420
Average IBI **Reading-Apple iPhone 6 vs. Reading-Samsung Galaxy S6**	1.000

*Statistically significant.

Table 5.6: Pairwise comparisons for Maximum and Average IBI during the reading task.

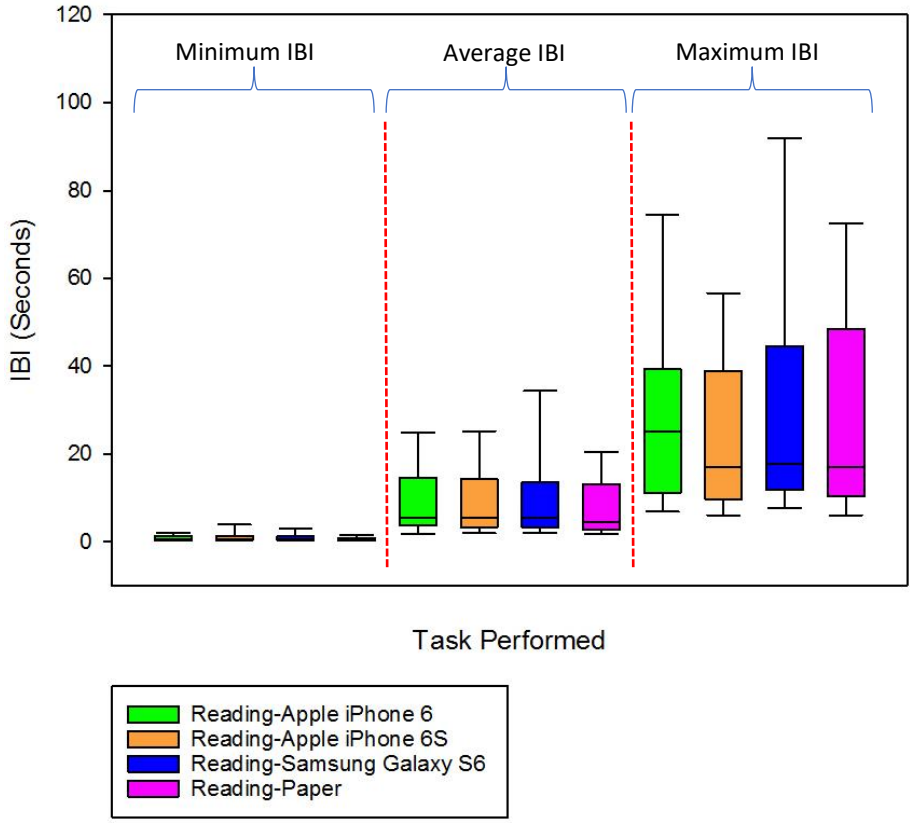


Figure 5.12: Box representing median and interquartile range for Minimum, Average and Maximum IBI values during the reading task.

There was no significant difference in the Minimum IBI between the 4 platforms [$\chi^2(3) = 7.242$ $p=0.065$]. In contrast, Maximum IBI [$\chi^2(3) = 9.456$, $p=0.024$] and Average IBI [$\chi^2(3) = 22.660$, $p<0.0005$] showed significant differences between the platforms assessed. *Post-hoc* analysis (Table 5.6) revealed that participants had a longer Maximum IBI when reading on Samsung Galaxy S6 compared to Apple iPhone 6S ($p_{adj}=0.034$). Furthermore, reading on paper produced significantly shorter Average IBI compared to Apple iPhone 6 ($p_{adj}=0.007$), Apple iPhone 6S ($p_{adj}=0.029$) and Samsung Galaxy S6 ($p_{adj}<0.0005$).

5.4.1.3 Binocular OFTA NIBUT During the Reading Task

The mean and standard deviations (±SD) for the Binocular OFTA NIBUT (seconds) during the reading task are shown in Table 5.7 and Figure 5.13.

Task & Platform	Binocular OFTA NIBUT (seconds) (Mean±SD)
Reading-Apple iPhone 6	7.58±9.27
Reading-Apple iPhone 6S	7.60±9.23
Reading-Samsung Galaxy S6	9.06±17.39
Reading-Paper	6.67±5.66

Table 5.7: Descriptive statistics for Binocular OFTA NIBUT during the reading task.

Pairwise Comparison (Task & Platform)	Adjusted P Value for Pairwise Comparison
Reading-Apple iPhone 6S vs. Reading-Paper	0.004*
Reading-Paper vs. Reading-Apple iPhone	0.378
Reading-Paper vs. Reading-Samsung Galaxy S6	0.304
Reading-Apple iPhone 6 vs. Reading-Samsung Galaxy S6	1.000
Reading-Apple iPhone 6 vs. Reading-Apple iPhone 6S	0.694
Reading-Samsung Galaxy S6 vs. Reading-Apple iPhone 6S	0.837

*Statistically significant.

Table 5.8: Pairwise comparisons for Binocular OFTA NIBUT during the reading task.

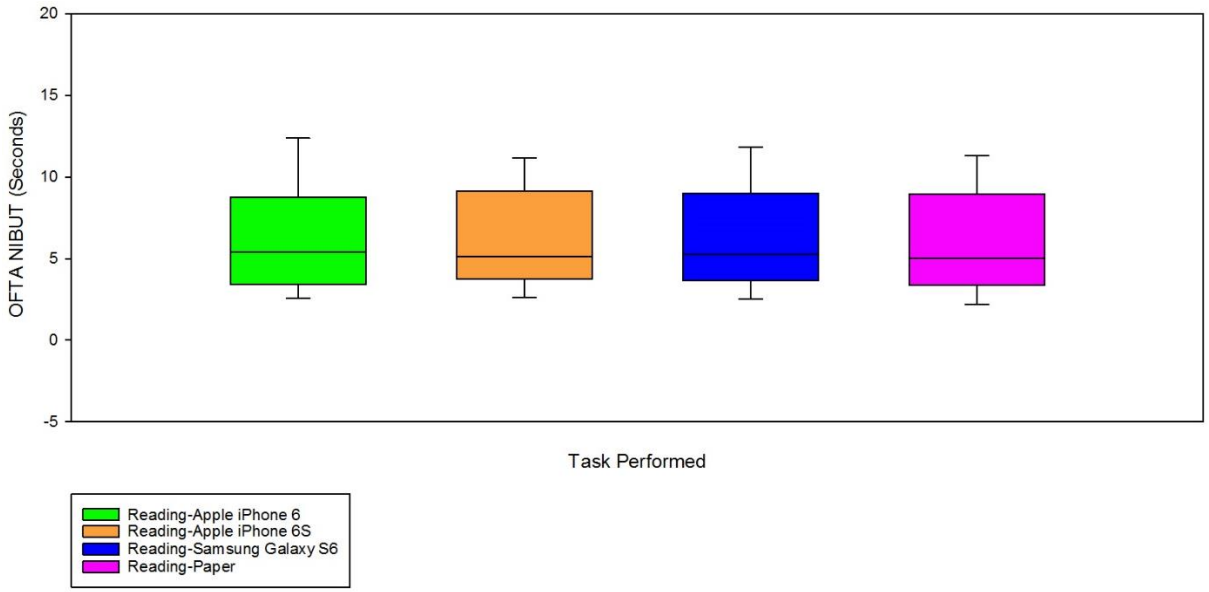


Figure 5.13: Box representing median and interquartile range for Binocular OFTA NIBUT during the reading task.

A significant difference was observed between measures of NIBUT when performing the reading task on the various platforms [$\chi^2(3) = 11.972$, p=0.007]. *Post-hoc* analysis revealed

that participants had a longer NIBUT when reading on an Apple iPhone 6S compared to the Paper (p_{adj}=0.004) (Table 5.8).

5.4.1.4 OPI During the Reading Task

The mean and standard deviations (±SD) for the OPI during the reading task were shown in Table 5.9 and Figure 5.14.

Task & Platform	OPI (Mean±SD)
Reading-Apple iPhone 6	0.96±0.49
Reading-Apple iPhone 6S	1.04±0.63
Reading-Samsung Galaxy S6	0.95±0.49
Reading-Paper	1.14±0.67

Table 5.9: Ocular Protection Index (OPI) during the reading task.

Pairwise Comparison (Task & Platform)	Adjusted P Value for Pairwise Comparison
Reading-Samsung Galaxy S6 vs. Reading-Paper	0.034*
Reading-Samsung Galaxy S6 vs. Reading-Apple iPhone 6	1.000
Reading-Samsung Galaxy S6 vs. Reading-Apple iPhone 6S	1.000
Reading-Apple iPhone 6 vs. Reading-Apple iPhone 6S	1.000
Reading-Apple iPhone 6 vs. Reading-Paper	0.103
Reading-Apple iPhone 6S vs. Reading-Paper	0.763

*Statistically significant.

Table 5.10: Pairwise comparisons for OPI during the reading task.

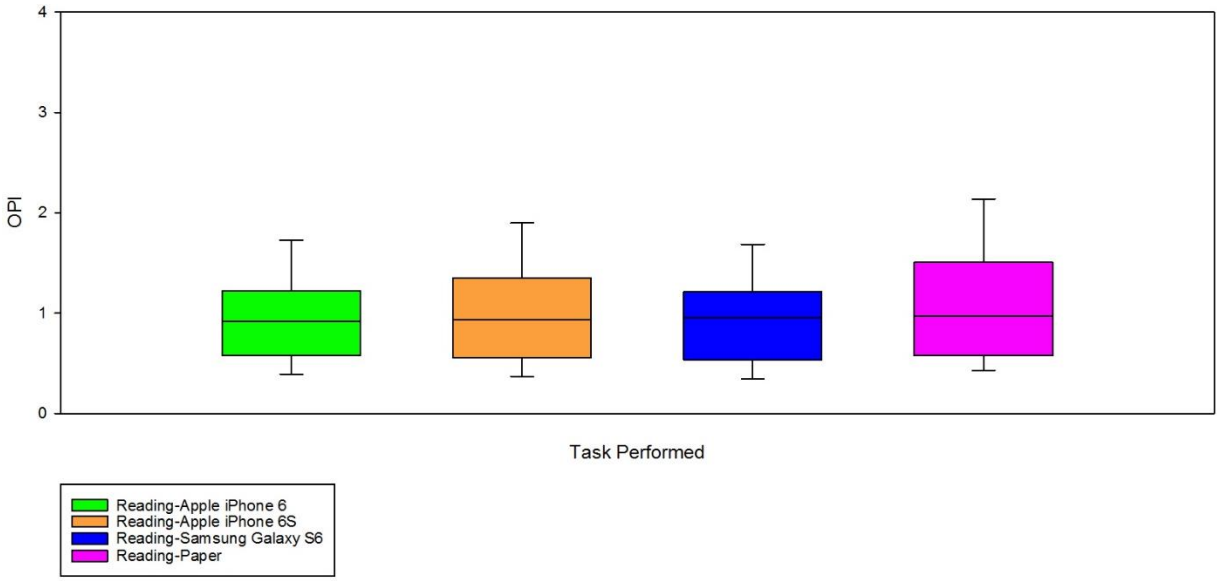


Figure 5.14: Box representing median and interquartile range for OPI during the reading task.

OPI was found to show significant differences when performing a reading task on different platforms [$\chi^2(3) = 9.036$ p=0.029]. *Post-hoc* analysis revealed that participants had a lower OPI when reading on Samsung Galaxy S6 compared to paper (p_{adj}=0.034) (Table 5.10).

5.4.2 Blink and Tear Film Characteristics During the Gaming Task

5.4.2.1 Blink Rate During the Gaming Task

Table 5.11 and Figure 5.15 display the mean and standard deviations (±SD) for the blink rate throughout the gaming task.

Task & Platform	Blink Rate (Blink/minute) (Mean±SD)
Gaming-Apple iPhone 6	8.84±7.36
Gaming-Apple iPhone 6S	9.59±7.34
Gaming-Samsung Galaxy S6	8.85±7.25
Gaming-Paper	10.70±8.36
Gaming-Nokia 5210	11.94±8.44
Gaming-Apple Smart Watch	9.44±6.36

Table 5.11: Blink rate during the gaming task.

Pairwise Comparison (Task & Platform)	Adjusted P Value for Pairwise Comparison
Gaming-Apple iPhone 6 vs. Gaming-Nokia 5210	0.002*
Gaming-Samsung Galaxy S6 vs. Gaming-Nokia 5210	0.001*
Gaming-Samsung Galaxy S6 vs. Gaming-Apple iPhone 6	1.000
Gaming-Samsung Galaxy S6 vs. Gaming-Apple Smart Watch	1.000
Gaming-Samsung Galaxy S6 vs. Gaming-Apple iPhone 6S	0.982
Gaming-Samsung Galaxy S6 vs. Gaming-Paper	0.063
Gaming-Apple iPhone 6 vs. Gaming-Apple Smart Watch	1.000
Gaming-Apple iPhone 6 vs. Gaming-Apple iPhone 6S	1.000
Gaming-Apple iPhone 6 vs. Gaming-Paper	0.086
Gaming-Apple Smart Watch vs. Gaming-Apple iPhone 6S	1.000
Gaming-Apple Smart Watch vs. Gaming-Paper	1.000
Gaming-Apple Smart Watch vs. Gaming-Nokia 5210	0.449
Gaming-Apple iPhone 6S vs. Gaming-Paper	1.000
Gaming-Apple iPhone 6S vs. Gaming-Nokia 5210	0.573
Gaming-Paper vs. Gaming-Nokia 5210	1.000

*Statistically significant.

Table 5.12: Pairwise comparisons for blink rate during the gaming task.

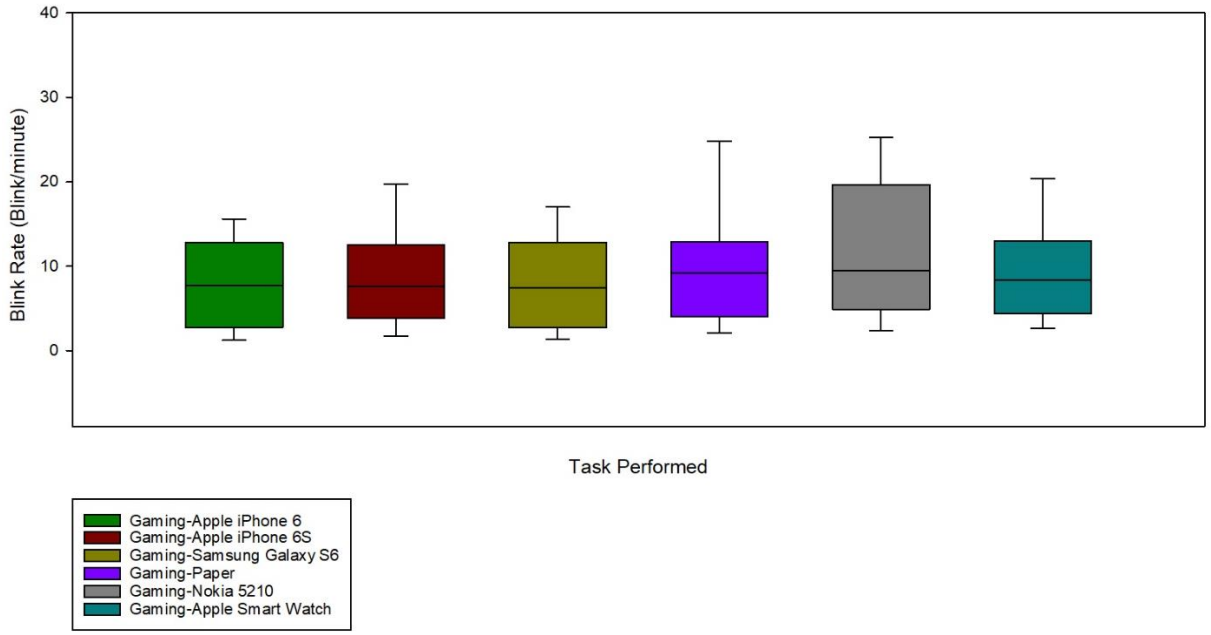


Figure 5.15: Box representing median and interquartile range for blink rate during the gaming task.

When considering the gaming task, the blink rate was significantly different between the various platforms [$\chi^2(5) = 23.981$, $p<0.0005$]. *Post-hoc* analysis showed that the blink rate was significantly higher with the Nokia 5210 when compared to both the iPhone 6 ($p_{adj}=0.002$) and the Samsung Galaxy S6 ($p_{adj}=0.001$) (Table 5.12).

5.4.2.2 Minimum, Maximum and Average IBI During the Gaming Task

The mean and standard deviations (±SD) for the Minimum, Maximum and Average IBI during the gaming task are displayed in Table 5.13 and Figure 5.16.

IBI Metric	Task & Platform	IBI (seconds) (Mean±SD)
Minimum IBI	Gaming-Apple iPhone 6	4.26±12.98
	Gaming-Apple iPhone 6S	1.49±3.04
	Gaming-Samsung Galaxy S6	1.68±3.69
	Gaming-Paper	0.89±1.59
	Gaming-Nokia 5210	0.84±1.02
	Gaming-Apple Smart Watch	0.94±1.17
Maximum IBI	Gaming-Apple iPhone 6	42.94±32.67
	Gaming-Apple iPhone 6S	40.96±32.90
	Gaming-Samsung Galaxy S6	42.14±36.40
	Gaming-Paper	39.30±28.79
	Gaming-Nokia 5210	32.53±24.33
	Gaming-Apple Smart Watch	37.34±23.11
Average IBI	Gaming-Apple iPhone 6	16.39±21.09
	Gaming-Apple iPhone 6S	11.84±10.70
	Gaming-Samsung Galaxy S6	14.88±17.91
	Gaming-Paper	10.87±10.67
	Gaming-Nokia 5210	9.72±8.96
	Gaming-Apple Smart Watch	10.56±8.85

Table 5.13: Descriptive statistics for Minimum, Maximum and Average IBI during the gaming task.

Pairwise Comparison (Task & Platform)	Adjusted P Value for Pairwise Comparison
Gaming-Apple iPhone 6 vs. Gaming-Nokia 5210	0.009*
Gaming-Samsung Galaxy S6 vs. Gaming-Nokia 5210	0.002*
Gaming-Nokia 5210 vs. Gaming-Paper	1.000
Gaming-Nokia 5210 vs. Gaming-Apple iPhone 6S	0.529
Gaming-Nokia 5210 vs. Gaming-Apple Smart Watch	0.268
Gaming-Paper vs. Gaming-Apple iPhone 6S	1.000
Gaming-Paper vs. Gaming-Apple Smart Watch	1.000
Gaming-Paper vs. Gaming-Apple iPhone 6	0.268
Gaming-Paper vs. Gaming-Samsung Galaxy S6	0.070
Gaming-Apple iPhone 6S vs. Gaming-Apple Smart Watch	1.000
Gaming-Apple iPhone 6S vs. Gaming-Apple iPhone 6	1.000
Gaming-Apple iPhone 6S vs. Gaming-Samsung Galaxy S6	1.000
Gaming-Apple Smart Watch vs. Gaming-Apple iPhone 6	1.000
Gaming-Apple Smart Watch vs. Gaming-Samsung Galaxy S6	1.000
Gaming-Apple iPhone 6 vs. Gaming-Samsung Galaxy S6	1.000

*Statistically significant.

Table 5.14: Pairwise comparisons for Average IBI during the gaming task.

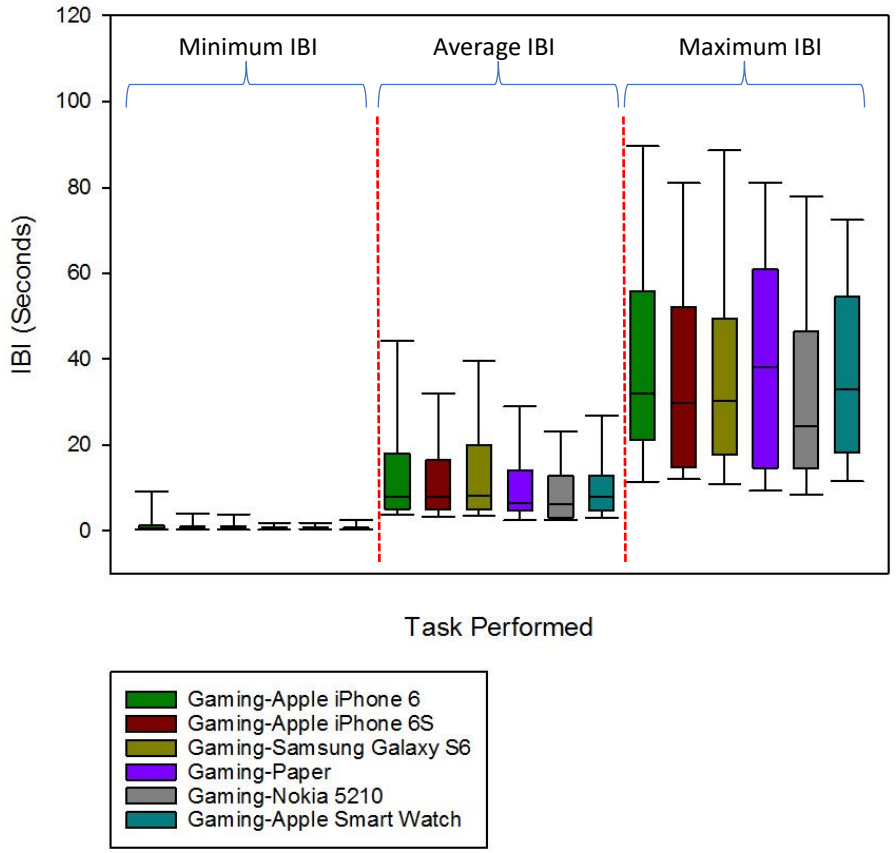


Figure 5.16: Box representing median and interquartile range for Minimum, Average and Maximum IBI during the gaming task.

There was no significant difference in the Minimum IBI [$\chi^2(5) = 10.030$, p=0.074] and Maximum IBI [$\chi^2(5) = 8.913$, p=0.113] but significant variation was observed for Average IBI [$\chi^2(5) = 20.983$, p=0.001] between the 6 platforms. *Post-hoc* analysis revealed that compared to the Nokia 5210, participants had significantly longer Average IBI when playing games on the Apple iPhone 6 (p_{adj}=0.009) and Samsung Galaxy S6 (p_{adj}=0.002) (Table 5.14).

5.4.2.3 Binocular OFTA NIBUT During the Gaming Task

The mean and standard deviations (±SD) for the Binocular OFTA NIBUT (seconds) during the gaming task are shown in Table 5.15 and Figure 5.17. No significant difference was found in the NIBUT results during the gaming task [$\chi^2(5) = 5.581$, p=0.349].

Task & Platform	Binocular OFTA NIBUT (seconds) (Mean±SD)
Gaming-Apple iPhone 6	8.14±11.22
Gaming-Apple iPhone 6S	7.95±9.31
Gaming-Samsung Galaxy S6	7.57±7.46
Gaming-Paper	7.67±8.54
Gaming-Nokia 5210	6.91±6.40
Gaming-Apple Smart Watch	7.21±6.34

Table 5.15: Descriptive statistics for Binocular OFTA NIBUT during the gaming task.

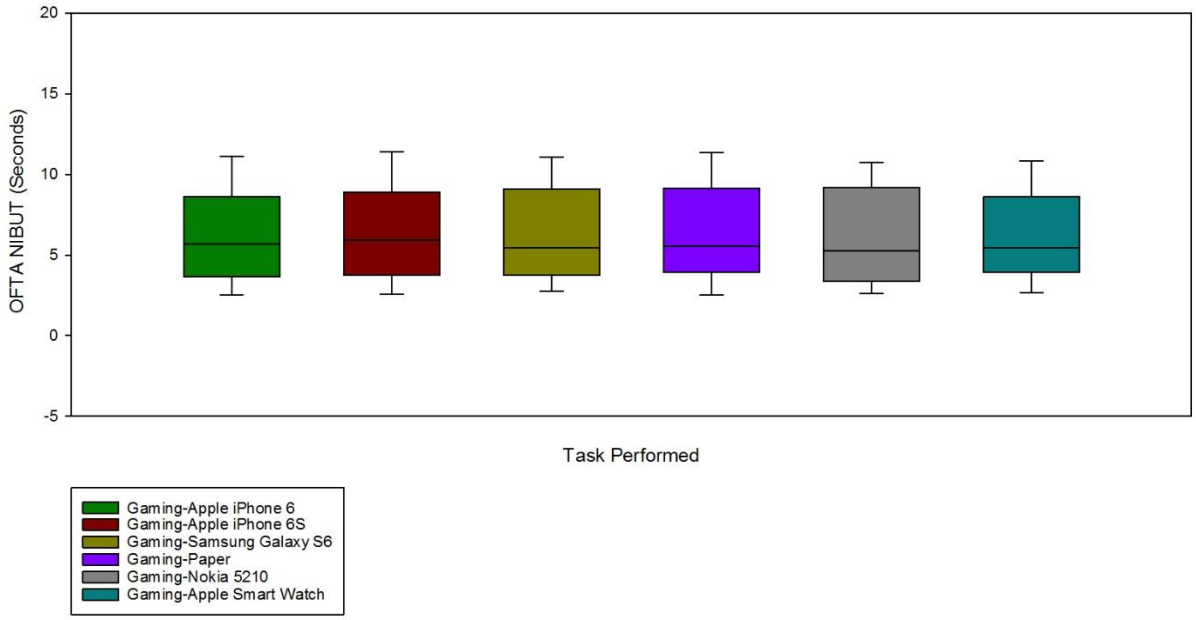


Figure 5.17: Box representing median and interquartile range for Binocular OFTA NIBUT during the gaming task.

5.4.2.4 OPI During the Gaming Task

The mean and standard deviations (±SD) for the OPI during the gaming task are shown in Table 5.16 and Figure 5.18.

Task & Platform	OPI (Mean±SD)
Gaming-Apple iPhone 6	0.74±0.45
Gaming-Apple iPhone 6S	0.84±0.46
Gaming-Samsung Galaxy S6	0.73±0.38
Gaming-Paper	0.89±0.47
Gaming-Nokia 5210	0.93±0.48
Gaming-Apple Smart Watch	0.81±0.38

Table 5.16: Ocular Protection Index (OPI) during the gaming task.

Pairwise Comparison (Task & Platform)	Adjusted P Value for Pairwise Comparison
Gaming-Apple iPhone 6 vs. Gaming-Paper	0.024*
Gaming-Apple iPhone 6 vs. Gaming Nokia 5210	0.037*
Gaming-Apple iPhone 6 vs. Gaming-Samsung Galaxy S6	1.000
Gaming-Apple iPhone 6 vs. Gaming-Apple Smart Watch	0.846
Gaming-Apple iPhone 6 vs. Gaming-Apple iPhone 6S	0.186
Gaming-Samsung Galaxy S6 vs. Gaming-Apple Smart Watch	1.000
Gaming-Samsung Galaxy S6 vs. Gaming-Apple iPhone 6S	0.982
Gaming-Samsung Galaxy S6 vs. Gaming-Nokia 5210	0.268
Gaming-Samsung Galaxy S6 vs. Gaming-Paper	0.186
Gaming-Apple Smart Watch vs. Gaming-Apple iPhone 6S	1.000
Gaming-Apple Smart Watch vs. Gaming-Nokia 5210	1.000
Gaming-Apple Smart Watch vs. Gaming-Paper	1.000
Gaming-Apple iPhone 6S vs. Gaming-Nokia 5210	1.000
Gaming-Apple iPhone 6S vs. Gaming-Paper	1.000
Gaming-Nokia 5210 vs. Gaming-Paper	1.000

*Statistically significant.

Table 5.17: Pairwise comparisons for OPI during the gaming task.

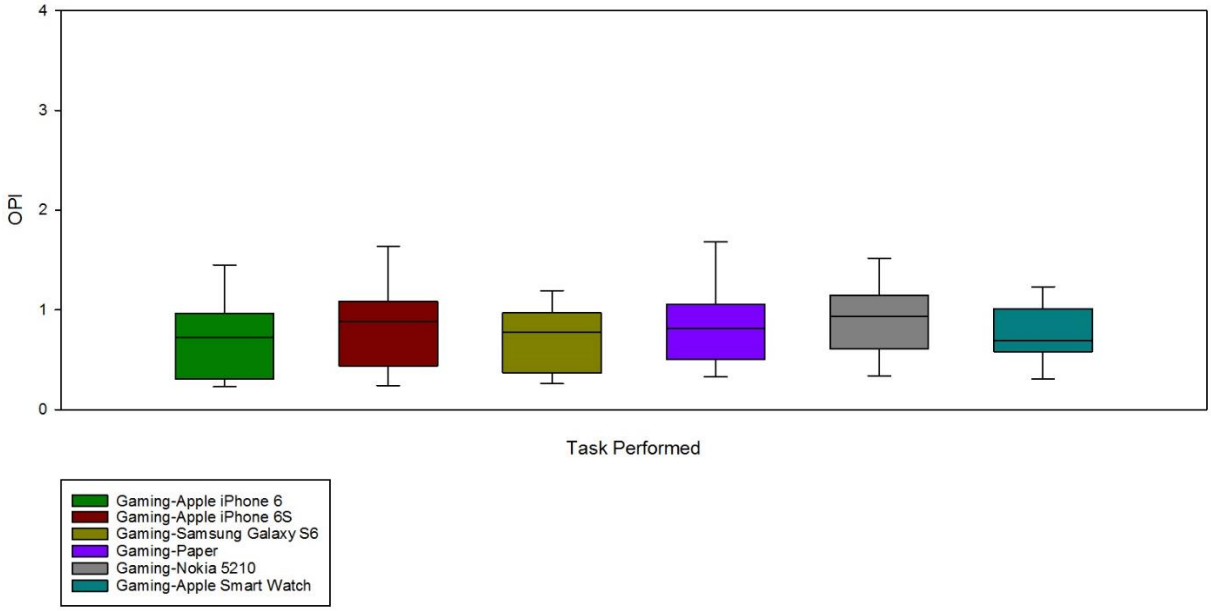


Figure 5.18: Box representing median and interquartile range for OPI during the gaming task.

A significant difference was found in the OPI results during the gaming task [$\chi^2(5) = 16.723$, p=0.005]. *Post-hoc* analysis revealed that compared to the Apple iPhone 6, participants had a

significantly higher OPI when playing games on Paper (p_{adj}=0.024) and Nokia 5210 (p_{adj}=0.037) (Table 5.17).

5.4.3 Changes in Blink and Tear Film Characteristics Throughout the Studies (Baseline vs. Reading vs. Gaming)

5.4.3.1 Blink Rate (Baseline vs. Reading vs. Gaming)

The mean and standard deviations (±SD) for the blink rate at baseline was 20.81±15.65 blink/minute. A significant interaction was observed between the baseline blink rate and choice of task [$\chi^2(10) = 93.858$, $p<0.0005$].

		Baseline	Reading				Gaming				
			iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	Apple Smart Watch
Reading	**iPhone 6**	0.002*									
	iPhone 6S	0.003*	1.000								
	Samsung Galaxy S6	<0.0005*	1.000	1.000							
	Paper	1.000	0.787	0.917	0.145						
Gaming	**iPhone 6**	<0.0005*	0.235	0.197	1.000	<0.0005*					
	iPhone 6S	<0.0005*	1.000	1.000	1.000	0.002*	1.000				
	Samsung Galaxy S6	<0.0005*	0.114	0.094	0.639	<0.0005*	1.000	1.000			
	Paper	<0.0005*	1.000	1.000	1.000	0.145	1.000	1.000	0.639		
	Apple Smart Watch	<0.0005*	1.000	1.000	1.000	0.001*	1.000	1.000	1.000	1.000	
	Nokia 5210	0.014*	1.000	1.000	1.000	1.000	0.049*	1.000	0.022*	1.000	1.000

The p values presented in this table had been adjusted (p_{adj}) and the symbol * denote statistical significance.

Table 5.18: Pairwise comparisons for blink rate (Baseline vs. Reading vs. Gaming).

The *post-hoc* comparisons were shown in Table 5.18. *Post-hoc* analysis revealed that the blink rate measured at baseline was greater than the blink rate during each of the gaming tasks (Apple iPhone 6: p_{adj}<0.0005, Apple iPhone 6S: p_{adj}<0.0005, Samsung Galaxy S6: p_{adj}<0.0005, Nokia 5210: p_{adj}=0.014, Apple Smart Watch: p_{adj}<0.0005, Paper: p_{adj}<0.0005) and reading tasks (Apple iPhone 6: p_{adj}=0.002, Apple iPhone 6S: p_{adj}=0.003, Samsung Galaxy S6: p_{adj}<0.0005, with the exception of reading on the paper platform (p_{adj}=1.00) (Table 5.18). In addition, the blink rate while playing games on Samsung Galaxy S6 was significantly lower compared to the blink rate while playing games on Nokia 5210 (p_{adj}=0.022) and reading on paper (p_{adj}<0.0005). Playing games on Apple iPhone 6 also significantly reduced the blink rate compared to playing games on Nokia 5210 (p_{adj}=0.049) and reading on paper (p_{adj}<0.0005). Reading on paper were found to significantly increase the blink rate compared to playing games on Apple Smart Watch (p_{adj}=0.001) and playing games on Apple iPhone 6S (p_{adj}=0.002).

5.4.3.2 Minimum IBI (Baseline vs. Reading vs. Gaming)

The mean baseline measurement of Minimum IBI was 2.35$\pm$9.09 seconds. A significant interaction was observed between the baseline Minimum IBI and choice of task [$\chi^2(10)$ = 27.380, p=0.002].

		Baseline	Reading				Gaming				
			iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	Apple Smart Watch
Reading	iPhone 6	1.000									
	iPhone 6S	1.000	1.000								
	Samsung Galaxy S6	1.000	1.000	1.000							
	Paper	1.000	1.000	1.000	1.000						
Gaming	iPhone 6	1.000	1.000	1.000	1.000	1.000					
	iPhone 6S	1.000	1.000	0.965	1.000	1.000	1.000				
	Samsung Galaxy S6	1.000	1.000	1.000	1.000	1.000	1.000	1.000			
	Paper	1.000	0.053	0.005*	0.005*	1.000	0.056	1.000	1.000		
	Apple Smart Watch	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.185	
	Nokia 5210	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.965	1.000

The p values presented in this table had been adjusted (p_{adj}) and the symbol *denote statistical significance.

Table 5.19: Pairwise comparisons for Minimum IBI (Baseline vs. Reading vs. Gaming).

Post-hoc results in Table 5.19 showed that playing games on paper produced a significantly shorter amount of Minimum IBI compared to reading on Samsung Galaxy S6 (p_{adj}=0.005) and reading on Apple iPhone 6S (p_{adj}=0.005).

5.4.3.3 Maximum IBI (Baseline vs. Reading vs. Gaming)

The mean baseline values for Maximum IBI were 18.35±20.83 seconds. A significant interaction was observed between the baseline Maximum IBI and choice of task [$\chi^2(10)$ = 100.690, p<0.0005].

		Baseline	Reading				Gaming				
			iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	Apple Smart Watch
Reading	**iPhone 6**	0.019*									
	iPhone 6S	0.709	1.000								
	Samsung Galaxy S6	0.001*	1.000	1.000							
	Paper	0.489	1.000	1.000	1.000						
Gaming	**iPhone 6**	<0.0005*	0.064	0.001*	0.787	0.001*					
	iPhone 6S	<0.0005*	0.828	0.023*	1.000	0.038*	1.000				
	Samsung Galaxy S6	<0.0005*	0.064	0.001*	0.787	0.001*	1.000	1.000			
	Paper	<0.0005*	0.351	0.007*	1.000	0.012*	1.000	1.000	1.000		
	Apple Smart Watch	<0.0005*	0.073	0.001*	0.872	0.002*	1.000	1.000	1.000	1.000	
	Nokia 5210	<0.0005*	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

The p values presented in this table had been adjusted (p_{adj}) and the symbol * denote statistical significance.

Table 5.20: Pairwise comparisons for Maximum IBI (Baseline vs. Reading vs. Gaming).

Post-hoc analysis revealed that the Maximum IBI was significantly shorter at baseline than for all of the gaming tasks (Apple iPhone 6: p_{adj}<0.0005, Apple iPhone 6S: p_{adj}<0.0005, Samsung Galaxy S6: p_{adj}=0.001, Nokia 5210: p_{adj}<0.0005, Apple Smart Watch: p_{adj}<0.0005, Paper: p_{adj}<0.0005). The Maximum IBI was also significantly shorter at baseline when compared to the values obtained during the reading tasks with the Apple iPhone 6 (p_{adj}=0.019) and Samsung Galaxy S6 (p_{adj}=0.001) (Table 5.20). In addition, Maximum IBI was significantly shorter when reading on Apple iPhone 6S compared to playing games on Apple iPhone 6S (p_{adj}=0.023), playing games on paper (p_{adj}=0.007), playing games on Apple Smart Watch (p_{adj}=0.001), playing games on Apple iPhone 6 (p_{adj}=0.001) and playing games on Samsung Galaxy S6 (p_{adj}=0.001). Furthermore, Maximum IBI was significantly shorter when reading on paper compared to playing games on Apple iPhone 6S (p_{adj}=0.038), playing games on paper (p_{adj}=0.012), playing games on Apple Smart Watch (p_{adj}=0.002), playing games on Apple iPhone 6 (p_{adj}=0.001) and playing games on Samsung Galaxy S6 (p_{adj}=0.001).

5.4.3.4 Average IBI (Baseline vs. Reading vs. Gaming)

The mean baseline values for Average IBI were 7.34±14.22 seconds. A significant interaction was observed between the baseline Average IBI and choice of task [$\chi^2(10) = 90.879$, p<0.0005].

		Baseline	Reading				Gaming				
			iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	Apple Smart Watch
Reading	**iPhone 6**	0.009*									
	iPhone 6S	0.027*	1.000								
	Samsung Galaxy S6	<0.0005*	1.000	1.000							
	Paper	1.000	0.872	1.000	0.064						
Gaming	**iPhone 6**	<0.0005*	0.249	0.100	1.000	<0.0005*					
	iPhone 6S	<0.0005*	1.000	1.000	1.000	0.004*	1.000				
	Samsung Galaxy S6	<0.0005*	0.038*	0.013*	0.574	<0.0005*	1.000	1.000			
	Paper	0.001*	1.000	1.000	1.000	0.137	1.000	1.000	0.296		
	Apple Smart Watch	<0.0005*	1.000	1.000	1.000	0.001*	1.000	1.000	1.000	1.000	
	Nokia 5210	0.046*	1.000	1.000	1.000	1.000	0.060	1.000	0.007*	1.000	0.965

The p values presented in this table had been adjusted (p_{adj}) and the symbol * denote statistical significance.

Table 5.21: Pairwise comparisons for Average IBI (Baseline vs. Reading vs. Gaming).

The Average IBI values were shorter at baseline when compared to each gaming task (Apple iPhone 6: p_{adj}<0.0005, Apple iPhone 6S: p_{adj}<0.0005, Samsung Galaxy S6: p_{adj}<0.0005, Paper: p_{adj}=0.001, Nokia 5210: p_{adj}=0.046, Apple Smart Watch: p_{adj}<0.0005) as well as the reading task (Apple iPhone 6: p_{adj}=0.009, Apple iPhone 6S: p_{adj}=0.027, Samsung Galaxy S6: p_{adj}<0.0005) (Table 5.21). When comparing between the reading and gaming task, reading on paper has significantly shorter Average IBI compared to playing games on Apple iPhone 6S (p_{adj}=0.004), playing games on Apple Smart Watch (p_{adj}=0.001), playing games on Apple iPhone 6 (p_{adj}<0.0005) and playing games on Samsung Galaxy S6 (p_{adj}<0.0005). In addition, playing games on Samsung Galaxy S6 produced significantly longer Average IBI compared to reading on Apple iPhone 6S (p_{adj}=0.013), playing games on Nokia 5210 (p_{adj}=0.007) and reading on Apple iPhone 6 (p_{adj}=0.038).

5.4.3.5 Binocular OFTA NIBUT (Baseline vs. Reading vs. Gaming)

The mean baseline values for NIBUT were 9.79$\pm$11.26 seconds. A significant interaction was observed between the baseline Binocular OFTA NIBUT and choice of task [$\chi^2(10) = 77.178$, p<0.0005].

		Baseline	Reading				Gaming				
			iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	Apple Smart Watch
Reading	iPhone 6	<0.0005*									
	iPhone 6S	<0.0005*	1.000								
	Samsung Galaxy S6	<0.0005*	1.000	1.000							
	Paper	<0.0005*	1.000	0.371	1.000						
Gaming	iPhone 6	<0.0005*	1.000	1.000	1.000	1.000					
	iPhone 6S	<0.0005*	1.000	1.000	1.000	0.185	1.000				
	Samsung Galaxy S6	<0.0005*	1.000	1.000	1.000	1.000	1.000	1.000			
	Paper	<0.0005*	1.000	1.000	1.000	1.000	1.000	1.000	1.000		
	Apple Smart Watch	<0.0005*	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	
	Nokia 5210	<0.0005*	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

The p values presented in this table had been adjusted (p_{adj}) and the symbol * denote statistical significance.

Table 5.22: Pairwise comparison for Binocular OFTA NIBUT (Baseline vs. Reading vs. Gaming).

The Binocular OFTA NIBUT measurements at baseline was significantly higher than all the NIBUT measurements taken during the reading and gaming tasks (p_{adj}<0.0005) (Table 5.22). For Binocular OFTA NIBUT, there was no significant differences between any of the reading and gaming task (p_{adj} >0.05).

5.4.3.6 OPI (Baseline vs. Reading vs. Gaming)

The mean baseline values for OPI was 2.09±0.99. A significant interaction was observed between the OPI and choice of task [$\chi^2(10) = 82.253$, p<0.0005].

		Baseline	Reading				Gaming				
			iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	iPhone 6	iPhone 6S	Samsung Galaxy S6	Paper	Apple Smart Watch
Reading	iPhone 6	<0.0005*									
	iPhone 6S	<0.0005*	1.000								
	Samsung Galaxy S6	<0.0005*	1.000	1.000							
	Paper	0.023*	1.000	1.000	1.000						
Gaming	iPhone 6	<0.0005*	1.000	1.000	1.000	0.003*					
	iPhone 6S	<0.0005*	1.000	1.000	1.000	1.000	1.000				
	Samsung Galaxy S6	<0.0005*	1.000	0.709	1.000	0.008*	1.000	1.000			
	Paper	<0.0005*	1.000	1.000	1.000	1.000	1.000	1.000	0.872		
	Apple Smart Watch	<0.0005*	1.000	1.000	1.000	0.574	1.000	1.000	1.000	1.000	
	Nokia 5210	<0.0005*	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

The p values presented in this table had been adjusted (p_{adj}) and the symbol * denote statistical significance.

Table 5.23: Pairwise comparison for OPI (Baseline vs. Reading vs. Gaming).

The OPI values at baseline was significantly higher than the OPI values during the gaming (Apple iPhone 6: p_{adj}<0.0005, Apple iPhone 6S: p_{adj}<0.0005, Samsung Galaxy S6: p_{adj}<0.0005, Paper: p_{adj}<0.0005, Nokia 5210: p_{adj}<0.0005, Apple Smart Watch: p_{adj}<0.0005) and reading tasks (Apple iPhone 6: p_{adj}<0.0005, Apple iPhone 6S: p_{adj}<0.0005, Samsung Galaxy S6: p_{adj}<0.0005, Paper: p_{adj}=0.023) (Table 5.23). In addition, OPI values when reading on paper was significantly higher compared to the OPI values when playing games on Apple iPhone 6 (p_{adj}=0.003) and playing games on Samsung Galaxy S6 (p_{adj}=0.008).

5.4.4 Changes in Blink and Tear Film Characteristics with Regards to Baseline

The changes in Blink Rate, Minimum IBI, Maximum IBI, Average IBI, NIBUT and OPI (baseline compared to each task and platform) can be seen in Table 5.24 below.

Task & Platform	Mean Average Changes					
	Blink Rate (Blink/minute)	Minimum IBI (seconds)	Maximum IBI (seconds)	Average IBI (seconds)	NIBUT (seconds)	OPI
Reading-Apple iPhone 6	7.47±11.10	0.67±4.70	-12.83±21.99	-4.02±6.75	2.22±2.30	1.13±0.88
Reading-Apple iPhone 6S	6.96±11.29	0.42±5.06	-7.19±22.07	-4.03±7.38	2.19±2.33	1.05±0.89
Reading-Samsung Galaxy S6	7.52±9.31	-1.41±6.09	-15.55±17.99	-5.93±9.42	0.73±6.54	1.14±0.84
Reading-Paper	4.09±10.87	0.88±4.66	-10.20±18.12	-2.45±4.55	3.12±6.16	0.95±0.88
Gaming-Apple iPhone 6	11.98±14.00	-1.91±12.34	-24.59±20.61	-9.05±13.52	1.66±1.71	1.35±1.06
Gaming-Apple iPhone 6S	11.23±13.11	0.86±9.62	-18.47±19.29	-4.50±12.43	1.85±2.44	1.24±1.08
Gaming-Samsung Galaxy S6	11.97±12.80	0.67±6.45	-23.79±22.47	-7.54±8.30	2.23±4.27	1.36±0.96
Gaming-Paper	10.13±11.86	1.46±7.67	-20.95±24.68	-3.53±12.71	2.13±3.01	1.20±0.99
Gaming-Nokia 5210	8.88±12.85	1.50±9.11	-14.18±16.73	-2.38±11.25	2.89±5.30	1.16±1.05
Gaming-Apple Smart Watch	11.38±12.11	1.40±8.87	-18.99±18.76	-3.22±11.71	2.58±5.37	1.28±1.02

Table 5.24: The mean average changes in the investigated parameters (baseline compared to each task and platform).

5.4.5 Number of Participants with NIBUT less than 10 seconds

Table 5.25 below showed the number of participants with <10 seconds NIBUT.

Task	Number of Participants		
	NIBUT 10 seconds or higher	NIBUT <10 seconds	Total
Baseline	11	22	33
Reading-Apple iPhone 6	6	27	33
Reading-Apple iPhone 6S	6	27	33
Reading-Samsung Galaxy S6	6	27	33
Reading-Paper	6	27	33
Gaming-Apple iPhone 6	6	27	33
Gaming-Apple iPhone 6S	6	27	33
Gaming-Samsung Galaxy S6	6	27	33
Gaming-Paper	7	26	33
Gaming-Nokia 5210	5	28	33
Gaming-Smart Watch	5	28	33

Table 5.25: Number of participants with <10 seconds NIBUT.

5.4.6 Correlation Between the Baseline Blinking and Tear Film Characteristics and the Subjective Assessment of Dry Eye

The OSDI had a mean score of 5.17±2.91 while the McMonnies mean score was 3.70±2.05. There was no significant correlation between OSDI scores and all Binocular OFTA metrics for both reading and gaming tasks (Figure 5.19). The correlation between McMonnies score and all the other metrics were also not significant, except for 'Minimum IBI' which showed a moderately-weak significant correlation (Figure 5.20).

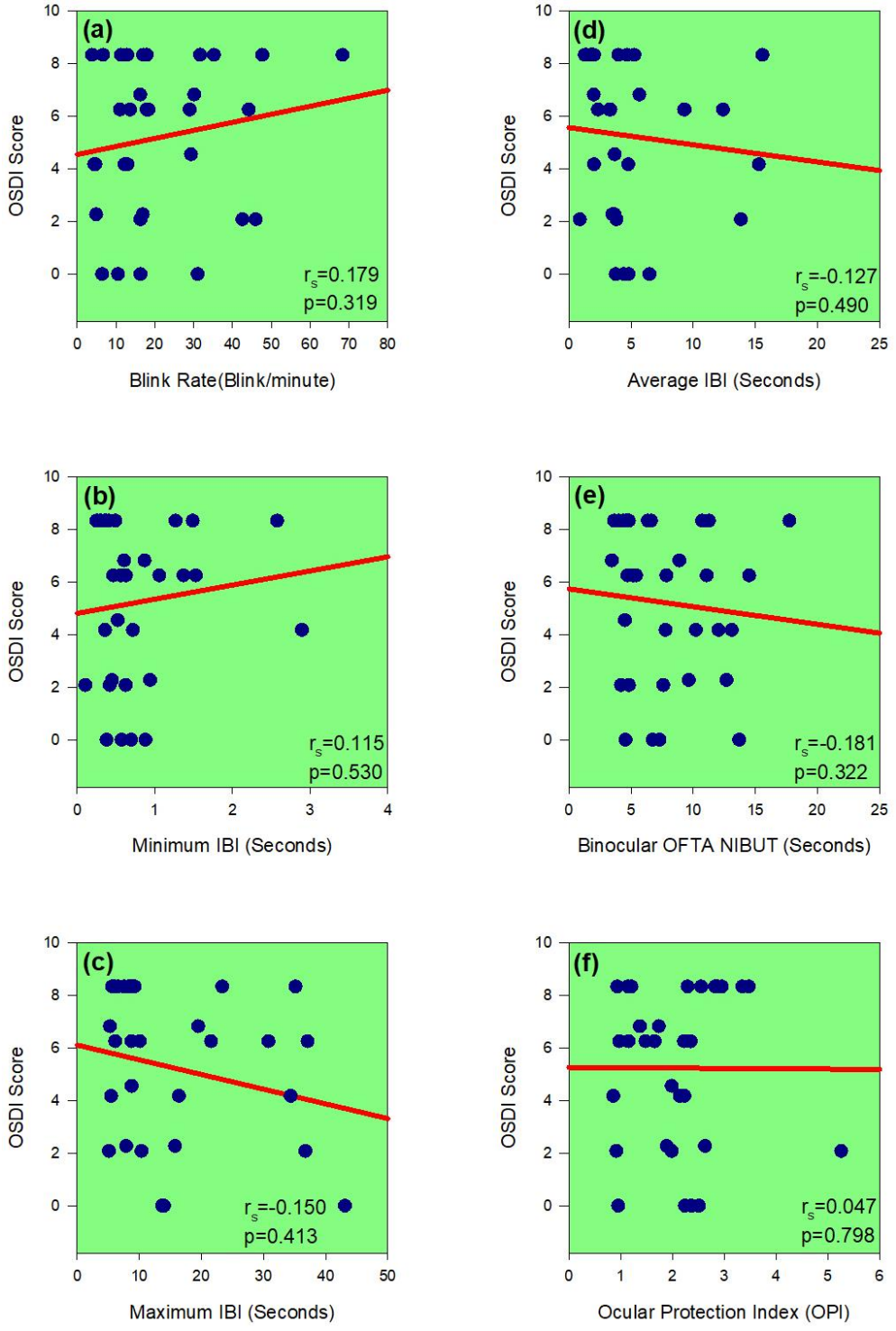


Figure 5.19: Spearman's correlation between OSDI Score and (a) Blink Rate, (b) Minimum IBI, (c) Maximum IBI, (d) Average IBI, (e) Binocular OFTA NIBUT, (f) Ocular Protection Index.

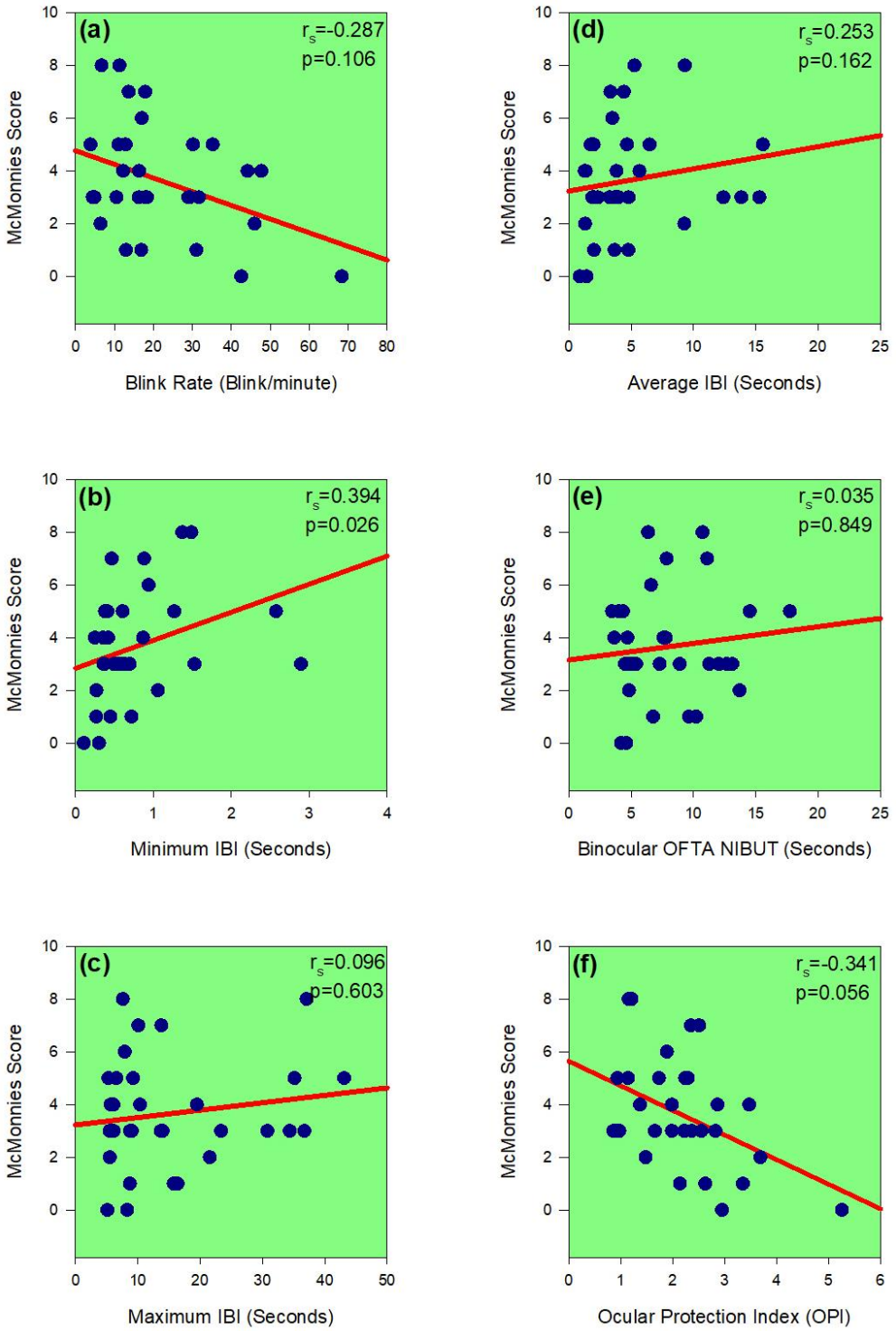


Figure 5.20: Spearman's correlation between McMonnies Score and (a) Blink Rate, (b) Minimum IBI, (c) Maximum IBI, (d) Average IBI, (e) Binocular OFTA NIBUT, (f) Ocular Protection Index.

5.5 Discussion

A significant body of literature suggests that blink rates are affected by the cognitive difficulty of the task being conducted (Holland & Tarlow, 1972, 1975; Martins & Carvalho, 2015; Wong et al., 2002; York et al., 1971). Despite this known association, few studies have examined the effect of the host platform on the blink rate whilst maintaining task difficulty. In this study, it was found that blink rate was significantly reduced when participants observed the reading task on all three smart devices in comparison to the paper platform. Although it is unclear if VDTs are analogous to smart devices, Argiles et al., (2015) found similar results to that of the present study when comparing blink rate with VDT and paper copy. Conversely, Chu et al., (2014) found that blink rate was similar with VDT when compared to hard copy. These disparate reports highlight the ambiguity surrounding the effect of visual ergonomics on the eye.

In this study, the distance and angular position of all platforms, as well as the size of letter and font were kept consistent. Thus, the task difficulty should have been similar across the four platforms. The luminance was also similar; however, an intrinsic difference exists between the smart device screens and the paper copy. All of the smart devices used in this study used backlit screens whereas the paper copy luminance is dependent on illuminance from an external light source. It is common for smart devices to use backlit screens in order to improve the visibility of the displayed material in low light, however, some smart devices such as the Amazon Kindle (Amazon Inc., Seattle, Washington) need to be externally lit. Given the inherent difference between these two methods of lighting, it is conceivable that backlit screens may have an influence on the blink rate. To test this hypothesis future studies should incorporate smart devices without an internal light source to determine if this is a significant factor. The screen refresh rate also needs to be considered. All smart devices tested in this

experiment ran with a 60 Hz refresh rate. Jaschinski et al., (1996) examined the effect of VDT refresh rates on blink rate and reported that lower frequencies resulted in longer inter-blink intervals; the lower refresh rates in their study (between 55 and 90 Hz) matched that of the smartphones in the present study. Holland & Tarlow, (1975) suggested that blinking occurs between visual fixations and may be timed so as not to interfere with significant visual input. Cognitive process may be disrupted by sudden change in visual input because component processes or display areas in visual perception, imaging and operational memory are shared (Holland & Tarlow, 1975). Blinking, causes a brief blackout period and produce a sudden change in the visual input (Holland & Tarlow, 1975). Blink rate is low when information memory is operating, and cognitive processes utilising display areas accessible to visual input are disrupted during the blackout period of a blink (Holland & Tarlow, 1975).

There may also be a psychological factor that influences blink rate. Human factors research suggest that there is an innate preference towards reading from paper when compared to screen based text (Cakir et al., 1980). Muter et al., (1982) found that this preference was generally associated with the tactile nature of the material rather than specific factors related to the screen itself. This bias towards the paper copy is likely to influence blink rate and may partly contribute towards the findings.

For the first time, the binocular OFTA enables a real-time assessment of NIBUT whilst participants are viewing a smart device. It is known that in between blinks, the tear film becomes progressively thinner and dry spots develop over the cornea (Holly, 1973). This causes the tear film to become irregular and can reduce image quality (Tutt et al., 2000). Incomplete blinks do not maintains the tear film but instead destabilize the tear film and predispose the eye to dryness (Hirota et al., 2013). The longer the IBI, the greater the negative

effect on the tear film. Given that the blink rate is affected by the platform on which the reading material is viewed on, it is conceivable that tear break up time is also influenced. The results from this study revealed that NIBUT during the reading task was longer when the participants viewed the material on paper in comparison to the Apple iPhone 6S. Furthermore, during the reading task, OPI was found to be higher on paper in comparison with the Samsung Galaxy S6. These observations are indicative of a possible influence of smart devices on NIBUT changes, although the fact that these differences were only identified on an isolated number of platform suggests that either the variability in measuring NIBUT with the OFTA over shadows any clinical changes or NIBUT is minimally affected by the platform choice relative to blink rate.

In regards to the gaming task, NIBUT was similar during the gaming task across all platforms and the only results of note were the longer IBI with both the Apple iPhone 6 and Samsung Galaxy S6 when compared to the Nokia 5210. Standardising the gaming task between the 6 platforms was challenging and hence there were several unwanted disparities. Technical limitations meant that a snake game was used on the Nokia 5210 rather than the maze game. It is likely that the snake game has a different cognitive load when compared to the maze game which may have influenced the blink rate. Cardona et al., (2011) examined the blink rate whilst participants played 2 different VDT games (one game was easy while the other game was harder) and found that blink rate was lower when participants were playing the harder VDT game due to the greater cognitive load and higher concentration levels (Cardona et al., 2011). This theory is supported by the fact that all other platforms which used an equivalent game provided similar IBI. To conclusively determine the influence of the type of game on blink rate, both a maze game and snake game should be performed on the same

platform and the differences in blink rate assessed. Another confounding factor was that the Nokia 5210 had a lower luminance when compared to the other smartphones as it was not possible to adjust the brightness sufficiently. Furthermore, interacting with the maze games on the smart devices required the user to touch the screen, whereas the paper platform required the participants to mark the maze with a pencil; which may be another confounding variable.

The aim of the study was to examine the effect of different smart devices on blink and tear film characteristics whilst engaging on either a reading or gaming task. The study design was not focused on determining the difference in these clinical parameters between baseline and following each task. The presentation of the platforms was randomized for both the reading and gaming task, however, the randomization was only performed within each task group (i.e. reading and gaming) and not between both tasks. As such, the results are presented with the reading task in isolation, followed by the gaming task in isolation and then the with all results compared together. This last comparison which occurs between tasks and with the baseline values, need to be considered in view of a possible order effect influencing the data.

The baseline blink rate that was found in this study was comparable to those reported by other researchers (Carney & Hill, 1982; Doughty, 2001; Ousler et al., 2002). Compared to baseline, the reduction in blink rate when participants were performing their reading and gaming task were also comparable to other studies that have noted a reduction in blink rate when participants were exposed to VDT related task (Kazuo & Nakamori, 1993; Patel et al., 1991; Schlote et al., 2004; Tsubota, 1998). In accordance with the literature, the present investigation showed a significant increase in IBI when participants were reading (Cho et al.,

1997). Our study was unable to compare the average IBI of gaming task to other studies because most researchers only mention the blink rate in their study and not the average IBI.

The baseline values for Binocular OFTA NIBUT were significantly higher than all the reading and gaming task on all platforms. This finding are similar to what previous researchers have found (Cardona et al., 2011; Sweeney et al., 2013). The decrease in tear stability has been reported with VDT use (Himebaugh et al., 2009; Jansen et al., 2010) and this was attributed to reduced blink rate and frequent incomplete blink (Teoh et al., 2012). Moreover, measures of OPI during reading and gaming task on all platforms were less than 1.0 (Table 5.10 and Table 5.18) due to decreased NIBUT and increased average IBI. These results suggest that the cornea was prone to relatively long periods of exposure whilst engaging in all tested tasks (Ousler et al., 2008). It is important to note that this is the first time that the NIBUT measurements used to derive OPI were assessed in real-time and hence it is unclear how the published normative values relate to these results.

There was a statistically significant difference in NIBUT values where a comparison was made between the baseline and each post task value (Table 5.22). Willcox et al., (2017) proposed that participants with a NIBUT value of <10 seconds are at greater risk of dry eye. Interestingly, on inspection of Table 5.25, 22 participants had a NIBUT value of <10 seconds at baseline but following all tasks, the number of participants falling into this category increased. If reading is considered in isolation (Table 5.8), NIBUT values were different with the paper and iPhone 6S. However, if examining change from baseline (Table 5.24) no such statistical significance was found, indicating that any variations in NIBUT were small and were unlikely to be of clinical significance. Blink rate decreased from baseline when reading and gaming on all

platforms. This change was statistically different for all devices with the exception of reading on paper where a small non-significant change of 4.09±10.87 blink/minute was observed.

It was interesting to note that none of the metrics that were assessed correlated with the participant's perception of dry eye as assessed by both the McMonnies and OSDI, possibly yet again highlighting the multifactorial nature of dry eyes.

5.6 Conclusion

This study concluded that:

- Blink rate was reduced when participants observed the reading task on all three smart devices in comparison to paper.
- During the reading task, (i) Average IBI was longer on Apple iPhone 6 compared to paper and (ii) Samsung Galaxy S6 showed higher Maximum IBI compared to Apple iPhone 6.
- NIBUT during the reading task was longer when participants viewed the material on paper in comparison to the Apple iPhone 6S.
- During the gaming task, Average IBI was longer with both the Apple iPhone 6 and Samsung Galaxy S6 when compared to the Nokia 5210.
- Blink rate was found to be faster at baseline when compared with the blink rate when conducting all tasks with the exception of reading on paper.
- NIBUT was longer at baseline when compared to all inter-task measurements (reading and gaming).

Chapter 6: Accommodative Response to Targets on Smartphone and Smart Watch

6.1 Introduction

Examination of the accommodative response (AR) to a stimulus is valuable in clinical practice (Rosenfield et al., 1996). The average lag of accommodation is between 0.25 D and 0.50 D for children and young adults (Scheiman & Wick, 2014). The magnitude of the accommodative lag is relative to the demands of the stimulus (McClelland & Saunders, 2003; Millodot, 2015). Under near work conditions, high levels of accommodative lag are strongly associated with asthenopic symptoms (Chase et al., 2009; Tosha et al., 2009; Momeni-Moghaddam et al., 2014).

With the increasing popularity of smart devices i.e. smartphone, tablet and smart watch, the human accommodative system is challenged by a wide variety of electronic visual stimuli (Hayes et al., 2007; Do et al., 2011; Plaza et al., 2011; Puspitasari & Ishii, 2016). The ubiquitious use of computers have been linked to a condition termed Computer Vision Syndrome (CVS) which manifests as symptoms of eyestrain, ocular discomfort, headache, dry eye sensation, blurry vision and diplopia (Blehm et al., 2005; Burns, 1995; Lie & Watten, 1994; Parihar et al., 2016; Portello, 2012; Scheiman, 1996). Salibello and Nilsen (1995), proposed that 90% of the population who use computers for more than 2 hours a day experience vision-related symptoms (Salibello & Nilsen, 1995); the incidence and severity of such symptoms increased when more than 4 hours per day were spent working on a computer (Rossignol et al., 1987; Collier & Rosenfield, 2011; Thorud et al., 2012). More recently, the term Digital Eye Strain (DiES) has been introduced which encompasses both eye and vision problems relating to modern electronic displays such as smartphones and electronic reading devices as well as the traditional computer VDUs (Rosenfield, 2016).

The visual task complexity with electronic displays can be more diverse when compared to non-electronic material i.e. font sizes of electronic displays vary significantly (Bababekova et al., 2011) and the VA demands when viewing a webpage on a smartphone range from 6/5.9 to 6/28.5 (mean of 6/15.1) (Bababekova at al., 2011). As such to allow comfortable reading for a sustained period, a certain degree of acuity is required and reading a text size at, or close to the threshold of resolution for an extended period may cause significant discomfort (Ko et al., 2014). Kochurova et al., (2015) concluded that for a normal and healthy young person, sustained and comfortable reading could be achieved if the text size was at least twice the individual's visual acuity. Given that the smallest text size on the smartphone is approximately 6/6 (Bababekova et al., 2011), this would suggest that a near VA of 6/3 was required to facilitate comfortable reading. In clinical practice, the assessment of near vision is limited and patients are rarely tested to threshold. Given this limitation, it is unclear what proportion of the population are unable to perceive the level of hyperacuity required for adequate smartphone viewing (Rosenfield, 2016).

Tosha et al., (2009) measured AR monocularly on the right eye of participants using the Grand Seiko WAM-5500 while participants were looking at a 2 cm high-contrast Michelson star symbol at 300, 50, 33, 25, and 20 cm distance. Participants were divided into high (n = 15) or low visual discomfort groups (n = 16) based on their scores on the Conlon Visual Discomfort Survey. The study showed that participants in the higher visual discomfort group displayed increased accommodative lag (typically after at least 30 s of sustained fixation). The authors noted that this accommodative fatigue was only apparent for very close targets (20 to 25 cm) and not with targets at conventional reading distances (33 to 50 cm) (Tosha et al., 2009).

Given these observations, it could be proposed that sustained use of smartphones (assuming that they are used at a close working distance) may lead to greater accommodative fatigue.

Traditional clinical methods of assessing accommodation such as dynamic retinoscopy, accommodative facility and push-up test provide limited characterisation of accommodative system and fail to relate to real life visual demands. More recently, open field auto refractors have been modified to acquire the accommodative dynamic curve (Figure 6.1). The procedure is based on assessing the subject's refractive error changes whilst viewing targets of varying accommodative stimulus in real-time. There are numerous metrics that have been used to describe the accommodative dynamic curve and there is significant variability in the way they are derived:

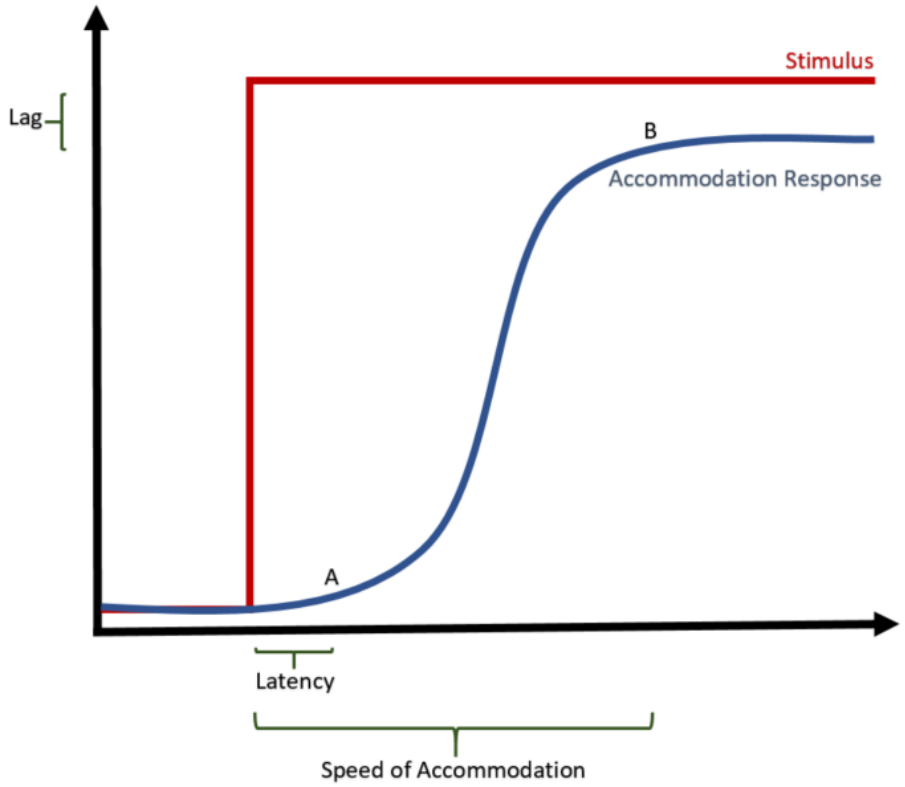


Figure 6.1: Typical AR/Stimulus response curve (accommodation phase).

i. Accommodative lag (ALag).

Accommodative lag (ALag) is defined as the difference between the accommodative stimulus and the actual amount of accommodation elicited by the crystalline lens. Clinically, ALag is measured using Nott Dynamic Retinoscopy (Leat & Gargon, 1996) or the Monocular Estimate Method (MEM) of dynamic retinoscopy (Rouse et al., 1982). For Nott Dynamic Retinoscopy, a near fixation target is viewed by the patient whilst the practitioner alters their own working distance to identify the point of neutrality (Leat & Gargon, 1996) while for MEM, neutrality is achieved by adding positive spherical lenses (Rouse et al., 1982). When comparing both methods, studies have shown that MEM provides a higher measure of ALag when compared to Nott Dynamic Retinoscopy (Tassinari, 2000). In research, open field autorefractors (Winn et al., 1989), abberometers (Kanda et al., 2012) and photorefractors (Anderson et al., 2010) have been used to calculate accommodative Lag. Using these devices, the participant focuses on a target of known accommodative demand whilst the refractive response is recorded. The difference between the demand and response gives the magnitude of accommodative lag. This can be conducted using both static and dynamic measurements of the refractive status. Dynamic measurements have an inherent advantage as they reduce the impact of single erroneous measurements, can assess the response in respect to a moving stimulus and can allow an assessment of accommodative microfluctuations (provided that the instrument has sufficient resolution) (Chen et al., 2017; Yeo et al., 2006).

ii. Mean velocity of accommodation (MeanVA) and disaccommodation (MeanVDA).

Mean velocity of accommodation (MeanVA) is defined by the time needed to travel from A to B divided by the accommodation differences between A and B (Figure 6.1). MeanVA is calculated as the absolute value of the dioptric change divided by the time over the interval

10 to 90% of the total step, covering 80% of the absolute values (Aldaba et al., 2015; Heron et al., 2001). The mean velocity of discommodation (MeanVDA) is measured using the same method but using the section of the response curve that corresponds to disaccommodation (Aldaba et al., 2015).

iii. Speed of accommodation (SOA).

Speed of accommodation (SOA) was defined as the speed needed for accommodation to reach point B (maximum accommodation response), from the moment the stimulus was introduced to the eye (Figure 6.1). Earlier studies had investigated the SOA using a crude reaction-time methods and step stimuli, and reported an SOA were slower for older participants (Allen, 1956; Temme & Morris, 1989). In contrast, Lockhart & Shi, (2010) used a velocity curve to mathematically determine the SOA by dividing the differences between one preceding and one succeeding the 'spherical equivalent value' by the time interval between them (Lockhart & Shi, 2010).

iv. Speed of disaccommodation (SODA).

Speed of disaccommodation (SODA) was defined as the speed needed for accommodation to reach the minimum accommodation response (during the disaccommodation phase), from the moment the stimulus was removed from the eye. The SODA was also investigated using the same methods to investigate SOA (described above) and it was found that SODA were typically faster than SOA (Allen, 1956; Temme & Morris, 1989).

v. Accommodation latency (ALat).

Accommodation latency (ALat) was defined as the time needed for the accommodation to start (point A in Figure 6.1), following the introduction of an accommodative stimulus (Mordi & Ciuffreda, 2004). The methods of identifying the point whereby accommodation is initiated

vary between studies. Schor et al., (1999) advocated that this point could be determined by determining the first of three data points where the accommodative values sequentially rose followed by a sequence of four values where no consecutive points reduced in accommodation. Anderson et al., (2010) proposed that the first of five consecutive points of accommodation increases should be used as the value to determine latency. These methods all involve the visual inspection of the refractive data rather than using regression fitting for determining the parameters.

vi. Disaccommodation latency (DALat).

Disaccommodation latency (DALat) was defined as the time needed for the accommodation to start decreasing, directly after the removal of the stimulus from the eye (Anderson et al., 2010). This has been calculated by determining the time between the offset of the near stimulus and the initiation of the disaccommodative response (Anderson et al., 2010; Kasthurirangan & Glasser, 2005, 2006).

Despite the widespread use of smartphones and smart watch, there is an absence of studies examining the effect of these devices on AR. Studies that have examined AR with VDU screens are not directly transferable given the difference in the display screen characteristics and the closer working distance.

6.2 Objective

The primary outcome of this study is to determine the differences in AR between a target displayed on paper, smartphone and smart watch. The secondary aim is to determine if the characteristics of a target effects AR.

6.3 Methodology

This chapter comprised of 2 separate experiments that utilized similar experimental protocols and set-up:

6.3.1 Experiment 1

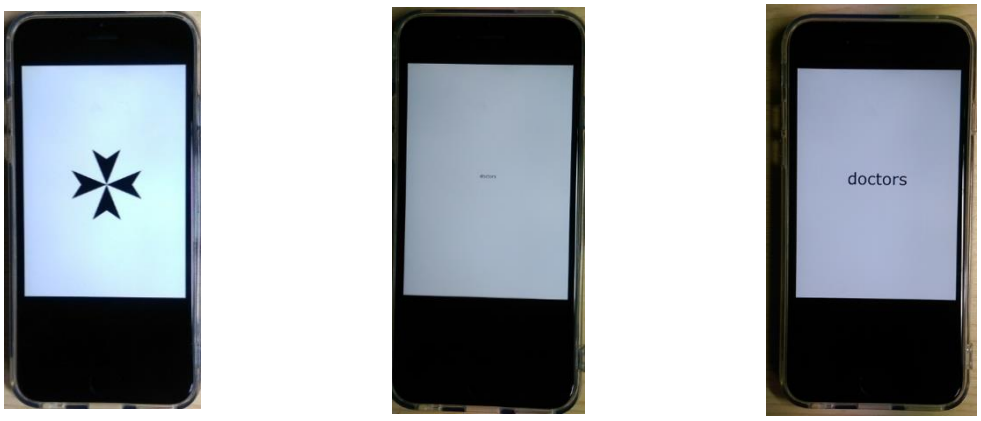
The AR in this experiment was measured while participants viewed a standardised target (N5 sized letter) across three platforms (paper, Apple iPhone 6 and Apple Smart Watch) (Figure 6.2).

N5 letters on paper N5 letters on Smartphone N5 letters on Smart watch

Figure 6.2: Target and platform combinations for experiment 1.

6.3.2 Experiment 2

The AR in this experiment was measured while participants viewed targets that differed in spatial characteristics; isotropic (Maltese cross) and anisotropic (N5 and N20 sized letters) contours target were assessed (Figure 6.3). An Apple iPhone 6 was used to display three different targets.



Maltese cross on Smartphone N5 letters on Smartphone N20 letters on Smartphone

Figure 6.3: Target and platform combinations for experiment 2.

6.3.3 Ethical Approval

Ethical approval for this study was obtained from the Research Ethics Committee, Faculty of Health & Human Sciences and Peninsula School of Medicine & Dentistry, Plymouth University. The letter of approval can be seen in the Appendix B (reference number 15/16-468). Prior to the start of data collection, participants were fully informed of the experiment and all relevant questions were answered accordingly. Written consent was obtained before the start of data collection.

6.3.4 Sample Size

The sample size was calculated using the software G*Power, version 3.1.9.2 (Faul et al., 2007; Prajapati et al., 2010). Previous studies examining accommodative response have used variable population sizes (range 4 to 27 participants) (Koh & Charman, 1998; Lin & Jiang, 2013; Montés-micó et al., 2017; Owens, 1980; Poltavski et al., 2012). Sample size calculations for this study were based upon a repeated measures ANOVA model with a moderate effect size of 0.25 (Cohen, 1988, 1992), a significance level of $p<0.05$ with a power of 80%. According to

the G*Power calculations, a total sample size of 51 participants were required for this experiment.

6.3.5 Inclusion and Exclusion Criteria

Participants were recruited from the staff and student population of Plymouth University using convenience sampling. The inclusion and exclusion criteria of the study are as follows:

6.3.5.1 Inclusion Criteria

- Completed a comprehensive eye examination within the last 12 months.
- Able to see decimal 0.50 at 30 cm and has at least 6.50 D accommodation.
- Aged between 18 and 33 years old.

6.3.5.2 Exclusion Criteria

- History of any form of ocular surgery including LASIK.
- Experiencing binocular or monocular diplopia.
- Problems focusing image at near or distance.
- Suffering any form of ocular or systemic diseases.
- Participation in any other pharmacological studies.
- Pregnant or breast feeding.
- Taking medications.

6.3.6 Target Characteristics

The Verdana font style was used for the fixation targets for both experiments as it demonstrates the clearest legibility for both capital letters and lowercase words (Sheedy et al., 2005). A font size N5 was selected as it is comparable to the text size used in newspaper, telephone directory and smartphones (Ciuffreda et al., 1990; Legge & Bigelow, 2011; Sanders & Sanders, 2007). A larger font of N20 was also assessed as it is an equivalent size to magazines titles (Legge & Bigelow, 2011). A Maltese cross was chosen as the third target as it has been used extensively in accommodation experiments. A Maltese cross has details at

multiple orientations, contains broad spatial frequency content (Mathews & Kruger, 1994), covers a large area of the central field (Ciuffreda, 1991) and provides a good cue to central fixation (Kruger et al., 2004). All the targets were matched for luminance, illuminance and contrast and were within the range regarded as suitable for comfortable ergonomic viewing (Anshel, 2005). The characteristics of the targets used in this experiment can be seen in Table 6.1 below.

Stimulus – Platform	Luminance* (cd/m^2)	Illuminance^ (lux)	Contrast (Weber)
N20 – Apple iPhone 6	142.3	568.0	0.9979
N5 – Apple iPhone 6	144.5	579.0	0.9979
N5 – Apple Smart Watch	135.9	581.0	0.9939
N5 – Paper	145.9	578.0	0.9747
Maltese Cross - Apple iPhone 6	146.1	581.3	0.9979

^ Measured using Konica Minolta Luminance Meter LS-150.
* Measured using CHY 230 Light Meter.

Table 6.1: Luminance, illuminance and contrast of the targets used in this experiment.

This measurement was also in accordance with the recommended minimum level of at least 35 cd/m^2 display luminance for a visual display unit (VDU) (North, 1993). The contrast for each target was calculated using Weber's contrast formula. All targets showed more than 0.90 contrast (Table 6.1) and were similar to conventional vision chart contrast levels (Benjamin, 2006). The size for the Verdana N5 letter, Verdana N20 letter and Maltese cross were 0.9073 mm, 4.9090 mm and 24.1407 mm, respectively.

6.3.7 Experiment Procedure

AR was investigated during two separate experiments, utilizing the same protocol. For the first experiment, evaluation of AR was performed when participants viewed a near target consisting of Verdana N5 letters on paper, Apple iPhone 6 and Apple Smart Watch. During the

second experiment, AR was conducted when participants viewed a near target consisting of a Maltese cross, Verdana N5 letters and Verdana N20 letters on Apple iPhone 6.

AR was measured objectively on both eyes of participants using an infrared binocular autorefractor, Grand Seiko WAM-5500 (Grand Seiko Co. Ltd., Hiroshima, Japan). The contralateral eye was occluded and participants were asked to wear daily disposable soft contact lenses if their refractive error is greater than -0.50 DS, +0.75 DS or -0.75 DC (1 Day Acuvue Moist, Johnson & Johnson Vision Care, Ireland) to correct the refractive error if present.

The Grand Seiko WAM-5500 has been used extensively in studies investigating accommodation (Aldaba et al., 2015; Chen et al., 2017; Green et al., 2011; Oliveira et al., 2012; Poltavski et al., 2012; Szostek et al., 2015; Yeo et al., 2013) and myopia (Borsting et al., 2010; Lin et al., 2013) and has been shown to be a reliable and valid method for measuring refraction objectively (Sheppard & Davies, 2010).

A motorised Badal lens system was used to alternate the accommodative stimulus between zero and three dioptres. The system consisted of a 2 inch, +5.00 meniscus badal lens and a Maltese cross placed one focal length away from the lens, (20 cm) to simulate a distance target (0 D stimulus). A motorised cog and pinion system was used to translate the variety of smart devices in and out of the visual axis at a distance of 3.00 D. The autorefractor was set to record measurements at a rate of 5 Hz for six full cycles and the the motorised cog and pinion system was syncronised to the autorefractors real-time measurments.

A cog and pinion was purchased from HPC Gears (Derbyshire, United Kingdom) and attached to a motor to move the smart devices. The specifications of the cog and pinion needed to

ensure that a quarter turn of the motor translated to approximately 10 cm of lateral travel. A modulus (MOD) of 2 was chosen to minimise the size of the cog and ensure that its weight was minimised. Using Equations 6.1, 6.2 and 6.3 it was determined that the Pitch Circle Diameter (PCD) of the gear (the diameter of a circle that encompasses the contact points on a gear) needed to be 127, the number of teeth (t) was calculated as 64 and the outside diameter (ØD) was calculated to be 131.

$$Pitch\ circle\ diamter, PCD = \mathrm{D}istance\ of\ travel \times 4\pi \qquad \text{Equation 6.1}$$

$$Number\ of\ teeth\ (t) = \frac{PCD}{MOD} \qquad \text{Equation 6.2}$$

$$\emptyset D = (t + 2) \times MOD \qquad \text{Equation 6.3}$$

Where:

PCD = Pitch Circle Diameter (mm)

DoT = Distance of travel (mm)

t = Number of teeth

ØD = Outside diameter of the gear

The closest match to these specifications was a cog (MOD 2) (Figure 6.4) that had a PCD equal to 128 mm, ØD of 132 mm and 64 teeth which provides a lateral translation of 101 mm (Equation 6.1).

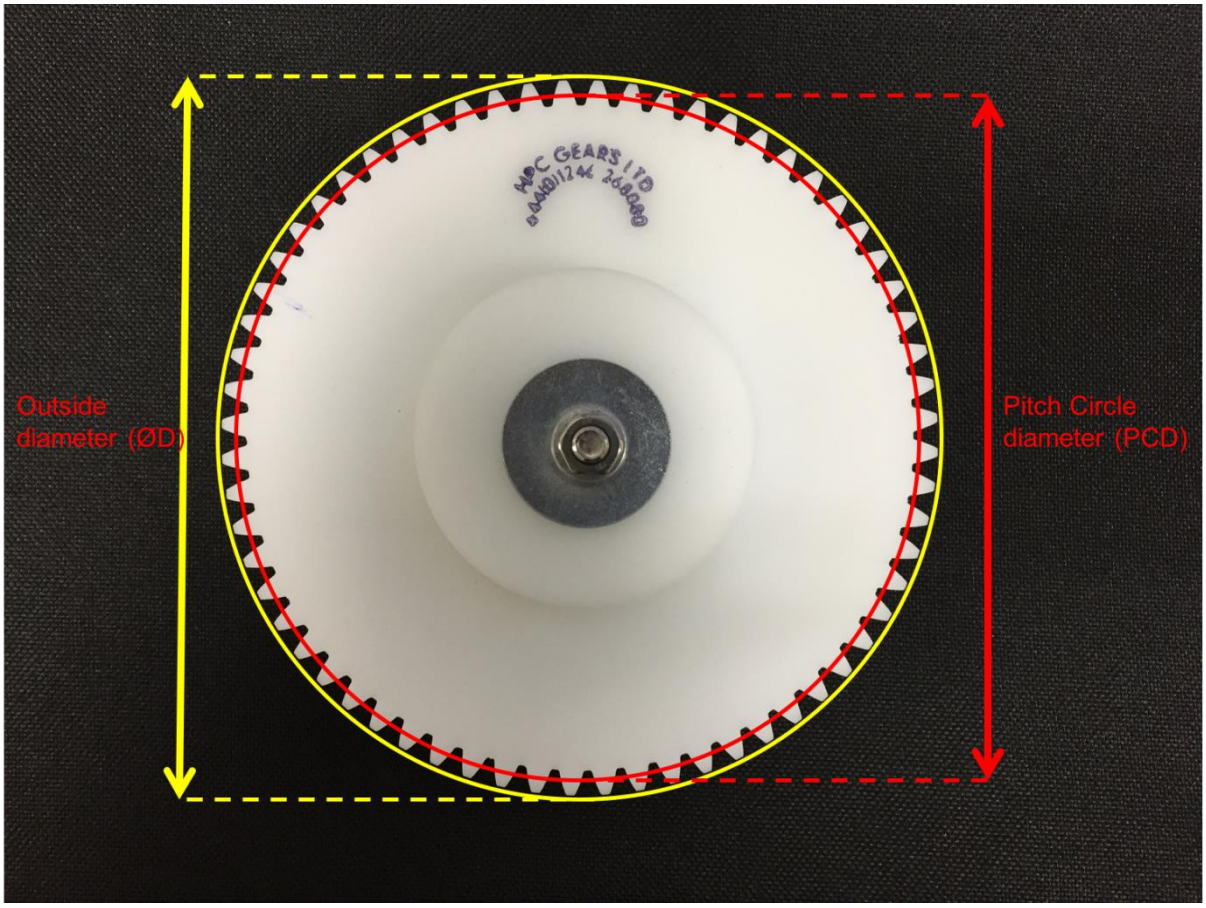


Figure 6.4: Image of the cog used for the AR experiments.

AR was measured continuously for a total of 6 cycles for each of the near targets. The order of presentation was randomized to reduce bias. The schematic plan for the AR experiment can be seen in Figure 6.5 and the finalized set-up for can be seen in Figure 6.6.

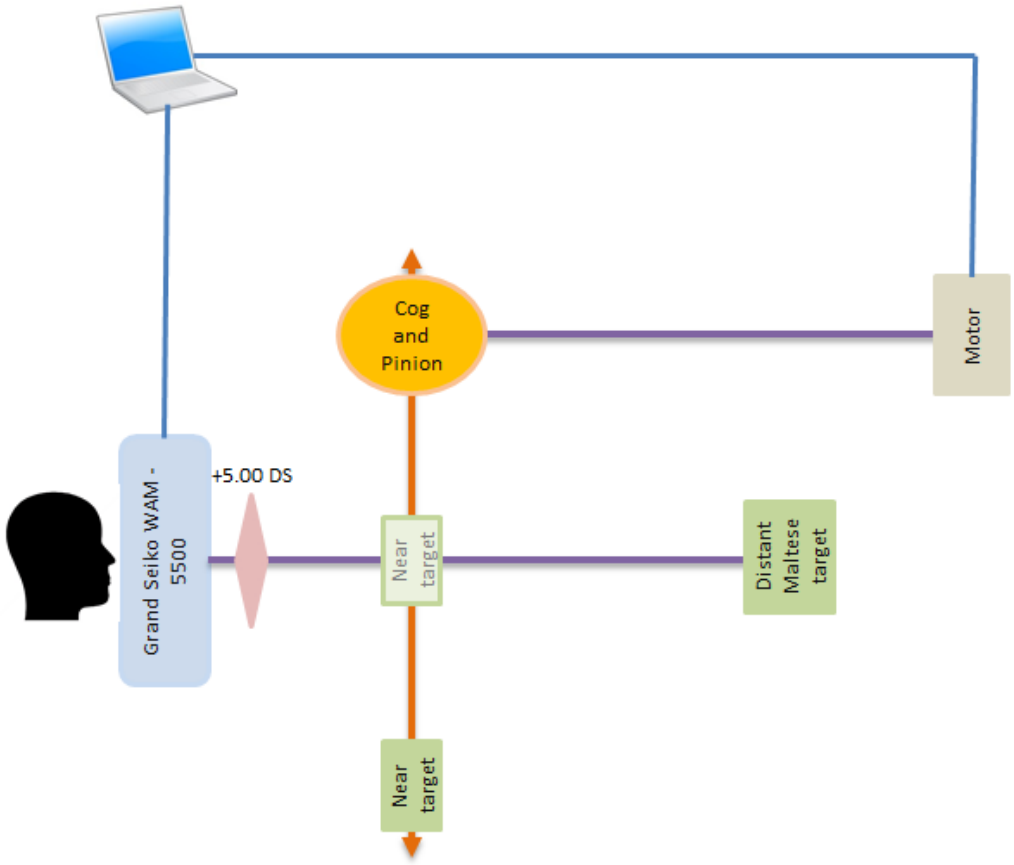


Figure 6.5: Schematic plan for the AR experiment. Near target was changed to appropriate target depending on the experiment conducted.

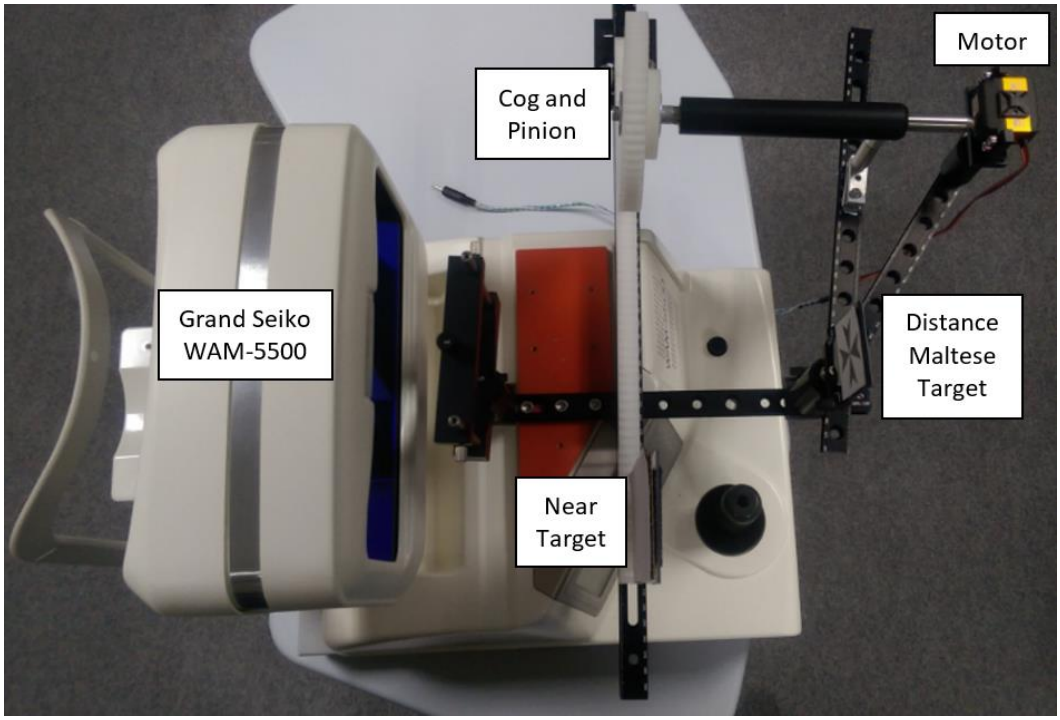


Figure 6.6: General set up for the AR experiments.

The AR data sets were exported to an Excel spreadsheet. To minimise fatigue, a 5-minute break time was introduced before the start of the next cycle with a different near target. During this 5-minute break, participants were instructed not to perform any near task and to look at a 6/60 letter located at 6 m away (Oliveira et al., 2012; Xiong & Muraki, 2014).

6.3.8 Accommodative Response Measurement

Figure 6.7: Side view of the set up for the AR experiments.

Measurement of AR was initiated using the 5 near targets as an accommodative stimulus (Figure 6.2 and Figure 6.3). The distant target was a Maltese cross and was kept constant throughout the experiment. Using the DynaWAM system (Figure 6.7), the near target was introduced in front of participant's line of sight for 5 seconds and then, moved so that the participant could fixate on the 0.00 D accommodative demand Maltese cross for 5 seconds. This process was continued for a total of 6 cycles for each near target. The order of presentation was randomized and a 5-minute break time was introduced during each near

target change (after completing 6 cycles for each near target). Participants were instructed to 'look at the target and keep the target as clear as possible at all times' as this instruction were found to elicit a more precise AR compared to other verbal instructions (Ciuffreda & Hokoda, 1985; Stark & Atchison, 1994).

6.3.9 Data Analysis

The parameters (AR and time) consist of 446 sampling points with a sampling rate of 5 Hz and a recording time of 30 seconds. For each participants, 5 cycles of accommodative and disaccommodation change were examined. For accommodative change the sampling points were identified as the first until the last data point where the near target was present. For disaccommodative change this range spanned across the data points where the distance target was present.

The data was exported to MATLAB (MATLAB R2016b, The MathWorks Inc.), where a sigmoidal regression curve function was fitted to each data set Equation 6.4.

$$y = a + \left[\frac{b}{1+e^{\left[-\left(\frac{x-d}{c}\right)\right]}}\right] \qquad \text{Equation 6.4}$$

$$x = \left[c\left(-Log10\left(\frac{b}{(y-a)} - 1\right)\right)\right] + d \qquad \text{Equation 6.5}$$

$$y_{99} = \frac{(b-a)}{100} \times 99 + a$$ Equation 6.6

$$y_{01} = \frac{(b-a)}{100} + a$$ Equation 6.7

Where a was the minimum, b was the asympotote of the curve, c was the mid-point, and d was the gradient of the slope at the midpoint.

Equation 6.5 was used to identify the time point at which a specific accommodative value was found. Equation 6.6 was used to determine the value of 99% of the maximum accommodative response (y_{99}) relative to the minimum value and Equation 6.7 was used to calculate the value for 1% of the accommodative response (y_{01}).

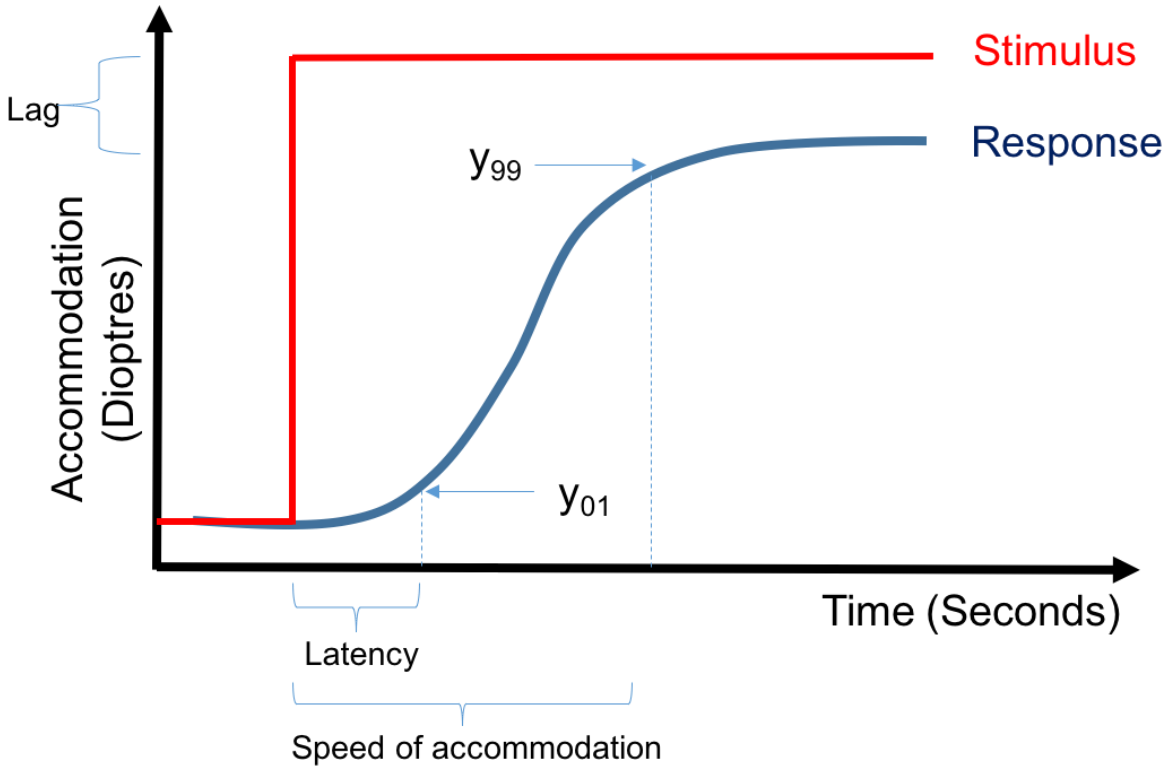


Figure 6.8: Description of the investigated accommodation parameters.

The graphical illustration of the accommodative parameters that were investigated are illustrated in Figure 6.8. Rather that using visual inspection of the data set for calculating the metrics discribing accommodation, all of the AR metrics were derived using the non-linear regression curves. Accommodative lag (ALag) was calculated as the difference between the accommodative stimulus and value b (the asympote of the sigmoidal function). Accommodative latency (ALat) was defined as the time between the initiation of the accommodative stimulus and y_{01} (the point where 1% of the accommodative response was reached). Speed of accommodation was designated as the time between the initiation of the accommodative stimulus and y_{99} (the point where 99% of the accommodative response was reached). The value d was used as the speed of accommodation (SOA) and the mean velocity of accommodation was calculated as the difference between the values y_{99} and y_{01} divided by the time between these two points.

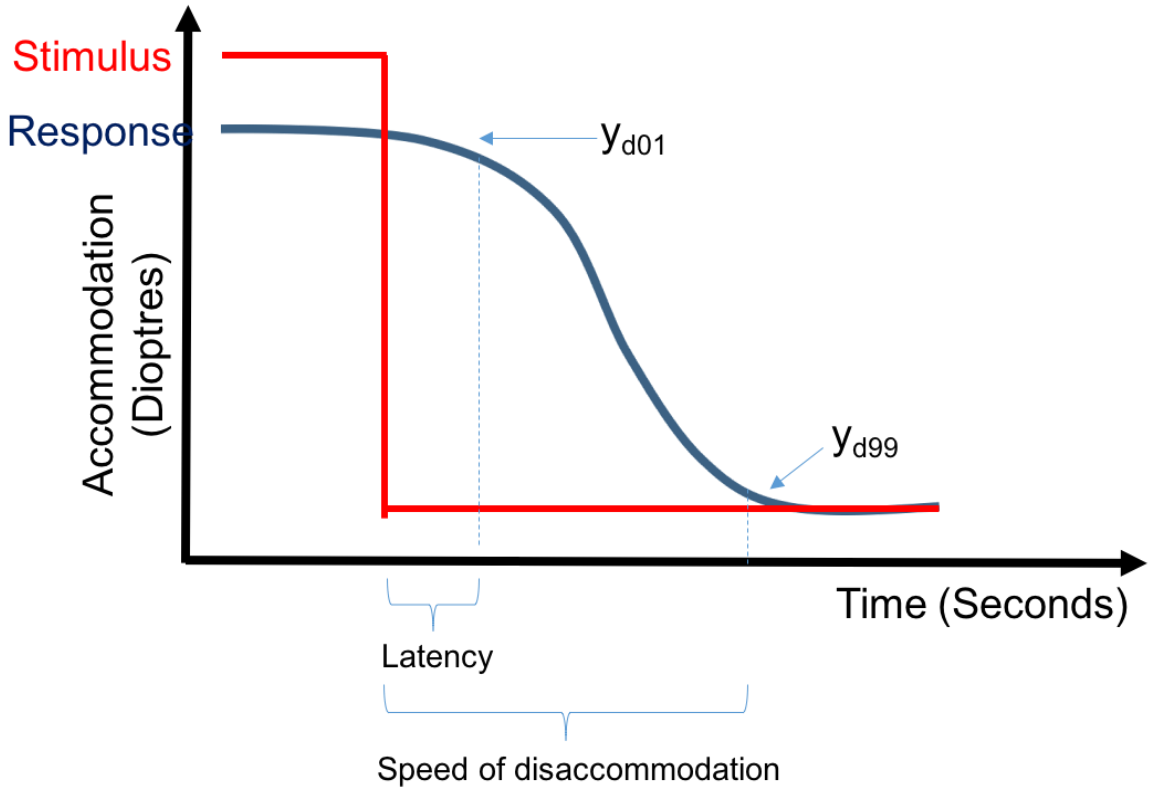


Figure 6.9: Description of the investigated disaccommodation parameters.

The graphical illustration on the disaccommodation parameters that were investigated are shown in Figure 6.9. Disaccommodative latency (DALat) was defined as the time between the removal of of the disaccommodative stimulus and y_{d01}. Speed of disaccommodation (SODA) was the time between the removal of the stimulus and y_{d99}. The methods used to calculated SOA and MeanVA were used to calculate the mean velocity of disaccommodation (MeanVDA) and Speed of disaccommodation (SODA). Data were assessed in SPSS Statistics version 23.0 (IBM Corp., Armonk, New York).

The first AR cycle was omitted from the analysis as to account for possible accommodative errors associated with the beginning of the task. Consequently, AR values of more than 10 D were removed as these values were attained when a blink occurred and also because values greater than 10 D were considered to be the outside of the normal physiological AR variation

of the human eye (Campbell & Westheimer, 1960). The data set was then tested for normality distribution using SPSS (histogram, Shapiro-Wilk, Z-score for skewness and Z-score for Kurtosis) so that further analysis using appropriate statistical test could be performed. Visual inspection of histograms along with the Sharpiro-Wilks tests were used to determine the distribution of the data and it was found to be non-normally distributed. Therefore, Friedman tests (χ) were used to determine if there were any significant differences between the groups. Where applicable, *post-hoc* testing using Wilcoxon signed-rank tests (Z) was conducted to determine the significant pairwise comparison and a Bonferroni correction applied to reduce Type 1 error. For the pair-wise comparison, the *p*-value adjustment was done automatically by SPSS (Adjusted Significance, p_{adj}) and remained at $p_{adj}<0.05$ as suggested by IBM Corporation, (2012) and Lund & Lund, (2014).

6.4 Results

A total of 58 participants (26 males, 32 females) with a mean age of 22.67$\pm$4.18 years old were recruited in this study. Participants had a mean RX (spherical equivalent) of -0.69$\pm$1.49 DS. Participants from the first AR experiment also participated in the second AR experiment.

6.4.1 Accommodative Response When Viewing Verdana N5 Letters on Paper, Apple iPhone 6 and Apple Smart Watch

For ease of referencing, Verdana N5 letters on paper will be referred as N5 Paper, Verdana N5 letters on Apple iPhone 6 will be referred as N5 Phone and Verdana N5 letters on Apple Smart Watch will be referred as N5 Watch. The accommodative response metrics were shown in Table 6.2 and Figure 6.10. The Friedman test (χ) results were shown in Table 6.3 and the significant *post-hoc* pairwise comparisons were shown in Figure 6.10.

Task & Platform	Mean±SD		
	N5 Paper	**N5 Phone**	**N5 Watch**
Accommodation Lag [ALag] * (Diopter)	0.9052±0.2635	0.9212±0.3277	0.7845±0.3460
Mean Velocity of Accommodation [MeanVA] * (Diopter/second)	0.7668±0.5025	0.5774±0.4107	0.4974±0.3177
Mean Velocity of Disaccommodation [MeanVDA] * (Diopter/second)	0.7193±0.6200	0.6836±0.4946	0.4690±0.4423
Speed of Accommodation [SOA] (Diopter/second)	2.1641±0.4623	2.2755±0.4137	2.2877±0.5261
Speed of Disaccommodation [SODA] * (Diopter/second)	1.2272±0.3397	1.3159±0.4102	1.1169±0.2520
Accommodation Latency [ALat] * (Second)	1.3007±0.4378	1.6286±0.3619	1.5844±0.4431
Disaccommodation Latency [DALat] (Second)	0.4689±0.2852	0.5323±0.4421	0.5234±0.3200

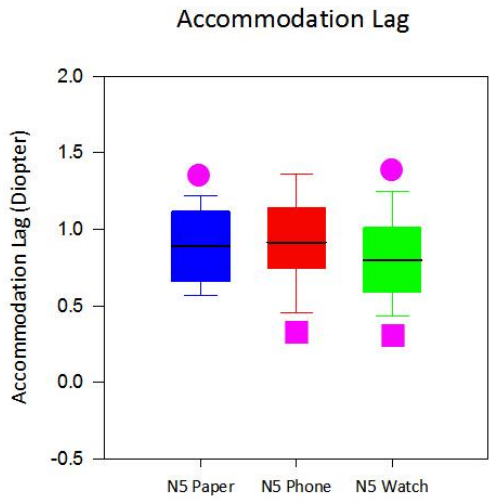
*Statistically significant.

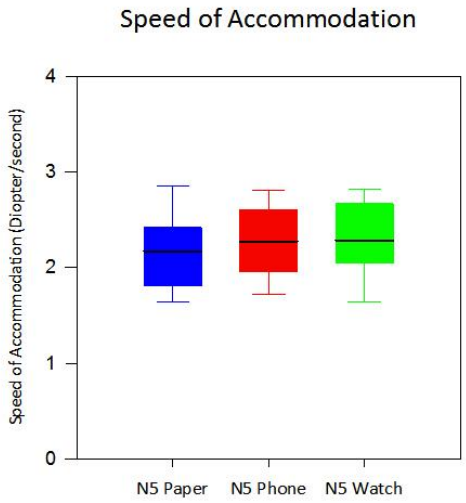
Table 6.2: Descriptive statistics for the accommodation parameter investigated in the first experiment.

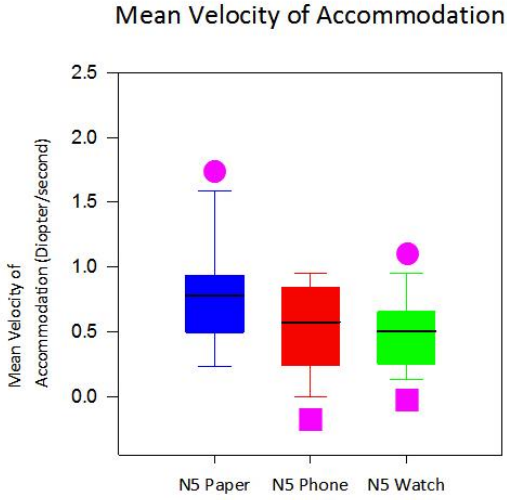
AR Parameter	Friedman Results
Accommodation Lag (ALag)	$\chi^2_2 = 10.945$, $p=0.004$*****
Mean Velocity of Accommodation (MeanVA)	$\chi^2_2 = 10.511$, $p=0.005$*****
Mean Velocity of Disaccommodation (MeanVDA)	$\chi^2_2 = 13.240$, $p=0.001$*****
Speed of Accommodation (SOA)	$\chi^2_2 = 2.259$, $p=0.323$
Speed of Disaccommodation (SODA)	$\chi^2_2 = 8.109$, $p=0.017$*****
Accommodation Latency (ALat)	$\chi^2_2 = 25.368$, $p<0.0005$*****
Disaccommodation Latency (DALat)	$\chi^2_2 = 4.044$, $p=0.132$

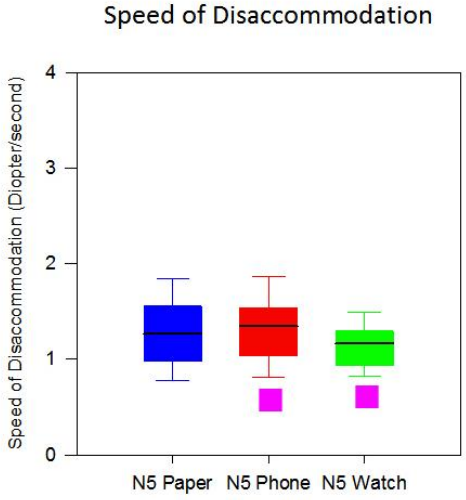
*Statistically significant.

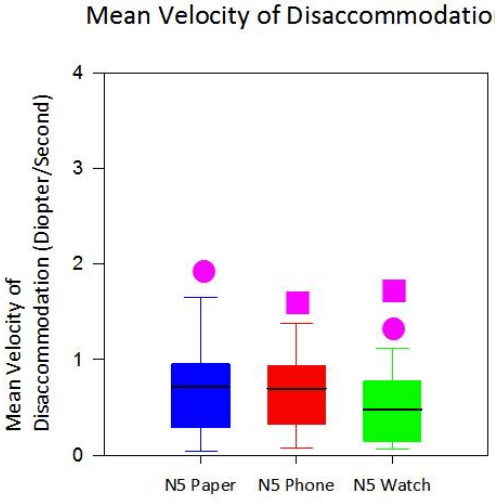
Table 6.3: Friedman results for the first experiment.

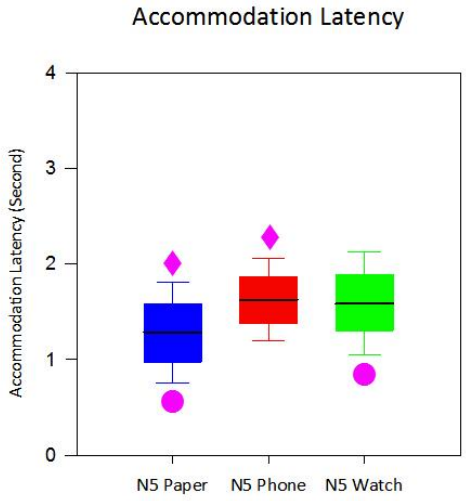

Accommodation Lag
Accommodation Lag (Diopter)
2.0
1.5
1.0
0.5
0.0
-0.5
N5 Paper
N5 Phone
N5 Watch

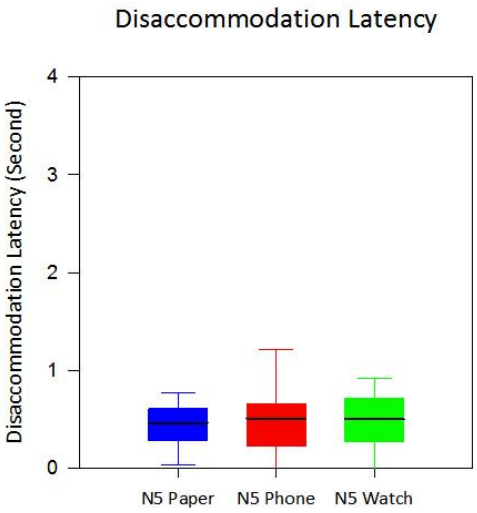

Speed of Accommodation
Speed of Accommodation (Diopter/second)
4
3
2
1
0
N5 Paper
N5 Phone
N5 Watch


Mean Velocity of Accommodation
Mean Velocity of Accommodation (Diopter/second)
2.5
2.0
1.5
1.0
0.5
0.0
N5 Paper
N5 Phone
N5 Watch


Speed of Disaccommodation
Speed of Disaccommodation (Diopter/second)
4
3
2
1
0
N5 Paper
N5 Phone
N5 Watch


Mean Velocity of Disaccommodation
Mean Velocity of Disaccommodation (Diopter/Second)
4
3
2
1
0
N5 Paper
N5 Phone
N5 Watch


Accommodation Latency
Accommodation Latency (Second)
4
3
2
1
0
N5 Paper
N5 Phone
N5 Watch



Legends:

N5 Paper.
N5 Phone.
N5 Watch.
Significant differences between N5 Watch – N5 Paper.
Significant differences between N5 Watch – N5 Phone.
Significant differences between N5 Phone – N5 Paper.

Figure 6.10: Box representing median and interquartile range for the results of the first experiment.

Friedman test showed significant differences in ALag, MeanVA, MeanVDA, SODA and ALat when viewing N5 Paper, N5 Phone and N5 Watch (Table 6.3). *Post-hoc* analysis revealed a difference in ALag between the N5 Watch and N5 Paper (Z = 2.765, p_{adj}=0.017) as well as between N5 Watch and N5 Phone (Z = 2.956, p_{adj}=0.009). *Post-hoc* analysis of MeanVA showed differences between N5 Watch and N5 Paper (Z = 2.991, p_{adj}=0.008) as well as between N5 Watch and N5 Phone (Z = 2.579, p_{adj}=0.030). Pairwise comparison of MeanVDA identified a difference between N5 Watch and N5 Paper (Z = 3.200, p_{adj}=0.004) as well as between N5 Watch and N5 Phone (Z = 3.100, p_{adj}=0.006). Pairwise comparison on SODA showed a difference between the N5 Watch and N5 Phone (Z = 2.670, p_{adj}=0.023). *Post-hoc* assessment of ALat showed significant differences between N5 Watch and N5 Paper (Z = -4.496, p_{adj}<0.0005) as well as between N5 Paper and N5 Phone (Z = -4.215, p_{adj}<0.0005).

Friedman's test revealed that the differences were not statistically significant for SOA (χ^2_2 = 2.259, *p*=0.323) and DALat (χ^2_2 = 4.044, *p*=0.132) respectively (Table 6.3).

6.4.2 Accommodative Response When Viewing Maltese cross, Verdana N5 Letters and Verdana N20 Letters on Apple iPhone 6

Friedman tests (χ) were conducted to investigate the changes in the 7 AR parameters when viewing Maltese cross (Maltese), Verdana N5 letters (N5) and Verdana N20 letters (N20) on Apple iPhone 6. The accommodative response metrics can be seen in Table 6.4 and Figure 6.11.

Task & Platform	Mean±SD		
	Maltese	N5	N20
Accommodation Lag [ALag] * (Diopter)	1.0668±0.3828	0.9212±0.3277	1.0130±0.3776
Mean Velocity of Accommodation [MeanVA] (Diopter/second)	0.7282±0.5244	0.5774±0.4107	0.6307±0.4729
Mean Velocity of Disaccommodation [MeanVDA] (Diopter/second)	0.5706±0.4909	0.6836±0.4946	0.6078±0.4884
Speed of Accommodation [SOA] (Diopter/second)	2.4138±0.4937	2.2755±0.4138	2.2715±0.5199
Speed of Disaccommodation [SODA] * (Diopter/second)	1.2730±0.4930	1.3159±0.4102	1.1605±0.3752
Accommodation Latency [ALat] * (Second)	1.5916±0.3933	1.6286±0.3619	1.4883±0.3716
Disaccommodation Latency [DALat] (Second)	0.5545±0.3720	0.5323±0.4421	0.6096±0.3583

*Statistically significant.

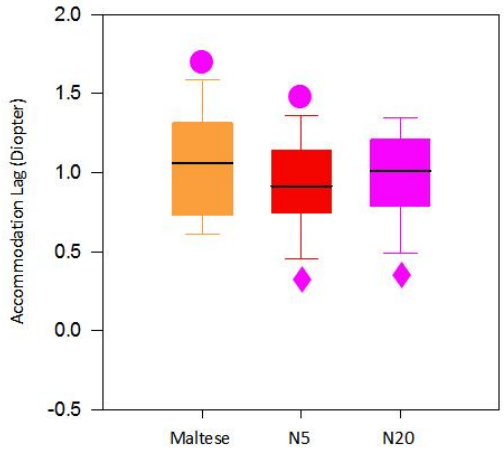
Table 6.4: Descriptive statistics for the accommodation parameter investigated in the second experiment.

AR Parameter	Friedman Results
Accommodation Lag (ALag)	$\chi^2_2 = 14.109$, $p=0.001$*
Mean Velocity of Accommodation (MeanVA)	$\chi^2_2 = 2.711$, $p=0.258$
Mean Velocity of Disaccommodation (MeanVDA)	$\chi^2_2 = 1.960$, $p=0.375$
Speed of Accommodation (SOA)	$\chi^2_2 = 5.393$, $p=0.067$
Speed of Disaccommodation (SODA)	$\chi^2_2 = 6.873$, $p=0.032$*
Accommodation Latency (ALat)	$\chi^2_2 = 6.035$, $p=0.049$*
Disaccommodation Latency (DALat)	$\chi^2_2 = 2.978$, $p=0.226$

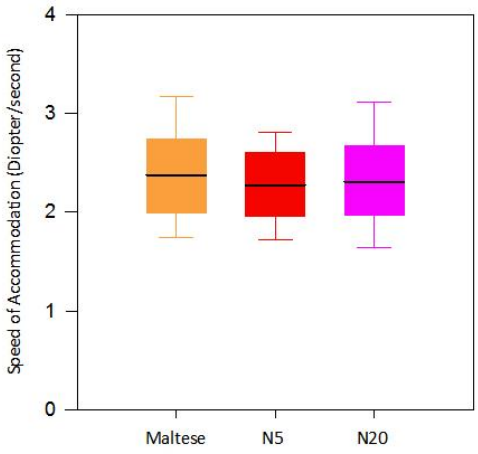
*Statistically significant.

Table 6.5: Friedman results for the second experiment.

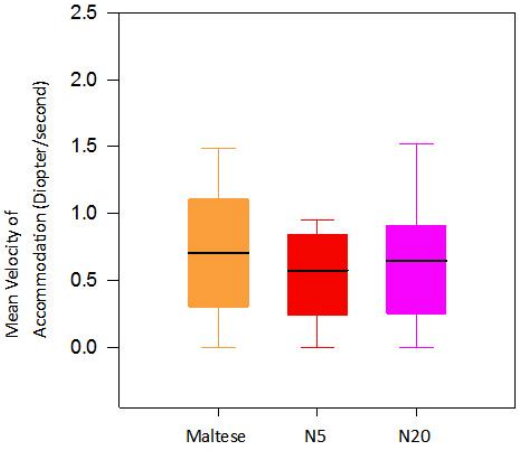
Accommodation Lag



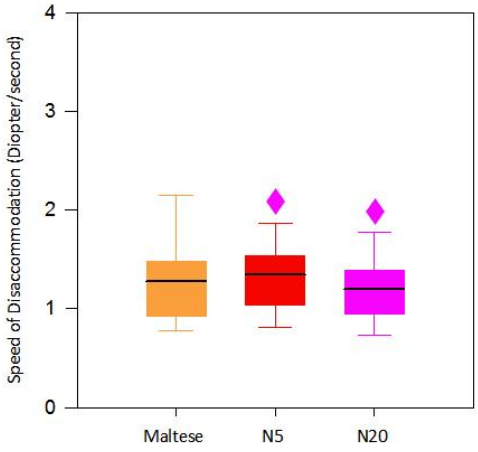
Speed of Accommodation



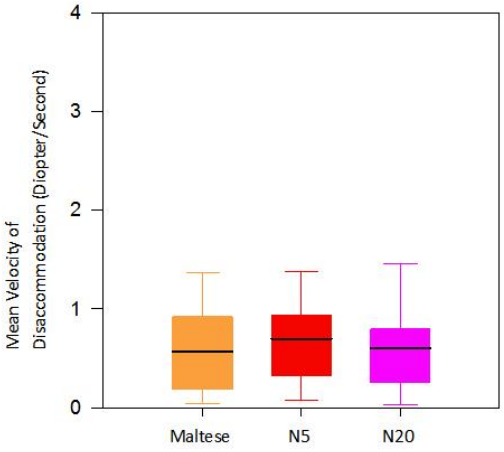
Mean Velocity of Accommodation



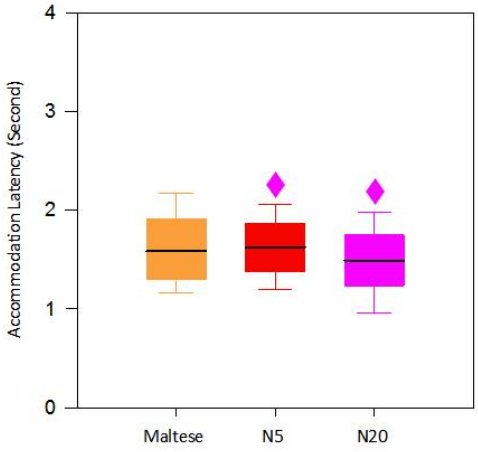
Speed of Disaccommodation

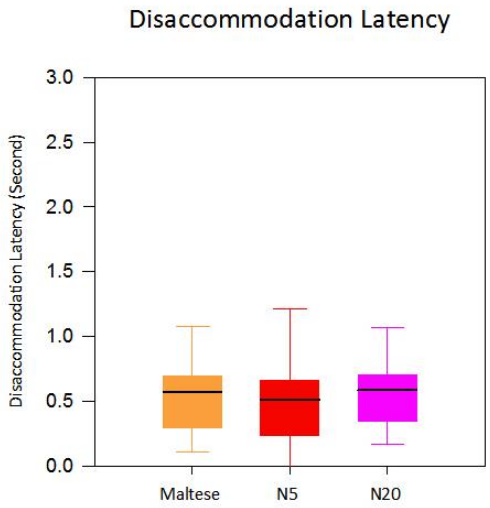


Mean Velocity of Disaccommodation



Accommodation Latency





Legends:

Maltese Phone.
N5 Phone.
N20 Phone.
Significant differences between N5 – Maltese.
Significant differences between N20 – N5.

Figure 6.11: Box representing median and interquartile range for the results of the second experiment.

Friedman test showed statistically significant differences in ALag, SODA and ALat when viewing Maltese, N5 and N20 on Apple iPhone 6 (Table 6.5; Figure 6.11). ALag differ significantly between the 3 targets ($\chi^2_2 = 14.109$, p=0.001). *Post-hoc* testing for ALag revealed significant differences between N5 and Maltese (Z = 3.623, p_{adj}=0.001) and between N5 and N20 (Z = -2.670, p_{adj}=0.023). Friedman's test also revealed that SODA was significantly different between the 3 targets ($\chi^2_2 = 6.873$, p=0.032). *Post-hoc* analysis on measures of SODA showed significant pairwise differences between N5 and N20 (Z = 2.574, p_{adj}=0.030). Similarly, Friedman's test showed significant differences for ALat ($\chi^2_2 = 6.035$, p=0.049). Pairwise comparison on ALat showed significant differences between N5 and N20 (Z = 2.435, p_{adj}=0.045). Friedman's test revealed that the differences were not statistically significant for MeanVA ($\chi^2_2 = 2.711$, p=0.258), MeanVDA ($\chi^2_2 = 1.960$, p=0.375), SOA ($\chi^2_2 = 5.393$, p=0.067) and DALat ($\chi^2_2 = 2.978$, p=0.226) respectively (Table 6.5).

6.5 Discussion

6.5.1 Accommodative Response When Viewing Verdana N5 Letters on Paper, Apple iPhone 6 and Apple Smart Watch

The results from this study demonstrated significant differences in the accommodative response when viewing a letter target on paper, smartphone and smart watch. Participants had a longer accommodative latency with the smartphone and smart watch when compared to the paper version of the N5 letter. There are several factors that may have contributed to this delayed initiation of the accommodative response. It is possible that the resolution of the target may have influenced the latency speed: The Verdana N5 letters on paper had a resolution of 1200 x 1200 dots per inch (dpi), whilst the smartphone and smart watch had a resolution of 326 pixels per inch (ppi). Another explanation might be contributed to screen reflections (Collins et al., 1994) that might be present on both the Smartphone and Smart Watch. In this current experiment, the presence of reflections or glare was controlled subjectively during the experiment (the examiner controlled the lighting around the experiment).

In addition, both the smartphone and smart watch were backlit device while the paper target was externally illuminated. The differences in lighting methods might contribute to the results in this study. This was because Alpern, (1958) had shown that accommodation significantly varies in accordance with the level of retinal illuminance and Shahnavaz & Hedman, (1984) had shown that lighting conditions does affect accommodation. To expand this study, a non-backlit display screen should be used to determine the influence of this feature. This could be achieved by using the device, Kindle Paperwhite (Amazon Inc., Seattle, Washington) that uses E-ink, which is a type of frontlit display and has no refresh rate (Siegenthaler et al., 2012a; Siegenthaler et al., 2012b).

Participants had a lesser accommodative lag and a slower accommodative velocity when viewing the smart watch in comparison to both the smartphone and paper. This suggests that there is greater accommodative accuracy when viewing a smart watch. It is difficult to account for this difference given that participants viewed the same target (Verdana N5 letters) and luminance, illuminance and contrast were controlled. It is unlikely that the in-display resolution may have explained these differences given that both the smartphone and smart watch had a had a resolution of 326 pixels per inch (ppi). It is more likely that the differences in the size of the platforms influences the results from this experiment. The size of the platform (display) was similar for paper and Apple iPhone 6 (138.1 x 67.0 mm) while for the Apple Smart Watch, the size was 42 x 35.9 mm. It is possible that the smaller display size for Apple Smart Watch may have resulted in a 'crowding' effect. Otero et al., (2017) found that accurate accommodation was assisted by peripheral depth cues. It can be proposed that the smart watch's surround provided depth cues that were not present on the paper and smartphone. The assertion that a larger display leads to a more accurate accommodative response has some interesting implications and indicates a preference in the visual system towards larger devices such as tablet devices. Furthermore, comparing a smaller paper target mounted on the smart watch with the electronic display would provide insight into the effects of the depth cues. To confirm this proposition, a study involving several different size devices is warranted.

Surprisingly, review of the current literature did not provide many articles that specifically investigated the changes in AR when presented with targets of different sizes (either hardcopy or VDT based) or crowding. In one such study, Hue et al., (2014) reported that the mean accommodative response was significantly lower (larger ALag or a greater difference

between the accommodative stimulus and response values) when reading from an Apple Ipod, compared to hardcopy material (size matched to Apple Ipod). The investigators attributed this differences to source of the stimulus, where hardcopy was printed while Apple Ipod uses pixel format for the letters (Hue et al., 2014). Thus, accurate inferences to the results obtained from this study were unable to be made.

6.5.2 Accommodative Response When Viewing Maltese cross, Verdana N5 Letters and Verdana N20 Letters on Apple iPhone 6

Studies assessing objective measures of accommodation often utilise Badal optometers as they allow a consistent angular image size regardless of the vergence demands; provided that the eye is located one focal length away from the badal lens (Subbaram & Bullimore, 2002; Aldaba et al., 2017). Despite this universal acceptance of the Badal system there is still much variation in the stimulus used in accommodation studies. In the present study, a higher accommodative lag was found upon viewing the Maltese cross relative to the letter targets. Schmid et al., (2005) found that accommodative lag was reduced with smaller letter targets (a higher accommodative accuracy was achieved when viewing smaller letter targets). The investigators postulated that smaller size letters requires a greater accommodative accuracy to be seen clearly and thus, provides a lesser lags of accommodation compared to larger letters (Schmid et al., 2005). It is also reported that accommodation responses are more accurate the greater the cognitive demand (Iwasaki, 1993). Perhaps, lesser amount of cognitive demands was elicited when looking onto Maltese cross and the N20 letters compared to N5. These could explain why such results were found in this current study.

In contrast, Win-Hall et al., (2007) found that the accommodative response was more accurate when using a star stimulus target in comparison to letters of decreasing angular size.

In comparison, Lovasik et al., (1987) found that the size of the letter target did not have any influence on the accommodative response. Whereas, Owens, (1980) proposed that the accommodative response is sensitive to mid spatial frequencies and asserted that high-resolution targets were not required for accommodation. These previous studies assessed accommodation with a static target and did not assess the dynamic response of the accommodation system – this contrast may explain why their findings are in juxtaposition with those of the present study.

In this study luminance and contrast was carefully controlled: Utilising a single device to display the targets allowed for a standardised background illumination. This was important given that previous research has shown that accommodation is influenced by luminance contrast (Wolfe & Owens, 1981). Fincham, (1951) also noted that longitudinal chromatic aberration was important for stimulating accommodation. This factor was consistent across all three targets however, it would be interesting to vary the colour contrast of the various targets to determine the effect on accommodative dynamics.

Interestingly the speed of disaccommodation and accommodative latency were both delayed with the N20 letters when compared to N5. These results suggest that spatial frequency is an important driver of accommodation and disaccommodation when an anisotropic contours target is used. Further research in warranted to understand why different targets yield variable accommodative response, even when presented on the same platform (smartphone).

6.6 Conclusion

This study concluded that:

- There was a significant difference in accommodative latency, accommodative lag, mean velocity of accommodation and mean velocity of disaccommodation, when viewing a smart watch when compared to the smartphone and paper copy.
- Accommodative lag, mean velocity of accommodation and mean velocity of disaccommodation were significantly lower when participants were viewing N5 letters on smart watch compared to N5 letters on paper or smartphone.
- Speed of disaccommodation was significantly lower when participants were viewing N5 letters on smart watch compared to N5 letters on smartphone.
- Accommodation latency was significantly lower when participants were viewing N5 letters on paper compared to N5 letters on smartphone or smart watch.
- Accommodative lag was significantly lower when participants were viewing N5 letters as opposed to N20 letters and Maltese cross on a smartphone.
- Accommodative latency and speed of disaccommodation were significantly faster when participants viewed the N20 letters as opposed to the N5 letters.

Chapter 7: The Relationship Between Duration of Smartphone Use and Symptoms of Dry Eye

7.1 Introduction

With the ever-growing use of smart devices, eye and vision problems relating to these platforms need to be identified. The term computer vision syndrome (CVS) has been recognised for almost 20 years but much of the research relating to this has been based upon traditional VDT screens (Nakaishi & Yamada, 1999; Kozeis, 2009; Logaraj et al., 2014; Courtin et al., 2016; Ranasinghe et al., 2016; Al-Rashidi & Alhumaidan, 2017; Caterina et al., 2018; Mowatt et al., 2018; Sheppard & Wolffsohn, 2018). More recently, classification of ocular symptoms associated with digital devices such as tablets and smartphones have used terminology such as visual fatigue and digital eye strain (DES) (Benedetto et al., 2013; Gowrisankaran & Sheedy, 2014; Parihar et al., 2016; Rosenfield, 2016; The Vision Council, 2016; Maducdoc et al., 2017). Typical symptoms encompassed under these terms include headaches, musculoskeletal pain in the neck and shoulder, eyestrain, blurred vision and dry eyes (Waersted et al., 2010; Thorud et al., 2012; Gowrisankaran & Sheedy, 2014; Kawashima et al., 2015; Rosenfield, 2016; Kim et al., 2017; Kumar & Amarnath, 2017; Munshi et al., 2017; Randolph, 2017; Coles-Brennan et al., 2018; Mowatt et al., 2018).

Several studies have reported that the mean duration of smartphone use is approximately 2 hours per day (Moon et al., 2014; Sadagopan et al., 2017), although more recent market surveys have suggested that this duration may be longer (EMarketer, 2017). In addition, investigators have indicated that per session, smartphones are typically used for short periods of time for checking the time, emails and news updates (Falaki et al., 2010; Oulasvirta et al., 2012). Despite the median smartphone session length being <1 minute (Falaki et al., 2010), certain activities such as playing games and using map based applications (apps) have been

shown to be associated with session times of >1 hour (Falaki et al., 2010; The Vision Council, 2016; Lee et al., 2017; Statista, 2017). Currently, much of the literature on smart phone usage habits is reliant upon questionnaires based subjective reports (Oulasvirta et al., 2012; Moon et al., 2014; Haug et al., 2015; Moon et al., 2016; Lee et al., 2017; Marty-Dugas et al., 2017; Papaconstantinou et al., 2017; Santos et al., 2017) while a few studies have utilized more complex methodologies that involve manual extraction of data from the participant's smartphone (Falaki et al., 2010; Soikkeli et al., 2011; Andrews et al., 2015). However, issues relating to breach of participant privacy during extraction of data from their smartphone (Kotz et al., 2016) has meant most researchers have preferred to use the questionnaire based method instead. Although questionnaires overcome the problems relating to privacy issues, they are limited by their subjective nature and thus prone to inaccuracies relating to poor recall and report of smartphone usage history (Pecoraro et al., 1979; Bush et al., 1989; Heliovaara et al., 1993; Paganini-Hill & Chao, 1993) .

On review of the literature, there is a paucity of literature on the associations between smartphone use and eye related symptoms (Moon et al., 2014; Park et al., 2014; Kim et al., 2016; Moon et al., 2016; Antona et al., 2018) as most of the work has been focused on investigating computer based VDTs and their impact on visual comfort (Nakaishi & Yamada, 1999; Wolkoff et al., 2005; Nakamura et al., 2010; Agarwal et al., 2013; Zhu et al., 2013; Hirota et al., 2013; Uchino et al., 2013; Jomoah, 2014; Wu et al., 2014; Courtin et al., 2016; Tauste et al., 2016). Of the few studies to have assessed DES in smartphone users, Long et al., (2017) observed the shorter working distance to be associated with increased eyestrain after 60 minutes of use. Moon et al., (2014), Park et al., (2015) and Park et al., (2017) all reported a strong association with smartphone use and dry eyes amongst both primary and high school

children and university students. Moreover, Moon et al., (2016) showed children in urban areas to have a higher risk factor for dry eye due to the longer duration of smartphone use when compared to those living in rural areas. Interestingly, the observations of Moon et al., (2014), Park et al., (2015) and Park et al., (2017) are suggestive of an association between smartphone use and dry eyes but the applicability of their findings to other populations are limited by their studies being carried out on only a selective population, namely of Korean origin. Indeed large epidemiology studies have identified significant regional differences in dry eyes with data suggesting higher prevalence of dry eye amongst Asian populations (Patel et al., 1995; Yeh et al., 2015; Stapleton et al., 2017). It is unclear why such differences occur but consideration must be given to geographic, climatic and environmental variations (Stapleton et al., 2017). Consistent with the global trend, Asian countries show an increase rate of smartphone use (Munezawa et al., 2011; Statista, 2018b) and the ocular effects of these devices on eyes that may already be predisposed to dry eyes is of significant clinical interest.

7.2 Objective

The primary objective of this study was to examine the relationship between both subjective and objective measures of length of smartphone use and self-reported symptoms of dry eye. The prevalence of dry eyes in the general Caucasian population is approximately 14.5% (Paulsen et al., 2014) whereas in comparison, the prevalence among Malaysians is approximately 48.8% (Aljarousha et al., 2018). Hence, a secondary objective was to explore whether differences in smartphone usage habits and ocular comfort exist between the ethnic groups, which may provide some insight into population differences in the occurrence of dry eye. A questionnaire based evaluation of the daily usage pattern of smartphone and other VDTs (tablet, smart watch, PC, TV and hand held electronic games) amongst participants from

the United Kingdom, UK (data collected in UK) and Malaysia, MY (data collected in Malaysia) was carried out. Furthermore, an exploratory study on both ethnic groups was also conducted using smartphone apps to investigate other objective metrics for characterising smartphone use and to assess if the 'time spent on smartphone' obtained via subjective questionnaires was comparable to objective measures.

7.3 Methods

7.3.1 Ethical Approval

Ethical approval was obtained from Research Ethics Committee, Faculty of Health & Human Sciences and Peninsula School of Medicine & Dentistry, Plymouth University (Appendix C, reference number 17/18-902). Prior to the start of data collection, participants were fully informed of the experiment and all relevant questions were answered accordingly. Written consent was obtained before the start of data collection.

7.3.2 Sample Size

The sample size was calculated using the software G*Power, version 3.1.9.2 (Prajapati et al., 2010; Faul et al., 2007). Previous studies that have assessed smartphone use via questionnaires have used variable sample sizes (range from 54 to 1824 participants) (Joo & Sang, 2013; Moon et al., 2014; Antona et al., 2018; Cha & Seo, 2018). Sample size calculations for this study were based upon a bivariate correlation model with a moderate effect size of 0.25 (Cohen, 1992; Cohen, 1988), a significance level of $p<0.05$ with a power of 80%. According to the G*Power calculations, a total sample size of 202 participants was required for this study.

7.3.3 Inclusion and Exclusion Criteria

Participants were recruited from the staff and student population of University of Plymouth (UK) and International Islamic University Malaysia (MY) using convenience sampling. The inclusion and exclusion criteria of the study are listed below.

7.3.3.1 Inclusion Criteria

- Completed a comprehensive eye examination within the last 12 months.
- Possess a smartphone and are able to view the display screen clearly.
- Older than 18 years and younger than 40 years old.
- Willing to participate in the study.

7.3.3.2 Exclusion Criteria

- Did not own a smartphone.
- History of any form of ocular surgery including LASIK.
- Participation in a pharmacological studies occurring concurrently.
- Suffering any form of ocular or systemic diseases.
- Pregnant or breast feeding.
- Taking medications.

7.3.4 Length of Smartphone Use and Assessment of the Symptoms of Dry Eye

The length of smartphone use was assessed via questionnaires and apps while symptoms of dry eye were investigated using validated questionnaires.

7.3.4.1 Frequency of Smart Device Use Questionnaire

This study assessed the length of smartphone use by developing the 'Frequency of Smart Device Use' questionnaire which was based on the work of Moon et al., (2014) and Moon et

al., (2016). This questionnaire can be seen in Appendix E (Study 17/18-902 CASE REPORT FORM) and participants were asked to answer all relevant questions in this questionnaire. The parameters assessed from the questionnaires can be seen in Table 7.1.

Parameters Assessed	Definition
Duration of Smartphone Use	Total amount of time spent (minutes) per day viewing the smartphone's display screen.
Duration of Tablet Use	Total amount of time spent (minutes) per day viewing the tablet's display screen.
Duration of Smart Watch Use	Total amount of time spent (minutes) per day viewing the smart watch's display screen.
Duration of PC Use	Total amount of time spent (minutes) per day viewing the PC's display screen.
Duration of Watching TV	Total amount of time spent (minutes) per day watching the TV.
Duration of Playing Hand Held Video Games	Total amount of time spent (minutes) per day playing hand held video games.
Duration of Gaming on TV	Total amount of time spent (minutes) per day playing console games on TV.
Duration of Sleep	Amount of sleep (minutes) per day.
Duration of Outdoor Activity	Amount of outdoor activity conducted per day (minutes).

Table 7.1: Definition of investigated parameters via the Frequency of Smart Device Use questionnaire.

7.3.4.2 Monitoring the Length of Smartphone Use via Apps

Due to technical limitations, the same apps for monitoring smartphone usage were not available on both the Android and Apple operating systems. Therefore, on the Android operating system, an application called QualityTime (ZeroDesktop Inc., California) was used while on the Apple iOS operating system, Moment app (Kevin Holesh, Pittsburgh) was employed. Both of these apps have similar functions and were able to passively track the smartphone use of the participants. Participants were instructed to download the respective apps from either Google Play store or Apple App store.

Once the apps were installed on to the participant's smartphone, participants were asked to use their smartphone normally for 7 consecutive days. On the 8th day, participants were instructed to access their apps and write down the output from the apps, from day 1 to 7 on the appropriate section of the Study 17/18-902 CASE REPORT FORM, Appendix E. The outputs assessed can be seen in Table 7.2.

Parameters Assessed	Definition
Smartphone's Screen Time	Total amount of time spent (minutes) per day viewing the smartphone's display screen.
Smartphone's Number of Pickups	Number of time per day the smartphone's display screen is unlocked or accessed.
Smartphone's Shortest Duration	Shortest amount of time (minutes) the smartphone's display screen is being used per day.
Smartphone's Longest Duration	Longest amount of time (minutes) the smartphone's display screen is being used per day.
Smartphone's Average Duration Per Use	The average amount of time spent (minutes) viewing the smartphone during each interaction/use.

Table 7.2: Definition of investigated parameters (apps).

Participants were asked not to include smartphone usage related to conventional voice phone call, but to include video calls; since conventional voice phone call does not requires looking at the display screen. This was feasible as both apps provided measures of length of time spent on normal voice calls.

7.3.4.3 Self-Reported Symptoms of Dry Eye Questionnaires

The McMonnies (McMonnies, 1986; Nichols et al., 2004) and OSDI (Schiffman et al., 2000) validated questionnaires were used in this study. The McMonnies questionnaire functions as a screening test to discriminate individuals with dry eye from a normal population and is not an instrument to grade either dry eye symptom severity or its effect on vision-related function

(Schiffman et al., 2000). In contrast, the OSDI assess the symptoms and severity related to dry eye and their effect on vision (Dougherty et al., 2011). The OSDI is reliable in assessing dry eye (Grubbs et al., 2014; Amparo et al., 2015; Novack et al., 2017) while the McMonnies is a good screening tool for dry eye (Tang et al., 2016). As such, both questionnaires were used in a synergistic manner in this study. Participants were asked to answer all the relevant questions in both sets of questionnaires.

7.3.5 Data Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, New York). Initial data inspection was through a visual method (histogram) followed by assessment of the Sharpiro-Wilks test and Z-scores for skewness and Kurtosis; the tests confirmed the data to show a non-normal distribution. Descriptive statistics of all the parameters investigated were presented separately for both the MY and UK data and then after combining the two datasets (MY+UK). To assess if there were any significant differences in smartphone usage habits between the MY and UK cohorts, a Mann Whitney U test was performed for each metric assessed with the questionnaire and smartphone app (Field, 2005; de Winter & Dodou, 2010). A Wilcoxon signed-rank tests (Z) was also performed to investigate the differences between the Duration of Smartphone Use (obtained via questionnaires) and Smartphone's Screen Time (obtained via apps). Norman, (2010) and Schober et al., (2018) advocate that Spearman's rank order correlation can be performed on ordinal ranked data. Thus, in this study, Spearman's rank order correlation was conducted to investigate the relationship between the Duration of Smartphone Use and Smartphone's Screen Time (the significance values were Bonferroni adjusted (p_{adj}) to minimise the chance of a type 1 error). Mann Whitney U test was also performed to investigate if there were any differences in OSDI

and McMonnies scores between the MY and UK groups. Lastly, Spearman's rank order correlation was also performed to assess the relationship between both the McMonnies and OSDI scores with all the investigated parameters described in Tables 7.1 and 7.2.

7.4 Results

7.4.1 Descriptive Statistics for MY, UK and combination of MY and UK data

A total of 468 participants were recruited for this study and out of these, 254 participants completed the study. The response rate for MY was 67.31% while for the UK it was 28.21%. The demographic characteristics of the study population can be seen in Table 7.3.

Demographic Data	Results		
	MY	UK	MY and UK
Number of Participants (N)	210	44	254
Age (Years) Mean±SD	23.57±4.75	22.61±2.89	23.41±4.49
Number of Males (%)	86 (40.95%)	13 (29.50%)	99 (38.97%)
Number of Females (%)	124 (59.05%)	31 (70.50%)	155 (61.03%)

Table 7.3: Demographic of the study populations.

Since 9 parameters from the Frequency of Smart Device Use questionnaire were based on ordinal range values (Duration of Smartphone Use, Duration of Tablet Use, Duration of Smart Watch Use, Duration of PC Use, Duration of Watching TV, Duration of Playing Hand Held Video Games, Duration of Gaming on TV, Duration of Sleep and Duration of Outdoor Activity), these were presented as frequency distribution charts (Figure 7.1 to Figure 7.9) (Sullivan & Artino, 2013).

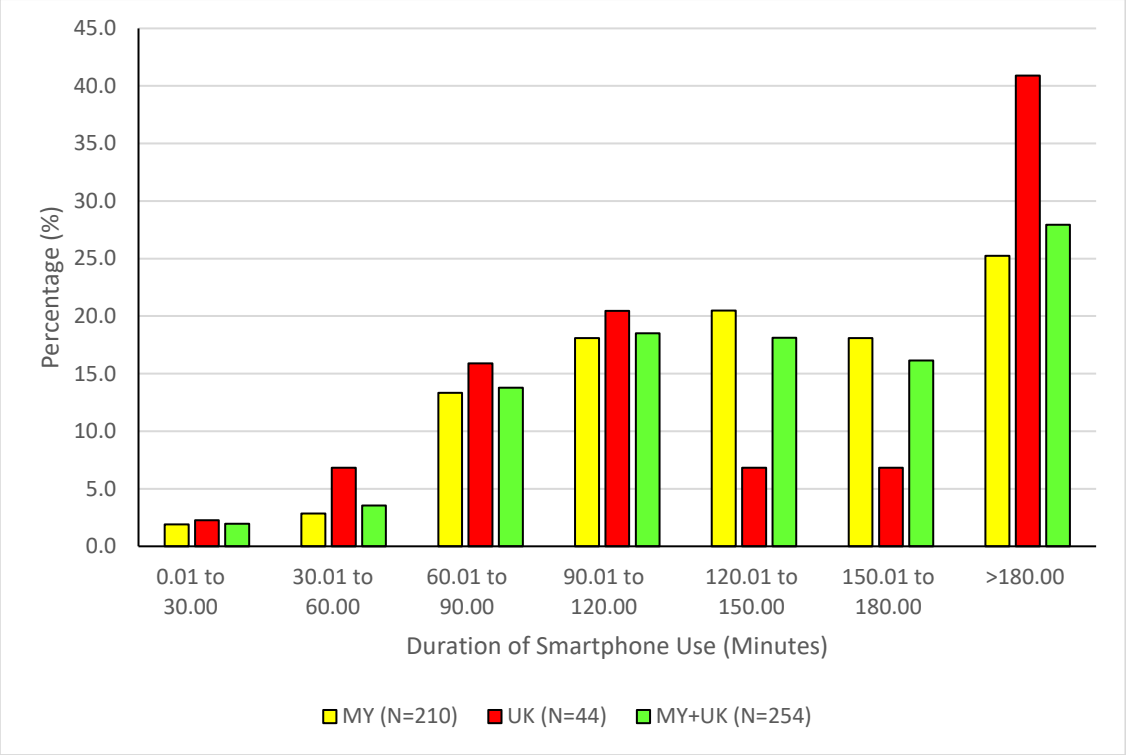


Figure 7.1: Bar chart showing the frequency distribution for 'Duration of Smartphone Use (Minutes)'.

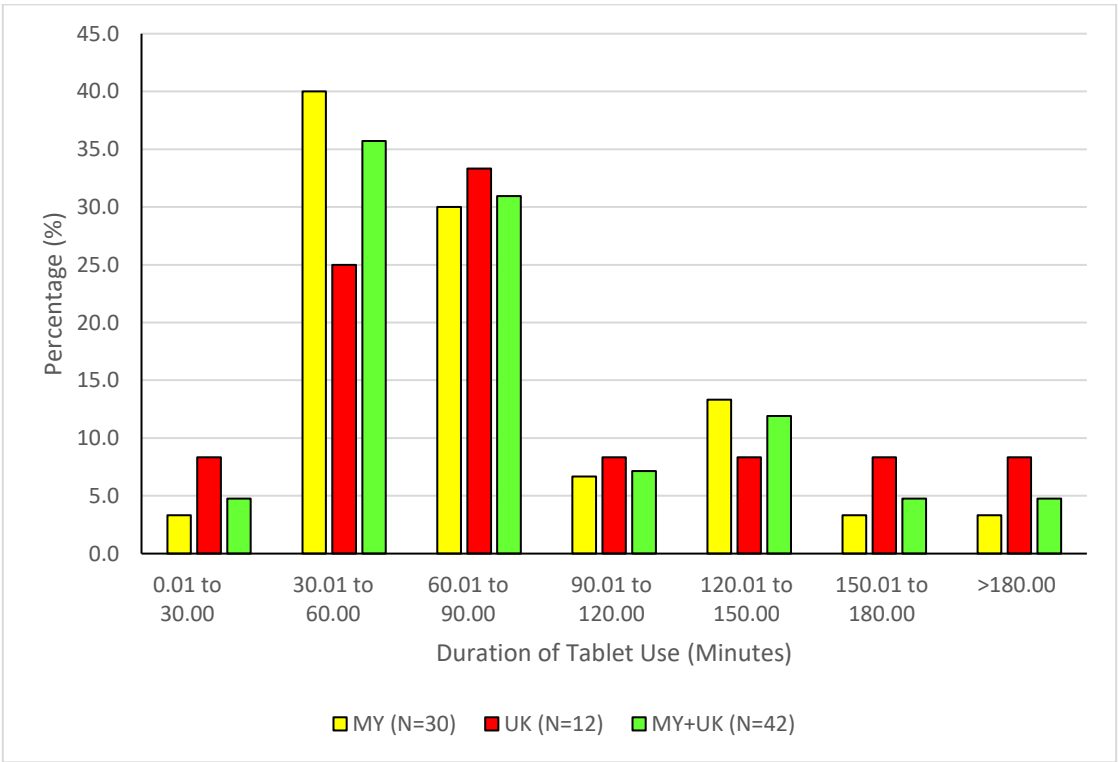


Figure 7.2: Bar chart showing the frequency distribution for 'Duration of Tablet Use (Minutes)'.

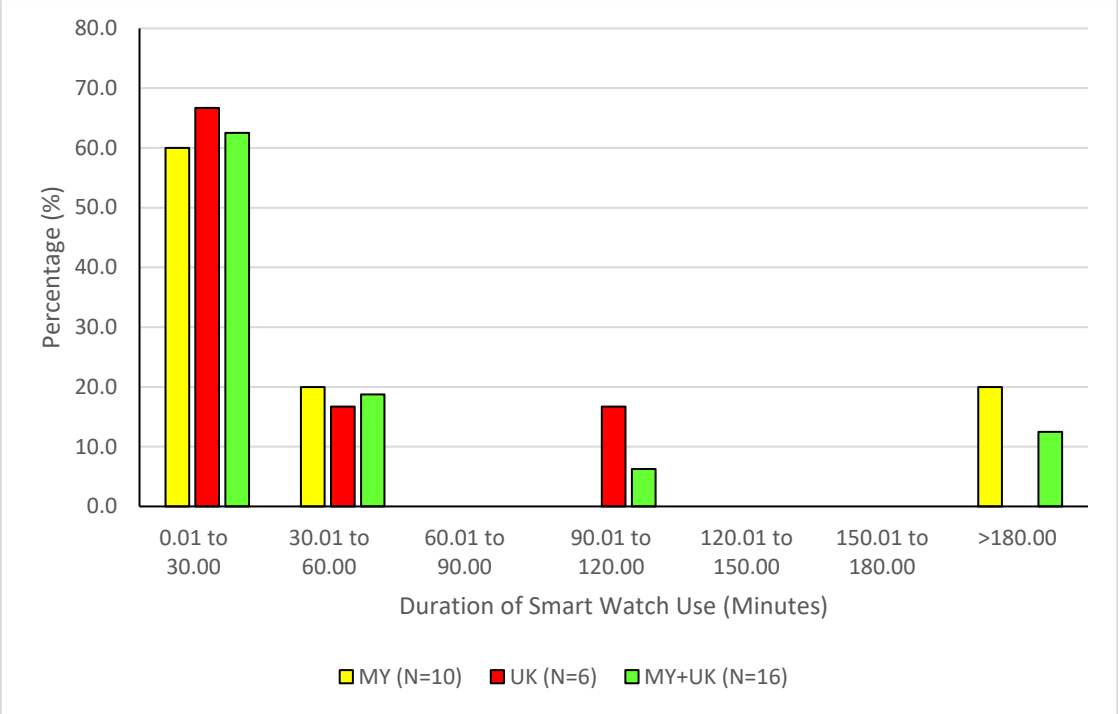


Figure 7.3: Bar chart showing the frequency distribution for 'Duration of Smart Watch Use (Minutes)'.

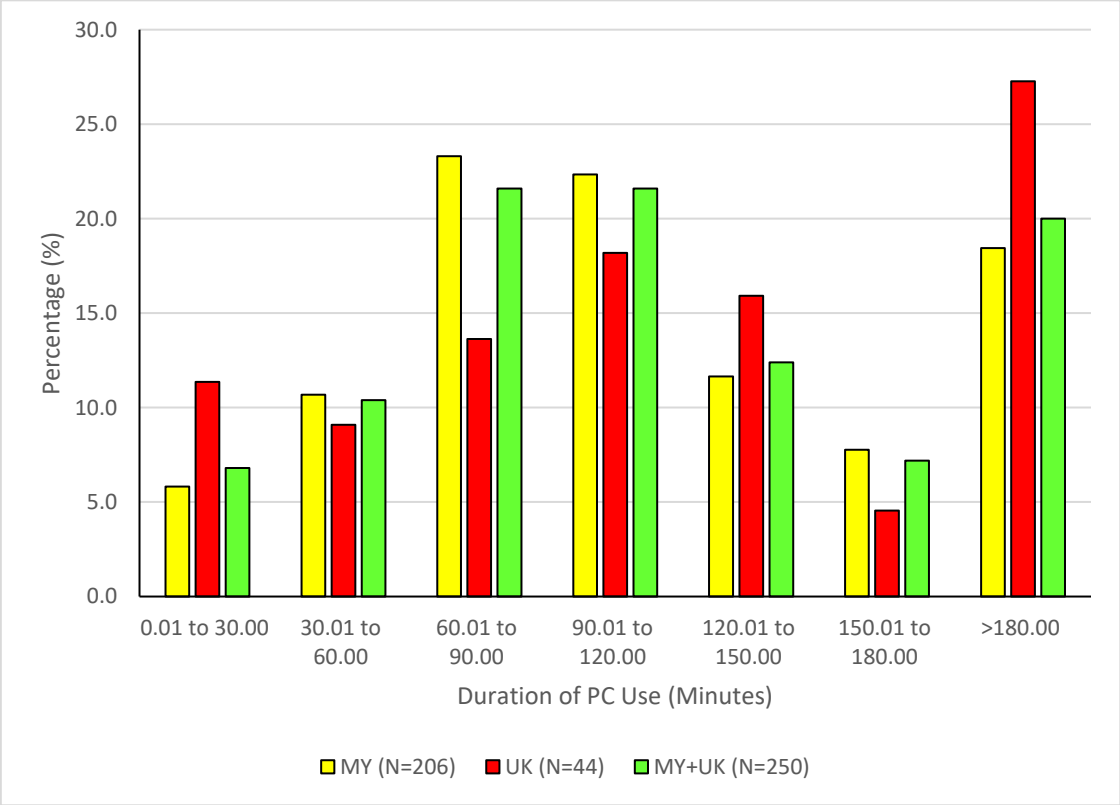


Figure 7.4: Bar chart showing the frequency distribution for 'Duration of PC Use (Minutes)'.

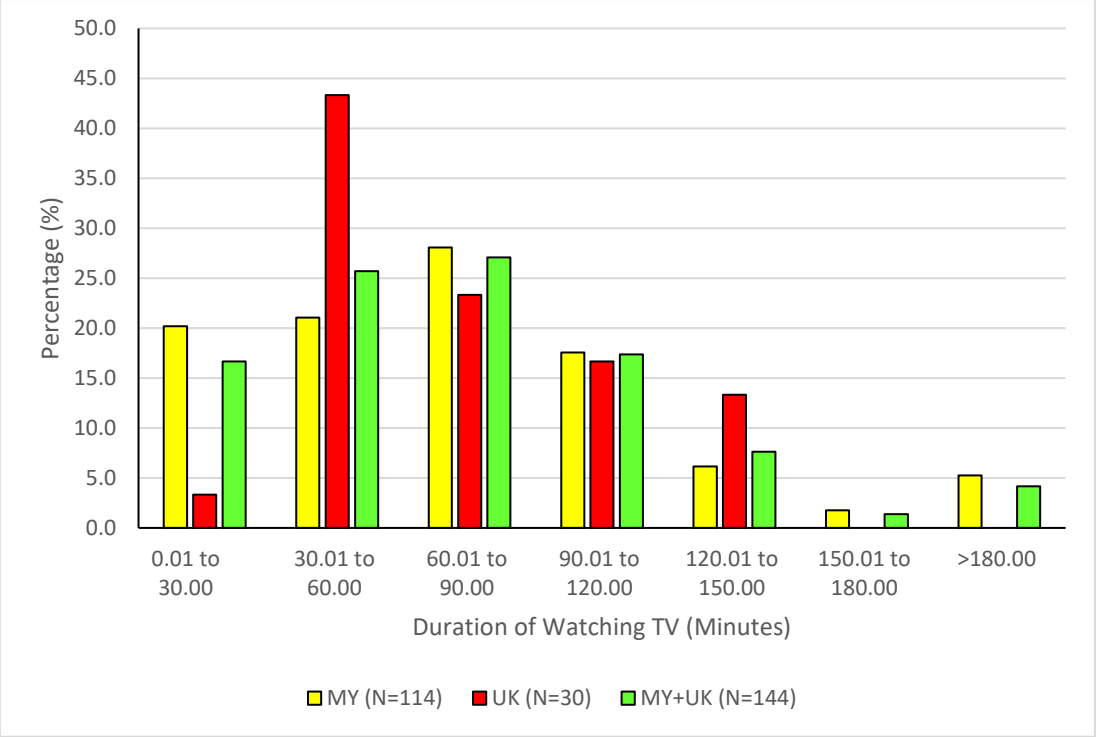


Figure 7.5: Bar chart showing the frequency distribution for 'Duration of Watching TV (Minutes)'.

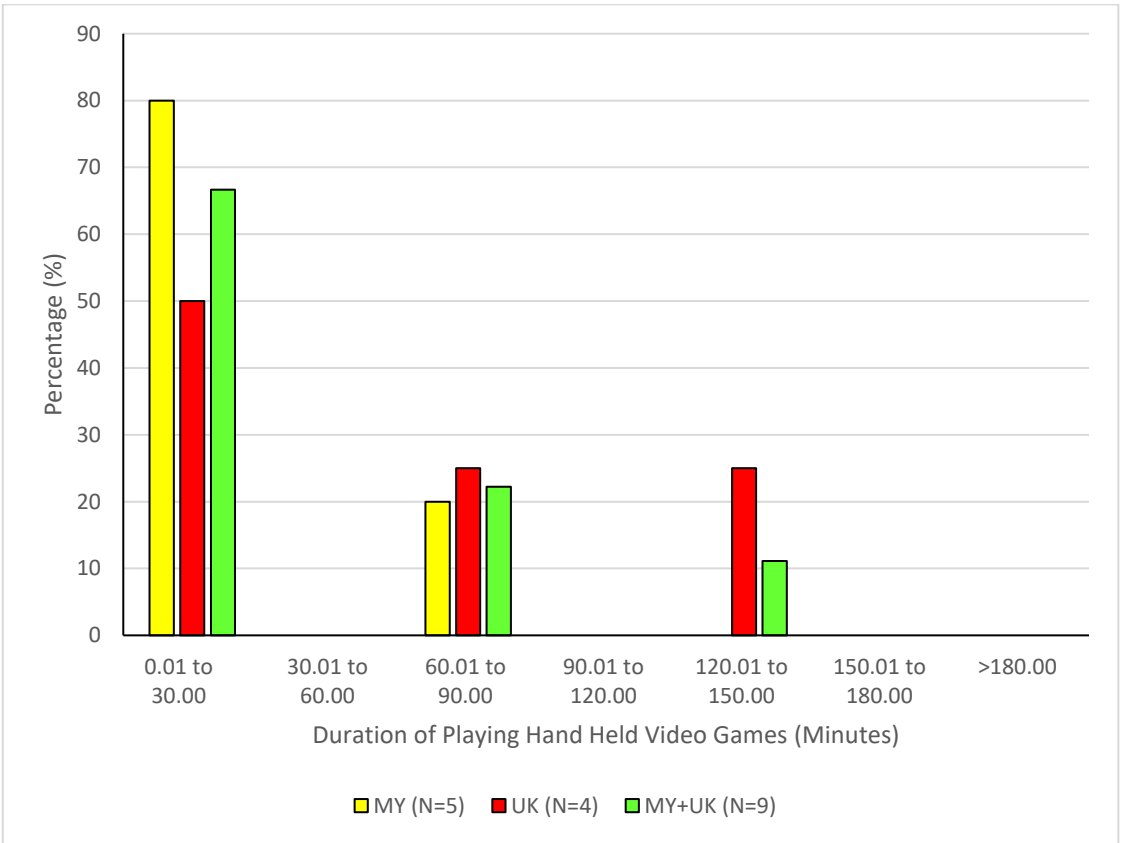


Figure 7.6: Bar chart showing the frequency distribution for 'Duration of Playing Hand Held Video Games (Minutes)'.

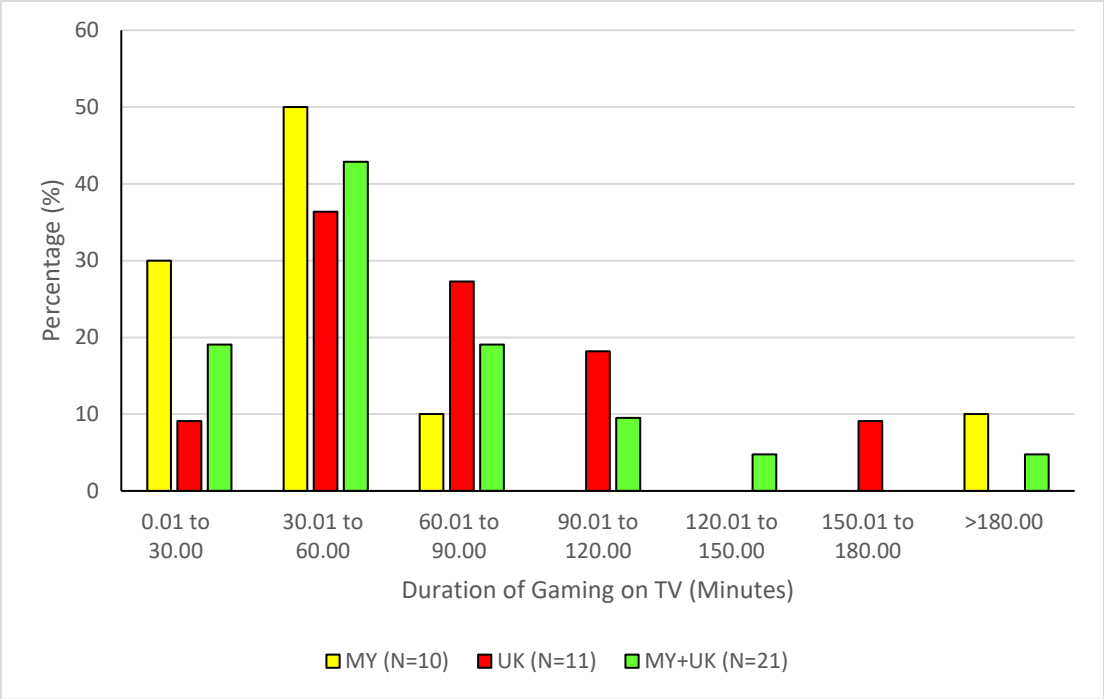


Figure 7.7: Bar chart showing the frequency distribution for 'Duration of Gaming on TV (Minutes)'.

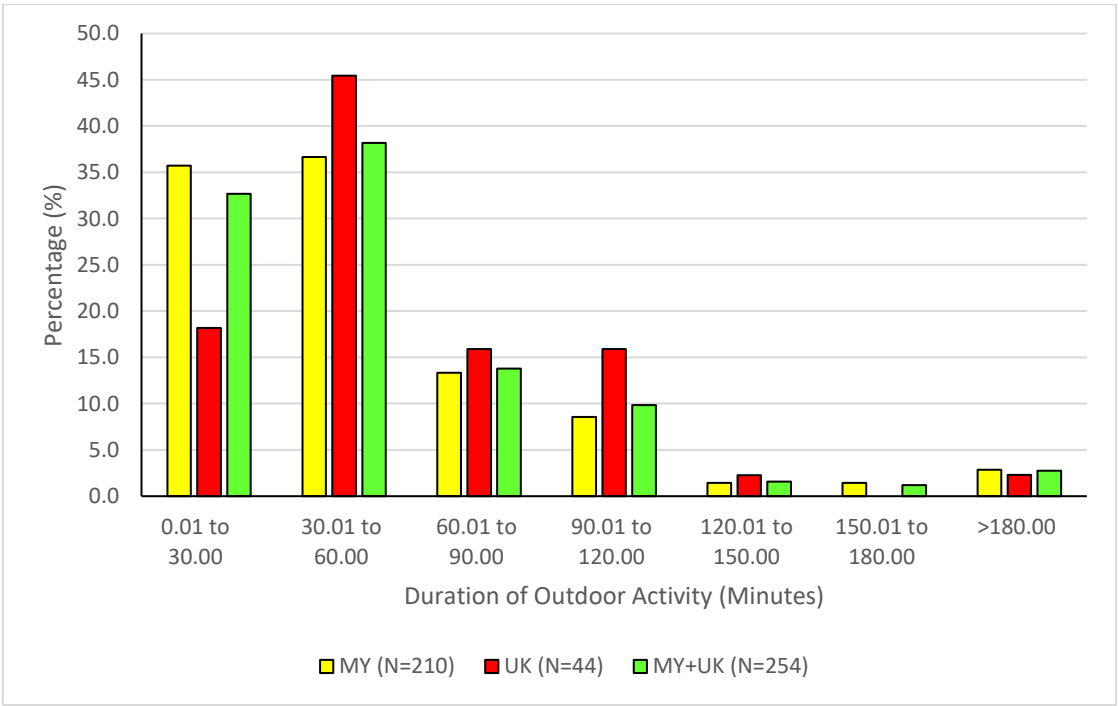


Figure 7.8: Bar chart showing the frequency distribution for 'Duration of Outdoor Activity (Minutes)'.

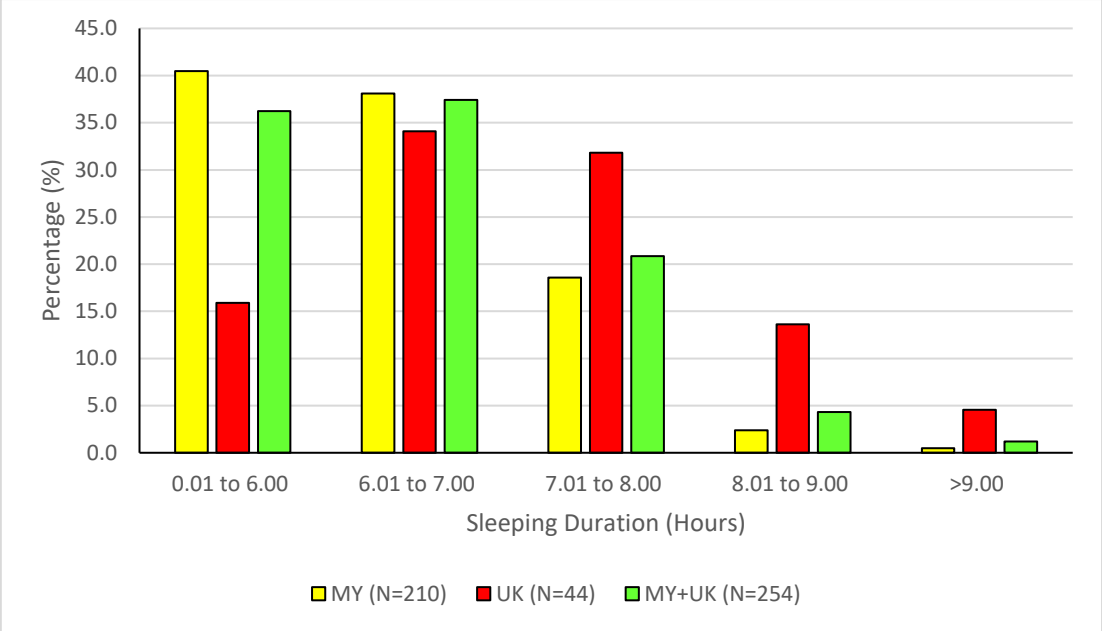


Figure 7.9: Bar chart showing the frequency distribution for 'Duration of Sleep (Hours)'.

7.4.2 Comparison of Smartphone Usage via the Frequency of Smart Device Use questionnaire between MY and UK participants

Other than Duration of Sleep and Duration of Outdoor Activity, Mann Whitney U test (Table 7.4) revealed no significant differences between the MY and UK data. Duration of Sleep for MY participants was significantly lower (mean rank=118.96) than the UK participants (mean rank=168.26), $U=2826.5$, $z=-4.288$, $p<0.0005$. In addition, Duration of Outdoor Activity for MY was significantly lower (mean rank=123.49) than the UK data (mean rank=146.63), $U=3778.5$, $z=-1.995$, $p=0.023$.

Investigated Parameters from Questionnaires	Mann Whitney U test Results
Duration of Smartphone Use	U=4526.5, z=-0.215, *p*=0.831
Duration of Tablet Use	U=161.5, z=-0.536, *p*=0.603
Duration of Smart Watch Use	U=27.0, z=-0.376, *p*=0.749
Duration of PC Use	U=4210.0, z=-0.752, *p*=0.454
Duration of Watching TV	U=1657.5, z=-0.265, *p*=0.793
Duration of Playing Hand Held Video Games	U=6.5, z=-1.025, *p*=0.405
Duration of Gaming on TV	U=34.0, z=-1.552, *p*=0.219
Duration of Sleep	U=2826.5, z=-4.288, *p*<0.0005*
Duration of Outdoor Activity	U=3778.5, z=-1.995, *p*=0.023*

*Statistically significant, *p*<0.05

Table 7.4: Results for the Mann Whitney U test on the data from the Frequency of Smart Device Use questionnaire.

7.4.3 Combining Data from QualityTime and Moment apps for Analysis

Although 2 different apps were being used to monitor smartphone usage, both apps were considered interchangeable due to their similar functionality. To validate this supposition, a pilot study was conducted on 5 participants using both apps. This was done by asking each participant to perform a series of tasks on both the Android (QualityTime) and Apple (Moment) based smartphone simultaneously for 1 hour. The tasks involved can be seen in Table 7.5 below. The investigator monitored the time throughout the designated task.

Task Number	Task to Perform
1	Watch you National Geographic on YouTube video (https://www.youtube.com/watch?v=JZf9TUDYmME) for 15 minutes
2	Close the phone display for 12 minutes
3	Access Facebook for 7 minutes
4	Close the phone display for 3 minutes
5	Read from a food blog (https://greatist.com/eat/best-food-blogs-2016) for 5 minutes
6	Close the phone display for 1 minutes
7	View a video on you tube (video clip-song) (https://www.youtube.com/watch?v=9LMDg6awPq8&list=RDGMEMQ1dJ7wXfLlqCjwV0xfSNbAVM9LMDg6awPq8&start_radio=1) for 3 minutes
8	Close the phone display for 14 minutes
Total Duration of all task is 1 hour	

Table 7.5: Flow of task for QualityTime vs. Moment apps.

Results showed that the output produced from both apps were identical within the limits of the resolution of the applications. As such, it was assumed that the results from the two apps were interchangeable and the data from both apps were combined and analysed together in subsequent analysis. The descriptive data for the combined apps that were used in subsequent analysis can be seen in Table 7.6.

The results from the apps-based parameters (Smartphone's Screen Time, Smartphone's Number of Pickups, Smartphone's Shortest Duration, Smartphone's Longest Duration and Smartphone's Average Duration Per Use) can be seen in Table 7.7 and Figure 7.10.

7.4.4 Comparison of Smartphone Usage via the apps between MY and UK participants

All participants who completed the questionnaire were invited to download an app onto their smartphone and record their smartphone usage habits over a 7-day period. A total of 76 participants completed this element of the study (Table 7.6).

Investigated Parameters	Results		
	MY	UK	MY and UK
Number of Participants (N)	58 QualityTime=41 Moment=17	18 QualityTime=6 Moment=12	76 QualityTime=47 Moment=29
Age (Years) Mean±SD	25.05±4.63	22.56±2.36	24.46±4.32
Number of Males (%)	10 (17.24%)	2 (11.10%)	12 (15.79%)
Number using quality time (%)	48 (82.76%)	16 (88.90%)	64 (84.21%)

Table 7.6: Descriptive data on participants involved in assessing smartphone usage via apps.

Smartphone's Screen Time for the MY participants was significantly longer (mean rank=42.34) when compared to the UK individuals (mean rank=26.14). In addition, Smartphone's Longest Duration for MY was significantly longer (mean rank=42.81) compared to the UK data (mean rank=24.61). Other investigated parameters showed no significant difference between both groups (Table 7.7, Table 7.8 and Figure 7.10).

Investigated Parameters	Mean±SD		
	MY	UK	MY and UK
Smartphone's Screen Time (Minutes)	262.38±112.10	183.82±111.28	243.77±116.14
Smartphone's Number of Pickups	117.59±112.59	80.63±70.71	108.83±104.97
Smartphone's Shortest Duration (Minutes)	1.27±1.96	1.45±0.86	1.32±1.76
Smartphone's Longest Duration (Minutes)	49.09±31.92	31.07±19.42	44.82±30.32
Smartphone's Average Duration Per Use (Minutes)	6.97±9.14	3.19±2.17	6.08±8.19

Table 7.7: Output from the smartphone apps.

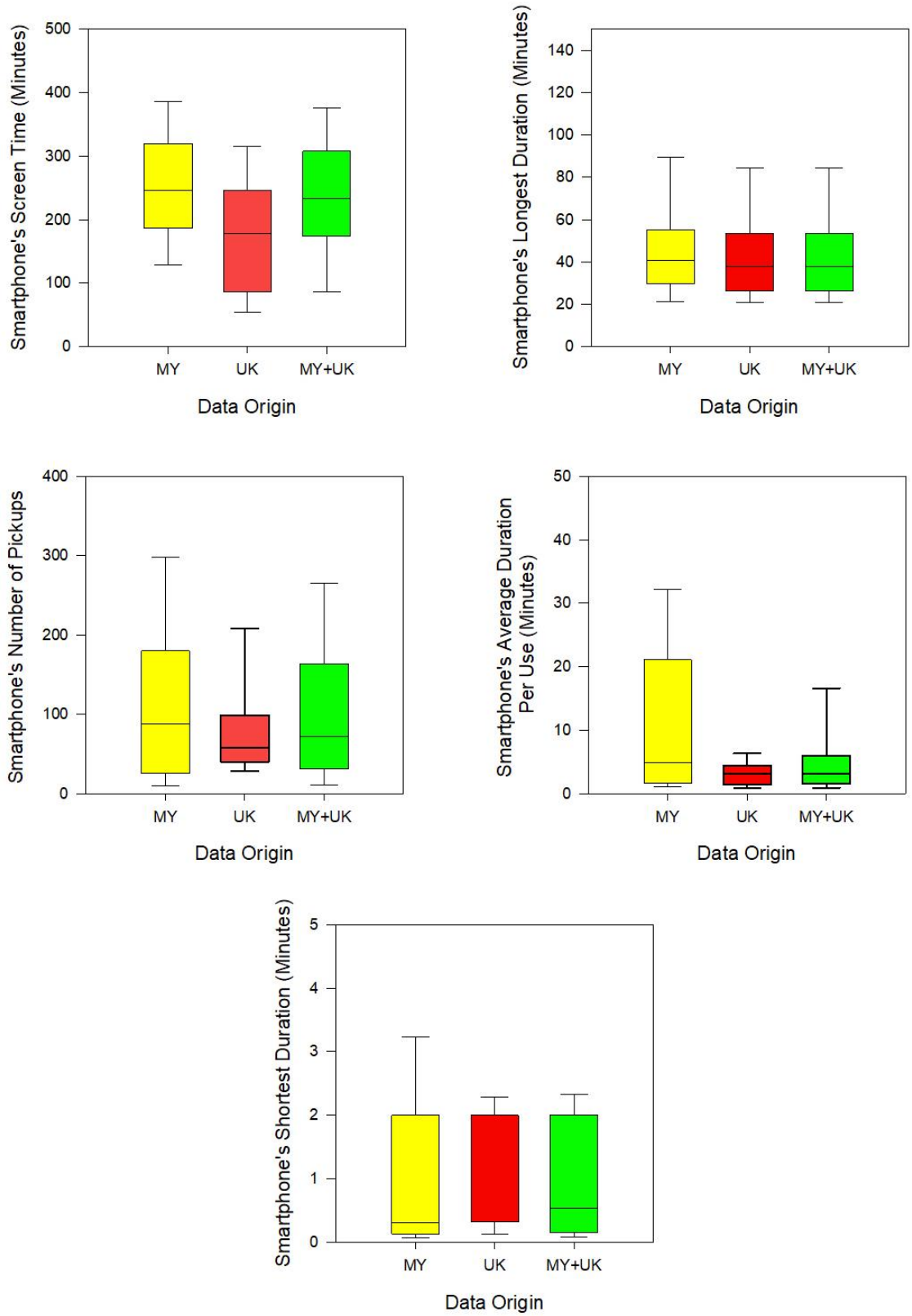


Figure 7.10: Box plot representing median and interquartile range for the apps-based data from MY, UK and combination of MY+UK.

Investigated Parameters from Apps	Mann Whitney U test Results
Smartphone's Screen Time	U=299.5, z=-2.719, *p*=0.007*
Smartphone's Number of Pickups	U=472.5, z=-0.605, *p*=0.545
Smartphone's Shortest Duration	U=362.5, z=-1.958, *p*=0.050
Smartphone's Longest Duration	U=272.0, z=-3.054, *p*=0.002*
Smartphone's Average Duration Per Use	U=451.0, z=-0.867, *p*=0.386

*Statistically significant, $p<0.05$

Table 7.8: Results for the Mann Whitney U test for comparison of Smartphone app data between MY and UK (Apps).

7.4.5 Comparing Questionnaire and App Assessment of 'Time Spent per Day on Smartphone'

The amount of time spent per day on a smartphone was obtained using 2 methods; (i) Questionnaires-Duration of Smartphone Use (ordinal data), and (ii) Apps-Smartphone's Screen Time (continuous data). To allow comparison of these two methods, the App's 'Smartphone Screen Time' metric was converted to ordinal data using the same ordinal rank cut-off used in the smart device usage questionnaires for the question 'Duration of Smartphone Use' (Figure 7.11). After the conversion, Wilcoxon signed-rank tests (Z) showed a significant difference in the results obtained via both methods ($Z = -4.163$, $p<0.0005$); the amount of time spent per day on smartphones was significantly higher when assessed using the apps as opposed to the response from the questionnaire. Although both parameters were significantly different, Spearman's correlation showed a significant moderate (Cohen, 1988) strength between both parameters ($p<0.0005$, $r_s=0.445$), as can be seen in Figure 7.12.

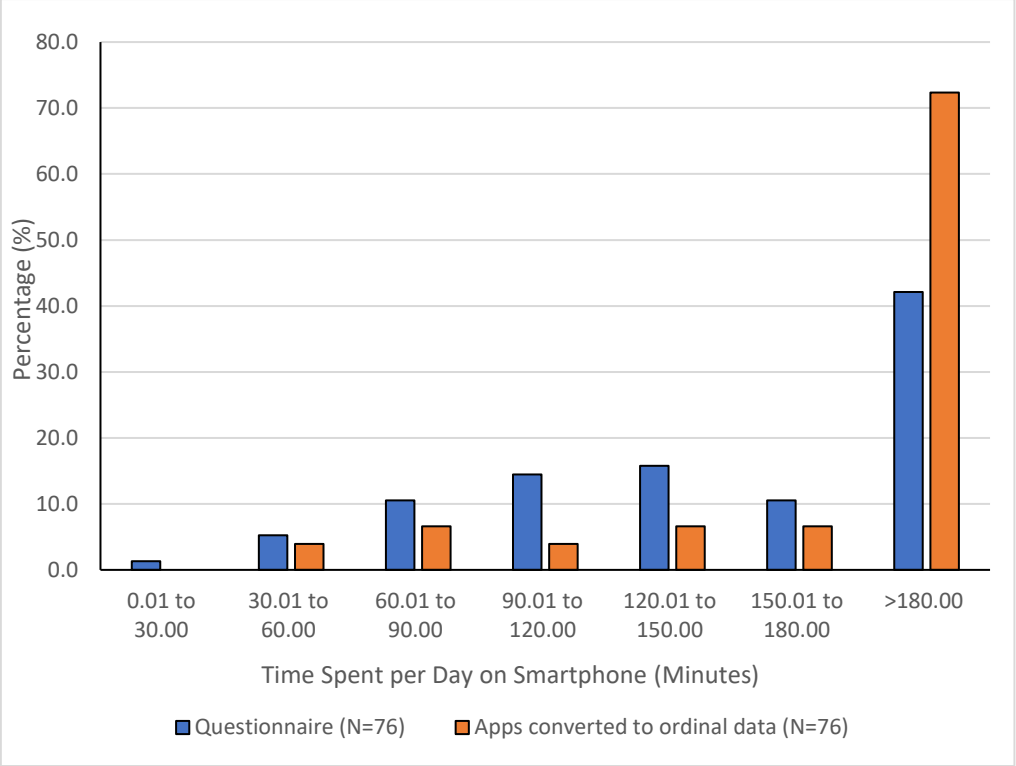
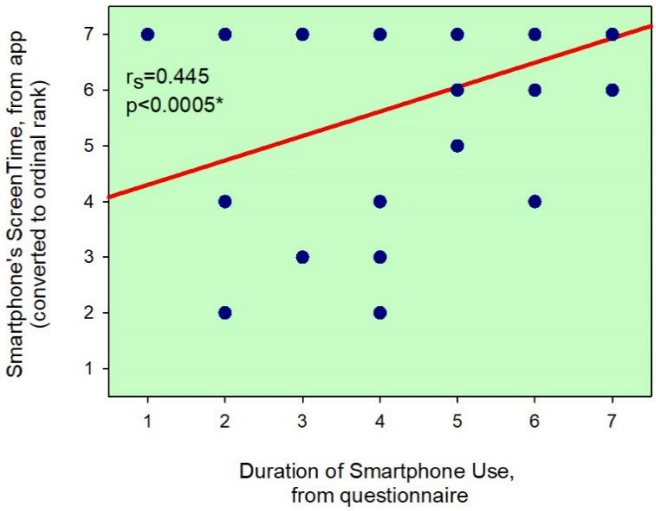


Figure 7.11: Bar chart showing the frequency distribution for 'Time Spent per Day on Smartphone (Minutes)' obtained from questionnaire and the converted apps data.



*Statistically significant, $p<0.05$

Each number on the x-axis and y-axis represent:

1	0.01 to 30.00 minutes
2	30.01 to 60.00 minutes
3	60.01 to 90.00 minutes
4	90.01 to 120.00 minutes
5	120.01 to 150.00 minutes
6	150.01 to 180.00 minutes
7	>180.00 minutes

Figure 7.12: Spearman's correlation for Time Spend per Day on Smartphone between questionnaire (Duration of Smartphone Use) and app (Smartphone's Screen Time) that was converted to ordinal rank.

7.4.6 Comparing OSDI Score and McMonnies Score between MY and UK participants

The results for OSDI score and McMonnies score for this study can be seen in Table 7.9 below. Mann Whitney U test showed no significant differences (p>0.05) between MY and UK participants for both OSDI and McMonnies scores (Table 7.10).

Investigated Parameters	Mean±SD		
	MY	UK	MY and UK
OSDI Score	10.79±12.94	10.01±9.80	10.65±12.44
McMonnies Score	3.62±2.91	4.57±3.47	3.79±3.03

Table 7.9: Results for OSDI score and McMonnies score for the investigated population.

Investigated Parameters	Mann Whitney U test Results
OSDI Score	U=4421.5, z=-0.451, p=0.652
McMonnies Score	U=3860.5, z=-1.726, p=0.084

Table 7.10: Mann Whitney results for OSDI score and McMonnies score between MY and UK.

7.4.7 Correlation Between OSDI Score and McMonnies Score with the Investigated Parameters

The Spearman's rank order correlations were investigated and presented in order of MY population, UK population and MY+UK population.

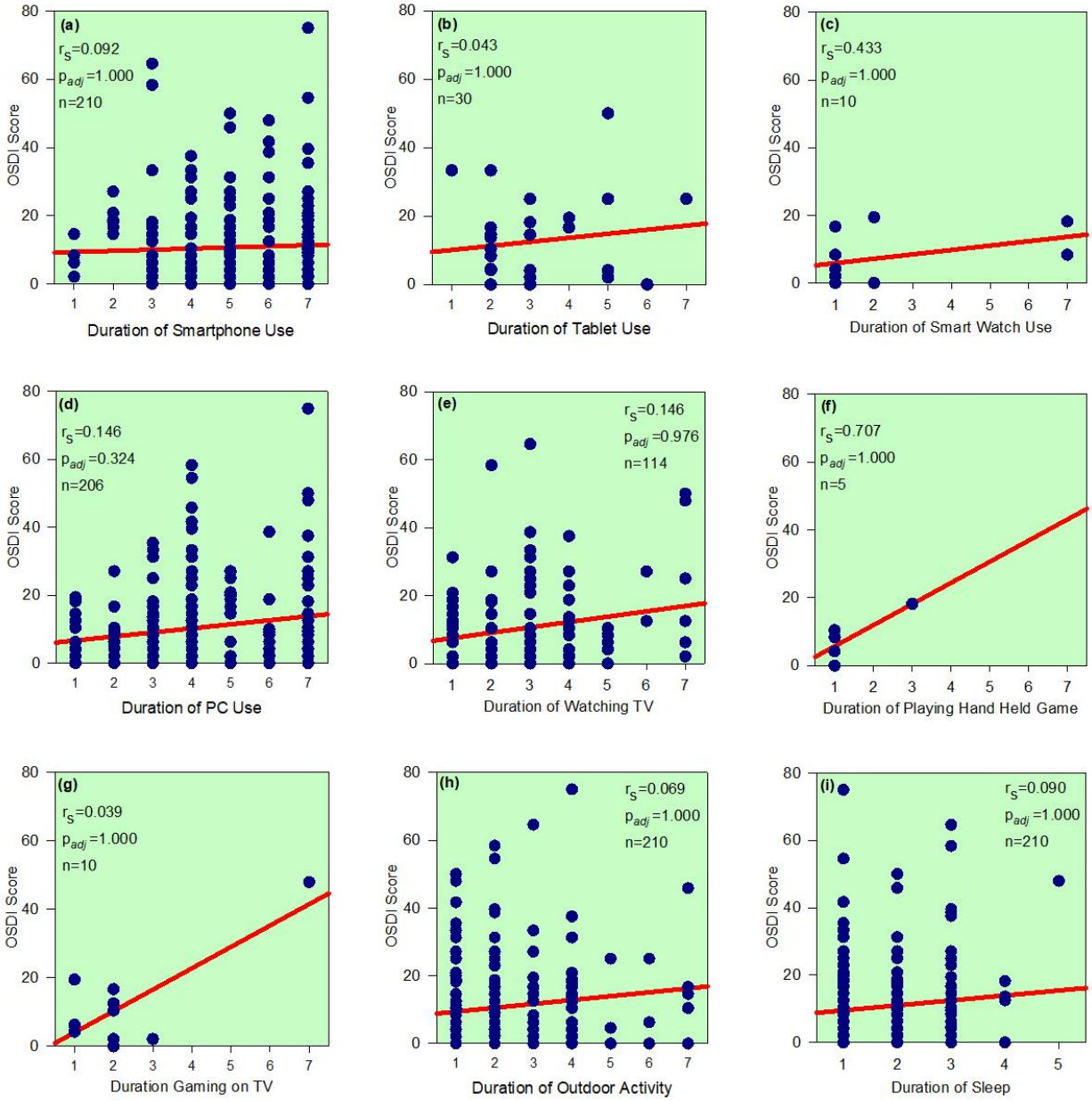
7.4.7.1 MY Population

For the MY population, the Spearman's rank order correlations between OSDI score and McMonnies score for the investigated parameters can be seen in Table 7.11, Table 7.12, Figure 7.13, Figure 7.14, Figure 7.15 and Figure 7.16. There was no significant correlation

between OSDI score with any of the investigated parameters while the McMonnies score only correlated significantly and weakly with Duration of Smartphone Use (r_s=0.217, p_{adj}=0.018).

	Investigated Parameters	Spearman's Correlation [r_s, Adjusted p value (p_{adj})]
From Questionnaires	**Duration of Smartphone Use (n=210)**	0.092, p_{adj}=1.000
	Duration of Tablet Use (n=30)	0.043, p_{adj}=1.000
	Duration of Smart Watch Use (n=10)	0.433, p_{adj}=1.000
	Duration of PC Use (n=206)	0.146, p_{adj}=0.324
	Duration of Watching TV (n=114)	0.146, p_{adj}=0.976
	Duration of Playing Hand Held Video Games n=5)	0.707, p_{adj}=1.000
	Duration of Gaming on TV (n=10)	0.039, p_{adj}=1.000
	Duration of Sleep (n=210)	0.090, p_{adj}=1.000
	Duration of Outdoor Activity (n=210)	0.069, p_{adj}=1.000
From Apps	**Smartphone's Screen Time (n=58)**	0.020, p_{adj}=1.000
	Smartphone's Number of Pickups (n=58)	-0.136, p_{adj}=1.000
	Smartphone's Shortest Duration (n=58)	-0.019, p_{adj}=1.000
	Smartphone's Longest Duration (n=58)	-0.010, p_{adj}=1.000
	Smartphone's Average Duration Per Use (n=58)	0.119, p_{adj}=1.000

Table 7.11: Spearman's correlation between OSDI score and the investigated parameters for the MY participants.



For (a) to (h), each number on the x-axis represent:

1	0.01 to 30.00 minutes
2	30.01 to 60.00 minutes
3	60.01 to 90.00 minutes
4	90.01 to 120.00 minutes
5	120.01 to 150.00 minutes
6	150.01 to 180.00 minutes
7	>180.00 minutes

For (i), each number on the x-axis represent:

1	0.01 to 6.00 hours
2	6.01 to 7.00 hours
3	7.01 to 8.00 hours
4	8.01 to 9.00 hours
5	>9.00 hours

Figure 7.13: Spearman's correlation plots between OSDI score with the investigated parameters derived from the questionnaire data from the MY group.

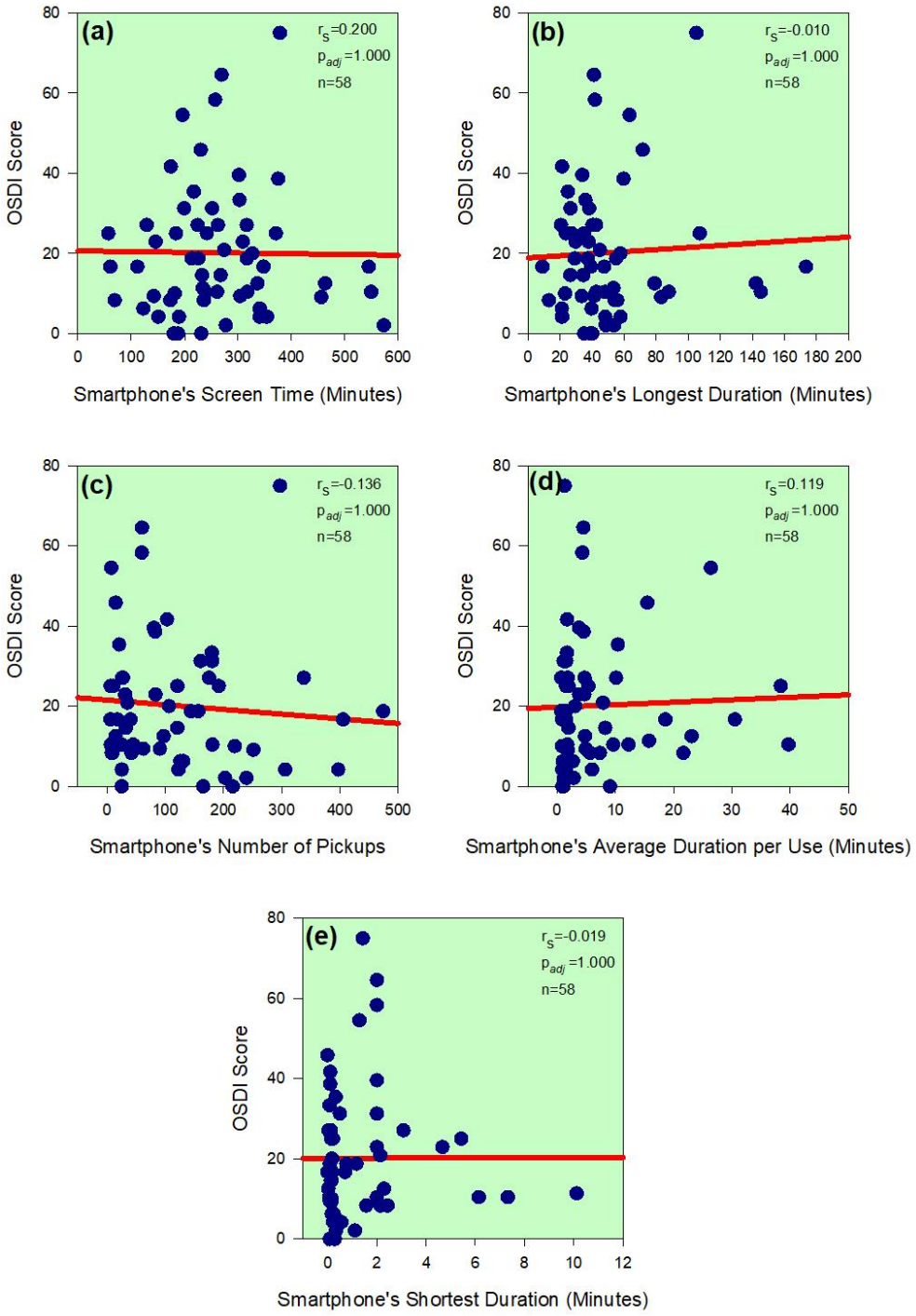
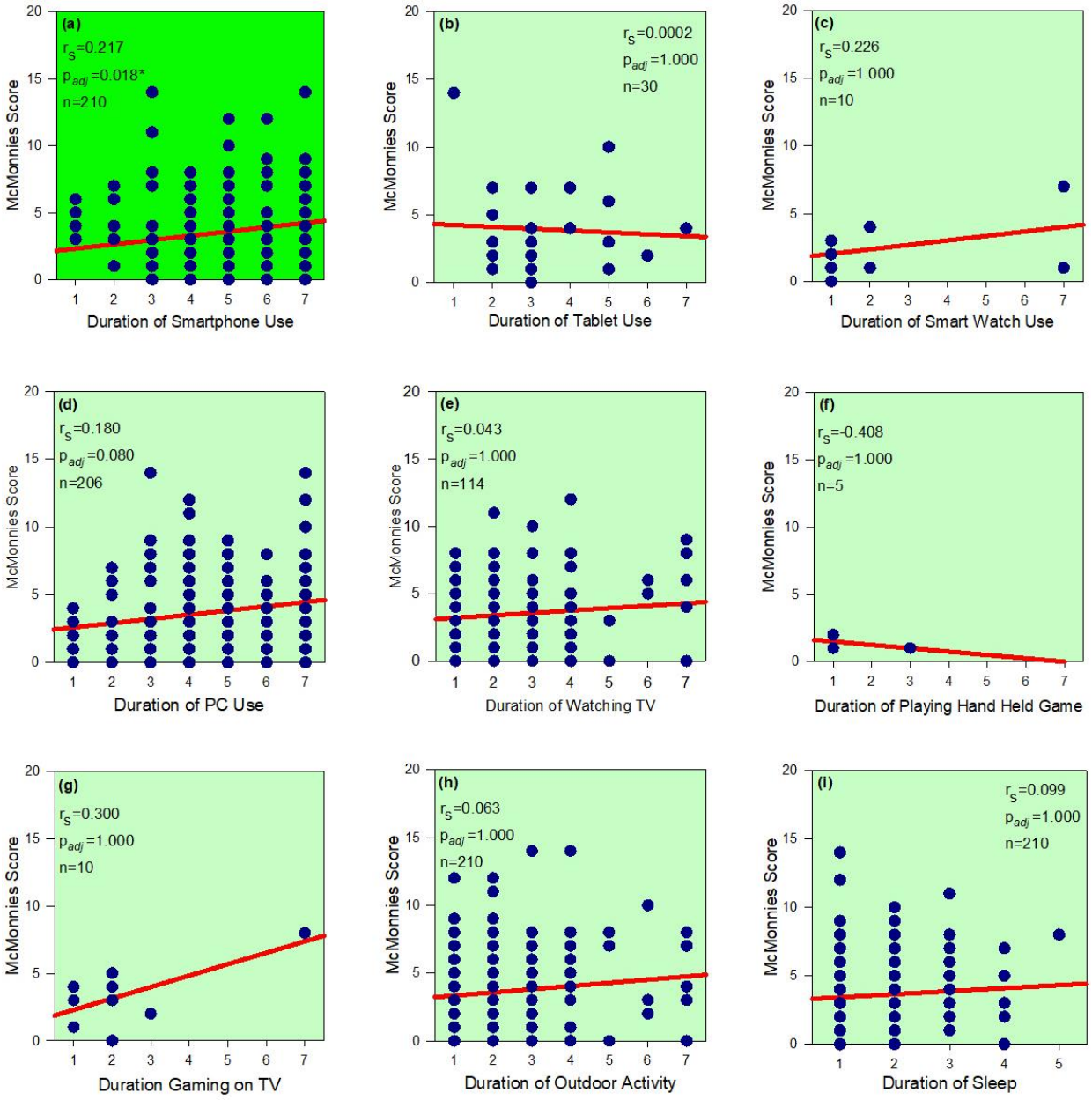


Figure 7.14: Spearman's correlation plots between OSDI score with the investigated parameters derived from the app data from the MY group.

Investigated Parameters		Spearman's Correlation [r_s, Adjusted p value (p_{adj})]
From Questionnaires	**Duration of Smartphone Use (n=210)**	0.217, p_{adj}=0.018*
	Duration of Tablet Use (n=30)	0.0002, p_{adj}=1.000
	Duration of Smart Watch Use (n=10)	0.226, p_{adj}=1.000
	Duration of PC Use (n=206)	0.180, p_{adj}=0.080
	Duration of Watching TV (n=114)	0.043, p_{adj}=1.000
	Duration of Playing Hand Held Video Games (n=5)	-0.408, p_{adj}=1.000
	Duration of Gaming on TV (n=10)	0.300, p_{adj}=1.000
	Duration of Sleep (n=210)	0.099, p_{adj}=1.000
	Duration of Outdoor Activity (n=210)	0.063, p_{adj}=1.000
From Apps	**Smartphone's Screen Time (n=58)**	0.180, p_{adj}=0.875
	Smartphone's Number of Pickups (n=58)	-0.078, p_{adj}=1.000
	Smartphone's Shortest Duration (n=58)	-0.027, p_{adj}=1.000
	Smartphone's Longest Duration (n=58)	0.159, p_{adj}=1.000
	Smartphone's Average Duration Per Use (n=58)	0.141, p_{adj}=1.000

*Statistically significant, p_{adj} <0.05

Table 7.12: Spearman's correlation between McMonnies score and the investigated parameters for the MY participants.



*Statistically significant, p_{adj} <0.05 (note the different shade of green in comparison to the other plots).

For (a) to (h), each number on the x-axis represent:

1	0.01 to 30.00 minutes
2	30.01 to 60.00 minutes
3	60.01 to 90.00 minutes
4	90.01 to 120.00 minutes
5	120.01 to 150.00 minutes
6	150.01 to 180.00 minutes
7	>180.00 minutes

For (i), each number on the x-axis represent:

1	0.01 to 6.00 hours
2	6.01 to 7.00 hours
3	7.01 to 8.00 hours
4	8.01 to 9.00 hours
5	>9.00 hours

Figure 7.15: Spearman's correlation plots between McMonnies score with the investigated parameters derived from the questionnaire data from the MY group.

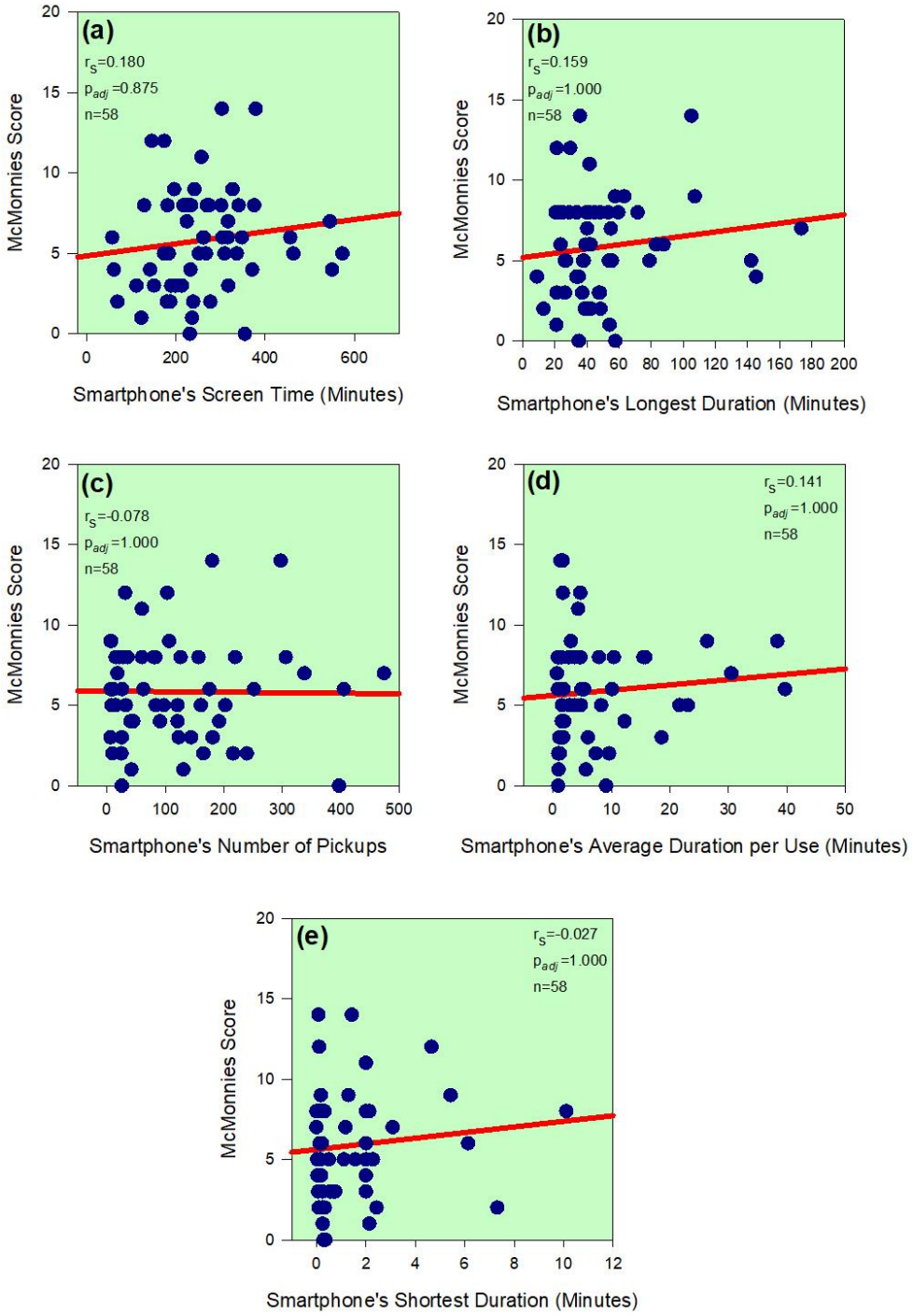


Figure 7.16: Spearman's correlation plots between McMonnies score with the investigated parameters derived from the app data from the MY group.

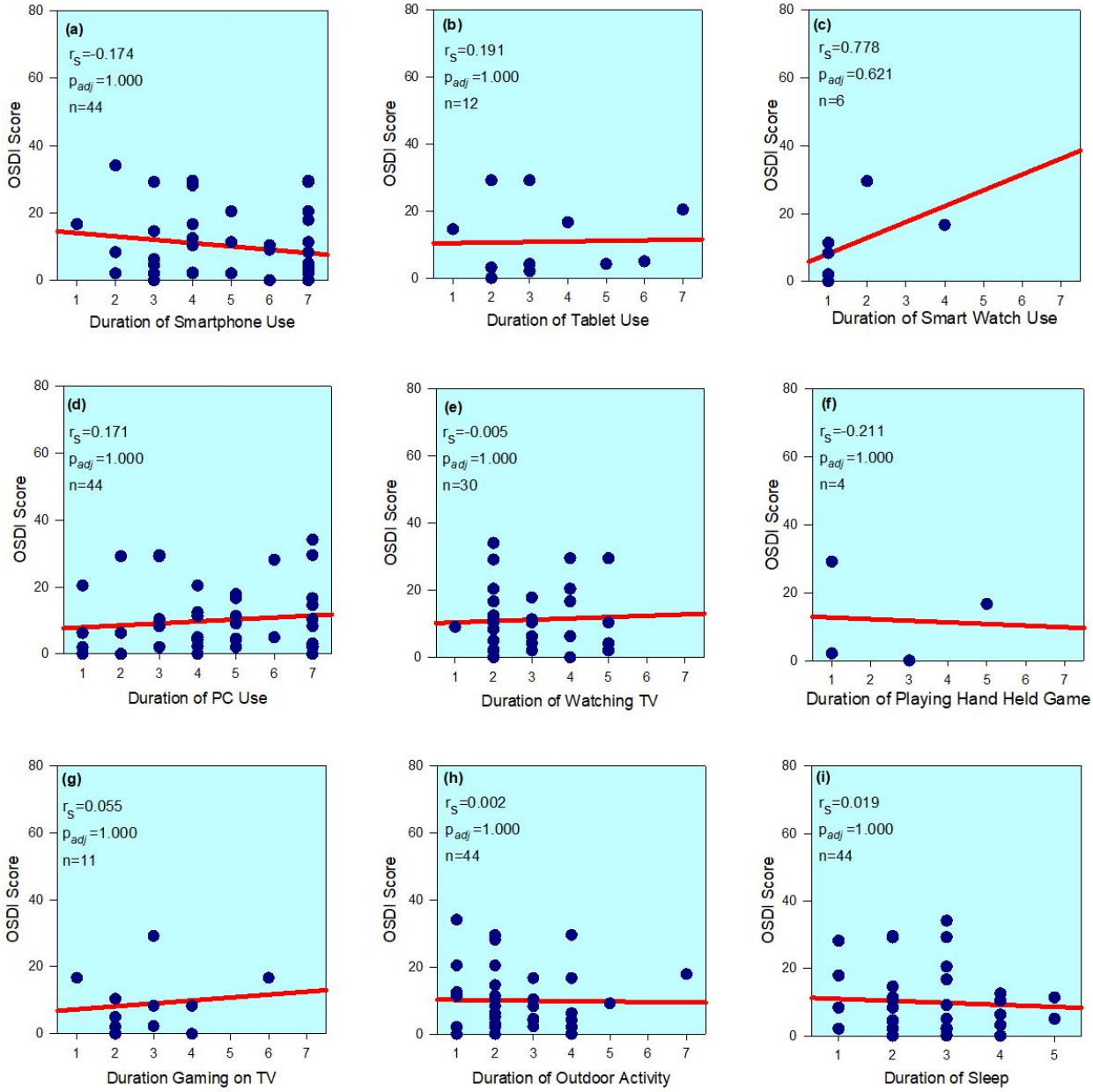
7.4.7.2 UK Population

For the UK population, the Spearman's rank order correlations between OSDI score and McMonnies score with the investigated parameters can be seen in Table 7.13, Table 7.14,

Figure 7.17, Figure 7.18, Figure 7.19 and Figure 7.20. With the UK population, there was no significant correlation between either the OSDI score or McMonnies score with any of the investigated parameters.

Investigated Parameters		Spearman's Correlation [r_s, Adjusted p value (p_{adj})]
From Questionnaires	**Duration of Smartphone Use (n=44)**	-0.174, p_{adj}=1.000
	Duration of Tablet Use (n=12)	0.191, p_{adj}=1.000
	Duration of Smart Watch Use (n=6)	0.778, p_{adj}=0.621
	Duration of PC Use (n=44)	0.171, p_{adj}=1.000
	Duration of Watching TV (n=30)	-0.005, p_{adj}=1.000
	Duration of Playing Hand Held Video Games (n=4)	-0.211, p_{adj}=1.000
	Duration of Gaming on TV (n=11)	0.055, p_{adj}=1.000
	Duration of Sleep (n=44)	0.019, p_{adj}=1.000
	Duration of Outdoor Activity (n=44)	0.002, p_{adj}=1.000
From Apps	**Smartphone's Screen Time (n=18)**	-0.040, p_{adj}=1.000
	Smartphone's Number of Pickups (n=18)	-0.017, p_{adj}=1.000
	Smartphone's Shortest Duration (n=18)	0.404, p_{adj}=0.480
	Smartphone's Longest Duration (n=18)	-0.023, p_{adj}=1.000
	Smartphone's Average Duration Per Use (n=18)	0.032, p_{adj}=1.000

Table 7.13: Spearman's correlation between OSDI score and the investigated parameters for the UK participants.



For (a) to (h), each number on the x-axis represent:

1	0.01 to 30.00 minutes
2	30.01 to 60.00 minutes
3	60.01 to 90.00 minutes
4	90.01 to 120.00 minutes
5	120.01 to 150.00 minutes
6	150.01 to 180.00 minutes
7	>180.00 minutes

For (i), each number on the x-axis represent:

1	0.01 to 6.00 hours
2	6.01 to 7.00 hours
3	7.01 to 8.00 hours
4	8.01 to 9.00 hours
5	>9.00 hours

Figure 7.17: Spearman's correlation plots between OSDI score with the investigated parameters derived from the questionnaires data from the UK group.

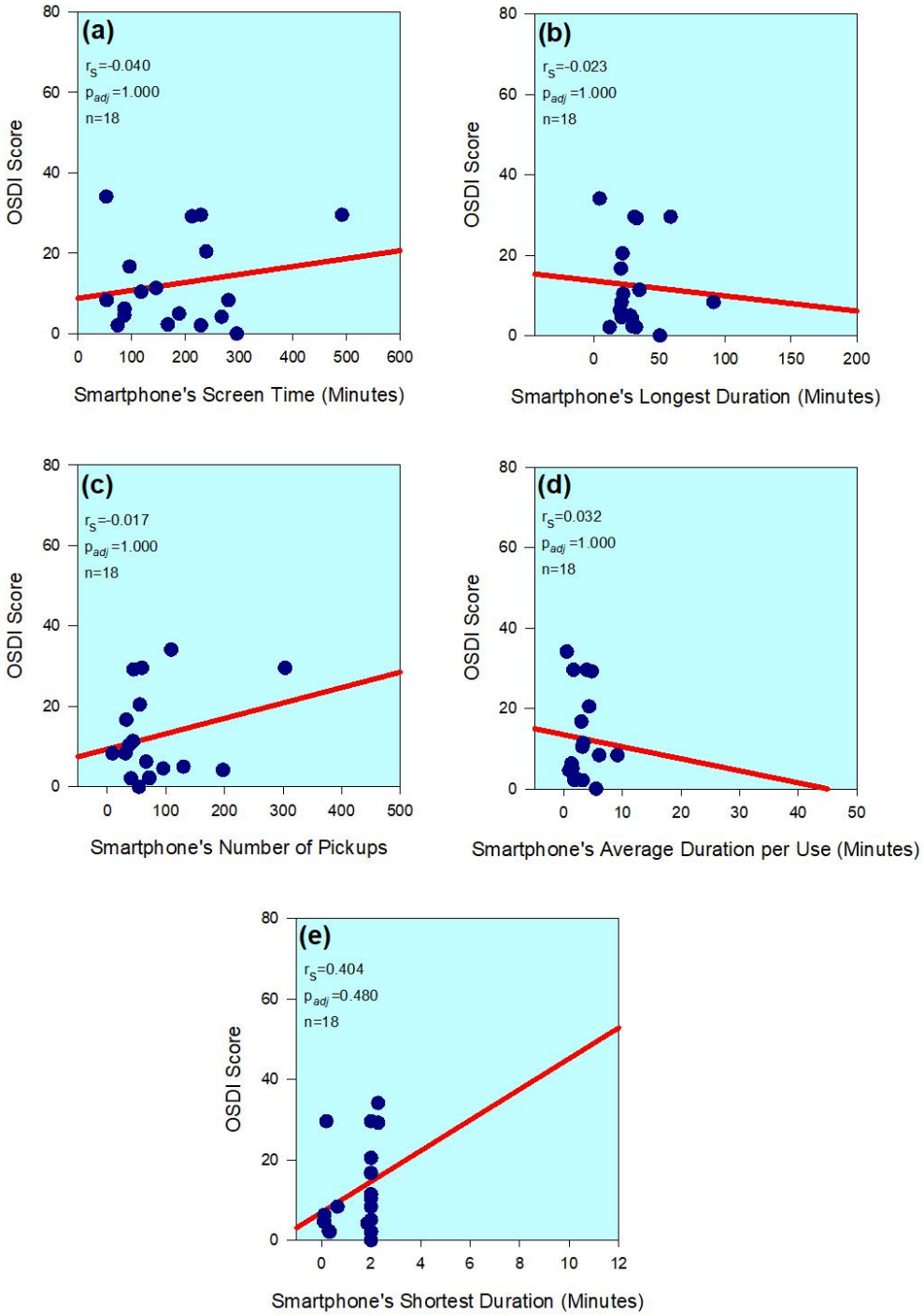
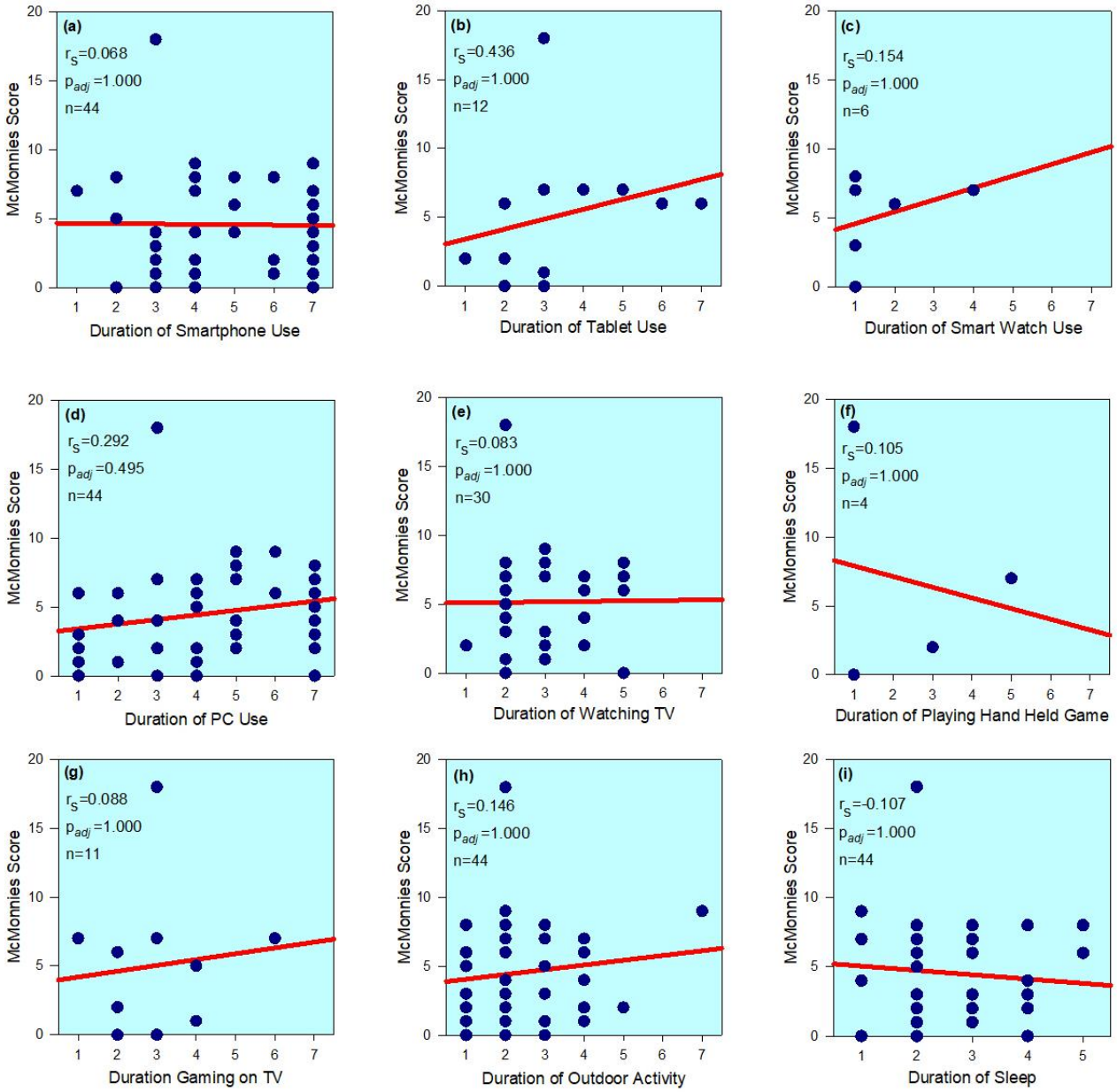


Figure 7.18: Spearman's correlation plots between OSDI score with the investigated parameters derived from the app data from the UK group.

Investigated Parameters		Spearman's Correlation [r_s, Adjusted p value (p_{adj})]
From Questionnaires	**Duration of Smartphone Use (n=44)**	0.068, p_{adj}=1.000
	Duration of Tablet Use (n=12)	0.436, p_{adj}=1.000
	Duration of Smart Watch Use (n=6)	0.154, p_{adj}=1.000
	Duration of PC Use (n=44)	0.292, p_{adj}=0.495
	Duration of Watching TV (n=30)	0.083, p_{adj}=1.000
	Duration of Playing Hand Held Video Games (n=4)	0.105, p_{adj}=1.000
	Duration of Gaming on TV (n=11)	0.088, p_{adj}=1.000
	Duration of Sleep (n=44)	-0.107, p_{adj}=1.000
	Duration of Outdoor Activity (n=44)	0.146, p_{adj}=1.000
From Apps	**Smartphone's Screen Time (n=18)**	0.086, p_{adj}=1.000
	Smartphone's Number of Pickups (n=18)	-0.086, p_{adj}=1.000
	Smartphone's Shortest Duration (n=18)	0.552, p_{adj}=0.090
	Smartphone's Longest Duration (n=18)	0.193, p_{adj}=1.000
	Smartphone's Average Duration Per Use (n=18)	0.079, p_{adj}=1.000

Table 7.14: Spearman's correlation between McMonnies score and the investigated parameters for the UK participants.



For (a) to (h), each number on the x-axis represent:

1	0.01 to 30.00 minutes
2	30.01 to 60.00 minutes
3	60.01 to 90.00 minutes
4	90.01 to 120.00 minutes
5	120.01 to 150.00 minutes
6	150.01 to 180.00 minutes
7	>180.00 minutes

For (i), each number on the x-axis represent:

1	0.01 to 6.00 hours
2	6.01 to 7.00 hours
3	7.01 to 8.00 hours
4	8.01 to 9.00 hours
5	>9.00 hours

Figure 7.19: Spearman's correlation plots between McMonnies score with the investigated parameters derived from the questionnaires data from the UK group.

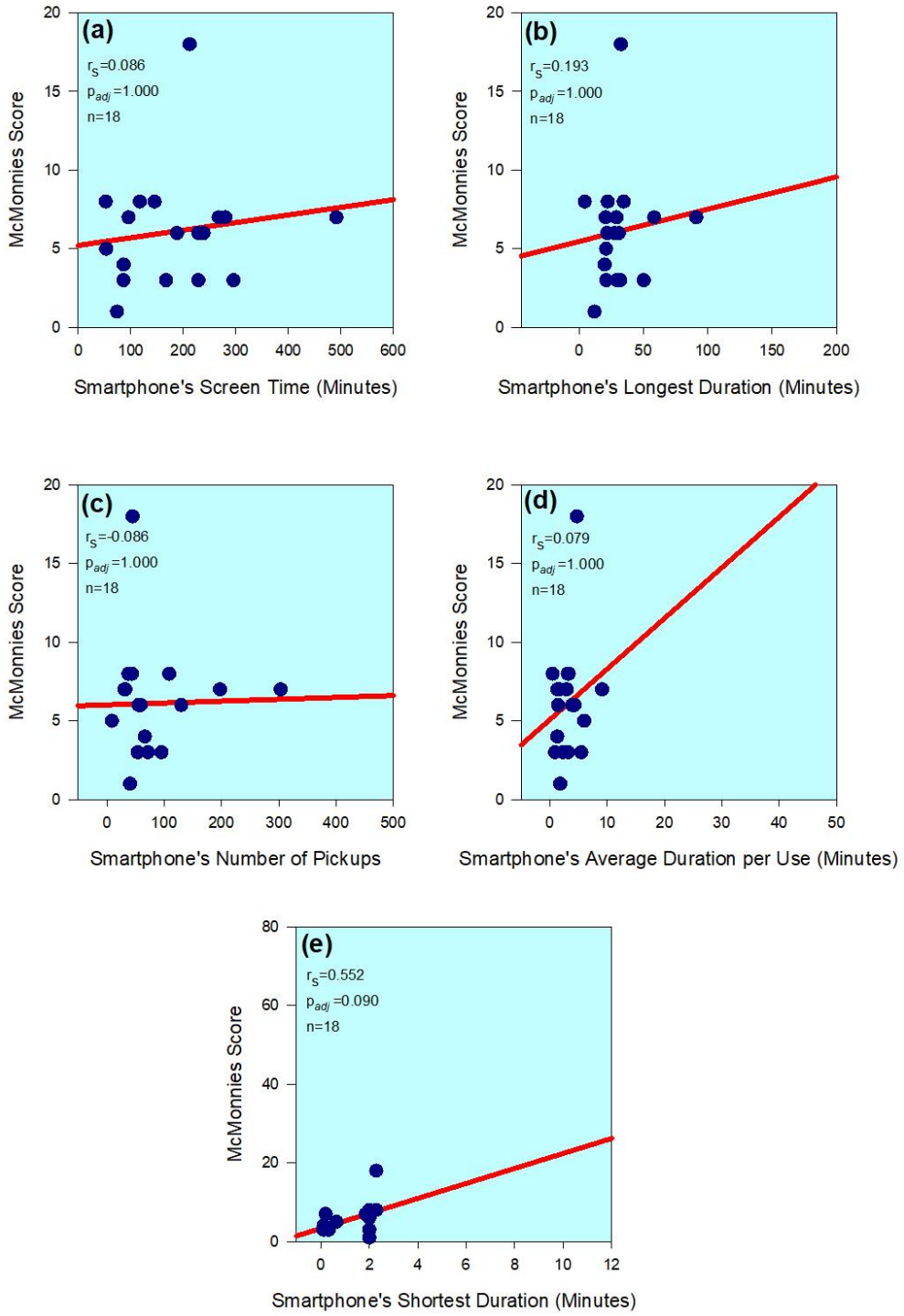


Figure 7.20: Spearman's correlation plots between McMonnies score with the investigated parameters derived from the app data from the UK group.

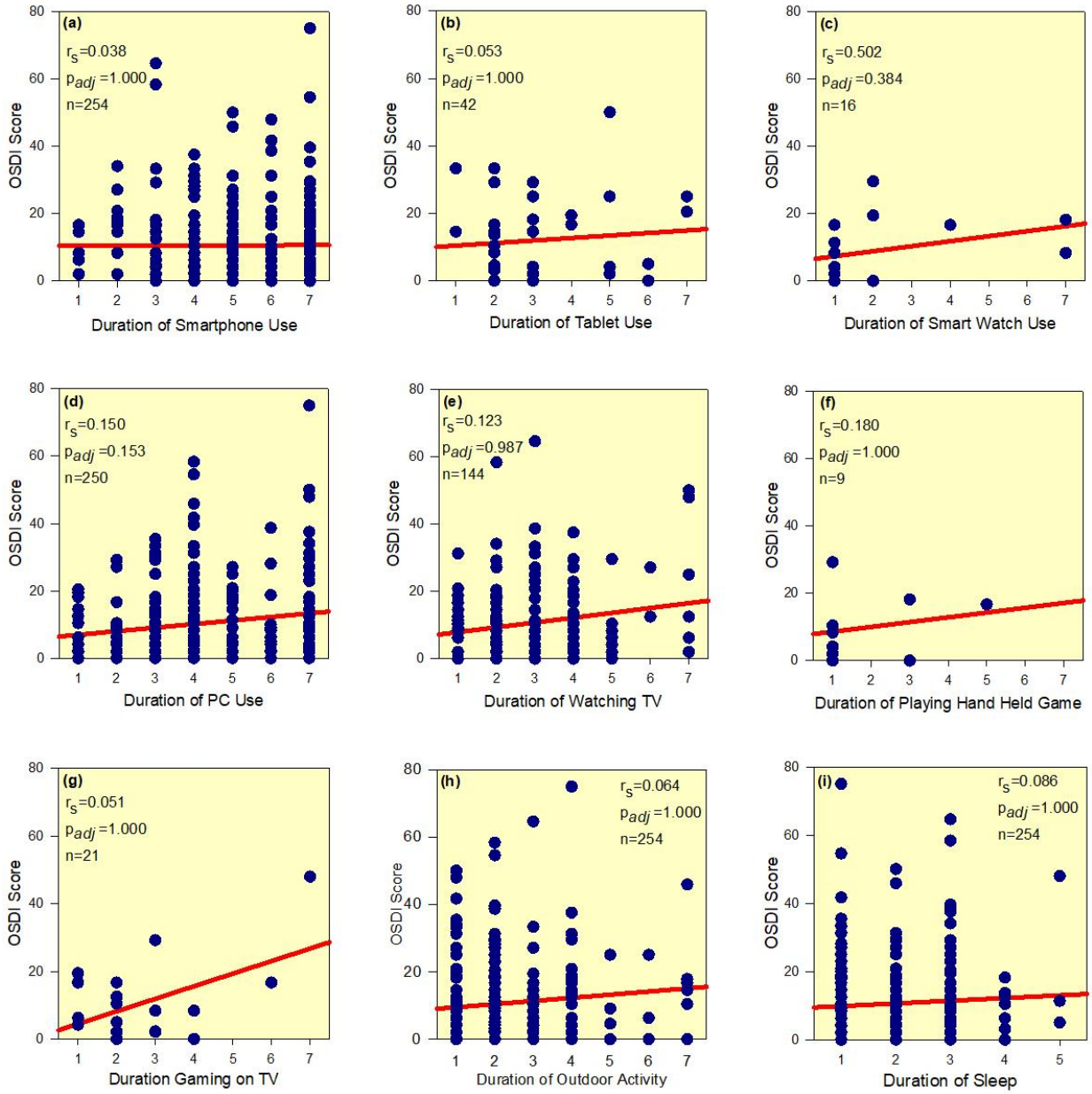
7.4.7.3 Combined MY+UK Population

For the combined MY+UK population, the Spearman's rank order correlations between OSDI score and McMonnies score with the investigated parameters can be seen in Table 7.15, Table

7.16, Figure 7.21, Figure 7.22, Figure 7.23 and Figure 7.24. There was no significant correlation between OSDI score with any of the investigated parameters. The McMonnies score only correlated significantly and weakly with Duration of Smartphone Use (r_s=0194, p_{adj}=0.016) and Duration of PC Use (r_s=0.209, p_{adj}=0.009).

Investigated Parameters		Spearman's Correlation [r_s, Adjusted p value (p_{adj})]
From Questionnaires	**Duration of Smartphone Use (n=254)**	0.038, p_{adj}=1.000
	Duration of Tablet Use (n=42)	0.053, p_{adj}=1.000
	Duration of Smart Watch Use (n=16)	0.502, p_{adj}=0.384
	Duration of PC Use (n=250)	0.150, p_{adj}=0.153
	Duration of Watching TV (n=144)	0.123, p_{adj}=0.987
	Duration of Playing Hand Held Video Games (n=9)	0.180, p_{adj}=1.000
	Duration of Gaming on TV (n=21)	0.051, p_{adj}=1.000
	Duration of Sleep (n=254)	0.086, p_{adj}=1.000
	Duration of Outdoor Activity (n=254)	0.064, p_{adj}=1.000
From Apps	**Smartphone's Screen Time (n=76)**	0.112, p_{adj}=1.000
	Smartphone's Number of Pickups (n=76)	-0.074, p_{adj}=1.000
	Smartphone's Shortest Duration (n=76)	0.017, p_{adj}=1.000
	Smartphone's Longest Duration (n=76)	0.080, p_{adj}=1.000
	Smartphone's Average Duration Per Use (n=76)	0.128, p_{adj}=1.000

Table 7.15: Spearman's correlation between OSDI score and the investigated parameters for the MY+UK participants.



For (a) to (h), each number on the x-axis represent:

1	0.01 to 30.00 minutes
2	30.01 to 60.00 minutes
3	60.01 to 90.00 minutes
4	90.01 to 120.00 minutes
5	120.01 to 150.00 minutes
6	150.01 to 180.00 minutes
7	>180.00 minutes

For (i), each number on the x-axis represent:

1	0.01 to 6.00 hours
2	6.01 to 7.00 hours
3	7.01 to 8.00 hours
4	8.01 to 9.00 hours
5	>9.00 hours

Figure 7.21: Spearman's correlation plots between OSDI score with the investigated parameters derived from the questionnaires data from the MY+UK group.

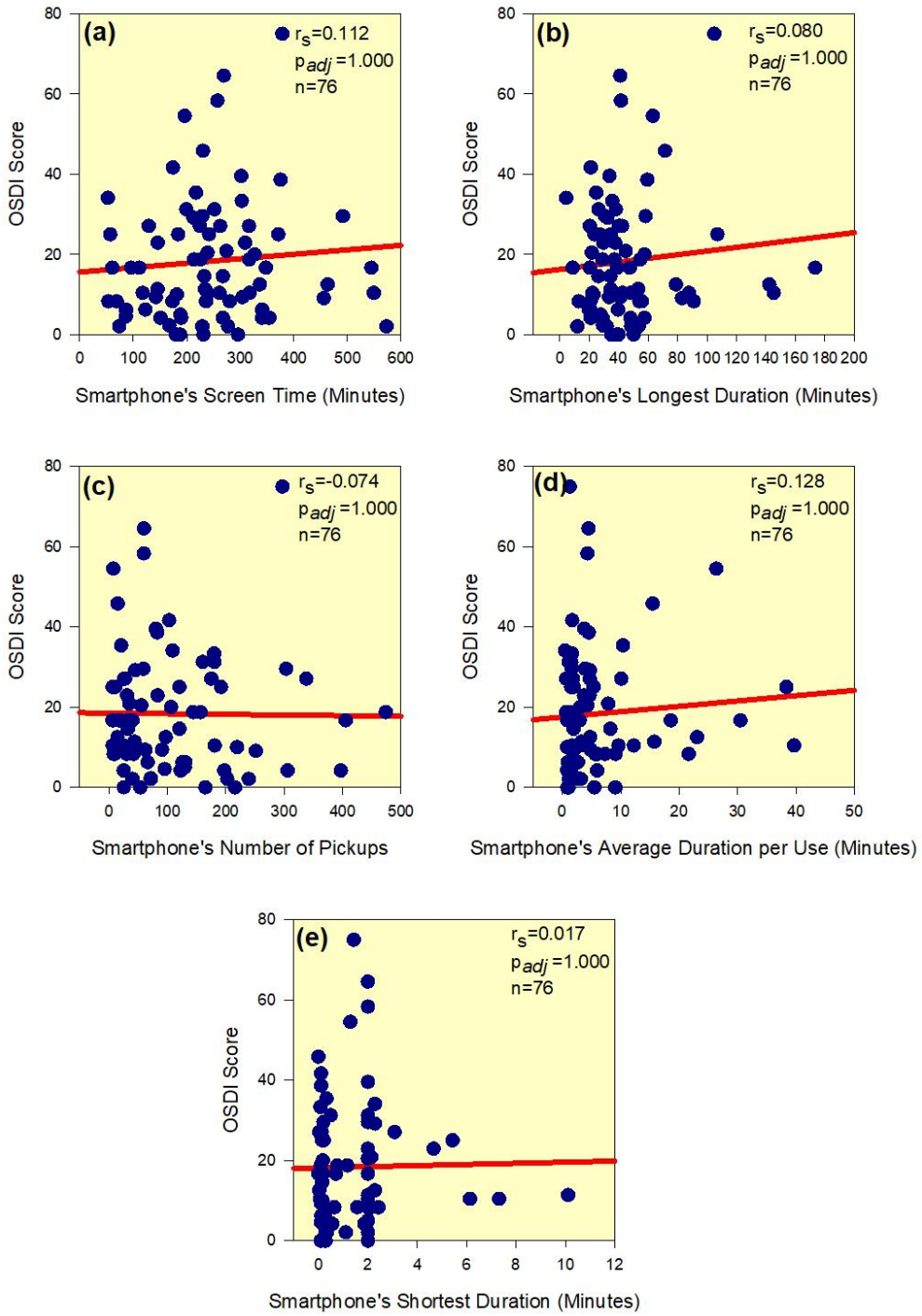
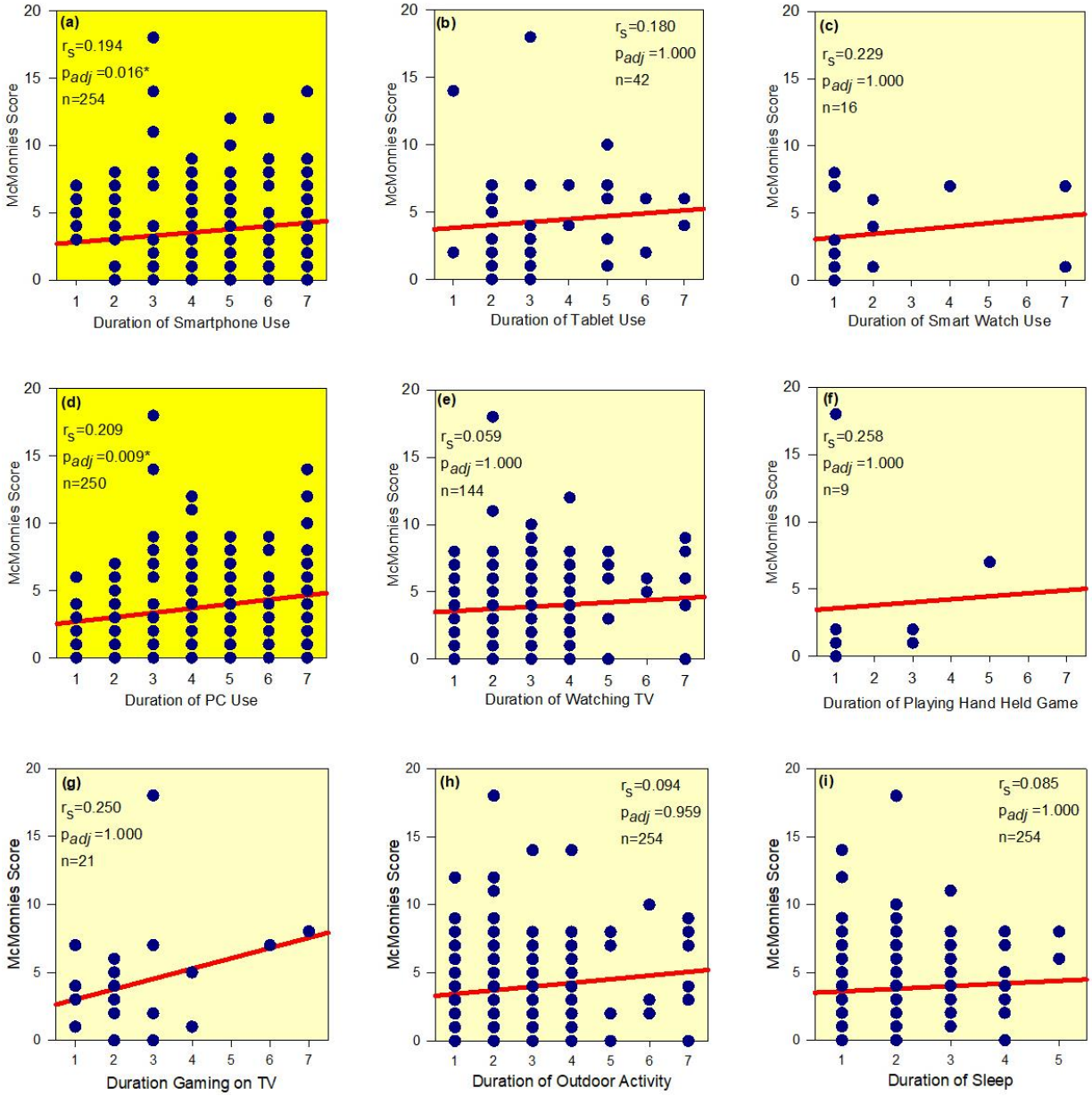


Figure 7.22: Spearman's correlation plots between OSDI score with the investigated parameters derived from the app data from the MY+UK group.

	Investigated Parameters	Spearman's Correlation [r_s, Adjusted p value (p_{adj})]
From Questionnaires	**Duration of Smartphone Use (n=254)**	0.194, p_{adj}=0.016*
	Duration of Tablet Use (n=42)	0.180, p_{adj}=1.000
	Duration of Smart Watch Use (n=16)	0.229, p_{adj}=1.000
	Duration of PC Use (n=250)	0.209, p_{adj}=0.009*
	Duration of Watching TV (n=144)	0.059, p_{adj}=1.000
	Duration of Playing Hand Held Video Games (n=9)	0.258, p_{adj}=1.000
	Duration of Gaming on TV (n=21)	0.250, p_{adj}=1.000
	Duration of Sleep (n=254)	0.085, p_{adj}=1.000
	Duration of Outdoor Activity (n=254)	0.094, p_{adj}=0.959
From Apps	**Smartphone's Screen Time (n=76)**	0.163, p_{adj}=0.800
	Smartphone's Number of Pickups (n=76)	-0.055, p_{adj}=1.000
	Smartphone's Shortest Duration (n=76)	0.075, p_{adj}=1.000
	Smartphone's Longest Duration (n=76)	0.142, p_{adj}=0.888
	Smartphone's Average Duration Per Use (n=76)	0.127, p_{adj}=0.888

*Statistically significant, p_{adj} <0.05

Table 7.16: Spearman's correlation between McMonnies score and the investigated parameters for the MY+UK participants.



*Statistically significant, p_{adj} <0.05 (note the different shade of yellow in comparison to the other plots).

For (a) to (h), each number on the x-axis represent:

1	0.01 to 30.00 minutes
2	30.01 to 60.00 minutes
3	60.01 to 90.00 minutes
4	90.01 to 120.00 minutes
5	120.01 to 150.00 minutes
6	150.01 to 180.00 minutes
7	>180.00 minutes

For (i), each number on the x-axis represent:

1	0.01 to 6.00 hours
2	6.01 to 7.00 hours
3	7.01 to 8.00 hours
4	8.01 to 9.00 hours
5	>9.00 hours

Figure 7.23: Spearman's correlation plots between McMonnies score with the investigated parameters derived from the questionnaires data from the MY+UK group.

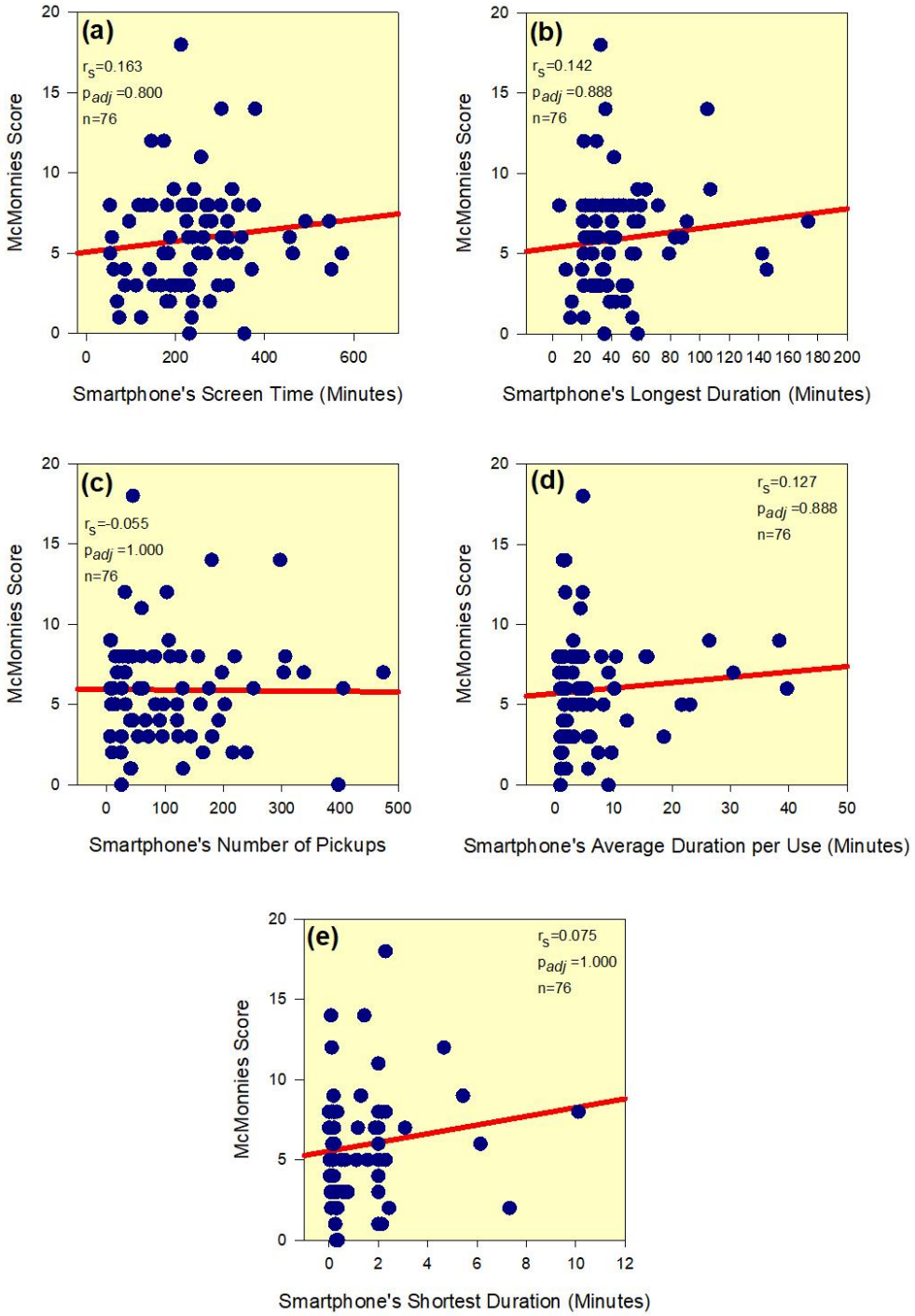


Figure 7.24: Spearman's correlation plots between McMonnies score with the investigated parameters derived from the app data from the MY+UK group.

7.5 Discussion

Albeit a weak relationship, the present study demonstrated a significant correlation between the results from the McMonnies questionnaire and the duration of smartphone use amongst

both the MY participants and the combined MY+UK group. There was also a significant association between the McMonnies score and the duration of time spent on the PC in the combined MY+UK group. No such correlations were observed for the UK group in isolation. However, given the smaller sample size, it is likely that there was insufficient power to detect this relationship within this sample alone. Nevertheless, the results of this study support the findings of Moon et al., (2014), Park et al., (2015) and Park et al., (2017) who all observed an association between smartphone use and dry eyes. Moreover, these results also provide tentative support for a negative association between the use of traditional VDT screens and dry eye (Tanahashi et al., 1986; Bergqvist and Knave, 1994; Uchino et al., 2008). It is important to note that the present investigation only assessed the subjective symptoms associated with dry eye and given that dry eye is a multifactorial disease, it is not possible to conclude a definitive link between these results and the relative risk of developing dry eye with smartphone and computer use.

Previous research investigating Caucasians and Asians (Patel et al., 1995; Yeh et al., 2015; Stapleton et al., 2017) suggests that there is a difference in dry eye prevalence between UK and Malaysian populations, although in this study, there was no significant difference between the McMonnies and OSDI scores. Again, the low number of UK participants who responded to the questionnaire has most likely resulted in limited statistical power. For the combined MY and UK data, the McMonnies score significantly correlated with Duration of Smartphone Use and Duration of PC Use, unlike the OSDI score. It is unclear why this trend was not mirrored by the OSDI data but this may be due to the nature of the two questionnaires; the OSDI questionnaire emphasizes the assessment of symptoms related to

dry eye (Dougherty et al., 2011) whilst the McMonnies questionnaire attempts to discriminate individuals with dry eye from non-dry eye sufferers (Schiffman et al., 2000).

According to the data derived from the questionnaire, no difference was found in the Duration of Smartphone Use between the UK and MY populations. Conversely, when examining the data from the apps, it can be seen that the MY population had significantly higher screen time on average when compared to the UK sample. In addition, the longest duration spent on the smartphone was greatest amongst MY participants. The disparity between the data acquired from the questionnaire and apps highlights the difficulty in interpreting the results of the subjective questionnaires. The study found that participants significantly underestimated the actual time spent looking at their smartphone when completing the questionnaire. Indeed, only a moderate correlation was found between the results from the questionnaire and app. These results are in agreement with Lee et al., (2017) who also noted that participants are poor at estimating their screen time.

One of the more surprising findings was the length of time participants spent on their smartphone. The average screen time, according to the apps, for the total study population was approximately 4 hours (MY=262.38$\pm$112.10 minutes; UK=183.82$\pm$111.28 minutes). The results from the questionnaire (Figure 7.1) show that 28% of participants reported spending more than 3 hours on their smartphone (MY=25%; UK=41%). In comparison, the participants in the study by Moon et al., (2014) had an average screen time of less than 1 hour; this may be explained by the age of the participants as the study was conducted on schoolchildren with an average age of 11 years. The study by Sadagopan et al., (2017) is more comparable as the participants were medical students with a mean age of 19 years. However, in Sadagopan et al., (2017) study, the screen time was approximately 2 hours per day; half of the screen time

found in the present study. Research conducted by market surveys give an estimation of mobile phone use more comparable with the results from the present study (EMarketer, 2017).

A notable limitation of the study relates to this higher than expected duration of smartphone use. The questionnaire given to participants to capture their smartphone use was based upon that utilised by Moon et al., (2014), which had a maximum cut-off for smartphone usage of 3 hours. In the present study, this resulted in a relatively high proportion of participants bracketing to this highest usage banding and thus, there was poor differentiation of the smartphone usage of these participants. Future studies should bracket their questionnaire to include higher smartphone usage categories.

When comparing the differences in the investigated parameters between participants from MY and UK, a significant difference was observed for Duration of Sleep, Duration of Outdoor Activity, Smartphone's Screen Time and Smartphone's Average Duration Per Use (Table 7.4 and Table 7.8). Results showed that on a daily basis, participants from MY slept less and performed less outdoor activity compared to the UK participants. However, on a daily basis, it was clear that MY participants spent more time on their smartphone and had the longest duration of smartphone interaction per session compared to the UK group.

There are a few limitations which are likely to influence the result of this study. One of the limitations is that the sample size of the UK group was smaller than expected and hence the statistical power was low when looking at this sample in isolation. As such, caution and care should be taken when interpreting the results that relate to the UK population. In addition, relatively few participants (N=76) were able to complete the app-based aspect of the study reporting issues relating to insufficient space for app instillation or software incompatibly. As

the sample size of this element of the study was particularly low, there is a risk that the actual population might not exhibit the findings that was evident in this investigation. In addition, although the pilot study showed that both apps were tracking smartphone usage in the same way over a 1 hour period, it is conceivable that subtle inherent differences between both apps that might lead to output discrepancies over a longer period of time.

Another limitation lies within the apps itself. The apps were known to calculate and record the use of smartphone when the display screen of the smartphone is accessed (turned on/off). As such, the time recorded by the app includes idle (turned on) display screen times when the participants are not looking at the devices. This may partly explain the higher screen time recorded by the app relative to the smartphone usage time derived from the questionnaire.

Although there are several limitations, this novel study provides much-needed insight with regards to smartphone usage pattern and dry eye symptoms.

7.6 Conclusion

This study concluded that:

- Participants who used their smartphone and personal computer more frequently manifested with higher scores on the McMonnies questionnaire.
- Screen time was higher amongst individuals from MY in comparison to those from the UK.
- Apps provided a higher value of screentime use when compared to values derived from subjective questionnaires.

Chapter 8: Summary and Conclusions

8.1 Introduction

Dry eye is a multifactorial disease that affects the ocular surface (Willcox et al., 2017). The prevalence of dry eye varies, but some studies have indicated the prevalence is as high as 50% in some populations (Stapleton et al., 2017). Since dry eye reduces the patient's quality of life this condition poses to be a significant public health concern (Paulsen et al., 2014; Uchino & Schaumberg, 2013). It is widely established that the use of VDT is linked to dry eye (Uchino et al., 2013). However, there is a significant paucity of literature exploring the relationship between smart device use and dry eye (Moon et al., 2014; Kim et al., 2016; Moon et al., 2016; Antona et al., 2018). There are numerous clinical and lab based methods for assessing dry eye, however none are able to evaluate the tear film stability in real-time using an open field system. As such, the principle objective of this thesis was to design, develop and validate a binocular device that is able to assess NIBUT non-invasively. Subsequently, the device was used to assess the impact of using smart devices on blink characteristics and non-invasive tear break up time (NIBUT). In addition, the ramifications of using smart devices on tear osmolarity and accommodation response were also investigated. The thesis also attempts to ascertain the smart devices usage habits of university students and evaluates its possible association with dry eyes.

8.2 Assessment of the Tear Film During Smart Device Use

Measurement of tear osmolarity is considered the 'objective gold standard' for the detection of dry eye (Farris, 1994). Chapter 3 investigated the changes in tear osmolarity levels pre- and post- smart device usage for reading and gaming tasks. Tear osmolarity values were similar following the reading task across the four platforms (Apple iPhone 6, Apple iPhone 6S, Samsung Galaxy S6 and paper) tested. However, tear osmolarity was reduced when

participants were engaged in the gaming task on the Nokia 5210 and Apple Smart Watch when compared to the maze game on paper. It was proposed that these finding may have been influenced by factors such as differences in luminance levels between the platforms, crowding effect from the smaller Apple Smart Watch and Nokia 5210 screen or by the inherent differences in the gaming task itself. It was also found that tear osmolarity values at baseline were higher than the subsequent values found after reading and playing games. This is in direct contrast to the results of Yazici et al., (2015) who observed a significant increase in tear osmolarity after exposure to a VDT task. Although the investigation showed statistically significant changes in tear osmolarity, these changes cannot be considered to be clinically significant (Eperjesi et al., 2012).

The study design in Chapter 3 required multiple readings of tear osmolarity to be taken, and the possibility of an order effect influencing the results, could not be dismissed. Prior to the present work, there has been no study that has assessed the effect of multiple tear osmolarity measurement being taken on a single day and thus, it is difficult to draw firm conclusions from this aspect of the investigation. Furthermore, the TearLab cannot be used to assess real-time tear osmolarity changes and thus, measurements were limited to pre- and post-exposure to smart device use. Thus, the purpose of Chapter 4 was to ascertain if the changes in tear osmolarity that were evident in Chapter 3 were caused by the consecutive repeated measures of tear osmolarity. In addition, the study also investigated the intraobserver variability of the osmolarity measurements. Eleven measurement of tear osmolarity were performed using the TearLab following a similar protocol to that of Chapter 3. There were no significant differences between the 11 tear osmolarity measurement and tear osmolarity values did not correlate with the number of measurements. Furthermore, a low CoV was observed, suggesting high

levels of repeatability. Although this Chapter 4 showed that tear osmolarity levels were not affected by repeated measures, there are still other factors that could influence tear osmolarity levels and these were discussed in Chapter 4.

As detailed in Chapter 3 and 4 there are several limitations when assessing the response of the tear film to a smart device. Therefore, a primary objective of this thesis was to assess and develop new methods of assessing the tear film using a non-invasive method whilst participants were actively engaged with a task on the smart devices. The Open Field Tear Film Analyzer (OFTA) is a novel monocular device that was designed and developed to measure blink rate and NIBUT whilst participants were engaged in a visual task. Chapter 2 describes the process by which the device was conceptualised, developed and validated for its reliability and reproducibility. The measures derived from the B&L Keratometer revealed the widest limits of agreement in comparison to the other devices. In addition, reliability statistics were strongest for the OFTA whilst reproducibility showed similar results between the OFTA and Oculus K5M. However, there was a significant difference in NIBUT results, along with a strong proportional bias and heteroscedasticity on the Bland and Altman plots, indicating that the results from the Oculus K5M are not interchangeable with those from the OFTA. Despite these differences, the OFTA was deemed a valid method for assessing NIBUT and was further developed in Chapter 5.

There were several limitations associated with OFTA discussed in Chapter 2. Being a monocular device, it failed to provide a binocular measurement of tear film stability. To comprehensively assess the impact of a given visual task on the eyes, it is vital that both eyes are evaluated simultaneously to determine the effect on the binocular tear film stability. As such, a binocular system may aid to understand how the tear film stability in the ipsilateral

eye affects blinking on the contralateral eye. Such an assessment would allow determination of the co-dependency of the bilateral blink response.

In Chapter 5, a binocular version of the OFTA was developed to investigate the changes in blink characteristics (blink rate, minimum inter blink interval, average inter blink interval and maximum inter blink interval), non-invasive break up time (NIBUT) and ocular protection index (OPI) during smart device use. The main findings from this novel study suggested that blink rate was reduced when participants observed the reading task on all three smart devices in comparison to paper. Additionally, NIBUT was found to be reduced when participants were reading from the Apple iPhone 6 relative to the hard copy. It was proposed that intrinsic differences between the platforms such as the screen refresh rate and type of luminance, or a psychological factor may have caused these differences. Blink rate was faster and NIBUT was longer at baseline when compared to all inter-task measurements, however, it is unclear whether an order effect may have influenced this result.

An interesting observation was that both tear osmolarity (Chapter 3) and blink rate (Chapter 5) were marginally better when engaging with a gaming task on the older Nokia 5210 phone in comparison to some of the more modern smart devices. These observations suggest that as the older generation of phones become functionally redundant newer smart devices may actually have a greater impact on the tear film and blink rate.

8.2.1 Limitations

There were several limitations concerning the assessment of the tear film during smart device use. The limited resolution of the video camera used to capture the reflections of the mires from the tear film in Chapters 2 and 5 was a significant restriction. For future studies, a video camera with a higher resolution will be used such that the visualization and detection of tear

break-up can be optimised. The OFTA uses a visible light source of 470 nm, which may influence the blink rate and tear film stability. In order to overcome this, the light source for the OFTA should also be change into an IR light source.

One of the limitations of Chapter 5 was the duration of the task engagement. Participants were only exposed to 5 minutes of smart device use which may have limited the ability to detect the changes in the investigated parameters which may have developed with more prolonged periods of smart device usage. This is particularly important as most smart device users are known to use the devices for an average of 2 hours per day (Moon et al., 2014; Sadagopan et al., 2017). The results of the present study may have also been affected by fatigue as the whole data collection process was conducted over 5 hours. Although regular rests were incorporated into the study design, fatigue may have had a cumulative effect on the results.

The current study failed to categorise blinks as complete or incomplete as Chu et al., (2014) assessed in their study. In the present protocol, a blink was considered when the upper eyelid covers at least half the pupil diameter. Retrospectively, a more thorough assessment could have been attained by assessing the number of complete and incomplete blinks. The time taken to analyse the OFTA videos was excessive and an objective method of image analysis is warranted in the future.

8.3 Smart Device Use and Accommodation

VDT usage is known to be associated with visual discomfort (Tosha et al., 2009; Parihar et al., 2016), but since smart devices are held at a shorter working distance these may pose a greater strain on the visual system. However, there is a distinct lack of literature assessing the accommodative response with smart device use. Chapter 6 investigated the accommodative

response to letter and Maltese target on a range of smart devices and hard copy. The results from this study demonstrated significant differences in the accommodative response (AR) when viewing a letter target on paper, smartphone and smart watch. Participants had a longer accommodative latency with the smartphone and smart watch when compared to the paper version of the N5 letter. This may have been due to differences in the display characteristics such as the resolution, method of illumination and refresh rate. In addition, participants had a greater accommodative lag and a slower accommodative velocity when viewing N5 letters on the smart watch in comparison to both the smartphone and paper. These observations suggest that the smaller screen on the smart watch may have created a crowding effect that contributed to the lack of accommodative accuracy. Accommodative lag was lower when using the higher detailed N5 letter rather than the N20 letter or Maltese cross suggesting that target detail is important for accommodative accuracy when viewing a smartphone.

8.3.1 Limitations

The main limitation of Chapter 6 was that the accommodative response measurements were assessed monocularly and therefore, failed to assess the typical binocular viewing environment. Although the participant's refractive error was corrected with soft contact lenses, the individuals were not grouped by refractive error and thus, differences in accommodation between myopes and hyperopes may have confounded the present results (McBrien & Millodot, 1986; Millodot, 2015). Furthermore, the current study only assessed changes in accommodative dynamics with short term smart device use and future work should aim to assess changes in these parameters over longer periods of time.

8.4 Smart Device Use and the Subjective Symptoms Associated with Dry Eye

The literature unequivocally suggests that VDT use contributes to the symptoms of dry eye. In comparison, there is limited evidence suggesting the relationship between dry eye and smart device use (Moon et al., 2014; Park et al., 2014; Moon et al., 2016). These previous studies (Moon et al., 2014; Moon et al., 2016) have examined this association via subjective questionnaires based upon on accurate recollection of smart device usage and dry eye symptoms. Chapter 7 evaluated the duration of smartphone and VDT usage and their association with subjective questionnaires of ocular comfort and dry eyes (OSDI and McMonnies). In an attempt to determine the reliability of questionnaires used to determine smartphone use habits, apps that capture smartphone screen-time were also implemented. To account for the variation in dry eyes across Caucasian and Asian populations (Patel et al., 1995; Yeh et al., 2015; Stapleton et al., 2017), whilst also considering differences in smart device usage across European and Asian countries (Osman et al., 2012; Statista, 2018b, 2018a) the study sought to investigate smartphone and VDT usage habits amongst University students in UK and Malaysia (MY). Results from the study showed that participants who used their smartphone and PC for a longer duration presented with higher McMonnies score. When considering the differences in smartphone usage between MY and UK, participants from MY had longer screen time compared to UK. Interesting, on comparing the subjective data on smartphone usage with the data from the apps, it was evident that participants significantly underestimated the total time spent on their smartphone; these observations question the validity of subjective questionnaires to evaluate smartphone use.

8.4.1 Limitations

Although the findings of Chapter 7 provide an interesting insight into the smart device usage habits of individuals from the UK and MY, there were several limitations to the investigation.

As the questionnaire utilised in the study was based upon the work of Moon et al., (2016), the question pertaining to smartphone usage time had a maximum cut-off of 3 hours. However, the present results showed that most participants used their smartphones for longer than 3 hours per day. As such, future studies should consider extending the cut-off so that a more accurate measure of smartphone use can be obtained. In the present investigation, the OSDI and McMonnies questionnaires were used as advocated in the Dry Eye Workshop II report (Wolffsohn et al., 2017). The Ocular Comfort Index (OCI) is an alternative questionnaire that assesses ocular surface irritation that was designed with Rasch analysis (Johnson & Murphy, 2007). The OCI is specifically targeted at dry eye symptoms alone whereas the OSDI provides a more holistic approach considering environmental factors. Future work should consider implementation of these specifically targeted Rasch validated questionnaires to further explore symptoms of dry eyes during smart device.

The maximum cut-off for smartphone usage was 3 hours. However, the present results showed that most participant used their smartphones for longer than 3 hours per day. As such, future studies should consider extending the cut-off so that a more accurate measure of smartphone use can be obtained. In the present investigation, the OSDI and McMonnies questionnaires were used as advocated in the Dry Eye Workshop II report (Wolffsohn et al., 2017). The Ocular Comfort Index (OCI) is an alternative questionnaire that assesses ocular surface irritation that was designed with Rasch analysis (Johnson & Murphy, 2007). The OCI is specifically targeted at dry eye symptoms alone whereas the OSDI provides a more holistic approach considering environmental factors. Future work should consider implementation of these specifically targeted Rasch validated questionnaires.

8.5 Conclusion

A novel non-invasive device that enables binocular real-time measurements of NIBUT and blinking characteristics was developed and validated. Reading from smart devices may have an impact on blink rate and the tear film, whilst the accommodative response was found to be affected by the viewing platform used. Length of time of smartphone and PC usage correlated significantly with symptoms of dry eyes, suggesting that prolonged periods of smart device use may be associated with dry eyes. Smart devices are ubiquitous in our daily lives and this thesis provides an initial assessment of the potential impact they may have on clinical and subjective parameters investigated. As such, this thesis paves the way for future research that will be focusing on the long-term effects of smart device use on the eyes.

Chapter 9: Appendix

A. Ethical Approval for OFTA Validation Experiment

RESEARCH WITH PLYMOUTH UNIVERSITY

12th November 2014

CONFIDENTIAL

Muhammad Afzam Shah Bin Abdul Rahim
Room FF01
Faculty of Health and Human Sciences
Peninsula Allied Health Centre
Plymouth University
Derriford Road
Plymouth PL6 8BH

Dear Muhammad

Application for Approval by Faculty Research Ethics Committee

Reference Number: 14/15-330
Application Title: **Sustained used of smartphones and its effect on accommodation, visual fatigue, intra-ocular pressure (IOP), blink rate and tear film stability in contact lens wearers and in non-contact lenswearers.**
Part I: Validation (repeatability, reproducibility and reliability) of Open Field Tearfilm Analyzer (OFTA)

I am pleased to inform you that the Committee has granted approval to you to conduct this research.

Please note that this approval is for three years, after which you will be required to seek extension of existing approval.

Please note that should any MAJOR changes to your research design occur which effect the ethics of procedures involved you must inform the Committee. Please contact Sarah Jones (email sarah.c.jones@plymouth.ac.uk).

Yours sincerely

S Jones

Professor Michael Sheppard, PhD, FAcSS
Chair, Research Ethics Committee -
Faculty of Health & Human Sciences and
Peninsula Schools of Medicine & Dentistry

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Professor Michael Sheppard
CQSW BSc MA PhD AcSS
Chair, Faculty Research Ethics Committee

B. Ethical Approval for Osmolarity, Binocular OFTA and Accommodative Response Experiment

RESEARCH WITH PLYMOUTH UNIVERSITY

26th October 2015

CONFIDENTIAL

Muhammad Afzam Shah Bin Abdul Rahim
Room FF01
Faculty of Health and Human Sciences
Peninsula Allied Health Centre
Plymouth University
Derriford Road
Plymouth
PL6 8BH

Dear Muhammad

Application for Approval by Faculty Research Ethics Committee

Reference Number: 15/16-468
Application Title: **Sustained used of smartphones and its effect on accommodation, visual fatigue, intra-ocular pressure (IOP), blink rate and tear film stability in contact lens wearers and in non-contact lens wearers**

I am pleased to inform you that the Committee has granted approval to you to conduct this research.

Please note that this approval is for three years, after which you will be required to seek extension of existing approval.

Please note that should any MAJOR changes to your research design occur which effect the ethics of procedures involved you must inform the Committee. Please contact Sarah Jones (email sarah.c.jones@plymouth.ac.uk).

Yours sincerely

S Jones

pp **Professor Michael Sheppard, PhD, FAcSS**
Chair, Research Ethics Committee -
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Professor Michael Sheppard
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Chair, Faculty Research Ethics Committee

C. Ethical Approval for Repeated Measures of Osmolarity and Duration of Smartphone Use and Dry Eye Symptoms Experiment

RESEARCH WITH PLYMOUTH UNIVERSITY

5th March 2018

CONFIDENTIAL

Muhammad Afzam Shah Bin Abdul Rahim
Room FF01
Faculty of Health and Human Sciences
Peninsula Allied Health Centre
Plymouth University
Derriford Road
Plymouth
PL6 8BH

Dear Muhammad,

Amendment to Approved Application

Amendment Reference Number: ***17/18-902***
Original application Reference Number: ***15/16-468***
Application Title: **Sustained used of smartphones and its effect on accommodation, visual fatigue, intra-ocular pressure (IOP), blink rate and tear film stability in contact lens wearers and in non-contact lens wearers. Part II: Binocular assessment of tear stability, blinking rate, accommodation and tear osmolarity during smartphone use.**

I am pleased to inform you that the Committee has granted approval to you for your amendment to the application approved on 26th October 2015. Please note that this approval is for one year from today's date (until 4th March 2019), after which you will be required to seek extension of existing approval.

Please note that should any MAJOR changes to your research design occur which effect the ethics of procedures involved you must inform the Committee. Please contact the committee administrator (email hssethics@plymouth.ac.uk).

Yours sincerely,

Professor Paul H Artes, PhD MCOptom
Professor of Eye and Vision Sciences
Co-Chair, Research Ethics Committee -
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Professor Paul H Artes, PhD
Co-Chair, Faculty HHS REB

D. Participants Information Sheet and Consent Form

EYE AND VISION RESEARCH WITH PLYMOUTH UNIVERSITY

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INVESTIGATING THE EFFECTS OF SMART PHONES ON OUR EYES
PART I: VALIDATION (REPEATABILITY, REPRODUCIBILITY AND RELIABILITY) OF OPEN FIELD TEARFILM ANALYZER (OFTA)

PARTICIPANT INFORMATION AND CONSENT LETTER

Muhammad Afzam Shah Bin Abdul Rahim is the principal investigator of this study and will work with the other clinical investigators from the School of Optometry, Plymouth University. They will perform all the clinical measurements as well as answer any questions that arise. Dr. Hetal Buckhurst (Director of Study), Prof. Dr. Christine Purslow and Assoc. Prof. Dr. Phillip Buckhurst (2nd and 3rd supervisor) will be overseeing this study.

INFORMATION RELATED TO YOUR PARTICIPATION

1. **What is this study about?**
   Our study group kindly invites you to participate in our study which is investigating the validity of the Open Field Tearfilm Analyzer (OFTA).

   Over the last 20 years, smartphones have become pivotal in our daily lives as they allow us to view emails, browse websites and even function as mobile entertainment devices. In the United Kingdom, 7 out of 10 adults own a smartphone. Data also shows that 98% of smartphones owner use their devices throughout the day. It was reported that 92% of smartphone users use their smartphone to send text messages to other phones while 84% of users use them to browse the internet. These data suggest that smartphones play an important role in our lives.

   Smartphones are mainly used at close working distance (distance between the user's eye and the smartphone screen) and a recent study suggested that these working distances differ significantly from those when reading hardcopy text. Since little is known about the effect of smartphones on the visual function, it is anticipated that these differences could lead to an excessive demand on both accommodation and vergence, resulting in ocular symptoms such as grittiness, dry eyes and tired eyes to develop. However, there are technical limitations in assessing real time changes on the tear film. Because of this, there has been limited information with regards to smartphone use and the tear film.

   A non-contact device called the Open Field Tearfilm Analyzer (OFTA) was designed in an attempt to assess real time changes in the tear layer stability. Since OFTA is a new instrument which has not been validated yet, the first part of this study will be assessing the validity (repeatability, reproducibility and reliability) of the OFTA. Once OFTA has been validated, it will be used to further investigate the effect of smartphone use on the visual function.

2. **Who may participate in this study?**
   This study will attempt to recruit 80 participants. This study only recruits healthy individuals that have never undergone any form of ocular surgery and are not currently taking any forms of medications that will affect the eyes. To be eligible for the study, you must be at least 18 years old. Your ocular health and status will be examined during the first initial screening/preliminary visit. We would appreciate if you can let us know if you are involved in any other research study.

Initials _____

EYE AND VISION RESEARCH WITH PLYMOUTH UNIVERSITY

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3. **What is the time commitment for this study?**
   This study comprises of three (3) visits which are at least 24 hours apart. The first visit is the preliminary visit, where we determine whether you are able to participate in this study or not. If you are eligible, baseline data will be collected during this visit by Investigator 1. The second visit (at least 24 hours after the first visit) is where the second set of data will be collected by Investigator 1. The third visit will be at least 24 hours after the second visit and a third set of data will be collected by Investigator 2 during this visit. Each visit will take about 1 hour for data collection.

4. **What is expected of me at these visits?**
   Although there are three (3) visits, the clinical examinations being performed on all visits are actually similar. Below are the lists of clinical examinations that will be performed on all visits:

   Subjective symptoms and ratings (questionnaires): Your personal details and medical history will be asked. Furthermore, you will be asked to grade the dryness of your eyes. You are also required to fill in the McMonnies and Ocular Surface Disease Index (OSDI) questionnaires.

   Visual acuity and refraction: You will be asked to look at a chart and read the lowest line that you can see (this will be done with you fixating on distance and near chart). After that, tests will be performed to determine the prescription of your eyes.

   Tear film assessment: Measurement of tear film stability will be conducted non-invasively using 3 different equipment (Bausch and Lomb Keratometer, Oculur Keratograph 5K and Open Field Tearfilm Analyzer (OFTA)). You will be asked to sit at an instrument, placing your chin and forehead against the chin rest and forehead rest and to fixate on the target. Before each measurement, you will be asked to blink three times and then hold your eyes open for as long as possible. The chin rest and forehead rest will be sanitized with alcohol swabs between each participant. Both eyes will be examined.

   Slit lamp examination: You will be asked to sit at an instrument. Your chin and forehead will be placed against the appropriate chin rest and forehead rest. The investigator will examine your ocular structures to determine your ocular health status. A sterile sodium fluorescein strip and lissamine green strip will be used to assess the ocular surface for any abnormalities (Sodium fluorescein will be used to assess the cornea while lissamine green will be used to assess the bulbar conjunctiva). Both eyes will be examined beginning with the right eye. The chin rest and forehead rest will be sanitized with alcohol swabs between each participant.

5. **Are there any risks associated with this study?**
   All the clinical examinations being performed in this study is non-invasive and adheres to the Declaration of Helsinki. Therefore, we do not anticipate any risk associated with this study. You may/may not feel slight discomfort/eye irritation during some of the study procedure. The discomfort/irritation is normally temporary in most cases. Please inform the investigator if you experience any form of discomfort/irritation.

6. **What are the benefits of participation in this study?**
   Unfortunately, this study is unlikely to benefit you directly. However, it will help the researchers at Plymouth University to have a better understanding on the validity of OFTA. Results from this study will aid future studies relating to smartphones and eye health.

Initials _____

EYE AND VISION RESEARCH WITH PLYMOUTH UNIVERSITY

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7. **Is there remuneration for participation?**
   Unfortunately, you will not get paid to participate in this study. No such claims can be made in any way.

8. **Can I withdraw from the study? Can my involvement be discontinued?**
   Yes. You are free to decide whether or not to participate in this study. Your decision will not influence the eye care available to you either at the School of Optometry or with your own Optometrist. The principal investigator may remove you from the study if the investigators believe it to be in your best interest. The Plymouth University's Office of Research Ethics could terminate your participation at any time.

9. **Confidentiality and security of data**
   All information you provide as a participant and any data we collect as a result of your participation in this study will remain confidential. You will be assigned an identification number, which will appear on all study records in place of your name. Any data collected in this investigation may be submitted for publication or used in presentations. Neither your name nor information disclosing your identity will be released or published without your explicit consent to the disclosure. For the purpose of monitoring the research, the Office of Research Ethics at the Plymouth University may inspect your study records at the School of Optometry. However, no records containing identifiable personal information will be permitted to leave the custody of the School of Optometry. Records from this study will be retained for a minimum of ten (10) years. Electronic records will be safely stored on a password protected server and hard copies will be securely stored in a record storage facility at the university. After ten (10) years, records will be confidentially disposed of in accordance with the guidelines laid out by the Plymouth University.

10. **Other important issues**
    If you have any questions regarding the study procedures, please do not hesitate to contact the principal investigator or the School of Optometry at (0)1752 600 600.

11. **Questions or concerns about participation in the study**
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DECLARATION OF INFORMED CONSENT

(Please insert your initials in the boxes, if you agree)

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☐ I am aware that this study has been reviewed and received ethics clearance through the Faculty Research Ethics Committee, and that if I have any concerns or questions about my participation in this study, I may contact Afzam Shah, principle investigator of this study +44 7584 423580 or at muhammad.abdulrahim@plymouth.ac.uk.

☐ I am aware that I may withdraw from the study at any time without affecting my relationship with the Plymouth University or School of Optometry. I am aware that the investigators reserve the right to discontinue my participation from the study at any time, either in regards to the research or the health of my eyes.

☐ I am aware that my participation in this study does not replace or constitute a complete eye examination in any way. During the study and after completion of the scheduled study visits, I agree to continue eye care at my regular eye care practitioner.

☐ I am aware that my participation in this study is voluntary, but that following study procedures is important to the success of the study. With full knowledge of this foregoing, I agree, of my own free will, to participate in this study. I also consent to the release of information from the study to my eye care practitioner, where relevant.

☐ I am aware that I will receive a copy of this information and consent letter. I am aware that by signing this form, I do not waive my legal rights or release the investigator(s) and/or involved institution(s) from their legal and professional responsibilities.

_____ _____
Signature of participant Date

_____
Printed name of participant

_____ _____
Signature of person explaining consent Date

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INVESTIGATING THE EFFECTS OF SMART PHONES ON OUR EYES
PART II: BINOCULAR ASSESSMENT OF TEAR STABILITY, ACCOMMODATION AND TEAR OSMOLARITY DURING SMARTPHONE USE

PARTICIPANT INFORMATION AND CONSENT LETTER

Muhammad Afzam Shah Bin Abdul Rahim is the principal investigator of this study and will work with the other clinical investigators from the School of Optometry, Plymouth University. They will perform all the clinical measurements as well as answer any questions that arise. Dr. Hetal Buckhurst (Director of Study), Prof. Dr. Christine Purslow and Dr. Phillip Buckhurst (2nd and 3rd supervisor) will be overseeing this study.

INFORMATION RELATED TO YOUR PARTICIPATION

1. **What is this study about?**
   Our study group kindly invites you to participate in our study which is investigating the effect of smartphone use on the tear film covering our eyes.

   Over the last 20 years, smartphones have become pivotal in our daily lives as they allow us to view emails, browse websites and even function as mobile entertainment devices. In the United Kingdom, 7 out of 10 adults own a smartphone. Data also shows that 98% of smartphones owner use their devices throughout the day. It was reported that 92% of smartphone users use their smartphone to send text messages to other phones while 84% of users use them to browse the internet. These data suggest that smartphones play an important role in our lives.

   Smartphones are mainly used at close working distance (distance between the user's eye and the smartphone screen) and a recent study suggested that these working distances differ significantly from those when reading hardcopy text. Since little is known about the effect of smartphones on the visual function, it is anticipated that these differences could lead to an excessive demand on both accommodation and vergence, resulting in ocular symptoms such as grittiness, dry eyes and tired eyes to develop. However, there are technical limitations in assessing real time changes on the tear film. Because of this, there has been limited information with regards to smartphone use and the tear film.

   To date, there has been no research that investigates the effect of smartphone use on the tear stability and accommodation. Therefore, it is imperative to investigate if smartphone use will cause changes to these ocular parameter (tear stability, tear osmolarity and accommodation).

2. **Who may participate in this study?**
   This study will attempt to recruit 80 participants. This study only recruits healthy individuals that have never undergone any form of ocular surgery and are not currently taking any forms of medications that will affect the eyes. To be eligible for the study, you must be at least 18 years old. Your eye health will be examined prior to enrolment into the study. We would appreciate if you can let us know if you are involved in any other research study.

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3. **What is the time commitment for this study?**
This study consists of only one visit which will take about 2 hours. During this visit, we will first determine whether you are able to participate in this study or not. If you are eligible, and once written consent has been obtained, data collection will start.

4. **What is expected of me at these visits?**
The clinical examinations that will be performed during this study are listed below.

Subjective symptoms and ratings (questionnaires): Your personal details and medical history will be asked. Furthermore, you will be asked to grade the dryness of your eyes. You are also required to fill in the McMonnies and Ocular Surface Disease Index (OSDI) questionnaires. The OSDI questionnaire asks about sensations and effects of dryness in a time period of the last week while the McMonnies questionnaire is more about general conditions like medication, diseases and sleeping habits.

Visual acuity and refraction: You will be asked to look at a chart and read the lowest line that you can see (this will be done with you fixating on distance and near chart). After that, tests will be performed to determine the prescription of your eyes.

Accommodation: While seated comfortably, you will be asked to look at a smartphone/conventional mobile phone display screen. At the same time, accommodation (focusing power of the eye) will be measured automatically and non-invasively using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (Grand Seiko Co. Ltd., Japan). Both eyes will be measured.

Tear osmolarity: While seated comfortably, a very small amount of tear fluid sample (50 nanoliter) will be collected from your eye (at the lower eyelid portion). This is done using the Test Card lab-on-a-chip technology, which is a small, single use, individually packed polycarbonate microchip from TearLab (TearLab Corp., Texas, USA). The osmolarity (viscosity) value of the tears will then be calculated automatically by the equipment. Both eyes will be measured.

Exposure to smartphone task: While seated comfortably, you are requested to read and play games on different modalities (3 smartphone, 1 conventional mobile phone, a smart watch and on actual printed paper material) in a randomized order. You will only be using each modality for 5 minutes. A 5 minute rest will be given before you move on to the subsequent modality, until you completed reading and playing games on all 6 modality. Simultaneously, while you are performing the designated task (reading and playing games on phones), measurements of tear stability will be conducted (see description below). Both eyes will be exposed to the aforementioned task.

Tear stability: Tear stability will be measured using the Open Field Tear film Analyzer (OFTA). You will be asked to sit at an instrument, placing your chin and forehead against the chin rest and forehead rest and to fixate on the target (smartphone/mobile phone/printed paper) for 5 minutes. The OFTA does not touch the eye (non-invasive instrument) and thus, ocular anesthesia is not required. Both eyes will be examined.

Slit lamp examination: You will be asked to sit at an instrument. Your chin and forehead will be placed against the appropriate chin rest and forehead rest. The investigator will examine your ocular structures to determine your ocular health status. A sterile sodium fluorescein strip and lissamine green strip will be used to assess the ocular surface for any abnormalities (Sodium fluorescein will be used to assess the cornea while lissamine green will be

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used to assess the bulbar conjunctiva). Both eyes will be examined beginning with the right eye. The chin rest and forehead rest will be sanitized with alcohol swabs between each participant.

5. **Are there any risks associated with this study?**
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6. **What are the benefits of participation in this study?**
Unfortunately, this study is unlikely to benefit you directly. However, it will help gain a better understanding on the effect of smartphone use on ocular parameter (tear stability, tear osmolarity and accommodation).

7. **Is there remuneration for participation?**
Unfortunately, you will not get paid to participate in this study.

8. **Can I withdraw from the study? Can my involvement be discontinued?**
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2. **Who may participate in this study?**
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3. **What is the time commitment for this study?**
This study consists of only one visit which will take about 2 hours. During this visit, we will first determine whether you are able to participate in this study or not. If you are eligible, and once written consent has been obtained, data collection will start. To examine the relationship between smart device use and the symptoms of dry eye, you will be asked to monitor your electronic smart device usage for one week.

4. **What is expected of me at these visits?**
The clinical examinations that will be performed during this study are listed below.

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surface for any abnormalities (Sodium fluorescein will be used to assess the cornea while lissamine green will be used to assess the bulbar conjunctiva). Both eyes will be examined beginning with the right eye. The chin rest and forehead rest will be sanitized with alcohol swabs between each participant.

Frequency of smart device use: Smart device use will be assessed via the use of a freely available app that monitor smart device use (Moment: Screen time tracker, Kevin Holesh; Quality Time, NComputing Global Inc.). You will be asked to download these applications onto your personal smart device and these applications will provide data on the total number of minutes per day spent on your smart device. You will also be asked to complete a questionnaire to quantify the overall usage of smart devices, VDU (including laptop), tablet, game console, smart watch and television.

5. **Are there any risks associated with this study?**
All the clinical examinations being performed in this study are actually common optometric procedures and adhere to the Declaration of Helsinki (which means that all the examinations conducted in this study will not harm the participants). Therefore, we do not anticipate any risk associated with this study. You may/may not feel slight discomfort/eye irritation during some of the study procedure. The discomfort/irritation is temporary. Please inform the investigator if you experience any form of discomfort/irritation.

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DECLARATION OF INFORMED CONSENT

(Please insert your initials in the boxes, if you agree)

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☐ I am aware that my participation in this study is voluntary, but that following study procedures is important to the success of the study. With full knowledge of this foregoing, I agree, of my own free will, to participate in this study.

_____ _____
Signature of participant Date

_____
Printed name of participant

_____ _____
Signature of person explaining consent Date

Initials _____

E. Case Report Form (CRF)

Study 14/15-330

CASE REPORT FORM

Muhammad Afzam Shah Bin Abdul Rahim
Plymouth University
Peninsula Allied Health Centre, Room FF01
Derriford Road, Plymouth, PL68BH
Tel: +44 (0)1752 586727 Fax: +44 (0)1752 588874

Patient number: | | |

VISIT 1 (Day 1):

Screening Visit & Baseline Data

SCREENING FORMS: SMARTPHONE AND THE EYES

INFORMED CONSENT
DEMOGRAPHY
MEDICAL HISTORY
OCULAR HISTORY
OCULAR SIGNS AND SYMPTOMS
INCLUSION AND EXCLUSION CRITERIA
OSDI©
MCMONNIES©
PATIENT STATUS
VISUAL ACUITY AND REFRACTION
TEAR BREAK UP TIME
SLIT LAMP EXAMINATION

Visit 1 (Day 1): Screening Visit & Baseline Data

Date:		Time:	

Day 2 and 3 time window	

V1- INFORMED CONSENT

Has the participant singed the informed consent?

☐ Yes
☐ No*

**If no, please STOP and complete "Patient status" first*

Informed consent was obtained on (DD/MM/YYYY): _____

The informed consent has to be signed before any procedure of the visit

V1- DEMOGRAPHY

Gender	Female	Male	N/A
Date of birth			
Occupation			
Ethnicity	Caucasian	Chinese	Indian
	Afro-Caribbean	Hispanic	Others:_____
Smoker	Current	Never	Former
	How much per day? _____ Stopped since when? _____		
Eye (iris) color	Dark blue	Light blue	Green
	Light brown	Dark brown	Others:_____

V1- MEDICAL HISTORY

General health	Good	Other:	
Medical history	None	Diabetes	Migraine
	Headache	High blood pressure	Rheumatism
	Stroke	Herpes	Thyroid
	Neck/shoulder pain	Cardiovascular	Multiple sclerosis
	Other:		
	Last visit to GP:		
Any allergies	None	Other:	

V1- OCULAR HISTORY

Ocular history	None	Macular disease/ARMD		Retinitis pigmentosa
	Glaucoma	Cataract		Visual field loss
	Others:			
	Allergy:			
	Last visit to optometrist: Reason:			
Contact lens wear	Yes	Never		Used to (since _____)
	If Yes, which lenses?	RGP	Hydrogel	SiHy
	Modality?	Daily	2 weekly	≥Monthly
Eye drops	Yes		No	

V1- OCULAR SIGNS AND SYMPTOMS

Ocular signs and symptoms		
Itchy eyelids	Yes	No
Rosacea	Yes	No
Crusting on the lashes	Yes	No
Crusting on the lid margin	Yes	No
Dry eye treatment		
Dry eye drops	Yes	No
Scrub/massage of the eyelids	Yes	No
Warm compression	Yes	No
Other adnexa and conjunctival abnormalities		
Pinguecula	Yes	No
Pterygium	Yes	No
Others: **Include drawings if necessary.*		

V1- INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria		
Older than 18 years and younger than 40 years	Yes	No
Completed a comprehensive eye examination within the last 12 months	Yes	No
SCL wear was stopped for a minimum of 2 day	Yes	No
RGP lens wear was stopped for a minimum of 1 week	Yes	No
Had signed the consent form	Yes	No
Exclusion criteria		
Pregnant or breast feeding	Yes	No
Application of any eye drops within the last 48 hours	Yes	No
Application of medication within the last 30 days which influences the body water regulatory system	Yes	No
Change of ocular therapy within the last 30 days	Yes	No
Permanent application of eye drops or ocular medication	Yes	No
On-going ocular treatment	Yes	No
Any forms of ocular pathology or history of refractive surgery	Yes	No
Any forms of systemic disease that may influence the water regulatory system	Yes	No
Participation in any other pharmacological studies	Yes	No
Abnormal binocular vision status	Yes	No
Abnormal accommodation status	Yes	No
History or currently experiencing dry eye disease	Yes	No

V1- OSDI®

Please answer the following by circling the most appropriate respond to you. Then, please fill in boxes A, B, C, D and E based on the instructions given.

1. HAVE YOU EXPERIENCED ANY OF THE FOLLOWING DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that is sensitive to light?	4	3	2	1	0
2. Eyes that feels gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0
Subtotal score for answer 1 to 5				(A)	

2. HAVE PROBLEMS WITH YOUR EYES LIMITING YOU IN PERFORMING ANY OF THE FOLLOWING DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine ATM?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A
Subtotal score for answer 6 to 9					(B)	

3. HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A

12. Areas that is air-conditioned?	4	3	2	1	0	N/A
Subtotal score for answer 10 to 12					(C)	

Please carefully calculate the portions below.

Add Subtotals A, B, C to Obtain D (D = Sum scores for all the questions answered)	(D)

Total Number of Questions Answered = E (Please DO NOT include questions answered N/A)	(E)

V1- MCMONNIES©

Please answer the following by circling the most appropriate respond to you.

Gender	Female	Male	
Age	≤24 years	25-45 years	≥46 years
Contact lens wear	Non-contact lens wearer	Hard contact lens wearer	Soft contact lens wearer

1. Have you ever had drops prescribed or other treatment for dry eyes?

Yes	No	Uncertain

2. Do you ever experience any of the following dry eye symptoms?

Soreness	Scratchiness	Dryness	Grittiness	Burning

3. How often do your eyes have these symptoms?

Never	Sometimes	Often	Constantly

4. Are your eyes usually sensitive to cigarette smoke, smog, air conditioning or central heating?

Yes	No	Sometimes

5. Do your eyes become very red and irritated when swimming?

Not applicable	Yes	No	Sometimes

6. Are your eyes dry and irritated when drinking alcohol?

Not applicable	Yes	No	Sometimes

7. Do you take or use any of the following?

Antihistamine tablets	Antihistamine eye drops	Diuretics (fluid tablets)
Tranquilizers	Oral contraceptives	Sleeping tablets

8. Do you suffer from arthritis?

Yes	No	Uncertain

9. Do you experience dryness of the nose, mouth, throat, chest or vagina?

Never	Sometimes	Often	Constantly

10. Do you suffer from thyroid abnormality?

Yes	No	Uncertain

11. Are you known to sleep with eyes partly open?

Yes	No	Sometimes

12. Do you have eye irritation as you wake from sleep?

Yes	No	Sometimes

Total score*	

**A score of over 20 is indicative of dry eye, while a total score of between 10 and 20 is suggestive of borderline dry eye disease.*

V1- PATIENT STATUS

Include into this study	Yes	No
*Please state reason if 'No'		
Signature		
Date		
Comment(s)		

V1- VISUAL ACUITY AND REFRACTION

Vision

RE Vision		LE Vision		BE Vision	

Refraction and Visual Acuity

Rx RE		VA:
Rx LE		VA:

V1- TEAR BREAK UP TIME

Examiner ID	

Order of tests and eye must be randomised

Bausch and Lomb Keratometer

	RE	LE
Measurement 1 (s)		
Measurement 2 (s)		
Measurement 3 (s)		

Oculus Keratograph 5M

	RE	LE
Measurement 1 (s)		
Measurement 2 (s)		
Measurement 3 (s)		

OFTA

TBUT recorded	RE	LE
Measurement 1 (s)	Yes No	Yes No
Measurement 2 (s)	Yes No	Yes No
Measurement 3 (s)	Yes No	Yes No

V1- SLIT LAMP EXAMINATION

Slit lamp recordings.

	RE	LE
Cornea		
Bulbar conjunctiva		

VISIT 2 (Day 2):
Data for Visit 2

VISUAL ACUITY AND REFRACTION
TEAR BREAK UP TIME
SLIT LAMP EXAMINATION

Visit 2 (Day 2)

Day 2 and 3 time window	

Date:		Time:	

V2- VISUAL ACUITY AND REFRACTION

Vision

RE Vision		LE Vision		BE Vision	

Refraction and Visual Acuity

Rx RE		VA:
Rx LE		VA:

V2- TEAR BREAK UP TIME

Examiner ID	

Order of tests and eye must be randomised

Bausch and Lomb Keratometer

	RE	LE
Measurement 1 (s)		
Measurement 2 (s)		
Measurement 3 (s)		

Oculus Keratograph 5M

	RE	LE
Measurement 1 (s)		
Measurement 2 (s)		
Measurement 3 (s)		

OFTA

TBUT recorded	RE	LE
Measurement 1 (s)	Yes No	Yes No
Measurement 2 (s)	Yes No	Yes No
Measurement 3 (s)	Yes No	Yes No

V2- SLIT LAMP EXAMINATION

Slit lamp recordings.

	RE	LE
Cornea		
Bulbar conjunctiva		

VISIT 3 (Day 3):
Data for Visit 3

VISUAL ACUITY AND REFRACTION
TEAR BREAK UP TIME
SLIT LAMP EXAMINATION

Visit 3 (Day 3)

Day 2 and 3 time window	

Date:		Time:	

V2- VISUAL ACUITY AND REFRACTION

Vision

RE Vision		LE Vision		BE Vision	

Refraction and Visual Acuity

Rx RE		VA:
Rx LE		VA:

V3- TEAR BREAK UP TIME

Examiner ID	

Order of tests and eye must be randomised

Bausch and Lomb Keratometer

	RE	LE
Measurement 1 (s)		
Measurement 2 (s)		
Measurement 3 (s)		

Oculus Keratograph 5M

	RE	LE
Measurement 1 (s)		
Measurement 2 (s)		
Measurement 3 (s)		

OFTA

TBUT recorded	RE	LE
Measurement 1 (s)	Yes No	Yes No
Measurement 2 (s)	Yes No	Yes No
Measurement 3 (s)	Yes No	Yes No

V3- SLIT LAMP EXAMINATION

Slit lamp recordings.

	RE	LE
Cornea		
Bulbar conjunctiva		

WITHDRAWAL FORM

Date of last visit or phone contact:

INFORMATION ABOUT STUDY TERMINATION

Reason for withdrawal from the study:

	Adverse effect to fluorescein or lissamine green.
	Other medical reason (give details)
	Lost to follow to follow up (what was the last action taken?)
	Other reason (give details)

Examiner ID	
Signature	
Date	

FLOW CHART

CLINICAL INVESTIGATION PROCEDURES	DAY 1 (BASELINE)	DAY 2	DAY 3
Informed consent	x		
Demography	x		
Medical history	x		
Ocular history	x		
Ocular signs and symptoms	x		
Inclusion and exclusion criteria	x		
OSDI®	x		
MCMONNIES®	x		
Patient status	x		
Visual acuity and refraction	x	x	x
Tear break up time B&L keratometer	x	x	x
Tear break up time	x	x	x
Tear break up time OFTA	x	x	x
Slit lamp examination	x	x	x

Study 15/16-468

CASE REPORT FORM

Muhammad Afzam Shah Bin Abdul Rahim
Plymouth University
Peninsula Allied Health Centre, Room FF01
Derriford Road, Plymouth, PL68BH
Tel: +44 (0)1752 586727 Fax: +44 (0)1752 588874

Patient number: | | |

Part I:

Screening Visit and Baseline Data

INFORMED CONSENT
DEMOGRAPHY
MEDICAL HISTORY
OCULAR HISTORY
OCULAR SIGNS AND SYMPTOMS
INCLUSION AND EXCLUSION CRITERIA
OSDI©
MCMONNIES©
PATIENT STATUS
VISUAL ACUITY AND REFRACTION

Part I: Screening Visit & Baseline Data

Date:		Time:	

PI- INFORMED CONSENT

Has the participant singed the informed consent?

☐ Yes
☐ No*

**If no, please STOP and complete "Patient status" first*

Informed consent was obtained on (DD/MM/YYYY): ☐

The informed consent has to be signed before any procedure of the visit

PI- DEMOGRAPHY

Gender	Female	Male	N/A
Date of birth			
Occupation			
Ethnicity	Caucasian	Chinese	Indian
	Afro-Caribbean	Hispanic	Others:_____
Smoker	Current	Never	Former
	How much per day? _____ Stopped since when? _____		
Eye (iris) color	Dark blue	Light blue	Green
	Light brown	Dark brown	Others:_____

PI- MEDICAL HISTORY

General health	Good	Other:	
Medical history	None	Diabetes	Migraine
	Headache	High blood pressure	Rheumatism
	Stroke	Herpes	Thyroid
	Neck/shoulder pain	Cardiovascular	Multiple sclerosis
	Other:		
	Last visit to GP:		
Any allergies	None	Other:	

PI- OCULAR HISTORY

Ocular history	None	Macular disease/ARMD		Retinitis pigmentosa
	Glaucoma	Cataract		Visual field loss
	Others:			
	Allergy:			
	Last visit to optometrist: Reason:			
Contact lens wear	Yes	Never		Used to (since _____)
	If Yes, which lenses?	RGP	Hydrogel	SiHy
	Modality?	Daily	2 weekly	≥Monthly
Eye drops	Yes		No	

PI- OCULAR SIGNS AND SYMPTOMS

Ocular signs and symptoms		
Itchy eyelids	Yes	No
Rosacea	Yes	No
Crusting on the lashes	Yes	No
Crusting on the lid margin	Yes	No
Dry eye treatment		
Dry eye drops	Yes	No
Scrub/massage of the eyelids	Yes	No
Warm compression	Yes	No
Other adnexa and conjunctival abnormalities		
Pinguecula	Yes	No
Pterygium	Yes	No
Others:		

**Include drawings if necessary.*

PI- INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria		
Older than 18 years and younger than 40 years	Yes	No
Completed a comprehensive eye examination within the last 12 months	Yes	No
SCL wear was stopped for a minimum of 2 day	Yes	No
RGP lens wear was stopped for a minimum of 1 week	Yes	No
Had signed the consent form	Yes	No
Exclusion criteria		
Pregnant or breast feeding	Yes	No
Application of any eye drops within the last 48 hours	Yes	No
Application of medication within the last 30 days which influences the body water regulatory system	Yes	No
Change of ocular therapy within the last 30 days	Yes	No
Permanent application of eye drops or ocular medication	Yes	No
On-going ocular treatment	Yes	No
Any forms of ocular pathology or history of refractive surgery	Yes	No
Any forms of systemic disease that may influence the water regulatory system	Yes	No
Participation in any other pharmacological studies	Yes	No
Abnormal binocular vision status	Yes	No
Abnormal accommodation status	Yes	No
History or currently experiencing dry eye disease	Yes	No

PI- OSDI©

Please answer the following by circling the most appropriate respond to you. Then, please fill in boxes A, B, C, D and E based on the instructions given.

1. HAVE YOU EXPERIENCED ANY OF THE FOLLOWING DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that is sensitive to light?	4	3	2	1	0
2. Eyes that feels gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0
Subtotal score for answer 1 to 5				(A)	

2. HAVE PROBLEMS WITH YOUR EYES LIMITING YOU IN PERFORMING ANY OF THE FOLLOWING DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine ATM?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A
Subtotal score for answer 6 to 9					(B)	

3. HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A

12. Areas that is air-conditioned?	4	3	2	1	0	N/A
Subtotal score for answer 10 to 12					(C)	

Please carefully calculate the portions below.

Add Subtotals A, B, C to Obtain D (D = Sum scores for all the questions answered)	(D)

Total Number of Questions Answered = E (Please DO NOT include questions answered N/A)	(E)

PI MCMONNIES©

Please answer the following by circling the most appropriate respond to you.

Gender	Female	Male	
Age	≤24 years	25-45 years	≥46 years
Contact lens wear	Non-contact lens wearer	Hard contact lens wearer	Soft contact lens wearer

1. Have you ever had drops prescribed or other treatment for dry eyes?

Yes	No	Uncertain

2. Do you ever experience any of the following dry eye symptoms?

Soreness	Scratchiness	Dryness	Grittiness	Burning

3. How often do your eyes have these symptoms?

Never	Sometimes	Often	Constantly

4. Are your eyes usually sensitive to cigarette smoke, smog, air conditioning or central heating?

Yes	No	Sometimes

5. Do your eyes become very red and irritated when swimming?

Not applicable	Yes	No	Sometimes

6. Are your eyes dry and irritated when drinking alcohol?

Not applicable	Yes	No	Sometimes

7. Do you take or use any of the following?

Antihistamine tablets	Antihistamine eye drops	Diuretics (fluid tablets)
Tranquilizers	Oral contraceptives	Sleeping tablets

8. Do you suffer from arthritis?

Yes	No	Uncertain

9. Do you experience dryness of the nose, mouth, throat, chest or vagina?

Never	Sometimes	Often	Constantly

10. Do you suffer from thyroid abnormality?

Yes	No	Uncertain

11. Are you known to sleep with eyes partly open?

Yes	No	Sometimes

12. Do you have eye irritation as you wake from sleep?

Yes	No	Sometimes

Total score*	

**A score of over 20 is indicative of dry eye, while a total score of between 10 and 20 is suggestive of borderline dry eye disease.*

PI- PATIENT STATUS

Include into this study	Yes	No
*Please state reason if 'No'		
Signature		
Date		
Comment(s)		

PI- VISUAL ACUITY AND REFRACTION

Distance Vision

RE Vision		LE Vision		BE Vision	

Distance Refraction and Visual Acuity

Rx RE		VA:
Rx LE		VA:

Near Acuity

RE Vision	
LE Vision	
RE VA	
LE VA	

Part II:

Exposure to Conventional Mobile Phones, Smartphones and Smart Watch

TEAR OSMOLARITY
BINOCULAR NON-INVASIVE TEAR STABILITY
BLINKING RATE
SLIT LAMP EXAMINATION

Part II- Exposure to Conventional Mobile Phones, Smartphones and Smart Watch

PII-TEAR OSMOLARITY

Order of tests and eye MUST BE randomised.

TearLab (Baseline: Pre-exposure to phone)

Baseline	Pre-Exposure Tear Osmolarity Value (mOsm/L)	
	RE	LE
Before looking straight ahead		
After looking straight ahead		

TearLab (Post-exposure to phone: reading)

Phone	Post-Exposure Tear Osmolarity Value (mOsm/L)	
	RE	LE
Phone 1		
Phone 2		
Phone 3		
Phone 4		

TearLab (Post-exposure to phone: playing games)

Phone	Post-Exposure Tear Osmolarity Value (mOsm/L)	
	RE	LE
Phone 1		
Phone 2		
Phone 3		
Phone 4		
Phone 5		
Phone 6		

PII-BINOCULAR NON-INVASIVE TEAR STABILITY AND BLINKING RATE (BASELINE AND READING)

Baseline

Looking Straight Ahead	Recorded using OFTA					
	RE			LE		
	1	2	3	1	2	3
Baseline (No task)	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No

Recorded using OFTA while reading for 5 minutes on each phone.
Order MUST BE randomized.

Phone	Recorded using OFTA					
	RE			LE		
	1	2	3	1	2	3
Phone 1	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Phone 2	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Phone 3	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Phone 4	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No

PII-BINOCULAR NON-INVASIVE TEAR STABILITY AND BLINKING RATE (PLAYING GAMES)

Recorded using OFTA while playing maze games for 5 minutes on each phone.
Order MUST BE randomized.

Phone	Recorded using OFTA					
	RE			LE		
	1	2	3	1	2	3
Phone 1	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Phone 2	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Phone 3	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Phone 4	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Phone 5	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Phone 6	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No

PII- SLIT LAMP EXAMINATION

Slit lamp recordings

Structures	RE	LE
Cornea		
Bulbar conjunctiva		

WITHDRAWAL FORM

Date of last visit or phone contact:

INFORMATION ABOUT STUDY TERMINATION

Reason for withdrawal from the study:

	Adverse effect to fluorescein or lissamine green.
	Other medical reason (give details)
	Lost to follow to follow up (what was the last action taken?)
	Other reason (give details)

Examiner ID	
Signature	
Date	

FLOW CHART

CLINICAL INVESTIGATION PROCEDURES	PART I	PART II
Informed consent	x	
Demography	x	
Medical history	x	
Ocular history	x	
Ocular signs and symptoms	x	
Inclusion and exclusion criteria	x	
OSDI®	x	
MCMONNIES®	x	
Patient status	x	
Visual acuity and refraction	x	
Tear osmolarity		x
Binocular non-invasive tear stability		x
Blinking rate		x
Slit lamp examination		x

Study 15/16-468

CASE REPORT FORM

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Derriford Road, Plymouth, PL68BH
Tel: +44 (0)1752 586727 Fax: +44 (0)1752 588874

Patient number: | | |

Part I:
Screening Visit and Baseline Data

INFORMED CONSENT
DEMOGRAPHY
MEDICAL HISTORY
OCULAR HISTORY
OCULAR SIGNS AND SYMPTOMS
INCLUSION AND EXCLUSION CRITERIA
PATIENT STATUS
VISUAL ACUITY AND REFRACTION

Part I: Screening Visit & Baseline Data

Date:		Time:	

PI- INFORMED CONSENT

Has the participant singed the informed consent?

☐ Yes
☐ No*

**If no, please STOP and complete "Patient status" first*

Informed consent was obtained on (DD/MM/YYYY): ☐

The informed consent has to be signed before any procedure of the visit

PI- DEMOGRAPHY

Gender	Female	Male	N/A
Date of birth			
Occupation			
Ethnicity	Caucasian	Chinese	Indian
	Afro-Caribbean	Hispanic	Others:_____
Smoker	Current	Never	Former
	How much per day? _____ Stopped since when? _____		
Eye (iris) color	Dark blue	Light blue	Green
	Light brown	Dark brown	Others:_____

PI- MEDICAL HISTORY

General health	Good	Other:	
Medical history	None	Diabetes	Migraine
	Headache	High blood pressure	Rheumatism
	Stroke	Herpes	Thyroid
	Neck/shoulder pain	Cardiovascular	Multiple sclerosis
	Other:		
	Last visit to GP:		
Any allergies	None	Other:	

PI- OCULAR HISTORY

Ocular history	None	Macular disease/ARMD		Retinitis pigmentosa
	Glaucoma	Cataract		Visual field loss
	Others:			
	Allergy:			
	Last visit to optometrist: Reason:			
Contact lens wear	Yes	Never		Used to (since _____)
	If Yes, which lenses?	RGP	Hydrogel	SiHy
	Modality?	Daily	2 weekly	≥Monthly
Eye drops	Yes		No	

PI- OCULAR SIGNS AND SYMPTOMS

Ocular signs and symptoms		
Itchy eyelids	Yes	No
Rosacea	Yes	No
Crusting on the lashes	Yes	No
Crusting on the lid margin	Yes	No
Dry eye treatment		
Dry eye drops	Yes	No
Scrub/massage of the eyelids	Yes	No
Warm compression	Yes	No
Other adnexa and conjunctival abnormalities		
Pinguecula	Yes	No
Pterygium	Yes	No
Others:		

**Include drawings if necessary.*

PI- INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria		
Older than 18 years and younger than 40 years	Yes	No
Completed a comprehensive eye examination within the last 12 months	Yes	No
Had signed the consent form	Yes	No
Exclusion criteria		
Pregnant or breast feeding	Yes	No
Experiencing binocular or monocular diplopia	Yes	No
Taking medications	Yes	No
Suffering any form of ocular or systemic diseases	Yes	No
Have problems focusing image at near or distance	Yes	No
History of any form of ocular surgery including LASIK	Yes	No
Participation in any other pharmacological studies	Yes	No

PI- PATIENT STATUS

Include into this study	Yes	No
*Please state reason if 'No'		
Signature		
Date		
Comment(s)		

PI- VISUAL ACUITY AND REFRACTION

Distance Vision

RE Vision		LE Vision		BE Vision	

Distance Refraction and Visual Acuity

Rx RE		VA:
Rx LE		VA:

Near Acuity

RE Vision	
LE Vision	
RE VA	
LE VA	

Part II:

Measurement of Accommodation Response (AR) Using Grand Seiko WAM-5500

N20 Letter on iPhone 6
Maltese cross iPhone 6
N5 Letter on iPhone 6
N5 Letter on Paper
N5 Letter on Smart Watch

Part II- Measurement of Accommodation Response (AR) Using Grand Seiko WAM-5500

Order of tests and eye MUST BE randomised.
Measure the RE only (in binocular view).

No.	Experiment	Data Collected
1	N20 Letter on iPhone 6	Yes / No
2	Maltese cross iPhone 6	Yes / No
3	N5 Letter on iPhone 6	Yes / No
4	N5 Letter on Paper	Yes / No
5	N5 Letter on Smart Watch	Yes / No

WITHDRAWAL FORM

Date of last visit or phone contact:

INFORMATION ABOUT STUDY TERMINATION

Reason for withdrawal from the study:

	Adverse effect to fluorescein or lissamine green.
	Other medical reason (give details)
	Lost to follow to follow up (what was the last action taken?)
	Other reason (give details)

Examiner ID	
Signature	
Date	

FLOW CHART

CLINICAL INVESTIGATION PROCEDURES	PART I	PART II
Informed consent	x	
Demography	x	
Medical history	x	
Ocular history	x	
Ocular signs and symptoms	x	
Inclusion and exclusion criteria	x	
Patient status	x	
Visual acuity and refraction	x	
N20 Letter on iPhone 6		x
Maltese cross iPhone 6		x
N5 Letter on iPhone 6		x
N5 Letter on Paper		x
N5 Letter on Smart Watch		x

Study 17/18-902

CASE REPORT FORM

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Derriford Road, Plymouth, PL68BH
Tel: +44 (0)1752 586727 Fax: +44 (0)1752 588874

Patient number: | | |

Part I:
Screening Visit and Baseline Data

INFORMED CONSENT
DEMOGRAPHY
MEDICAL HISTORY
OCULAR HISTORY
OCULAR SIGNS AND SYMPTOMS
INCLUSION AND EXCLUSION CRITERIA
OSDI©
MCMONNIES©
PATIENT STATUS
VISUAL ACUITY AND REFRACTION

Part I: Screening Visit & Baseline Data

Date:		Time:	

PI- INFORMED CONSENT

Has the participant singed the informed consent?

☐ Yes
☐ No*

**If no, please STOP and complete "Patient status" first*

Informed consent was obtained on (DD/MM/YYYY): ☐

The informed consent has to be signed before any procedure of the visit

PI- DEMOGRAPHY

Gender	Female	Male	N/A
Date of birth			
Occupation			
Ethnicity	Caucasian	Chinese	Indian
	Afro-Caribbean	Hispanic	Others:_____
Smoker	Current	Never	Former
	How much per day? _____ Stopped since when? _____		
Eye (iris) colour	Dark blue	Light blue	Green
	Light brown	Dark brown	Others:_____

PI- MEDICAL HISTORY

General health	Good	Other:	
Medical history	None	Diabetes	Migraine
	Headache	High blood pressure	Rheumatism
	Stroke	Herpes	Thyroid
	Neck/shoulder pain	Cardiovascular	Multiple sclerosis
	Other:		
	Last visit to GP:		
Any allergies	None	Other:	

PI- OCULAR HISTORY

Ocular history	None	Macular disease/ARMD		Retinitis pigmentosa
	Glaucoma	Cataract		Visual field loss
	Others:			
	Allergy:			
	Last visit to optometrist: Reason:			
Contact lens wear	Yes	Never		Used to (since _____)
	If Yes, which lenses?	RGP	Hydrogel	SiHy
	Modality?	Daily	2 weekly	≥Monthly
Eye drops	Yes		No	

PI- OCULAR SIGNS AND SYMPTOMS

Ocular signs and symptoms		
Itchy eyelids	Yes	No
Rosacea	Yes	No
Crusting on the lashes	Yes	No
Crusting on the lid margin	Yes	No
Dry eye treatment		
Dry eye drops	Yes	No
Scrub/massage of the eyelids	Yes	No
Warm compression	Yes	No
Other adnexa and conjunctival abnormalities		
Pinguecula	Yes	No
Pterygium	Yes	No
Others:		

**Include drawings if necessary.*

PI- INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria		
Aged between 18 and 35 years old	Yes	No
Completed a comprehensive eye examination within the last 12 months	Yes	No
SCL wear was stopped for a minimum of 2 day	Yes	No
RGP lens wear was stopped for a minimum of 1 week	Yes	No
Had signed the consent form	Yes	No
Exclusion criteria		
Pregnant or breast feeding	Yes	No
Application of any eye drops within the last 48 hours	Yes	No
Application of medication within the last 30 days which influences the body water regulatory system	Yes	No
Change of ocular therapy within the last 30 days	Yes	No
Permanent application of eye drops or ocular medication	Yes	No
On-going ocular treatment	Yes	No
Any forms of ocular pathology or history of refractive surgery	Yes	No
Any forms of systemic disease that may influence the water regulatory system	Yes	No
Participation in a pharmacological studies occurring concurrently.	Yes	No
Abnormal binocular vision status	Yes	No
Abnormal accommodation status	Yes	No
History or currently experiencing dry eye disease	Yes	No

PI- OSDI©

Please answer the following by circling the most appropriate respond to you. Then, please fill in boxes A, B, C, D and E based on the instructions given.

1. HAVE YOU EXPERIENCED ANY OF THE FOLLOWING DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that is sensitive to light?	4	3	2	1	0
2. Eyes that feels gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0
Subtotal score for answer 1 to 5				(A)	

2. HAVE PROBLEMS WITH YOUR EYES LIMITING YOU IN PERFORMING ANY OF THE FOLLOWING DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine ATM?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A
Subtotal score for answer 6 to 9					(B)	

3. HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A

12. Areas that is air-conditioned?	4	3	2	1	0	N/A
Subtotal score for answer 10 to 12					(C)	

Please carefully calculate the portions below.

Add Subtotals A, B, C to Obtain D (D = Sum scores for all the questions answered)	(D)

Total Number of Questions Answered = E (Please DO NOT include questions answered N/A)	(E)

PI MCMONNIES®

Please answer the following by circling the most appropriate respond to you.

Gender	Female	Male	
Age	≤24 years	25-45 years	≥46 years
Contact lens wear	Non-contact lens wearer	Hard contact lens wearer	Soft contact lens wearer

1. Have you ever had drops prescribed or other treatment for dry eyes?

Yes	No	Uncertain

2. Do you ever experience any of the following dry eye symptoms?

Soreness	Scratchiness	Dryness	Grittiness	Burning

3. How often do your eyes have these symptoms?

Never	Sometimes	Often	Constantly

4. Are your eyes usually sensitive to cigarette smoke, smog, air conditioning or central heating?

Yes	No	Sometimes

5. Do your eyes become very red and irritated when swimming?

Not applicable	Yes	No	Sometimes

6. Are your eyes dry and irritated when drinking alcohol?

Not applicable	Yes	No	Sometimes

7. Do you take or use any of the following?

Antihistamine tablets	Antihistamine eye drops	Diuretics (fluid tablets)
Tranquilizers	Oral contraceptives	Sleeping tablets

8. Do you suffer from arthritis?

Yes	No	Uncertain

9. Do you experience dryness of the nose, mouth, throat, chest or vagina?

Never	Sometimes	Often	Constantly

10. Do you suffer from thyroid abnormality?

Yes	No	Uncertain

11. Are you known to sleep with eyes partly open?

Yes	No	Sometimes

12. Do you have eye irritation as you wake from sleep?

Yes	No	Sometimes

Total score*	

**A score of over 20 is indicative of dry eye, while a total score of between 10 and 20 is suggestive of borderline dry eye disease.*

PI- PATIENT STATUS

Include into this study	Yes	No
*Please state reason if 'No'		
Signature		
Date		
Comment(s)		

PI- VISUAL ACUITY AND REFRACTION

Distance Vision

RE Vision		LE Vision		BE Vision	

Distance Refraction and Visual Acuity

Rx RE		VA:
Rx LE		VA:

Near Acuity

RE Vision	
LE Vision	
RE VA	
LE VA	

Part II:
Effect of Multiple Measurements of Tear Osmolarity

TEAR OSMOLARITY

Part II- Effect of Multiple Measurements of Tear Osmolarity

PII-TEAR OSMOLARITY

TearLab Measurements

Number of Measurements	Tear Osmolarity Value (mOsm/L) RE	Temperature	Humidity
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			
11.			

WITHDRAWAL FORM

Date of last visit or phone contact:

INFORMATION ABOUT STUDY TERMINATION

Reason for withdrawal from the study:

	Adverse effect to fluorescein or lissamine green.
	Other medical reason (give details)
	Lost to follow to follow up (what was the last action taken?)
	Other reason (give details)

Examiner ID	
Signature	
Date	

FLOW CHART

CLINICAL INVESTIGATION PROCEDURES	PART I	PART II
Informed consent	x	
Demography	x	
Medical history	x	
Ocular history	x	
Ocular signs and symptoms	x	
Inclusion and exclusion criteria	x	
OSDI©	x	
MCMONNIES©	x	
Patient status	x	
Visual acuity and refraction	x	
Tear osmolarity		x

Study 17/18-902

CASE REPORT FORM

Muhammad Afzam Shah Bin Abdul Rahim
Plymouth University
Peninsula Allied Health Centre, Room FF01
Derriford Road, Plymouth, PL68BH
Tel: +44 (0)1752 586727 Fax: +44 (0)1752 588874

Patient number: | | |

Part I:
Screening Visit and Baseline Data

INFORMED CONSENT
DEMOGRAPHY
MEDICAL HISTORY
OCULAR HISTORY
OCULAR SIGNS AND SYMPTOMS
OSDI©
MCMONNIES©
FREQUENCY OF SMART DEVICE USE
PATIENT STATUS

Part I: Screening Visit & Baseline Data

Date:		Time:	

PI- INFORMED CONSENT

Has the participant singed the informed consent?

☐ Yes
☐ No*

**If no, please STOP and complete "Patient status" first*

Informed consent was obtained on (DD/MM/YYYY): ☐

The informed consent has to be signed before any procedure of the visit

PI- DEMOGRAPHY

Gender	Female	Male	N/A
Date of birth			
Occupation			
Ethnicity	Caucasian	Chinese	Indian
	Afro-Caribbean	Hispanic	Others:_____
Smoker	Current	Never	Former
	How much per day? _____ Stopped since when?		

PI- MEDICAL HISTORY

General health	Good	Other:	
Medical history	None	Diabetes	Migraine
	Headache	High blood pressure	Rheumatism
	Stroke	Herpes	Thyroid
	Neck/shoulder pain	Cardiovascular	Multiple sclerosis
	Other:		
	Last visit to GP:		
Any allergies	None	Other:	

PI- OCULAR HISTORY

Ocular history	None	Macular disease/ARMD		Retinitis pigmentosa
	Glaucoma	Cataract		Visual field loss
	Others:			
	Allergy:			
	Last visit to optometrist: Reason:			
Contact lens wear	Yes	Never		Used to (since _____)
	If Yes, which lenses?	RGP	Hydrogel	SiHy
	Modality?	Daily	2 weekly	>Monthly
Eye drops	Yes		No	

PI- OSDI©

Please answer the following by circling the most appropriate respond to you. Then, please fill in boxes A, B, C, D and E based on the instructions given.

1. HAVE YOU EXPERIENCED ANY OF THE FOLLOWING DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that is sensitive to light?	4	3	2	1	0
2. Eyes that feels gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0
Subtotal score for answer 1 to 5				(A)	

2. HAVE PROBLEMS WITH YOUR EYES LIMITING YOU IN PERFORMING ANY OF THE FOLLOWING DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine ATM?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A
Subtotal score for answer 6 to 9					(B)	

3. HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that is air-conditioned?	4	3	2	1	0	N/A
Subtotal score for answer 10 to 12					(C)	

Please carefully calculate the portions below.

Add Subtotals A, B, C to Obtain D (D = Sum scores for all the questions answered)	(D)

Total Number of Questions Answered = E (Please DO NOT include questions answered N/A)	(E)

PI- MCMONNIES©

Please answer the following by circling the most appropriate respond to you.

Gender	Female	Male	
Age	≤24 years	25-45 years	≥46 years
Contact lens wear	Non-contact lens wearer	Hard contact lens wearer	Soft contact lens wearer

1. Have you ever had drops prescribed or other treatment for dry eyes?

Yes	No	Uncertain

2. Do you ever experience any of the following dry eye symptoms?

Soreness	Scratchiness	Dryness	Grittiness	Burning

3. How often do your eyes have these symptoms?

Never	Sometimes	Often	Constantly

4. Are your eyes usually sensitive to cigarette smoke, smog, air conditioning or central heating?

Yes	No	Sometimes

5. Do your eyes become very red and irritated when swimming?

Not applicable	Yes	No	Sometimes

6. Are your eyes dry and irritated when drinking alcohol?

Not applicable	Yes	No	Sometimes

7. Do you take or use any of the following?

Antihistamine tablets	Antihistamine eye drops	Diuretics (fluid tablets)
Tranquilizers	Oral contraceptives	Sleeping tablets

8. Do you suffer from arthritis?

Yes	No	Uncertain

9. Do you experience dryness of the nose, mouth, throat, chest or vagina?

Never	Sometimes	Often	Constantly

10. Do you suffer from thyroid abnormality?

Yes	No	Uncertain

11. Are you known to sleep with eyes partly open?

Yes	No	Sometimes

12. Do you have eye irritation as you wake from sleep?

Yes	No	Sometimes

Total score*	

**A score of over 20 is indicative of dry eye, while a total score of between 10 and 20 is suggestive of borderline dry eye disease.*

PI- FREQUENCY OF SMART DEVICE USE

Please put in a tick in the box (√) next to the answer of your choice.

1. Use smartphone?
   - Yes □ → go No. 2
   - No □ → go No. 5

2. Size of smartphone
   - 5 inch or smaller □
   - > 5 inch □

3. Purpose of smartphone use
   - Playing games □
   - Reading □
   - Messaging □
   - Watching videos □
   - Others (_____) □

4. Mean daily duration of smartphone use (viewing the screen, not making calls)?
   - 0.01-30.00 minutes □
   - 30.01-60.00 minutes □
   - 60.01-90.00 minutes □
   - 90.01-120.00 minutes □
   - 120.01-150.00 minutes □
   - 150.01-180.00 minutes □
   - Over 180.00 minutes □

5. Use tablet device?
   Yes ☐ → go No. 6
   No ☐ → go No. 9

6. Size of tablet
   9 inch or smaller (iPad mini, Amazon Fire, Kindle e Reader) ☐
   > 9 inch (iPad, Samsung Galaxy Tab) ☐

7. Purpose of tablet use
   Playing games ☐
   Reading ☐
   Messaging ☐
   Watching videos ☐
   Others (_____) ☐

8. Mean daily duration of tablet device use?
   0.01-30.00 minutes ☐
   30.01-60.00 minutes ☐
   60.01-90.00 minutes ☐
   90.01-120.00 minutes ☐
   120.01-150.00 minutes ☐
   150.01-180.00 minutes ☐
   Over 180.00 minutes ☐

9. Use Smart Watch device?
   Yes ☐ → go No. 10
   No ☐ → go No. 12

10. Purpose of Smart Watch use
    Playing games ☐
    Reading ☐
    Messaging ☐
    Watching videos ☐
    Others (_____) ☐

11. Mean daily duration of using Smart Watch?
    0.01-30.00 minutes ☐
    30.01-60.00 minutes ☐
    60.01-90.00 minutes ☐
    90.01-120.00 minutes ☐
    120.01-150.00 minutes ☐
    150.01-180.00 minutes ☐
    Over 180.00 minutes ☐

12. Use personal computer?
    Yes □ → go No. 13
    No □ → go No. 15

13. Purpose of computer use
    Playing games □
    Reading □
    Messaging □
    Watching videos □
    Others (_____) □

14. Mean daily duration of using a personal computer?
    0.01-30.00 minutes □
    30.01-60.00 minutes □
    60.01-90.00 minutes □
    90.01-120.00 minutes □
    120.01-150.00 minutes □
    150.01-180.00 minutes □
    Over 180.00 minutes □

15. Watch TV?
    Yes □ → go No. 16
    No □ → go No. 17

16. Mean daily duration watching TV?
    0.01-30.00 minutes □
    30.01-60.00 minutes □
    60.01-90.00 minutes □
    90.01-120.00 minutes □
    120.01-150.00 minutes □
    150.01-180.00 minutes □
    Over 180.00 minutes □

17. Playing hand held portable video games (Nintendo 3DS, Nintendo Switch, PS Vita)?
    Yes □ → go No. 18
    No □ → go No. 19

18. Mean daily duration of playing hand held portable video games?
    0.01-30.00 minutes □
    30.01-60.00 minutes □
    60.01-90.00 minutes □
    90.01-120.00 minutes □
    120.01-150.00 minutes □
    150.01-180.00 minutes □
    Over 180.00 minutes □

19. Playing TV or monitor based video games (PC, X Box, Play Station, Nintendo Switch-docked)?

Yes	□	→ go No. 20
No	□	→ go No. 21

20. Mean daily duration of playing TV or monitor based video games?

0.01-30.00 minutes	□
30.01-60.00 minutes	□
60.01-90.00 minutes	□
90.01-120.00 minutes	□
120.01-150.00 minutes	□
150.01-180.00 minutes	□
Over 180.00 minutes	□

21. Mean daily duration of sleeping?

0.01-6.00 hours	□
6.01-7.00 hours	□
7.01-8.00 hours	□
8.01-9.00 hours	□
Over 9.00 hours	□

22. Mean daily duration of outdoor activity?

0.01-30.00 minutes	□
30.01-60.00 minutes	□
60.01-90.00 minutes	□
90.01-120.00 minutes	□
120.01-150.00 minutes	□
150.01-180.00 minutes	□
Over 180.00 minutes	□

23. Please include details and the time spend on any other electronic display screen devices that you use, that have not been discussed above.

_____
_____
_____

Part II:
Smart Device Usage Pattern During 7 Days

OSDI©
MCMONNIES©
FREQUENCY OF SMART DEVICE USE
OUTPUT FROM MOMENT/QUALITY TIME

PII- OSDI© (During 7 Days)

Please answer the following by circling the most appropriate respond to you. Then, please fill in boxes A, B, C, D and E based on the instructions given.

1. HAVE YOU EXPERIENCED ANY OF THE FOLLOWING DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that is sensitive to light?	4	3	2	1	0
2. Eyes that feels gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0
Subtotal score for answer 1 to 5				(A)	

2. HAVE PROBLEMS WITH YOUR EYES LIMITING YOU IN PERFORMING ANY OF THE FOLLOWING DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine ATM?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A
Subtotal score for answer 6 to 9					(B)	

3. HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS DURING THE LAST WEEK?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that is air-conditioned?	4	3	2	1	0	N/A
Subtotal score for answer 10 to 12					(C)	

Please carefully calculate the portions below.

Add Subtotals A, B, C to Obtain D (D = Sum scores for all the questions answered)	(D)

Total Number of Questions Answered = E (Please DO NOT include questions answered N/A)	(E)

PII- MCMONNIES© (During 7 Days)

Please answer the following by circling the most appropriate respond to you.

Gender	Female	Male	
Age	≤24 years	25-45 years	≥46 years
Contact lens wear	Non-contact lens wearer	Hard contact lens wearer	Soft contact lens wearer

1. Have you ever had drops prescribed or other treatment for dry eyes?

Yes	No	Uncertain

2. Do you ever experience any of the following dry eye symptoms?

Soreness	Scratchiness	Dryness	Grittiness	Burning

3. How often do your eyes have these symptoms?

Never	Sometimes	Often	Constantly

4. Are your eyes usually sensitive to cigarette smoke, smog, air conditioning or central heating?

Yes	No	Sometimes

5. Do your eyes become very red and irritated when swimming?

Not applicable	Yes	No	Sometimes

6. Are your eyes dry and irritated when drinking alcohol?

Not applicable	Yes	No	Sometimes

7. Do you take or use any of the following?

Antihistamine tablets	Antihistamine eye drops	Diuretics (fluid tablets)
Tranquilizers	Oral contraceptives	Sleeping tablets

8. Do you suffer from arthritis?

Yes	No	Uncertain

9. Do you experience dryness of the nose, mouth, throat, chest or vagina?

Never	Sometimes	Often	Constantly

10. Do you suffer from thyroid abnormality?

Yes	No	Uncertain

11. Are you known to sleep with eyes partly open?

Yes	No	Sometimes

12. Do you have eye irritation as you wake from sleep?

Yes	No	Sometimes

Total score*	

**A score of over 20 is indicative of dry eye, while a total score of between 10 and 20 is suggestive of borderline dry eye disease.*

PII- FREQUENCY OF SMART DEVICE USE (During 7 Days)

Please put in a tick in the box (√) next to the answer of your choice.

1. Use smartphone?
   - Yes ◻ → go No. 2
   - No ◻ → go No. 5

2. Size of smartphone
   - 5 inch or smaller ◻
   - > 5 inch ◻

3. Purpose of smartphone use
   - Playing games ◻
   - Reading ◻
   - Messaging ◻
   - Watching videos ◻
   - Others (_____) ◻

4. Mean daily duration of smartphone use (viewing the screen, not making calls)?
   - 0.01-30.00 minutes ◻
   - 30.01-60.00 minutes ◻
   - 60.01-90.00 minutes ◻
   - 90.01-120.00 minutes ◻
   - 120.01-150.00 minutes ◻
   - 150.01-180.00 minutes ◻
   - Over 180.00 minutes ◻

5. Use tablet device?
   - Yes ◻ → go No. 6
   - No ◻ → go No. 9

6. Size of tablet
   - 9 inch or smaller (iPad mini, Amazon Fire, Kindle e Reader) ◻
   - > 9 inch (iPad, Samsung Galaxy Tab) ◻

7. Purpose of tablet use
   - Playing games ◻
   - Reading ◻
   - Messaging ◻
   - Watching videos ◻
   - Others (_____) ◻

8. Mean daily duration of tablet device use?
   - 0.01-30.00 minutes ◻
   - 30.01-60.00 minutes ◻
   - 60.01-90.00 minutes ◻
   - 90.01-120.00 minutes ◻
   - 120.01-150.00 minutes ◻
   - 150.01-180.00 minutes ◻
   - Over 180.00 minutes ◻

9. Use Smart Watch device?
   - Yes ◻ → go No. 10
   - No ◻ → go No. 12

10. Purpose of Smart Watch use
    - Playing games □
    - Reading □
    - Messaging □
    - Watching videos □
    - Others (_____) □

11. Mean daily duration of using Smart Watch?
    - 0.01-30.00 minutes □
    - 30.01-60.00 minutes □
    - 60.01-90.00 minutes □
    - 90.01-120.00 minutes □
    - 120.01-150.00 minutes □
    - 150.01-180.00 minutes □
    - Over 180.00 minutes □

12. Use personal computer?
    - Yes □ → go No. 13
    - No □ → go No. 15

13. Purpose of computer use
    - Playing games □
    - Reading □
    - Messaging □
    - Watching videos □
    - Others (_____) □

14. Mean daily duration of using a personal computer?
    - 0.01-30.00 minutes □
    - 30.01-60.00 minutes □
    - 60.01-90.00 minutes □
    - 90.01-120.00 minutes □
    - 120.01-150.00 minutes □
    - 150.01-180.00 minutes □
    - Over 180.00 minutes □

15. Watch TV?
    - Yes □ → go No. 16
    - No □ → go No. 17

16. Mean daily duration watching TV?
    - 0.01-30.00 minutes □
    - 30.01-60.00 minutes □
    - 60.01-90.00 minutes □
    - 90.01-120.00 minutes □
    - 120.01-150.00 minutes □
    - 150.01-180.00 minutes □
    - Over 180.00 minutes □

17. Playing hand held portable video games (Nintendo 3DS, Nintendo Switch, PS Vita)?
Yes □ → go No. 18
No □ → go No. 19

18. Mean daily duration of playing hand held portable video games?
0.01-30.00 minutes □
30.01-60.00 minutes □
60.01-90.00 minutes □
90.01-120.00 minutes □
120.01-150.00 minutes □
150.01-180.00 minutes □
Over 180.00 minutes □

19. Playing TV or monitor based video games (PC, X Box, Play Station, Nintendo Switch-docked)?
Yes □ → go No. 20
No □ → go No. 21

20. Mean daily duration of playing TV or monitor based video games?
0.01-30.00 minutes □
30.01-60.00 minutes □
60.01-90.00 minutes □
90.01-120.00 minutes □
120.01-150.00 minutes □
150.01-180.00 minutes □
Over 180.00 minutes □

21. Mean daily duration of sleeping?
0.01-6.00 hours □
6.01-7.00 hours □
7.01-8.00 hours □
8.01-9.00 hours □
Over 9.00 hours □

22. Mean daily duration of outdoor activity?
0.01-30.00 minutes □
30.01-60.00 minutes □
60.01-90.00 minutes □
90.01-120.00 minutes □
120.01-150.00 minutes □
150.01-180.00 minutes □
Over 180.00 minutes □

23. Please include details and the time spend on any other electronic display screen devices that you use, that have not been discussed above.

_____
_____
_____

Part II- OUTPUT FROM MOMENT/QUALITY TIME

Please write down the output from your Moment or Quality Time Apps in the table below.

Day 1	
Total screen time	
Number of pickups	
Individual timings	
Length of first pickup	
Length of second pickup	
Length of third pickup	
Length of fourth pickup	
Length of fifth pickup	
Length of sixth pickup	
Length of seventh pickup	
Length of eighth pickup	
Length of ninth pickup	
Length of tenth pickup	
Length of eleventh pickup	
Length of twelfth pickup	
Length of thirteenth pickup	
Length of fourteenth pickup	
Length of fifteenth pickup	
Length of sixteenth pickup	
Length of seventieth pickup	
Length of eighteenth pickup	
Length of nineteenth pickup	
Length of twentieth pickup	

Day 2	
Total screen time	
Number of pickups	
Individual timings	
Length of first pickup	
Length of second pickup	
Length of third pickup	
Length of fourth pickup	
Length of fifth pickup	
Length of sixth pickup	
Length of seventh pickup	
Length of eighth pickup	
Length of ninth pickup	
Length of tenth pickup	
Length of eleventh pickup	
Length of twelfth pickup	
Length of thirteenth pickup	
Length of fourteenth pickup	
Length of fifteenth pickup	
Length of sixteenth pickup	
Length of seventieth pickup	
Length of eighteenth pickup	
Length of nineteenth pickup	
Length of twentieth pickup	

Day 3	
Total screen time	
Number of pickups	
Individual timings	
Length of first pickup	
Length of second pickup	
Length of third pickup	
Length of fourth pickup	
Length of fifth pickup	
Length of sixth pickup	
Length of seventh pickup	
Length of eighth pickup	
Length of ninth pickup	
Length of tenth pickup	
Length of eleventh pickup	
Length of twelfth pickup	
Length of thirteenth pickup	
Length of fourteenth pickup	
Length of fifteenth pickup	
Length of sixteenth pickup	
Length of seventieth pickup	
Length of eighteenth pickup	
Length of nineteenth pickup	
Length of twentieth pickup	

Day 4	
Total screen time	
Number of pickups	
Individual timings	
Length of first pickup	
Length of second pickup	
Length of third pickup	
Length of fourth pickup	
Length of fifth pickup	
Length of sixth pickup	
Length of seventh pickup	
Length of eighth pickup	
Length of ninth pickup	
Length of tenth pickup	
Length of eleventh pickup	
Length of twelfth pickup	
Length of thirteenth pickup	
Length of fourteenth pickup	
Length of fifteenth pickup	
Length of sixteenth pickup	
Length of seventieth pickup	
Length of eighteenth pickup	
Length of nineteenth pickup	
Length of twentieth pickup	

Day 5	
Total screen time	
Number of pickups	
Individual timings	
Length of first pickup	
Length of second pickup	
Length of third pickup	
Length of fourth pickup	
Length of fifth pickup	
Length of sixth pickup	
Length of seventh pickup	
Length of eighth pickup	
Length of ninth pickup	
Length of tenth pickup	
Length of eleventh pickup	
Length of twelfth pickup	
Length of thirteenth pickup	
Length of fourteenth pickup	
Length of fifteenth pickup	
Length of sixteenth pickup	
Length of seventieth pickup	
Length of eighteenth pickup	
Length of nineteenth pickup	
Length of twentieth pickup	

Day 6	
Total screen time	
Number of pickups	
Individual timings	
Length of first pickup	
Length of second pickup	
Length of third pickup	
Length of fourth pickup	
Length of fifth pickup	
Length of sixth pickup	
Length of seventh pickup	
Length of eighth pickup	
Length of ninth pickup	
Length of tenth pickup	
Length of eleventh pickup	
Length of twelfth pickup	
Length of thirteenth pickup	
Length of fourteenth pickup	
Length of fifteenth pickup	
Length of sixteenth pickup	
Length of seventieth pickup	
Length of eighteenth pickup	
Length of nineteenth pickup	
Length of twentieth pickup	

Day 7	
Total screen time	
Number of pickups	
Individual timings	
Length of first pickup	
Length of second pickup	
Length of third pickup	
Length of fourth pickup	
Length of fifth pickup	
Length of sixth pickup	
Length of seventh pickup	
Length of eighth pickup	
Length of ninth pickup	
Length of tenth pickup	
Length of eleventh pickup	
Length of twelfth pickup	
Length of thirteenth pickup	
Length of fourteenth pickup	
Length of fifteenth pickup	
Length of sixteenth pickup	
Length of seventieth pickup	
Length of eighteenth pickup	
Length of nineteenth pickup	
Length of twentieth pickup	

WITHDRAWAL FORM

Date of last visit or phone contact:

INFORMATION ABOUT STUDY TERMINATION

Reason for withdrawal from the study:

	Adverse effect to fluorescein or lissamine green.
	Other medical reason (give details)
	Lost to follow to follow up (what was the last action taken?)
	Other reason (give details)

Examiner ID	
Signature	
Date	

FLOW CHART

CLINICAL INVESTIGATION PROCEDURES	PART I	PART II
Informed consent	x	
Demography	x	
Medical history	x	
Ocular history	x	
Ocular signs and symptoms	x	
OSDI©	x	
MCMONNIES©	x	
Frequency of smart device use	x	
Patient status	x	
OSDI©		x
MCMONNIES©		x
Frequency of smart device use		x
Output from Moment/Quality Time		x

F. Devices Specifications

The specifications of the device can be seen in Table F1. Throughout the investigation, the smart devices were fully charged before being used on each participant. In addition, only one participant was evaluated per day and in each case the devices were used for a maximum of 30 minutes. The 'battery saving' function was disabled to ensure constant brightness level throughout the studies. The mean±SD for luminance and illuminance for reading and gaming task measured before and after 30 minutes of use can be seen in Table F2; no significant difference was observed for luminance and illuminance levels before and after smart device usage. In addition, no glare sources were present within the room.

	Apple iPhone 6	**Apple iPhone 6S**	**Samsung Galaxy S6**	**Nokia 5210**	**Apple Smart Watch**
Cellular Network Technology	GSM, CDMA, HSPA, EVDO, LTE	GSM, CDMA, HSPA, EVDO, LTE	GSM, HSPA, LTE	GSM	None
Phone Size	138.1 x 67 x 6.9 mm	158.2 x 77.9 x 7.3 mm	143.4 x 70.5 x 6.8 mm	105.5 x 47.5 x 22.5 mm	42 x 35.9 x 10.5 mm
Display Type	LED-backlit IPS LCD, 16M colours	LED-backlit IPS LCD, 16M colours	Super AMOLED, 16M colours	Monochrome graphic	AMOLED, 16M colours
Display Size	4.7 inch	5.5 inch	5.1 inch	25 x 19 mm	1.65 inch
Display Resolution	750 x 1334 pixels (326 ppi)	1080 x 1920 pixels (401 ppi)	1440 x 2560 pixels (577 ppi)	5 lines	390 x 312 pixels (303 ppi)
Operating System	iOS 8	iOS 9	Android 5.0.2	None	watchOS 1.0

Table F1: Specifications of the devices.

Device and Task	Pre (Mean±SD)	Post (Mean±SD)	*p* value
Reading-Apple iPhone 6 (Luminance)	40.10±1.25	40.37±0.21	0.223
Reading-Apple iPhone 6S (Luminance)	45.37±0.25	45.53±1.04	0.106
Reading-Samsung Galaxy S6 (Luminance)	43.40±0.26	43.47±0.06	0.788
Reading-Apple iPhone 6 (Illuminance)	107.67±2.52	106.00±2.65	0.952
Reading-Apple iPhone 6S (Illuminance)	108.67±1.53	108.00±2.00	0.546
Reading-Samsung Galaxy S6 (Illuminance)	102.33±0.58	101.67±1.15	0.667
Gaming-Apple iPhone 6 (Luminance)	33.33±1.11	33.60±0.20	0.733
Gaming-Apple iPhone 6S (Luminance)	38.40±0.46	38.23±0.72	0.256
Gaming-Samsung Galaxy S6 (Luminance)	38.53±0.15	38.60±0.10	0.121
Gaming-Nokia 5210 (Luminance)	3.53±0.15	3.50±0.20	0.788
Gaming-Apple iPhone 6S (Luminance)	3.27±0.12	3.33±0.06	0.667

* Luminance was measured using Konica Minolta Luminance Meter LS-150 while Illuminance was measured using CHY 230 Light Meter.

Table F2: Luminance and Illuminance differences measured pre and post task.

G. Results for LE Osmolarity Analysis (from Chapter 3)

Osmolarity Changes following the use of Smartphones (Chapter 3-Left Eye Analysis)

Results

Thirty-three participants (14 males and 19 females) with a median age of 26 years old (First Quartile, Q_1=23 and Third Quartile, Q_3=30 years old) were assessed. Room temperature [median21.30 ^{0}C (Q_1=20.83 and Q_3=22.05 ^{0}C)] (Purslow & Wolffsohn, 2007; Wolkoff, 2008) and relative humidity [median 42.33% (Q_1=41.50 and Q_3=43.67%)] (Abusharha and Pearce, 2012) are known to affect the tear film and were controlled in this study.

Tear Osmolarity Following the Reading Task

The median tear osmolarity values for left eye (LE) following the reading task are displayed in Table F1 and Figure F1. For the reading task, there was no significant difference in osmolarity values between the 4 platforms [$\chi^2(3) = 0.769$, p=0.857]. The O

Task & Platform	Statistical Parameter	Tear Osmolarity (mOsm/L)
Reading-Apple iPhone 6	Median	286.00
	Q_1	281.50
	Q_3	293.00
Reading -Apple iPhone 6S	Median	288.00
	Q_1	282.50
	Q_3	292.00
Reading -Samsung Galaxy S6	Median	287.00
	Q_1	281.50
	Q_3	294.00
Reading -Paper	Median	289.00
	Q_1	281.50
	Q_3	293.00

Table G1: Descriptive statistics for LE tear osmolarity (reading task).

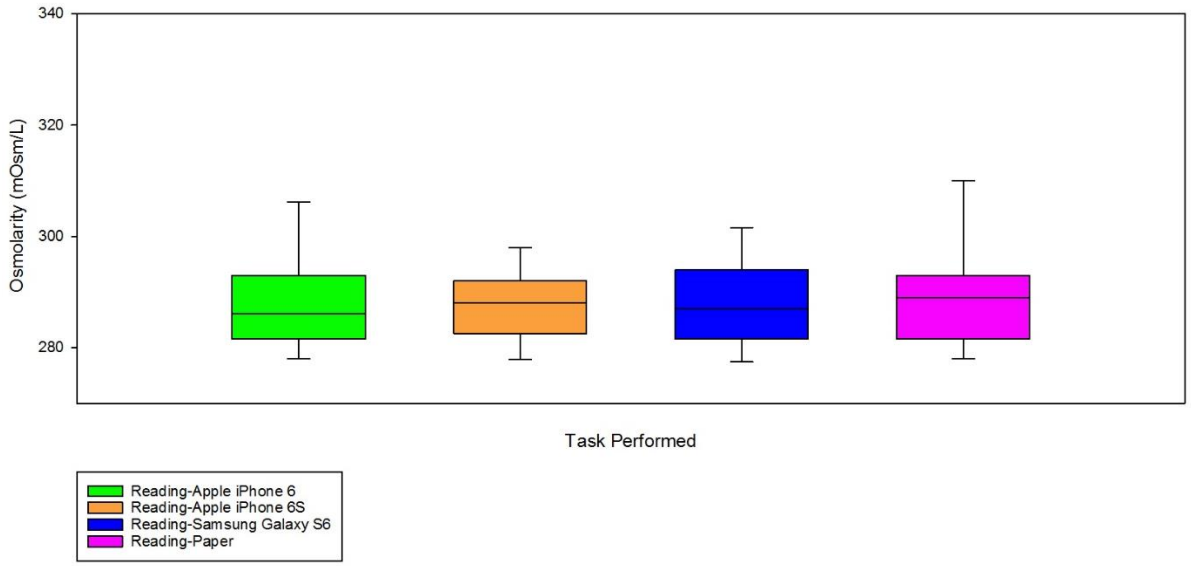

Figure G1: Box representing median and interquartile range for LE tear osmolarity values following the reading task.

Tear Osmolarity Following the Gaming Task

The tear osmolarity values following the gaming task are shown in Table F2 and Figure F2. For the gaming task, no significant difference in osmolarity values were found between the 6 platforms [$\chi^2(5) = 8.691$, p=0.122].

Task & Platform	Statistical Parameter	Tear Osmolarity (mOsm/L)
Gaming-Apple iPhone 6	Median	284.00
	Q_1	279.00
	Q_3	288.00
Gaming-Apple iPhone 6S	Median	283.00
	Q_1	279.00
	Q_3	286.00
Gaming-Samsung Galaxy S6	Median	283.00
	Q_1	280.50
	Q_3	290.50
Gaming-Paper	Median	285.00
	Q_1	280.00
	Q_3	288.50
Gaming-Nokia 5210	Median	283.00
	Q_1	280.00
	Q_3	287.50
Gaming-Apple Smart Watch	Median	281.00
	Q_1	278.00
	Q_3	284.50

Table G2: Descriptive statistics for LE tear osmolarity (gaming task).

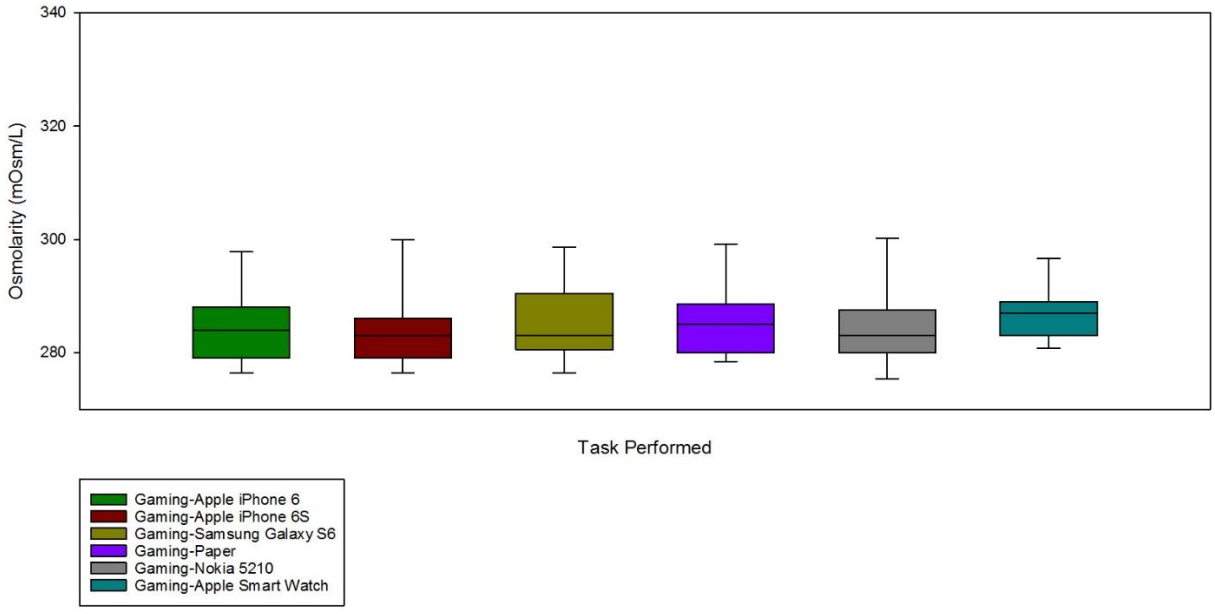

Figure G2: Box representing median and interquartile range for LE tear osmolarity values following the gaming task.

Influence of Repeated Measurements on Osmolarity Values

The median osmolarity values at baseline were 290 mOsms/L (Q_1=284 and Q_3=296 mOsm/L). A significant interaction was observed between baseline osmolarity and choice of task [χ^2 (10) = 53.945, p<0.0005]. *Post-hoc* analysis revealed that the osmolarity values were significantly higher at baseline than after the gaming tasks for 4 of the 6 platforms (Apple iPhone 6: p_{adj} =0.088, Apple iPhone 6S: p_{adj} =0.003, Samsung Galaxy S6: p_{adj} =0.022, Paper: p_{adj} =1.00, Nokia 5210: p_{adj} <0.002, Apple Smart Watch: p_{adj} <0.0005). In contrast, measures of osmolarity following the reading tasks for all platforms were not significantly different compared to baseline values (p_{adj} >0.05).

Correlation Between the Baseline Osmolarity Values and the Subjective Assessment of Dry Eye

The OSDI had a median score of 6.25 (Q_1=2.27 and Q_3=8.33) while the McMonnies median score was 3.00 (Q_1=3.00 and Q_3=5.00). No significant correlation was found between the baseline osmolarity values and both the McMonnies and OSDI score (Figure F3).

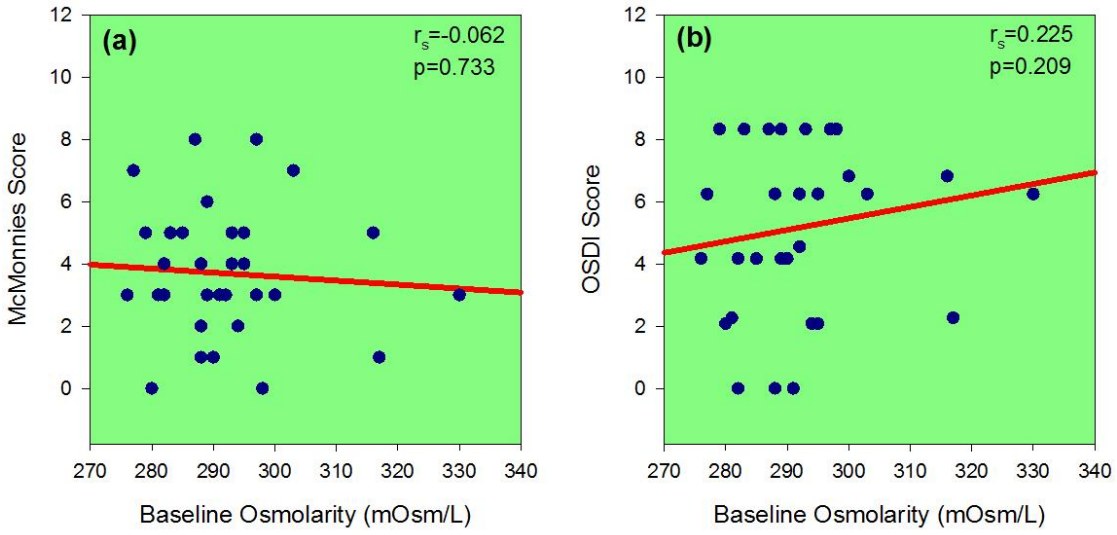

Figure G3: Spearman's correlation between (a) McMonnies Score and Baseline Osmolarity, (b) OSDI Score and Baseline Osmolarity.

Conclusion

The LE results showed similar trends with the RE results that was reported in Chapter 3.

H. The MATLAB code for AR Experiment

```
% curvefitting_PB_v1

clear all

filename = input ('Please input file name :   ', 's');

rawdata=xlsread(filename)

% for the first time taken to full accommdoative

x = rawdata(:,1);

y = rawdata(:,2);

[param]=sigm_fit(x,y)

[a] = param(1,1)

[b] = param(1,2)

[c] = param(1,3)

[d] = param(1,4)

if param(1,2)>param(1,1)
    [y91] = param(1,2)*.99
else
    [y91] = param(1,1)*.99
end

[x91] = (-(log10(((b-a)/(y91-a))-1))/d)+c

[starttime] = x(1,1)

[measurementnumbers] = x91 - x(1,1)

[time] = measurementnumbers * 0.125

% for first accommodative latancy

[y01] = (param(1,2)-param(1,1))/100 + param(1,1)

if param(1,2)>param(1,1)
    [y01] = (param(1,2)-param(1,1))/100 + param(1,1)
else
    [y01] = (param(1,1)-param(1,2))/100 + param(1,2)
end

[x01] = (-(log10(((b-a)/(y01-a))-1))/d)+c
[measurementnumbers01] = x01 - x(1,1)
[lag] = measurementnumbers01 * 0.125
```

```
% for the second time taken to full accommdoative

x2 = rawdata(:,5);

y2 = rawdata(:,6);

[param2]=sigm_fit(x2,y2)

[a2] = param2(1,1)

[b2] = param2(1,2)

[c2] = param2(1,3)

[d2] = param2(1,4)

if param2(1,2)>param2(1,1)
    [y92] = param2(1,2)*.99
else
    [y92] = param2(1,1)*.99
end

[x92] = (-(log10(((b2-a2)/(y92-a2))-1))/d2)+c2

[starttime2] = x2(1,1)

[measurementnumbers2] = x92 - x2(1,1)

[time2] = measurementnumbers2 * 0.125

% for second accommodative lag

[y02] = (param2(1,2)-param2(1,1))/100 + param2(1,1)

if param2(1,2)>param2(1,1)
    [y02] = (param2(1,2)-param2(1,1))/100 + param2(1,1)
else
    [y02] = (param2(1,1)-param2(1,2))/100 + param2(1,2)
end

[x02] = (-(log10(((b2-a2)/(y02-a2))-1))/d2)+c2
[measurementnumbers02] = x02 - x2(1,1)
[lag2] = measurementnumbers02 * 0.125

% for the third time taken to full accommdoative

x3 = rawdata(:,9);

y3 = rawdata(:,10);

[param3]=sigm_fit(x3,y3)

[a3] = param3(1,1)
```

```
[b3] = param3(1,2)

[c3] = param3(1,3)

[d3] = param3(1,4)

if param3(1,2)>param3(1,1)
    [y93] = param3(1,2)*.99
else
    [y93] = param3(1,1)*.99
end

[x93] = (-(log10(((b3-a3)/(y93-a3))-1))/d3)+c3

[starttime3] = x3(1,1)

[measurementnumbers3] = x93 - x3(1,1)

[time3] = measurementnumbers3 * 0.125

% for third accommodative lag

[y03] = (param3(1,2)-param3(1,1))/100 + param3(1,1)

if param3(1,2)>param3(1,1)
    [y03] = (param3(1,2)-param3(1,1))/100 + param3(1,1)
else
    [y03] = (param3(1,1)-param3(1,2))/100 + param3(1,2)
end

[x03] = (-(log10(((b3-a3)/(y03-a3))-1))/d3)+c3
[measurementnumbers03] = x03 - x3(1,1)
[lag3] = measurementnumbers03 * 0.125


% for the fourth time taken to full accommdoative

x4 = rawdata(:,13);

y4 = rawdata(:,14);

[param4]=sigm_fit(x4,y4)

[a4] = param4(1,1)

[b4] = param4(1,2)

[c4] = param4(1,3)

[d4] = param4(1,4)

if param4(1,2)>param4(1,1)
    [y94] = param4(1,2)*.99
else
    [y94] = param4(1,1)*.99
end
```

```
[x94] = (-(log10(((b4-a4)/(y94-a4))-1))/d4)+c4

[starttime4] = x4(1,1)

[measurementnumbers4] = x94 - x4(1,1)

[time4] = measurementnumbers4 * 0.125

% for fourth accommodative lag

[y04] = (param4(1,2)-param4(1,1))/100 + param4(1,1)

if param4(1,2)>param4(1,1)
    [y04] = (param4(1,2)-param4(1,1))/100 + param4(1,1)
else
    [y04] = (param4(1,1)-param4(1,2))/100 + param4(1,2)
end

[x04] = (-(log10(((b4-a4)/(y04-a4))-1))/d4)+c4

[measurementnumbers04] = x04 - x4(1,1)
[lag4] = measurementnumbers04 * 0.125

%for time taken to full disaccommodation

x5 = rawdata(:,3);

y5 = rawdata(:,4);

[param5]=sigm_fit(x5,y5)

[a5] = param5(1,1)

[b5] = param5(1,2)

[c5] = param5(1,3)

[d5] = param5(1,4)

if param5(1,2)>param5(1,1)
    [y95] = (param5(1,2)-param5(1,1))/100 + param5(1,1)
else
    [y95] = (param5(1,1)-param5(1,2))/100 + param5(1,2)
end

[x95] = (-(log10(((b5-a5)/(y95-a5))-1))/d5)+c5

[starttime5] = x5(1,1)

[measurementnumbers5] = x95 - x5(1,1)

[disaccommdation] = measurementnumbers5 * 0.125

%for disaccommodative lag

x6 = rawdata(:,3);
```

```
y6 = rawdata(:,4);

[param6]=sigm_fit(x6,y6)

[a6] = param6(1,1)

[b6] = param6(1,2)

[c6] = param6(1,3)

[d6] = param6(1,4)

if param6(1,2)>param6(1,1)
    [y96] = param6(1,2)*.99
else
    [y96] = param6(1,1)*.99
end

[x96] = (-(log10(((b6-a6)/(y96-a6))-1))/d6)+c6

[starttime6] = x6(1,1)

[measurementnumbers6] = x96 - x6(1,1)

[disaccommdationlag] = measurementnumbers6 * 0.125

%for time taken to full disaccommodation

x7 = rawdata(:,7);

y7 = rawdata(:,8);

[param7]=sigm_fit(x7,y7)

[a7] = param7(1,1)

[b7] = param7(1,2)

[c7] = param7(1,3)

[d7] = param7(1,4)

if param7(1,2)>param7(1,1)
    [y97] = (param7(1,2)-param7(1,1))/100 + param7(1,1)
else
    [y97] = (param7(1,1)-param7(1,2))/100 + param7(1,2)
end

[x97] = (-(log10(((b7-a7)/(y97-a7))-1))/d7)+c7

[starttime7] = x7(1,1)

[measurementnumbers7] = x97 - x7(1,1)

[disaccommdation2] = measurementnumbers7 * 0.125
```

```
%for disaccommodative lag

x8 = rawdata(:,7);

y8 = rawdata(:,8);

[param8]=sigm_fit(x8,y8)

[a8] = param8(1,1)

[b8] = param8(1,2)

[c8] = param8(1,3)

[d8] = param8(1,4)

if param8(1,2)>param8(1,1)
    [y98] = param8(1,2)*.99
else
    [y98] = param8(1,1)*.99
end

[x98] = (-(log10(((b8-a8)/(y98-a8))-1))/d8)+c8

[starttime8] = x8(1,1)

[measurementnumbers8] = x98 - x8(1,1)

[disaccommdationlag2] = measurementnumbers8 * 0.125
fjhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhffffffffffffffffffff

%for time taken to full disaccommodation

x9 = rawdata(:,11);

y9 = rawdata(:,12);

[param9]=sigm_fit(x9,y9)

[a9] = param9(1,1)

[b9] = param9(1,2)

[c9] = param9(1,3)

[d9] = param9(1,4)

if param9(1,2)>param7(1,1)
    [y99] = (param9(1,2)-param9(1,1))/100 + param9(1,1)
else
    [y99] = (param9(1,1)-param9(1,2))/100 + param9(1,2)
end

[x99] = (-(log10(((b9-a9)/(y99-a9))-1))/d9)+c9
fffffffffffffffffffffffffffffffjgh
```

```
[starttime9] = x9(1,1)

[measurementnumbers9] = x99 - x9(1,1)

[disaccommdation3] = measurementnumbers9 * 0.125

%for disaccommodative lag

x10 = rawdata(:,11);

y10 = rawdata(:,12);

[param10]=sigm_fit(x10,y10)

[a10] = param10(1,1)

[b10] = param10(1,2)

[c10] = param10(1,3)

[d10] = param10(1,4)

if param10(1,2)>param10(1,1)
    [y910] = param10(1,2)*.99
else
    [y910] = param10(1,1)*.99
end

[x910] = (-(log10(((b10-a10)/(y910-a10))-1))/d10)+c10

[starttime10] = x10(1,1)

[measurementnumbers10] = x910 - x10(1,1)

[disaccommdationlag3] = measurementnumbers10 * 0.125

%for time taken to full disaccommodation

x11 = rawdata(:,15);

y11 = rawdata(:,16);

[param11]=sigm_fit(x11,y11)

[a11] = param11(1,1)

[b11] = param11(1,2)

[c11] = param11(1,3)

[d11] = param11(1,4)

if param11(1,2)>param11(1,1)
    [y911] = (param11(1,2)-param11(1,1))/100 + param11(1,1)
else
```

```
    [y911] = (param11(1,1)-param11(1,2))/100 + param11(1,2)
end

[x911] = (-(log10(((b11-a11)/(y911-a11))-1))/d11)+c11

[starttime11] = x11(1,1)

[measurementnumbers11] = x911 - x11(1,1)

[disaccommdation4] = measurementnumbers11 * 0.125

%for disaccommodative lag

x12 = rawdata(:,15);

y12 = rawdata(:,16);

[param12]=sigm_fit(x12,y12)

[a12] = param12(1,1)

[b12] = param12(1,2)

[c12] = param12(1,3)

[d12] = param12(1,4)

if param12(1,2)>param12(1,1)
    [y912] = param12(1,2)*.99
else
    [y912] = param12(1,1)*.99
end

[x912] = (-(log10(((b12-a12)/(y912-a12))-1))/d12)+c12

[starttime12] = x12(1,1)

[measurementnumbers12] = x912 - x12(1,1)

[disaccommdationlag4] = measurementnumbers12 * 0.125


beep
subject = input('Please enter subject no :   ', 's');
activities = input('Please enter the testing activities :   ', 's');
trial = input('Please enter the trail number :   ', 's');
%group = input('Please enter Group no, Group 1= Normal, Group 2: Painful Gp
%:   ');


% Export to excel file

angname='Afzam01.xls';
fod = fopen(angname, 'a');
fprintf(fod, '%s\t',subject);
fprintf(fod, '%s\t',activities);
fprintf(fod, '%s\t',trial); % should analyse 3 trails in one matlab file
```

```
% fprintf(fod, '%7.4f\t',int_J_AP_L1);
% fprintf(fod, '%7.4f\t',J_ML_L1);
fprintf(fod, '%7.4f\t',time);
fprintf(fod, '%7.4f\t',time2);
fprintf(fod, '%7.4f\t',time3);
fprintf(fod, '%7.4f\t',time4);
fprintf(fod, '%7.4f\t',lag);
fprintf(fod, '%7.4f\t',lag2);
fprintf(fod, '%7.4f\t',lag3);
fprintf(fod, '%7.4f\t',lag4);
fprintf(fod, '%7.4f\t',disaccommdation);
fprintf(fod, '%7.4f\t',disaccommdation2);
fprintf(fod, '%7.4f\t',disaccommdation3);
fprintf(fod, '%7.4f\t',disaccommdation4);
fprintf(fod, '%7.4f\t',disaccommdationlag);
fprintf(fod, '%7.4f\t',disaccommdationlag2);
fprintf(fod, '%7.4f\t',disaccommdationlag3);
fprintf(fod, '%7.4f\t',disaccommdationlag4);
fprintf(fod, '%7.4f\t',a);
fprintf(fod, '%7.4f\t',a2);
fprintf(fod, '%7.4f\t',a3);
fprintf(fod, '%7.4f\t',a4);
fprintf(fod, '%7.4f\t',b);
fprintf(fod, '%7.4f\t',b2);
fprintf(fod, '%7.4f\t',b3);
fprintf(fod, '%7.4f\t',b4);
fprintf(fod, '%7.4f\t',c);
fprintf(fod, '%7.4f\t',c2);
fprintf(fod, '%7.4f\t',c3);
fprintf(fod, '%7.4f\t',c4);
fprintf(fod, '%7.4f\t',d);
fprintf(fod, '%7.4f\t',d2);
fprintf(fod, '%7.4f\t',d3);
fprintf(fod, '%7.4f\t',d4);
fprintf(fod, '%7.4f\t',a5);
fprintf(fod, '%7.4f\t',a7);
fprintf(fod, '%7.4f\t',a9);
fprintf(fod, '%7.4f\t',a11);
fprintf(fod, '%7.4f\t',b5);
fprintf(fod, '%7.4f\t',b7);
fprintf(fod, '%7.4f\t',b9);
fprintf(fod, '%7.4f\t',b11);
fprintf(fod, '%7.4f\t',c5);
fprintf(fod, '%7.4f\t',c7);
fprintf(fod, '%7.4f\t',c9);
fprintf(fod, '%7.4f\t',c11);
fprintf(fod, '%7.4f\t',d5);
fprintf(fod, '%7.4f\t',d7);
fprintf(fod, '%7.4f\t',d9);
fprintf(fod, '%7.4f\t',d11);
fprintf(fod, '%s\n',subject);
fclose(fod);
```

I. Appendix for Chapter 2: Validation of the Open Field Tear Film Analyzer (OFTA)

Results

Parameters	Median (Q_1; Q_3)
Participant's Age (years)	22.00 (20.25; 25.75)
Room temperature (^{0}C)	21.43 (20.88; 21.94)
Humidity (%RH)	42.00 (41.00; 42.67)

Table I1: Demographic of Chapter 2 study population, Median (Q_1; Q_3).

Instrument and Visit Number	NIBUT (s), Median (First Quartile, Q_1; Third Quartile, Q_3)		
	Visit 1	**Visit 2**	**Visit 3**
B&L Keratometer	10.69 (7.80; 21.12)	10.02 (6.73; 14.18)	10.19 (6.16; 16.44)
Oculus K5M	7.26 (5.52; 10.35)	8.12 (5.77; 11.89)	11.44 (6.92; 15.40)
OFTA	10.32 (7.90; 13.64)	12.34 (9.31; 16.03)	14.48 (8.29; 26.50)

Table I2: NIBUT values during V1, V2 and V3 obtained using the 3 instruments.

Bland and Altman plots during V1 and V2 (Reliability), Figure I1 (for all NIBUT values) and Figure I2 (for NIBUT ≤24 seconds)

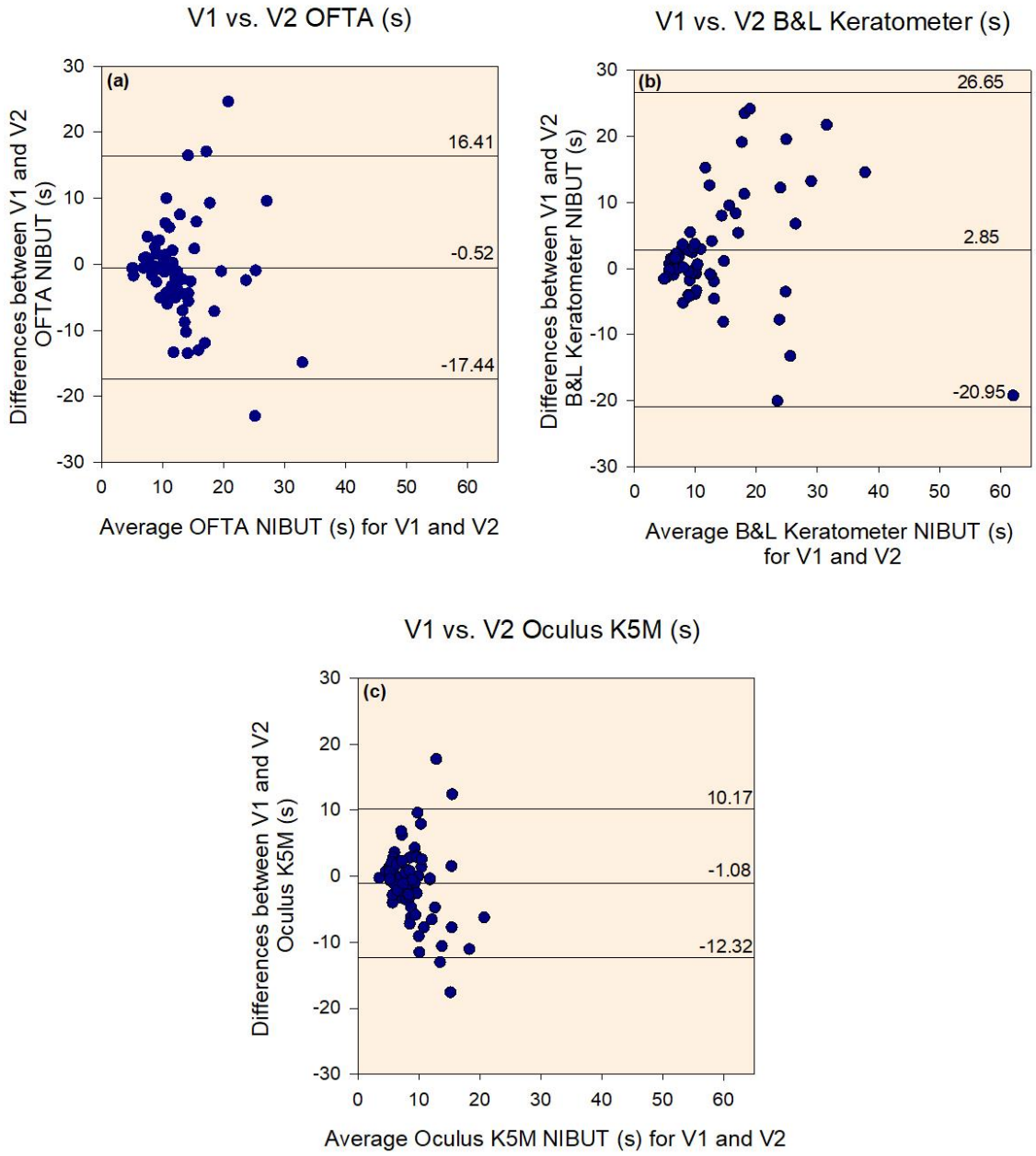

Figure I1: Bland and Altman reliability plots of NIBUT (non-transformed data, all NIBUT values) between V1 and V2 for (a) OFTA, (b) B&L Keratometer, (c) Oculus K5M.

Based on Figure I1, the Bland and Altman plots of the OFTA NIBUT during V1 and V2 had a mean difference of -0.52 seconds, with LoA of 16.41 to -17.44 seconds. The mean difference for B&L Keratometer NIBUT during V1 and V2 was 2.85 seconds, with LoA of 26.65 to -20.95

seconds. The mean difference for Oculus K5M NIBUT during V1 and V2 was -1.08 seconds, with LoA between 10.17 to -12.32 seconds.

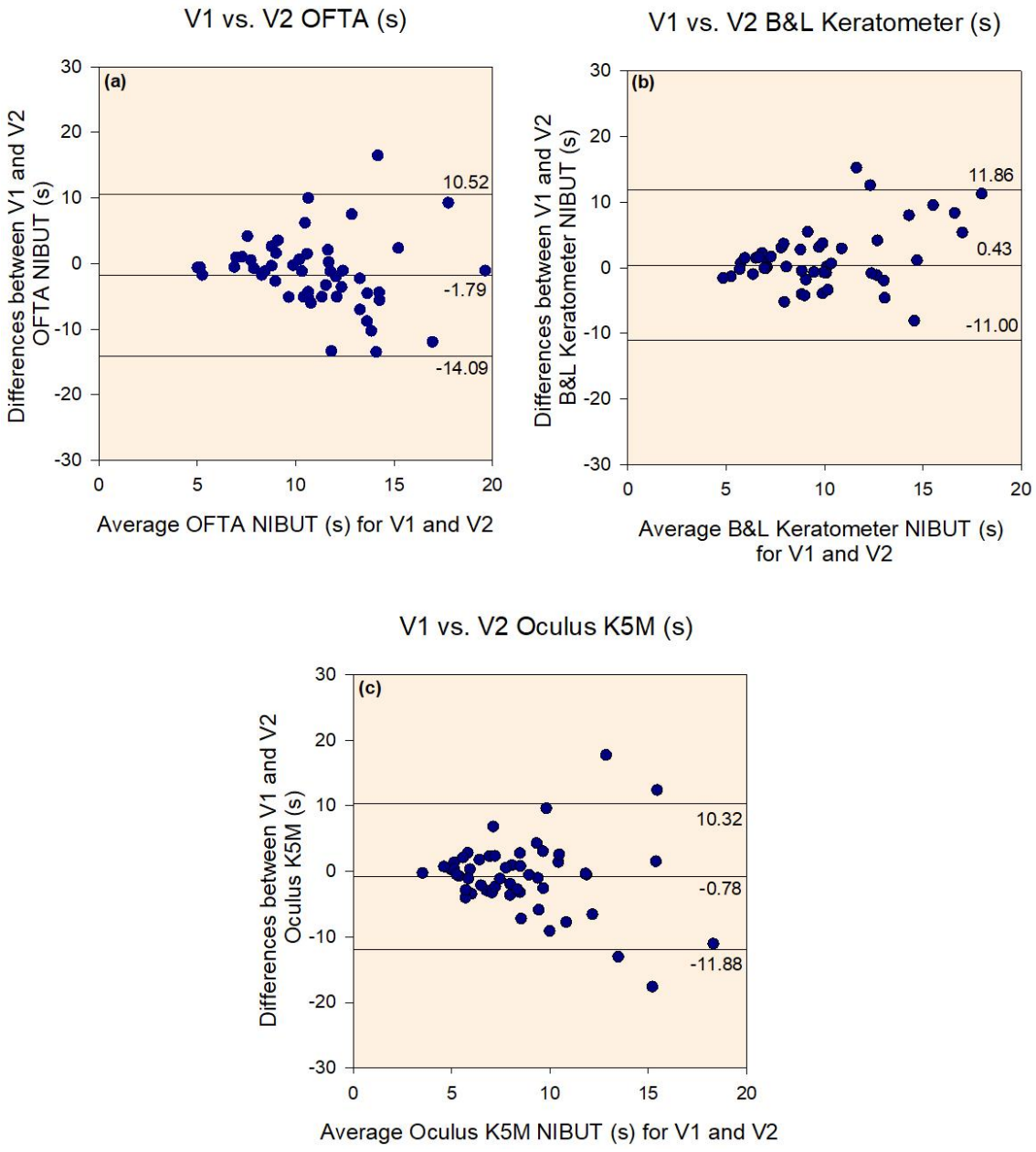

Figure I2: Bland and Altman reliability plots of NIBUT (non-transformed data, only NIBUT ≤24 seconds) between V1 and V2 for (a) OFTA, (b) B&L Keratometer, (c) Oculus K5M.

Based on Figure I2, the Bland and Altman plots of the OFTA NIBUT (only NIBUT ≤24 seconds) during V1 and V2 had a mean difference of -1.79 seconds, with LoA of 10.52 to -14.09 seconds. The mean difference for B&L Keratometer NIBUT (only NIBUT ≤24 seconds) during V1 and V2 was 0.43 seconds, with LoA of 11.86 to -11.00 seconds. The mean difference for Oculus K5M NIBUT (only NIBUT ≤24 seconds) during V1 and V2 was -0.78 seconds, with LoA between 10.32 to -11.88 seconds. The Bland and Altman plots in Figure I1 and Figure I2 demonstrate a heteroscedastic pattern. As such, Kendall's tau (τ) was calculated (Table I3 and Table I4).

Parameter	Kendall's τ (Original Data)	Heteroscedastic (Yes or No)	Kendall's τ (Log Data)	Kendall's τ (↑ or ↓)
V1 vs. V2 (OFTA)	-0.117	No	-0.069	↑
V1 vs. V2 (B&L Keratometer)	0.199	Yes	0.124	↓
V1 vs. V2 (Oculus K5M)	-0.172	No	-0.138	↑

Table I3: Kendall's τ for original data (all NIBUT values) and subsequent Kendall's τ after log transformation on the original data.

Parameter	Kendall's τ (Original Data)	Heteroscedastic (Yes or No)	Kendall's τ (Log Data)	Kendall's τ (↑ or ↓)
V1 vs. V2 (OFTA)	-0.243	No	-0.190	↑
V1 vs. V2 (B&L Keratometer)	0.004	No	-0.013	↓
V1 vs. V2 (Oculus K5M)	-0.082	No	-0.77	↓

Table I4: Kendall's τ for original data (only NIBUT ≤24 seconds) and subsequent Kendall's τ after log transformation on the original data.

As heteroscedasticity was confirmed based on the Kendall's tau calculations above, a new Bland and Altman reliability plots were plotted for 'all NIBUT values' (Figure 2.30 in Chapter 2) and 'only NIBUT ≤24 seconds' (Figure 2.31 in Chapter 2).

Bland and Altman plots during V1 and V3 (Reproducibility), Figure I3 (for all NIBUT values) and Figure I4 (for NIBUT ≤24 seconds)

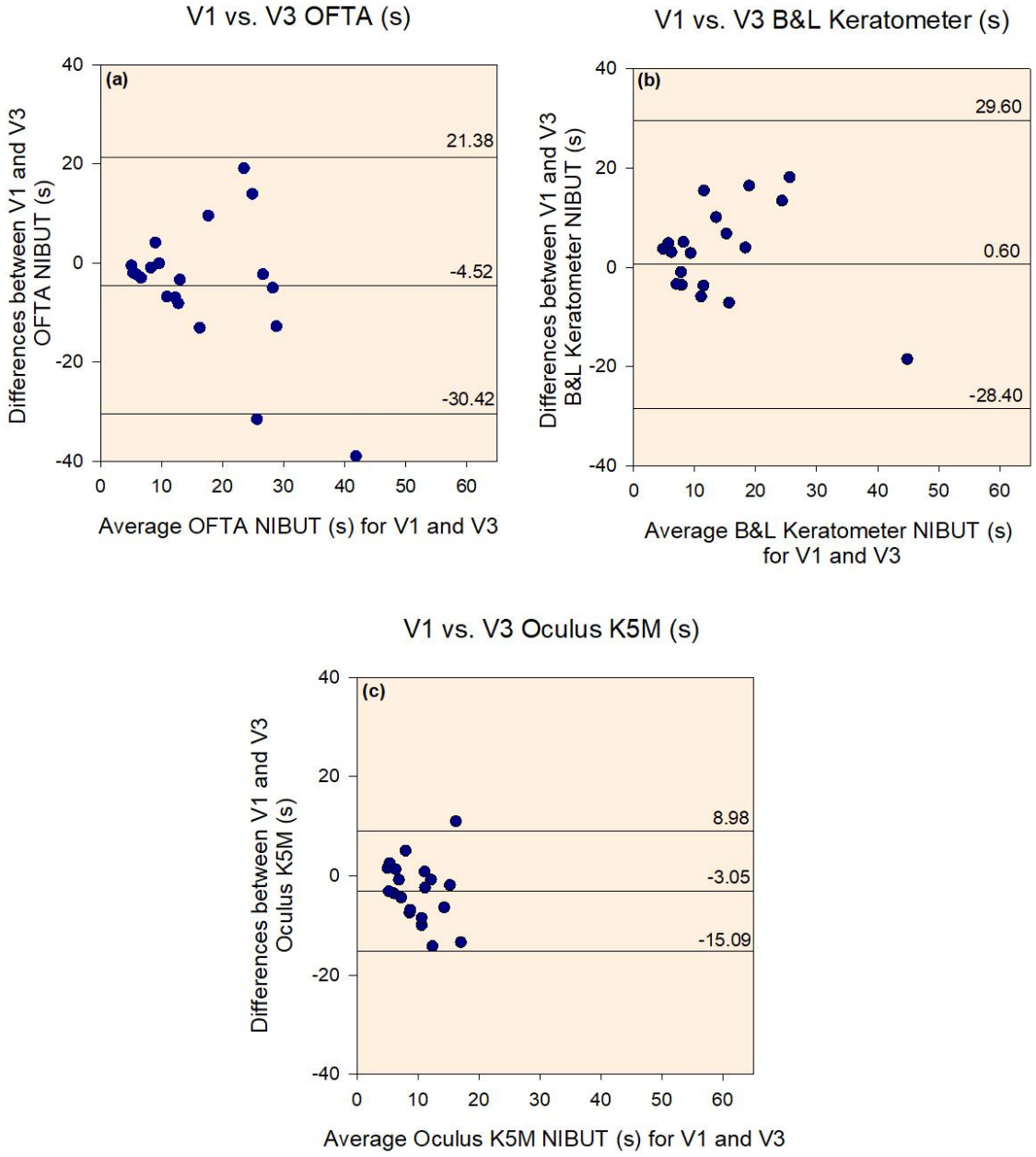

Figure I3: Bland and Altman reproducibility plots of NIBUT (non-transformed data, all NIBUT values) between V1 and V3 for (a) OFTA, (b) B&L Keratometer, (c) Oculus K5M.

Based on Figure I3, the Bland and Altman plots of the OFTA NIBUT during V1 and V2 had a mean difference of -0.52 seconds, with LoA of 16.41 to -17.44 seconds. The mean difference for B&L Keratometer NIBUT during V1 and V2 was 2.85 seconds, with LoA of 26.65 to -20.95 seconds. The mean difference for Oculus K5M NIBUT during V1 and V2 was -1.08 seconds, with LoA between 10.17 to -12.32 seconds.

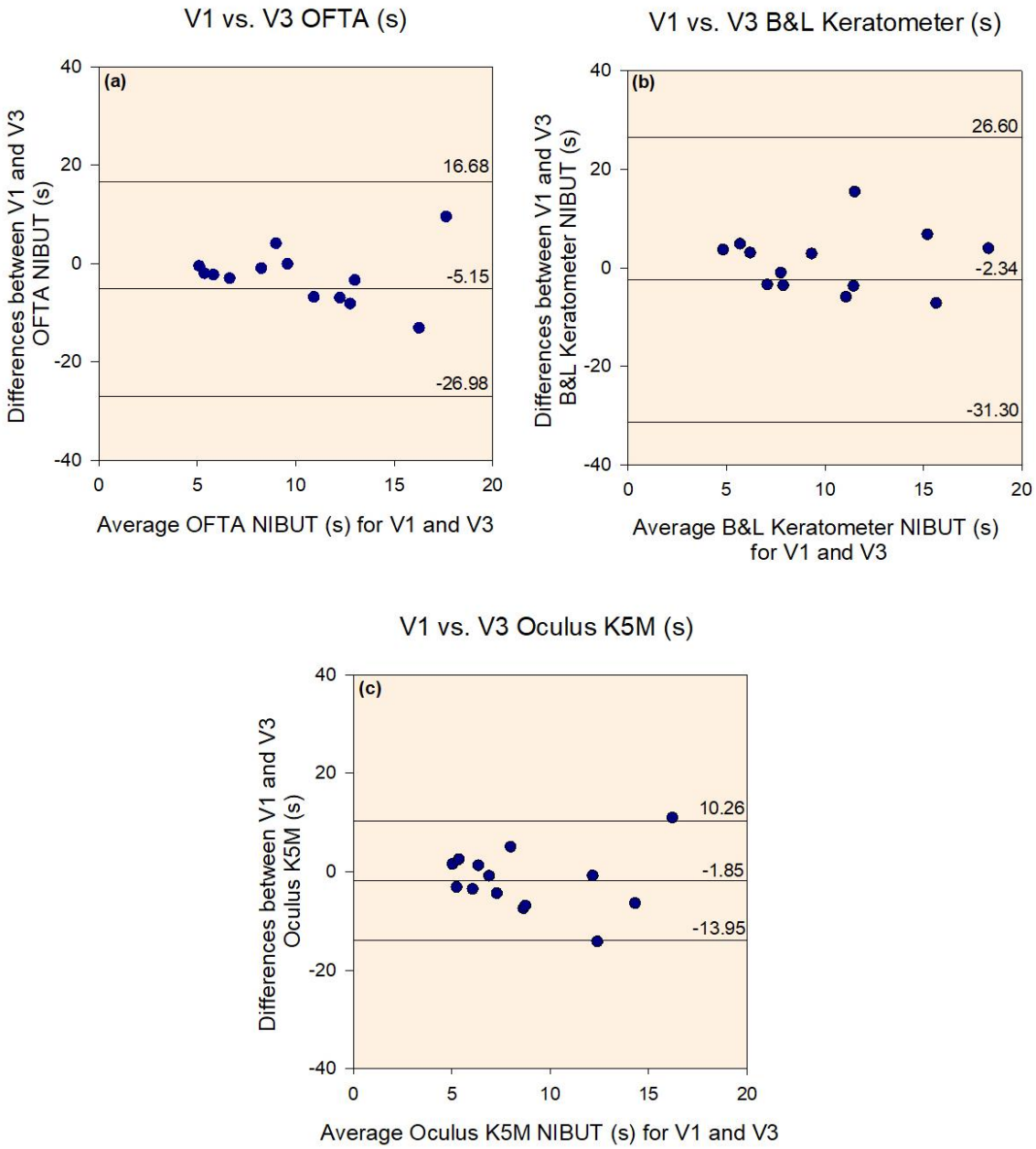

Figure I4: Bland and Altman reproducibility plots of NIBUT (non-transformed data, only NIBUT $\leq$24 seconds) between V1 and V3 for (a) OFTA, (b) B&L Keratometer, (c) Oculus K5M.

Based on Figure I4, the Bland and Altman plots of the OFTA NIBUT (only NIBUT ≤24 seconds) during V1 and V2 had a mean difference of -1.79 seconds, with LoA of 10.52 to -14.09 seconds. The mean difference for B&L Keratometer NIBUT (only NIBUT ≤24 seconds) during V1 and V2 was 0.43 seconds, with LoA of 11.86 to -11.00 seconds. The mean difference for Oculus K5M NIBUT (only NIBUT ≤24 seconds) during V1 and V2 was -0.78 seconds, with LoA between 10.32 to -11.88 seconds. The Bland and Altman plots in Figure I3 and Figure I4 demonstrate a heteroscedastic pattern. As such, Kendall's tau (τ) was calculated (Table I5 and Table I6).

Parameter	Kendall's τ (Original Data)	Heteroscedastic (Yes or No)	Kendall's τ (Log Data)
V1 vs. V2 (OFTA)	-0.274	No	-0.085
V1 vs. V2 (B&L Keratometer)	0.032	No	-0.116
V1 vs. V2 (Oculus K5M)	-0.242	No	-0.112

Table I5: Kendall's τ for original data (all NIBUT values) and subsequent Kendall's τ after log transformation on the original data.

Parameter	Kendall's τ (Original Data)	Heteroscedastic (Yes or No)	Kendall's τ (Log Data)	Kendall's τ (↑ or ↓)
V1 vs. V2 (OFTA)	-0.385	No	-0.297	↑
V1 vs. V2 (B&L Keratometer)	-0.275	No	-0.341	↓
V1 vs. V2 (Oculus K5M)	-0.209	No	-0.110	↑

Table I6: Kendall's τ for original data (only NIBUT ≤24 seconds) and subsequent Kendall's τ after log transformation on the original data.

As heteroscedasticity was confirmed based on the Kendall's tau calculations above, a new Bland and Altman reliability plots were plotted for 'all NIBUT values' (Figure 2.32 in Chapter 2) and 'only NIBUT $\leq$24 seconds' (Figure 2.33 in Chapter 2).

J. Appendix for Chapter 3: Osmolarity Changes Following the Use of Smartphones

Results

Parameters	Median (Q_1; Q_3)
Participant's Age (years)	26 (23; 30)
Room temperature (^{0}C)	21.30 (20.83; 22.05)
Humidity (%RH)	42.33 (41.50; 43.67)
Baseline Osmolarity (mOsm/L)	297 (289.50; 300.00)
OSDI Score	6.25 (2.27; 8.33)
McMonnies Score	3.00 (3.00; 5.00)

Table J1: Demographic of Chapter 3 study population, Median (Q_1; Q_3).

Tear Osmolarity Following the Reading task

Task & Platform	Tear Osmolarity (mOsm/L) Median (Q_1; Q_3)
Reading-Apple iPhone 6	292.00 (286.00; 303.00)
Reading-Apple iPhone 6S	292.00 (286.00; 299.00)
Reading-Samsung Galaxy S6	293.00 (287.00; 300.00)
Reading-Paper	292.00 (287.50; 299.50)

Table J2: Descriptive statistics for tear osmolarity (reading task).

Tear Osmolarity Following the Gaming Task

Task & Platform	Tear Osmolarity (mOsm/L) Median (Q_1; Q_3)
Gaming-Apple iPhone 6	288.00 (283.50; 293.00)
Gaming-Apple iPhone 6S	289.00 (285.00; 294.50)
Gaming-Samsung Galaxy S6	289.00 (284.00; 296.00)
Gaming-Paper	292.00 (285.50; 300.00)
Gaming-Nokia 5210	288.00 (282.00; 292.00)
Gaming-Apple Smart Watch	287.00 (283.00; 289.00)

Table J3: Descriptive statistics for tear osmolarity (gaming task).

K. Appendix for Chapter 4: Influence of Repeated Measurements on Tear Osmolarity

Results

Parameters	Median (Q_1; Q_3)
Participant's Age (years)	22 (19.50; 29.00)
Room Temperature (^{0}C)	21.82 (21.12; 22.33)
Humidity (%RH)	41.64 (41.64;42.82)
Baseline Osmolarity (mOsm/L)	297 (289.50; 300.00)
OSDI Score	6.25 (2.18; 13.07)
McMonnies Score	3.00 (2.00; 5.50)

Table K1: Demographic of Chapter 4 study population, Median (Q_1; Q_3).

Age, Gender and Osmolarity Differences between Osmolarity Study 1 (Chapter 3) and Osmolarity Study 2 (Chapter 4)

Parameter	Osmolarity Study 1 Median (Q_1; Q_3)	Osmolarity Study 2 Median (Q_1; Q_3)
Age (Years)	26.00 (23.00; 30.00)	22.00 (19.50; 29.00)
Gender	Male=14 (42.4%) Female=19 (57.6%)	Male=15 (45.5%) Female=18 (54.5%)
Tear Osmolarity (mOsm/L)	297.00 (289.50; 300.00)	295.09 (287.05; 301.27)

Table K2: Comparisons of age, gender and tear osmolarity between both experiments.

Effect of Repeated Measures on Tear Osmolarity (Osmolarity Study 2)

Measurement Number	Tear Osmolarity (mOsm/L) Median (Q_1; Q_3)
Measurement 1	294.00 (283.50; 303.50)
Measurement 2	292.00 (284.00; 299.00)
Measurement 3	297.00 (283.50; 304.00)
Measurement 4	297.00 (291.00; 309.00)
Measurement 5	296.00 (286.00; 305.00)
Measurement 6	293.00 (287.50; 300.50)
Measurement 7	294.00 (286.50; 300.00)
Measurement 8	293.00 (283.50; 305.00)
Measurement 9	290.00 (283.00; 297.00)
Measurement 10	291.00 (282.00; 306.50)
Measurement 11	297.00 (285.50; 305.00)

Table K3: Descriptive statistics (Median and interquartile range) for each measurement of tear osmolarity.

L. Appendix for Chapter 5: Binocular OFTA and Smart Devices

Results

Parameters	Median (Q_1; Q_3)
Participant's Age (Years)	26 (23; 30)
Room temperature (^{0}C)	21.30 (20.83; 22.05)
Humidity (%RH)	42.33 (41.50; 43.67)
Baseline Osmolarity (mOsm/L)	297 (289.50; 300.00)
Number of blinks within 5 minutes at baseline	81 (54; 153)
Blink rate at baseline (Blink/minute)	16.27 (10.73; 30.57)
Minimum IBI at baseline (seconds)	0.570 (0.373; 0.997)
Maximum IBI at baseline (seconds)	10.067 (7.043; 22.447)
Average IBI at baseline (seconds)	3.760 (2.005; 6.074)
Binocular OFTA NIBUT at baseline (seconds)	7.291 (4.657; 11.180)
OPI at baseline	2.141 (1.180; 2.591)
OSDI Score	6.25 (2.27; 8.33)
McMonnies Score	3.00 (3.00; 5.00)

Table L1: Demographic of Chapter 5 study population, Median (Q_1; Q_3).

Reading Task

Task & Platform	Total Blinks in 5 Minutes Median (Q_1; Q_3)
Reading-Apple iPhone 6	54 (21; 91)
Reading-Apple iPhone 6S	56 (21; 96)
Reading-Samsung Galaxy S6	56 (23; 95)
Reading-Paper	67 (23; 118)

Table L2: Descriptive statistics for total blinks in 5 minutes during the reading task.

Task & Platform	Blink Rate (Blink/minute) Median (Q_1; Q_3)
Reading-Apple iPhone 6	10.80 (10.80; 18.13)
Reading-Apple iPhone 6S	11.13 (4.20; 19.03)
Reading-Samsung Galaxy S6	11.27 (4.47; 19.00)
Reading-Paper	13.40 (4.60; 23.50)

Table L3: Total blinks in 5 minutes during the reading task converted to blink rate.

IBI Metric	Task & Platform	IBI (seconds) Median (Q_1; Q_3)
Minimum IBI	Reading-Apple iPhone 6	0.537 (0.393; 1.293)
	Reading-Apple iPhone 6S	0.600 (0.397; 1.342)
	Reading-Samsung Galaxy S6	0.627 (0.413; 1.303)
	Reading-Paper	0.583 (0.318; 0.867)
Maximum IBI	Reading-Apple iPhone 6	25.067 (11.067; 39.340)
	Reading-Apple iPhone 6S	16.933 (9.663; 38.908)
	Reading-Samsung Galaxy S6	17.833 (11.812; 44.560)
	Reading-Paper	16.987 (10.420; 48.427)
Average IBI	Reading-Apple iPhone 6	5.513 (3.686; 14.513)
	Reading-Apple iPhone 6S	5.368 (3.253; 14.350)
	Reading-Samsung Galaxy S6	5.426 (3.306; 13.475)
	Reading-Paper	4.502 (2.790; 13.163)

Table L4: Descriptive statistics for Minimum, Maximum and Average IBI during the reading task.

Task & Platform	Binocular OFTA NIBUT (seconds) Median (Q_1; Q_3)
Reading-Apple iPhone 6	5.391 (3.443; 8.771)
Reading-Apple iPhone 6S	5.100 (3.757; 9.138)
Reading-Samsung Galaxy S6	5.254 (3.663; 9.001)
Reading-Paper	5.051 (3.362; 8.962)

Table L5: Descriptive statistics for Binocular OFTA NIBUT during the reading task.

Task & Platform	OPI Median (Q_1; Q_3)
Reading-Apple iPhone 6	0.918 (0.578; 1.225)
Reading-Apple iPhone 6S	0.931 (0.560; 1.348)
Reading-Samsung Galaxy S6	0.953 (0.537; 1.212)
Reading-Paper	0.968 (0.575; 1.506)

Table L6: Ocular Protection Index (OPI) during the reading task.

Gaming Task

Task & Platform	Total Blinks in 5 Minutes Median (Q_1; Q_3)
Gaming-Apple iPhone 6	39 (14; 64)
Gaming-Apple iPhone 6S	38 (20; 63)
Gaming-Samsung Galaxy S6	37 (14; 64)
Gaming-Paper	46 (21; 65)
Gaming-Nokia 5210	47 (25; 98)
Gaming-Apple Smart Watch	42 (22; 65)

Table L7: Descriptive statistics for total blinks in 5 minutes during the gaming task.

Task & Platform	Blink Rate (Blink/minute) Median (Q_1; Q_3)
Gaming-Apple iPhone 6	7.73 (2.73; 12.83)
Gaming-Apple iPhone 6S	7.67 (3.83; 12.53)
Gaming-Samsung Galaxy S6	7.47 (2.73; 12.80)
Gaming-Paper	9.20 (4.07; 12.93)
Gaming-Nokia 5210	9.47 (4.90; 19.67)
Gaming-Apple Smart Watch	8.33 (4.43; 12.97)

Table L8: Total blinks in 5 minutes during the gaming task converted to blink rate.

IBI Metric	Task & Platform	IBI (seconds) Median (Q_1; Q_3)
Minimum IBI	Gaming-Apple iPhone 6	0.610 (0.328; 1.330)
	Gaming-Apple iPhone 6S	0.520 (0.317; 0.990)
	Gaming-Samsung Galaxy S6	0.560 (0.373; 0.983)
	Gaming-Paper	0.510 (0.310; 0.692)
	Gaming-Nokia 5210	0.473 (0.377; 0.875)
	Gaming-Apple Smart Watch	0.510 (0.413; 0.818)
Maximum IBI	Gaming-Apple iPhone 6	31.917 (21.085; 55.877)
	Gaming-Apple iPhone 6S	29.777 (14.781; 52.092)
	Gaming-Samsung Galaxy S6	30.300 (17.705; 49.448)
	Gaming-Paper	38.103 (14.552; 60.902)
	Gaming-Nokia 5210	24.240 (14.498; 46.423)
	Gaming-Apple Smart Watch	32.850 (18.302; 54.502)
Average IBI	Gaming-Apple iPhone 6	7.831 (4.964; 18.054)
	Gaming-Apple iPhone 6S	7.954 (4.916; 16.446)
	Gaming-Samsung Galaxy S6	8.130 (5.078; 19.859)
	Gaming-Paper	6.438 (4.608; 14.148)
	Gaming-Nokia 5210	6.279 (3.081; 12.722)
	Gaming-Apple Smart Watch	7.871 (4.722; 12.842)

Table L9: Descriptive statistics for Minimum, Maximum and Average IBI during the gaming task.

Task & Platform	Binocular OFTA NIBUT (seconds) Median (Q_1; Q_3)
Gaming-Apple iPhone 6	5.680 (3.650; 8.632)
Gaming-Apple iPhone 6S	5.938 (3.747; 8.901)
Gaming-Samsung Galaxy S6	5.441 (3.755; 9.108)
Gaming-Paper	5.542 (3.923; 9.134)
Gaming-Nokia 5210	5.239 (3.364; 9.185)
Gaming-Apple Smart Watch	5.476 (3.936; 8.594)

Table L10: Descriptive statistics for Binocular OFTA NIBUT during the gaming task.

Task & Platform	OPI Median (Q_1; Q_3)
Gaming-Apple iPhone 6	0.725 (0.310; 0.965)
Gaming-Apple iPhone 6S	0.884 (0.436; 1.085)
Gaming-Samsung Galaxy S6	0.774 (0.336; 0.969)
Gaming-Paper	0.815 (0.499; 1.056)
Gaming-Nokia 5210	0.936 (0.606; 1.150)
Gaming-Apple Smart Watch	0.6952 (0.579; 1.012)

Table L11: Ocular Protection Index (OPI) during the gaming task.

M. Appendix for Chapter 6: Accommodative Response to Targets on Smartphone and Smart Watch

Results

Parameters	Median (Q_1; Q_3)
Participant's Age (years)	21.00 (19.00; 26.00)
RX (spherical equivalent) Diopter	0.00 (-1.06; 0.00)

Table M1: Demographic of Chapter 6 study population, Median (Q_1; Q_3).

Accommodation Parameter	Statistical Parameter	N5 Paper	N5 Phone	N5 Watch
Accommodation Lag [ALag] * (Diopter)	Median	0.8968	0.9322	0.7292
	Q_1	0.6608	0.7627	0.5802
	Q_3	1.1184	1.1485	0.9423
Mean Velocity of Accommodation [MeanVA] * (Diopter/second)	Median	0.6631	0.6471	0.4953
	Q_1	0.4957	0.4133	0.3306
	Q_3	0.9546	0.8817	0.6080
Mean Velocity of Disaccommodation [MeanVDA] * (Diopter/second)	Median	0.6966	0.8109	0.3346
	Q_1	0.3500	0.2612	0.1621
	Q_3	0.9715	2.1517	0.7450
Speed of Accommodation [SOA] (Diopter/second)	Median	2.1377	2.3313	2.3049
	Q_1	1.8110	1.9603	2.0463
	Q_3	2.4176	2.5969	2.6635
Speed of Disaccommodation [SODA] * (Diopter/second)	Median	1.1744	1.2674	1.0577
	Q_1	0.9550	1.0093	0.9327
	Q_3	1.4438	1.5251	1.2623
Accommodation Latency [ALat] * (Second)	Median	1.2577	1.5520	1.6387
	Q_1	0.9623	1.3651	1.2595
	Q_3	1.5841	1.8712	1.8915
Disaccommodation Latency [DALat] (Second)	Median	0.5261	0.4883	0.5890
	Q_1	0.3250	0.3114	0.4200
	Q_3	0.6548	0.7049	0.7622

*Statistically significant.

Table M2: Descriptive statistics for the accommodation parameter investigated in the first experiment.

Accommodation Parameter	Statistical Parameter	Maltese	N5	N20
Accommodation Lag [ALag] * (Diopter)	Median	1.0378	0.9189	0.9894
	Q_1	0.7196	0.7428	0.7907
	Q_3	1.3172	1.1320	1.2063
Mean Velocity of Accommodation [MeanVA] (Diopter/second)	Median	0.7036	0.6226	0.6253
	Q_1	0.3868	0.4206	0.3484
	Q_3	1.2284	0.8720	0.9119
Mean Velocity of Disaccommodation [MeanVDA] (Diopter/second)	Median	0.4439	0.8109	0.5202
	Q_1	0.1993	0.2450	0.3872
	Q_3	1.0200	1.9577	0.7968
Speed of Accommodation [SOA] (Diopter/second)	Median	2.3613	2.2989	2.2114
	Q_1	2.0050	1.9564	1.9651
	Q_3	2.7545	2.6150	2.6229
Speed of Disaccommodation [SODA] * (Diopter/second)	Median	1.1186	1.2851	1.1296
	Q_1	0.9125	1.0680	0.9467
	Q_3	1.4878	1.5251	1.3835
Accommodation Latency [ALat] * (Second)	Median	1.5173	1.5520	1.5164
	Q_1	1.2865	1.3821	1.2403
	Q_3	1.8857	1.8712	1.7498
Disaccommodation Latency [DALat] (Second)	Median	0.5271	0.4590	0.5823
	Q_1	0.3579	0.3238	0.4183
	Q_3	0.7943	0.6824	0.6852

*Statistically significant.

Table M3: Descriptive statistics for the accommodation parameter investigated in the second experiment.

N. Appendix Chapter 7: The Relationship Between Duration of Smartphone Use and Symptoms of Dry Eye

Results

Demographic Data	Median (Q_1; Q_3)		
	MY	**UK**	**MY and UK**
Number of Participants (N)	210	44	254
Age (Years)	22.00 (20.00; 26.00)	22.00 (21.00; 24.00)	22.00 (20.00; 26.00)
Number of Males (%)	86 (40.95%)	13 (29.50%)	99 (38.97%)
Number of Females (%)	124 (59.05%)	31 (70.50%)	155 (61.03%)

Table N1: Demographic of the study populations.

Investigated Parameters	Median (Q_1; Q_3)		
	MY	**UK**	**MY and UK**
Number of Participants (N)	58 QualityTime=41 Moment=17	18 QualityTime=6 Moment=12	76 QualityTime=47 Moment=29
Age (Years)	23.00 (23.00; 25.25)	22.00 (20.00; 25.25)	23.00 (22.00; 25.00)
Number of Males (%)	10 (17.24%)	2 (11.10%)	12 (15.79%)
Number using quality time (%)	48 (82.76%)	16 (88.90%)	64 (84.21%)

Table N2: Descriptive data for the combined apps population.

Investigated Parameters	Median (Q_1; Q_3)		
	MY	**UK**	**MY and UK**
Smartphone's Screen Time (Minutes)	246.43 (186.64; 319.64)	177.71 (86.36; 245.79)	233.29 (173.32; 307.54)
Smartphone's Number of Pickups	87.07 (25.39; 180.18)	57.21 (39.71; 98.79)	71.64 (30.82; 163.93)
Smartphone's Shortest Duration (Minutes)	0.31 (0.13; 2.00)	2.00 (0.32; 2.00)	0.53 (0.15; 2.00)
Smartphone's Longest Duration (Minutes)	40.57 (29.55; 55.10)	28.43 (20.87; 33.11)	37.93 (26.40; 53.60)
Smartphone's Average Duration Per Use (Minutes)	3.39 (1.50; 8.45)	3.04 (1.43; 4.41)	3.10 (1.49; 5.99)

Table N3: Output from the apps.

Investigated Parameters	Median (Q_1; Q_3)		
	MY	**UK**	**MY and UK**
OSDI Score	6.25 (2.08; 15.10)	6.25 (2.08; 16.15)	6.25 (2.08; 15.10)
McMonnies Score	3.00 (1.00; 5.25)	4.00 (2.00; 7.00)	3.00 (1.75; 6.00)

Table N4: Results for OSDI score and McMonnies score for the investigated population.

Chapter 10: References

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