Investigations of visual changes associated with the menstrual cycle and pregnancy

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Abstract

Background: There is a paucity of information on visual effects associated with the menstrual cycle and pregnancy and the current literature is equivocal. There are currently no guidelines for eyecare professionals on when it is appropriate to prescribe spectacles.

Aim: To investigate, through scoping literature reviews and quantitative data analyses, possible visual changes and dry eye symptoms which are associated with the menstrual cycle and pregnancy.

Setting: The COVID pandemic only permitted online self-reported measurements using validated vision and dry eye questionnaires and a visual acuity test at peak progesterone, peak oestrogen, and menstruation stages of the menstrual cycle.

Methods: Scoping literature reviews provided an update on current knowledge. Novel online methodologies were developed, including use of eConsent and Web Apps for collecting data from the RAND NEI RQL 42, Sande dye questionnaires and the FrACT visual acuity test..

Participants: Despite wide promotion through multiple routes, only 44 participants were recruited of which only 15 completed data collection at 2 or more stages of the menstrual cycle.

Results: Baseline data on menarche and menstrual cycle duration is consistent with current literature. No statistically significant effects (tested using Wilcoxon's Signed Rank test) were found for five NEI RQL 42 subscales, Sande Dry questionnaire or the FrACT visual acuity measurements studied. Using Cohens d values for effect sizes, the far vision and Sande dry eye question 2 subscales, for the 2 questionnaires only completed cohort, had large effect sizes with the Sande dry eye question 2 subscale having a medium effect size for the all 3 questionnaires completed cohort. There was a trend suggesting greater visual difficulties and dry eye symptoms around the time of peak oestrogen which reduce towards menstruation.

Conclusion: Despite the disappointing lack of statistically significant findings, possibly due to insufficient data, the observed effect sizes for the far vision, glare and dry eye subscales indicate that future research in these areas might be most fruitful when considering visual changes associated with the menstrual cycle and pregnancy. This thesis provides the latest knowledge together with novel online methodologies that would enable further practice-based study of this topic and many others like it.

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COVID-19 impact statement

The COVID-19 pandemic has significantly impacted the research element of the professional doctorate, resulting in two changes to the study hypothesis, design and methods. In the period prior to the national lockdown, the research study received approval from the research ethics committees of the Institute of Optometry (IoO) and London South Bank University (LSBU). In conjunction with this process, the study gained support from local GP's, midwifery teams and a local obstetrics department, to facilitate participant recruitment.

In response to the COVID-19 pandemic, LSBU placed a moratorium on face-to-face research. This decision necessitated the researcher and supervisory team to investigate alternative aspects of vision during pregnancy and alternative methods of data collection. This resulted in a change in the study hypothesis to consider self-reported visual experiences during pregnancy, using a validated questionnaire via an online WebApp. Additional ethics approval was sought from IoO, LSBU and the HRA.

The changed study was promoted to multiple obstetric, midwifery teams and professional organisations to gain support to facilitate participant recruitment. However, professional teams were still in the recovery phase from the pandemic, with significant pressures on their time, and participant sign-up for the study was low. It was thought that this was due to pressures on the midwifery teams combined with the reported high anxiety levels of pregnant women. To support the professional doctorate, a new study was designed to investigate the any variations of vision during the menstrual cycle, using a self-reported validated vision questionnaire and online visual acuity test. This change required further approval from the research ethics committees and the re-development of the study webApp. The researcher requests that the effects of the COVID-19 pandemic be considered when assessing the research studies.

Glossary

Astigmatism	A refractive error in which the image of a point object is not a single point but two focal lines at different distances from the optical system.
Asthenopia	Any symptoms associated with the use of the eyes, typically eyestrain and headache.
Cycloplegia	Paralysis of the ciliary muscle of the eye resulting in dilatation of the pupil and paralysis of accommodation
Dizygotic twins	Two siblings who come from separate ova that are released at the same time from an ovary and are fertilized by separate sperm.
eConsenting	The use of remote, digital or online consenting
Hypermetropia	Refractive condition of the eye in which images of distant objects are focused behind the retina when accommodation is relaxed
Menarche	The first occurrence of menstruation
Menses	The time of menstruation
Monozygotic	Two siblings who come from the fertilization of a single ova by a single sperm, with the zygote then splitting into two.
Multiparous	Woman who have borne more than one child
Myopia	Refractive condition of the eye in which images of distant objects are focused in front of the retina when accommodation is relaxed
Nulliparous	A woman who has never given birth
Oligomenorrhea	An irregular menstrual cycle which may be longer than 35 days in duration
Ophthalmologist	A specialist in the branch of medicine concerned with the study and treatment of disorders and diseases of the eye.
Optometrist	A trained person who practices optometry with the aim of detecting defects in vision, signs of injury, ocular diseases or abnormality, and problems with general health

Ovum	A single cell released from either of the ovaries
Parturition	The action of giving birth
Polymenorrhea	A menstrual cycle which is shorter in duration than 21 days
Refraction	Process of measuring and correcting the refractive error of the eye
Refractive error-related quality of life	Refractive error-related quality of life is a measurement of the impact of refractive error on health, comfort, and happiness
Term	The normal duration of human pregnancy occurring between 37-42 weeks
Zygote	A fertilized ova

Abbreviations

AOP	Association of Optometrists
BCVA	Best corrected visual acuity
CCT	Central corneal thickness
CF	Correction factor
CoC	College of Optometrists
EDD	Expected delivery date
FrACT	Freiburg acuity & contrast test
FSH	Follicle stimulating hormone
GAG	Glygcosaminoglycan
GP	General medical practitioner
HCG	Human chorionic gonadotropin
HPL	Human placental lactogen
HRA	Health research authority
HRT	Hormone replacement therapy
IOP	Intra ocular pressure
IPD	Inter pupillary distance
LH	Luteinizing hormone
LMP	Last menstrual period
LMC	Local medical committee
LOC	Local optical committee
LOCSU	Local optical committee support unit
LPC	Local pharmacy committee
LSBU	London South Bank University
MSE	Mean spherical equivalent
NEI VFQ	National Eye Institute – Visual Function Questionnaire

NEI RQL	National Eye Institute – Refractive related Quality of Life
NICE	National Institute for Clinical Excellence
PMDD	Premenstrual dysphoric disorder
PMS	Pre-menstrual syndrome
QoL	Quality of life
QoV	Quality of vision
REC	Research ethics committee
RCM	Royal college of midwives
RCO	Royal college of ophthalmologists
RSVP	Refractive status and vision profile
SAP	Standard automated perimetry
SFHT	Sherwood Forest Hospital Trust
SSH	Sex steroid hormone
SWAP	Short wave automated perimetry
VA	Visual acuity
V	Vision

Study presentations & papers

Date	Location/journal	Audience	Topic
7.10.19	LSBU / F2F	Doctoral students	Review of Study A Vision and pregnancy
6.1.22	LSBU / virtual	Doctoral students	Study methods
3.3.22	LSBU / virtual	Student midwives	Ocular anatomy, vision and pregnancy – overview of the research study
21.2.23	LSBU / virtual	Student midwives	Ocular anatomy, vision and pregnancy, research and ethics applications
In preparation	Ophthalmic & Physiological Optics	Eye care practitioners & researchers	Review of visual changes during pregnancy & the menstrual cycle
In preparation	Ophthalmic & Physiological Optics	Eye care practitioners & researchers	Report of VIMC study

Chapter 1 Introduction

1.1 Chapter overview

The chapter starts with a brief overview of the research reported in this thesis and background to the research questions investigated. It will then introduce the physiological processes controlling menstruation and pregnancy and the roles which various hormones have within these processes. For readers who may be eye care professionals, terminology, definitions, and basic physiology relating to the menstrual cycle and pregnancy will be presented first. For readers who may be other health care professionals (e.g., midwives), terminology and definitions relating to vision and optometry will then be presented. The chapter then introduces the measurement of visual function and common vision defects. The potential link between the physiological processes controlling menstruation and pregnancy and vision defects will be considered.

1.2 Background

As primary eye care professionals, optometrists encounter women of all ages attending for both routine and symptom driven eye examinations and yet consideration is rarely given to the point in their menstrual cycle when the visual assessment takes place. Women may also attend for eye examinations during pregnancy for many reasons, extending from visual changes through to seeking reassurance about their ocular health and while there is a plethora of literature on the ocular pathology which can occur during pregnancy, there is a paucity of literature on the effects of pregnancy on more commonplace aspects of visual function, such as the refractive error (e.g., long-sightedness or short-sightedness). Given the potential for sight loss along with threat to life of mother and child, the importance of ocular pathology should not be under-estimated; however, the more prosaic complaints concerning eyes and vision for which pregnant women seek advice, such as eye strain (asthenopia) and blurred vision from refractive errors, should not be overlooked or dismissed.

1.3 Justification for the research

Anecdotal evidence from optometrists suggests that changes in refractive error can occur throughout the menstrual cycle and during pregnancy, along with dry eye symptoms, but the research data are inconclusive. Currently there are no clinical guidelines from the College of Optometrists (CoO) or any other professional organization advising on when it is appropriate to prescribe spectacles, either during the menstrual cycle or pregnancy.

1.4 Research aim

The research reported in this thesis investigates whether there are visual changes and dry eye symptoms during the menstrual cycle and pregnancy and also capture self-reported visual experiences during these periods.

1.5 Research objectives

1. To create clinical guidelines and protocols for optometrists and ophthalmologists on prescribing glasses during the menstrual cycle and pregnancy.
2. To provide non eye care healthcare professionals information on visual changes during pregnancy and the menstrual cycle.
3. To provide information to women on visual changes which can be expected during pregnancy or the menstrual cycle.

1.6 Study hypotheses

1.There are no statistically significant differences in the chosen NEI RQL questionnaire subscales, during pregnancy and the menstrual cycle.

2.There are no statistically significant differences in Sande dry eye questionnaire results, during pregnancy and the menstrual cycle.

3. There are no statistically significant differences in self-reported visual acuity measurements, during pregnancy and the menstrual cycle.

1.7 Menstrual cycle

The female reproductive cycle is underpinned by physiological changes, characterised primarily by periodic vaginal bleeding which arises from shedding of the uterine mucosae. The process starts between 10-16 years of age and may be considered as evolutionary adaptations to provide the opportunity for fertilization and pregnancy (Marques, Maderia and Gama, 2022).

1.7.1 Phases of the menstrual cycle

The menstrual cycle can be divided into different phases: menstruation when the uterine mucosae is shed, the luteal or secretory phase and the follicular or proliferative phase. The process of ovulation occurs towards the end of the follicular phase with changes to the uterus lining occurring during the luteal phase (Reed and Carr, 2018).

1.7.2 Duration of menstrual cycle

The duration of the menstrual cycle is known to vary, with a median duration of 28 days. Polymenorrhea is the term used to define menstrual cycles that are shorter than 21days, whereas oligomenorrhea is a term used to describe irregular menstrual cycles which may be as long as 35 days. The variation in cycle duration occurs during the follicular phase with the luteal phase being relatively constant at 14 days (Reed and Carr, 2018).

1.7.3 Hormones involved in the menstrual cycle

The menstrual cycle is under the control of fluctuating hormone levels (Speroff and Vande Wiele, 1971) and the cyclical process starts with the pituitary gland secreting the follicle stimulating hormone (FSH); this facilitates the development of a mature ovum, while concurrently stimulating the ovaries to secrete oestrogen. The FSH hormone is also secreted by the male and female adrenal glands which have a primary function in the development of secondary sexual characteristics.

During the normal menstrual cycle, oestrogen acts as negative feedback to the pituitary gland to halt the production and release of FSH, while simultaneously stimulating the pituitary gland to release luteinizing hormone (LH), which causes the ovarian follicle to burst and release the ovum. The remnants of the ovarian follicle are termed the corpus luteum and this tissue releases the hormone progesterone (Thiyagarajan, Bashit and Jeanmonod, 2022). The hormones of interest to this research are oestrogen and progesterone (Figure 1-1, Figure 1-2); both of these hormones are present in all tissues throughout the body, including ocular tissues (Gupta *et al.*, 2005).

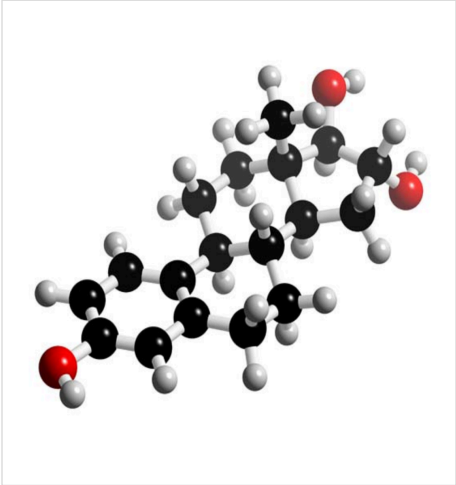

Figure 1-1 oestrogen molecule *

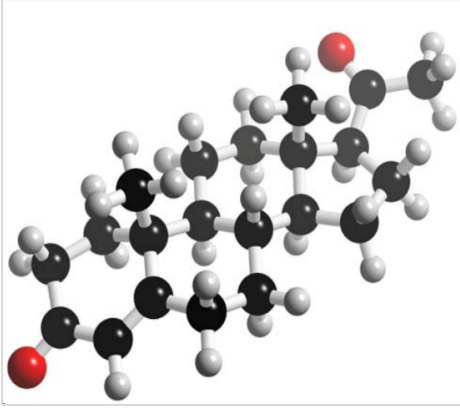

Figure 1-2 progesterone molecule *

Molecule key: Black = carbon (C); Red = oxygen (O); White = hydrogen (H)

* Images used under Adobe stock license agreement

1.7.4 Oestrogen production

Prior to the follicle releasing an ovum, it produces the hormone oestrogen. There are three major forms of physiological oestrogens in females: estrone (E1), which plays a role post-menopause, estradiol (E2) which is the most potent pre-menopausal form and estriol (E3) which is produced by the placenta during pregnancy. In pre-menopausal women, oestrogens are produced primarily in the ovaries, corpus luteum, and placenta. A small but significant amount of oestrogens can be produced by non-reproductive organs, such as the liver, heart, skin, and brain (Reed & Carr, 2018). Estradiol ligand hormone receptors have been found outside the reproductive organs (Thiyagarajan, Bashit and Jeanmonod, 2022; Williams and Lin, 2013).

1.7.5 Types of oestrogen receptors

In humans, there are two main subtypes of oestrogen receptor: Erα and Erβ and both are expressed in many cells and tissues. These receptors control key physiological functions in various organ systems: reproduction, skeletal, cardiovascular and central nervous systems, as well as in specific tissues (Paterni *et al.*, 2014). ERα is present mainly in mammary glands, uterus, ovary, bone, male reproductive organs (testes and epididymis), prostate (stroma), liver, adipose tissue and the eye. ERβ is found mainly in the prostate (epithelium), bladder, ovary, colon, adipose tissue, and immune system. The presence of the receptors has led to prospective therapeutic agents for prevention and treatment of a wide variety of pathological conditions, such as: cancer, metabolic and cardiovascular diseases, neurodegeneration, inflammation, and osteoporosis. E2 binds effectively to both ERα and Erβ receptors (Ogueta *et al.*, 1999; Guttridge, 1994).

1.7.6 HRT and oestrogen receptors

Although this is an expansive area and generally outside the scope of the review, it is worth highlighting that hormone replacement therapies (HRT) target both ERα and Erβ receptors, but can lead to an increased risk of breast and endometrial cancers along with thromboembolism (Williams and Lin, 2013).

Selective pharmacological agents have been developed and termed selective oestrogen receptor modulators (SERMs), which reduce the adverse effect by displaying tissue-selective agonist/antagonist activities (Martinkovich *et al.*, 2014).

1.8 Pregnancy

Pregnancy is the physiological state of a female carrying a developing fetus in the womb (Anderson and Ghaffarian, 2023), during this period levels of oestrogen and progesterone are increased to facilitate and support the environment for a potential fetus (Marieb, 1991).

1.8.1 Conception

The greatest chance for conception occurs during the follicular phase of the menstrual cycle (Mihm, Gangooly and Muttukrishna, 2011). If a fertilized ovum successfully implants into the endometrium, human chorionic gonadotropin (HCG) hormone is produced and released by the embryonic cells, which ultimately develop into the placenta (Guttmacher, Maddox and Spong, 2014; Betz and Fane, 2021). HCG levels are the earliest marker of pregnancy and can be detected 10 days after fertilization (Makrigiannakis *et al.*, 2017). Normal HCG levels for pre-menopausal women are between 0.02 to 0.8 IU/L and increase exponentially throughout the first trimester (Korevaar *et al*., 2015). This hormone stimulates the corpus luteum to produce progesterone, to support maintenance of the pregnancy (Pascual and Langaker, 2021; Soma-Pillay *et al.*, 2016; Mihm, Gangooly and Muttukrishna, 2011).

1.8.2 Phases of pregnancy

The duration of human pregnancy is on average 40 weeks or 280 days from the first day of the last menstrual period to the estimated date of delivery. Pregnancy is divided into three phases, each called a trimester and within each trimester significant developments occur with the fetus. The healthcare professionals supporting pregnant woman will undertake differing levels of maternal and foetal evaluation in each trimester. In the early phase more generalised health testing occurs which becomes more targeted as the pregnancy progresses, along with increasing parental education (Fowler, Mahdy and Jack, 2021).

1.8.3 Duration of pregnancy

By convention, the period from 3 weeks before, until 2 weeks after the expected delivery date (EDD) was considered 'term' (WHO, 2013). However, the American College of Obstetricians and Gynaecologists have suggested that the label 'term' be replaced by the designations early-term, full-term, late-term and post-term to more accurately describe deliveries occurring before, at or beyond 37 weeks of gestation (Spong, 2013).

1.8.4 Single versus multiple pregnancies

For natural or non-assisted pregnancies, a single pregnancy occurs when a sperm fertilizes an ovum creating a zygote, which then becomes implanted into the lining of the womb. Multiple pregnancies can occur if the zygote undergoes division into two, creating monozyotic (identical) twins or if the zygotes divide further leading to triplets, quadruplets, etc. Non-identical or fraternal (dizygotic) twins occur when two ova are released and become fertilised during the same menstrual cycle. The prevalence of multiple births in the UK was 15 in every 1000 maternities, which includes natural and assisted pregnancies (ONS, 2021). Greater levels of oestrogen occur with multiple births, which has the potential to have greater effects on the refractive error (Seravalli, Strambi and Tommaso, 2022).

1.8.5 Birth

Pregnancy ends with the delivery of the fetus. There are several theories as to how labour is initiated. One theory suggests that labour is initiated by the withdrawal of progesterone and the mechanical stretch experienced by the uterine wall (Myers and Elad, 2017). Another suggests that inflammatory mediators, such as prostaglandins, are vital in initiating uterine contractions (Ravanos *et al.*, 2015) which are sustained throughout labour and delivery by the release of oxytocin (Arrowsmith and Wray, 2014).

1.8.6 Hormones involved in pregnancy

During pregnancy the normal hormonal homeostasis, which controls the menstrual cycle is disrupted. The hormones having a significant role during pregnancy are follicle stimulating hormone (FSH), oestrogen, progesterone, human placental lactogen (HPL), relaxin, oxytocin and prolactin. Progesterone facilitates the creation of a suitable endometrial environment for implantation and maintenance of a fertilized ovum and the production of FSH and LH is diminished, with oestrogen and progesterone continuing to be produced by the corpus luteum and the placenta. Towards the end of the pregnancy, progesterone has a role of preparing the uterus for contraction during parturition.

1.9 Vision and the eye

The human senses have different measurable characteristics and the functional capability of the eye and visual system can be assessed in many ways. Visual acuity (VA) is a measurement of visual function and measures the spatial resolving power of the visual system, indicating the smallest angular size to be resolved (Davidson, 1991). Clinically, this is measured using an optotype chart, which uses high contrast letters of differing sizes; the most common types being a Snellen or Bailey Lovie LogMAR chart.

1.9.1 Definitions of vision

Vision is achieved through a combination of complex biological and neurological systems, which allow the body to interact and appreciate its surroundings (Sánchez, Somani and Salini, 2022). The human eye transduces a physical stimulus into a neural signal, to generate the perceived impression of the surroundings (Lodish *et al.*, 2021). There are many different functional aspects of vision which can be measured through objective and subjective tests, but clinically VA is the most common aspect of vision measured as it provides a standardised indicator of the functional ability of the eye and visual system. Donders, (1864) developed the term ‘visual acuity’ to describe the ‘sharpness of vision’ and defined it as the ratio between a subject's performance and a standard performance (Kniestedt and Stamper, 2003).

1.9.2 Visual acuity measurements

VA is generally measured using standardised vision charts having a range of targets, either letters or symbols, of varying sizes. There are different designs of chart but all are developed to be viewed under standardised conditions; the distance between the subject and chart, along with lighting levels. The testing distance and lighting levels can influence measurement. The most common type of vision chart is the Snellen chart (Snellen, 1862). Although widely used it has limitations, a significant one being that letter sizing does not have a logarithmic progression. This design limitation has been overcome with the LogMAR chart (Bailey and Lovie, 1976).

Both the Snellen and LogMAR charts can be found in clinical and research settings and are used routinely by all eye care health professionals. When recording acuity measurements, clinicians refer to 'vision' (V) as measurements without any refractive correction and 'visual acuity' (VA) when measurements are taken with any refractive correction used i.e. glasses or contact lenses (Millodot, 2009). Many test chart designs using various optotypes can be found outside clinical settings, such as online vision tests. However, a concern of individuals using these tests, is the lack of adherence to the standardised conditions (e.g. testing distance) which can give rise to misleading outcomes.

1.10 Optics of the eye

For optimal vision, light from the object of interest must be in sharp focus on the retina. If light is not focused on the retina it results in blurred vision. The ability of the eye to focus light onto the retina is provided by the refracting components of the eye; the cornea and the crystalline lens. The ophthalmic term for any focusing weakness of the eye is 'refractive error'. Refractive errors can vary in magnitude, from small clinically insignificant errors to those which when uncorrected are associated with visual impairment (WHO, 2013).

1.11 Refractive errors and their detection

Refractive errors are common eye disorders, which can cause difficulty with focusing (Table 1-1). These can impact an individual's ability to see clearly when looking at objects in the distance, such as road signs and or when viewing near vision objects, such as mobile phones or tablets. Williams *et al.* (2015) suggests that around 1 in 2 European adults have some form of refractive error. Refractive errors can be determined by an eye examination and treated with either corrective glasses, contact lenses or refractive surgery.

Within the UK, eye examinations are funded either through the NHS or privately. NHS eye examinations in England, Northern Ireland and Wales are commissioned centrally by the Department of Health, and delivered from participating optical practices. Activity data from NHSE indicates that there were over 13 million NHS eye examinations carried out in 2020 (NHSD, 2020). The activity data are collected based on eligibility criteria, which include broad age groupings but it is not possible to isolate the data for women of child-bearing ages; however, within the NHSD 2020 data, there were approximately 2.3 million NHS eye examinations, for females within the age group of 16-60 years. The only data collected by NHSE regarding refractive errors relates to whether a spectacle prescription was required and whether such prescriptions were considered stable or to have changed. There is no central information recording and gathering, for those who have private eye examinations.

2021 Census data for England and Wales gives a total population of 59.5 million, with 51% being female and of these 22% were of childbearing age (ONS, 2020). The census data also reports there were 624,828 live births in England and Wales (ONS, 2021). Although only an approximation, if half of mothers have a refractive error as Williams *et al.* (2015) suggest then potentially there could be 300,000 women who attend for an eye examination during their pregnancy.

1.11.1 Eye care professionals

In the UK, eye examinations are conducted by optometrists and ophthalmologists. There is some overlap between these roles in the UK; optometrists are allied health professionals primarily concerned with determining and correcting refractive errors, while ophthalmologists are medically qualified doctors who are primarily involved in the diagnosis and management of eye disease.

1.11.2 Types of refractive error

Common refractive errors are listed and defined in Table 1-1

Table 1-1 Common refractive errors

Myopia	Difficulty in seeing distant objects clearly without a spectacle correction, contact lenses or refractive surgery
Hypermetropia	Difficulty in seeing close objects clearly without the lens of the eye making a focusing effort (accommodation) or without a spectacle correction, contact lenses or refractive surgery
Astigmatism	Distorted vision which normally results from an irregularly curved cornea
Presbyopia	Difficulty in reading and other near vision tasks, and is linked to ageing and the eye's gradual loss of accommodation

(WHO, 2013; Bennett and Rabbetts, 1991)

1.11.3 Refractive error notation / mean spherical equivalent (MSE) and vector methods

There is a recognised standard notation for refractive errors, which facilitates transmission of information between eyecare professionals, for the benefit of the individual. Notation for refractive errors comprise of three components: sphere, cylinder, and axis; this is also known as the spectacle prescription. The refractive error/spectacle prescription can be written in two forms, with the cylinder being in either positive or negative form. For the analysis of refractive errors the concept of mean spherical equivalent (MSE) is used by many investigators (Hashemi *et al.*, 2016). This is a process of aggregation leading to a single number, which can be used easily for statistical analysis; half the cylindrical component is added to the spherical component. However, in doing this significant amounts of data can be lost, notably data on the axis direction. The difficulty in using the full refractive error for analysis lies with the appropriate inclusion of the astigmatism component but this can be achieved using a mathematical approach to convert the prescription into vector representation, which retains valuable data providing further detail (Thibos, Wheeler and Horner, 1997).

1.12 Hormones and refractive error

Clinical studies have considered the effects of hormones on refractive error with equivocal outcomes. However, the lack of agreement could be attributable to the differences in sample size and methods used to measure the refractive error (Gong *et al.*, 2015; Bergin, 1952). Sex steroid hormone (SSH) receptors have been found in the structures of the eye which are involved in the eyes ability to focus (Gupta *et al.*, 2005). Circulating oestrogen and progesterone hormones levels fluctuate throughout the menstrual cycle and pregnancy (Speroff and Vande Wiele, 1971). The hormone levels are presented in Table 1-2 and Table 1-3.

Table 1-2 Hormone daily production rate through the phases of the menstrual cycle

Hormone type	Early follicular	Pre-ovulatory	Mid luteal
Progesterone (ng/mL)	1	4	25
Estrone (ng/mL)	50	350	250
Estradiol (ng/mL)	36	380	250

(Baird and Fraser, 1974)

Table 1-3 Median hormone concentrations during pregnancy

Hormone type	1st trimester	2nd trimester	3 trimester
Progesterone (ng/mL)	25.6 (16.6–40.7)	48.1 (31.6–78.5)	130 (72.6–200)
Estrone (ng/mL)	0.93 (0.41–1.72)	4.28 (1.99–8.54)	11.5 (3.70–18.9)
Estradiol (ng/mL)	2.18 (1.16–3.59)	9.71 (5.33–15.1)	20.4 (12.8–32.9)

(Schock *et al.*, 2016)

10^{th}-90^{th} percentile range in brackets

1.13 Chapter summary

This chapter provides an outline of the research study. The physiological processes which control menstruation and pregnancy are described, along with the various hormones which are involved and their roles. The different types of refractive error have been described, along with the concept of visual acuity and an explanation of the measurement process.

Chapter 2 Literature reviews

2.1 Chapter overview

Chapter 1 provides an introduction to the research and outlines the aims, objectives and hypotheses. The physiological processes which control menstruation and pregnancy are described along with the different types of refractive error and the concept of visual acuity and its measurement. This chapter will present a summary of the literature on vision during the menstrual cycle and pregnancy, in relation to any potential effects on visual experience and refractive error.

2.2 Chapter aims

To support the research, literature reviews were performed to explore the current literature in relation to the influence of sex steroid hormones on visual acuity and refractive error along with visual symptoms reported during these physiological states.

2.3 Methodology

The type of literature review methodology used was a scoping review, as described by Pare *et. al*., (2015), although scoping reviews have similarities with other methodologies. The reviews were not based on the researchers' preconceived views, as found in narrative reviews and did not have a priori inclusion and exclusion criteria as found with systematic review methodologies. The aims of both reviews were to determine the breadth of extant literature and adopt a thematic construction to the analysis and synthesis of the data and identify any gaps in the literature. The database search methodology is described for each review, with the findings presented, in the following section.

2.4 Database searches

2.4.1 Vision in menstrual cycle

The search was last updated on 08.11.23. The searches were made using PubMed, Google Scholar, Cochrane Database of Systematic Reviews and clinical answers. The search strategy included keywords to find suitable materials: “menstrual cycle and vision”, “menstrual cycle and refractive error“, “menstrual cycle and corneal curvature”, “menstrual cycle and corneal thickness” and “menstrual cycle and crystalline lens”. Due to the paucity of literature, which is consistent with a narrative review on menstrual cycle and visual functions by Figueiredo *et al*. (2021), all studies between 1952 and 2023 were included.

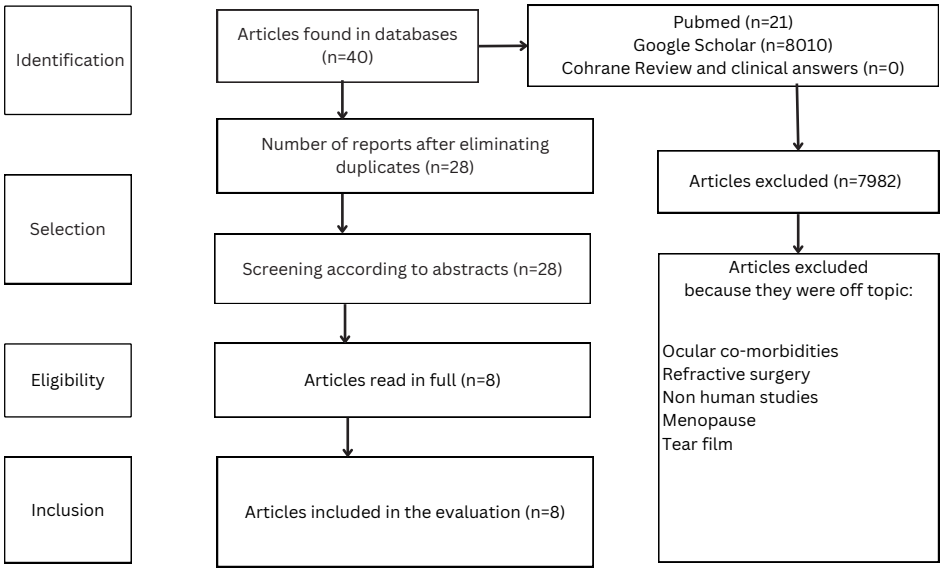

Figure 2-1 Results from database searches and selection process

2.4.2 Vision in pregnancy

The search was last updated on 08.11.23. The searches were made using PubMed, Google Scholar, Cochrane Database of Systematic Reviews and clinical answers. The search strategy included keywords to find suitable materials: “pregnancy and refractive error”, “pregnancy and visual acuity”, “pregnancy and corneal thickness”, “pregnancy and crystalline lens”, “pregnancy and oestrogen and vision” and “pregnancy and progesterone and vision”. All studies between 2000 and 2023 were included.

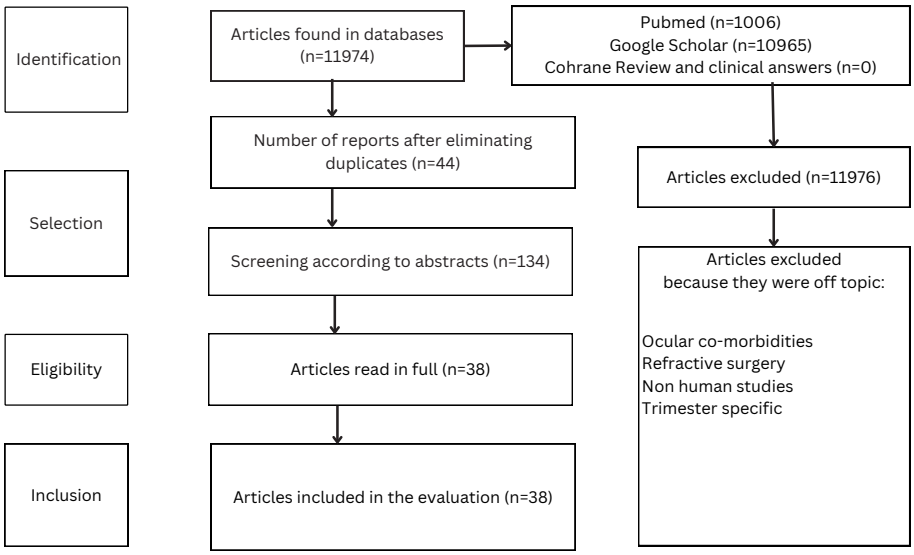

Figure 2-2 Results from database searches and selection process

2.5 Eligibility criteria

Only studies reported in English were selected. Case reports, reviews, animal studies were not selected. Conference posters and letters to the editor were excluded.

2.6 Selection

Publications were selected on the basis of relevance to the subject. With PubMed searches, all the items were selected based on the relevance of the title and then the abstract read; the same approach was taken for Google Scholar searches, but as a greater number of articles were returned the number was matched to the PubMed search and the same selection approach adopted. Other publications were identified from the bibliographies of these papers and included where relevant at the author's discretion. Articles were included if they made an original or significant contribution to the literature.

2.7 Analysis and synthesis

The reviews have been organised to discuss the main topics: refractive error, visual acuity, crystalline lens, corneal thickness, corneal curvature, sex hormones and pertinent miscellaneous items.

2.7.1 Menstrual cycle

2.7.1.1 Refractive error during menstruation

The hormonal changes during the menstrual cycle are well documented (Speroff and Vande Wiele, 1971) and their effects on refractive error have been investigated by Finkelstein (1887) and Bergin (1952). Both of these studies used small cohorts of participants and found less than 0.25D of clinical change in refractive error during the menstrual cycle.

Gong *et al.* (2015) used a cohort of 120 adolescents with a mean age of 15 +/- 10.4 years old and measured their refractive error and the interpupillary distance (IPD) 4 times during a single menstrual cycle. None of the data collections points coincided with ovulation, peak oestrogen or progesterone levels. The authors found statistically significant differences in the refractive error during the menstrual cycle, with increases in myopia.

A confounding factor, which may account for the findings, could be the increased levels of oestrogen during puberty. Interestingly they also found a statistically significant difference in the IPD measurement, implying that there would have to be structural differences affecting the positioning of the eye in the orbit or measurement errors. Erdem *et al.* (2007) investigated the refractive status and potential changes with 36 females, over a six-month period who were using hormone replacement therapy (HRT) and compared the pre-HRT refractive error to the 6 months post-HRT refractive error and found no statistically significant change. This suggests that HRT does not affect the refractive status, but no information on the type of HRT used was provided.

2.7.1.2 Visual effects of hormonal changes during menstruation

Hutchinson, Walker and Davidson (2014) suggest that oestrogen may play a role in vision and cite studies involving older females with the implication that lower oestrogen levels adversely affect ocular function, and suggest that appropriate levels oestrogen and in particular estradiol may be a factor in the maintenance of healthy visual function.

2.7.1.3 Visual acuity during menstruation

The effects of SSH on visual acuity will be discussed in Section 2.7.2.2.

2.7.1.4 Cornea

The effects of SSH on the cornea will be discussed in Section 2.7.2.7.

2.7.1.5 Corneal thickness and the menstrual cycle

Central corneal thickness (CCT) has also been found to vary during the menstrual cycle. In a small study which included six women, Leach *et al.* (1971) showed that the corneal thickness variation during the menstrual cycle closely paralleled the bimodal nature of the plasma oestrogen levels and that the maximum thickening occurred around ovulation. However, Soni (1980) found that the CCT was thinnest around ovulation and at a maximum in the luteal phase when the progesterone levels are highest.

The discrepancy between the findings of Leech *et al.* (1971) and Soni (1980) can be explained by a less accurate method of determining the point of ovulation used by Soni (1980). Findings by Kiely *et al.* (1983) and Goldich *et al.* (2011) supported those of Leech *et al.* (1971) and found there was significant variation in CCT during the menstrual cycle with the maximum thickness coinciding with the highest oestrogen level around ovulation and at the end of the cycle. Ghahfarokh *et al.* (2015) used an ultrasonic pachymeter and sensitive urine test to recognize the peak LH values as an indicator of ovulation and found the cornea to be at its thickest around ovulation and thinnest at the end of the menstrual cycle.

Variations of the CCT and corneal curvature have been shown to occur during the normal menstrual cycle and several studies have been performed considering refractive changes (Gong *et al.*, 2015; Bergin,1952; Finkelstein,1887). There are some differences between the results obtained but these could be explained by the age of the cohorts and differing measurement methods.

2.7.1.6 Crystalline lens

The effects of SSH on the crystalline lens will be discussed in Section 2.7.2.12.

2.7.1.7 Effects of the menstrual cycle on the conjunctiva

The conjunctiva is a thin transparent mucus membrane lining the posterior surface of the eyelids from the eyelid margin and reflected forward onto the anterior part of the eyeball where it merges with the corneal epithelium at the limbus (Millodot, 2009). The conjunctival tissue shows cyclical variations in the cellular structure of the epithelium during menstruation and menopause (Bajwa *et al.*, 2012). Oestrogen receptors are located on the conjunctival epithelium (Gupta *et al.*, 2005). Versura, Fresina and Campos (2007) applied hormonal cytology procedures to exfoliated cells in tear samples, which showed cellular changes peaking during the follicular phase, which correlate with subjective dry eye symptoms.

2.7.1.8 Effects of the menstrual cycle on the visual fields

Tate and Lynn (1977, cited in Henson 1993, pp. 1) defined visual fields as 'all the space that one eye can see at any given instant'. The commonly used instrument to assess visual fields is an automated perimeter. These standardised instruments provide clinical information on various performance aspects of the retina and visual pathway. The testing process is subjective, and it is known that changes in sensory and perceptual processes can occur during the menstrual cycle (Lanfair and Smith, 1974).

There are multiple visual field-testing paradigms; the most commonly used is 'standard automated achromatic perimetry' (SAP). Akar *et al.* (2005) found that using SAP there were no obvious differences during the menstrual cycle but using an alternative testing paradigm, short wavelength automated perimetry (SWAP), may be more sensitive to subtle sex hormone-dependent changes in healthy women and that clinicians should note the menstrual status of female patients if using SWAP. There were no comparable studies investigating visual field sensitivity.

2.7.1.9 Sensory impairments

Premenstrual syndrome (PMS) encompasses clinically significant somatic and psychological manifestations during the luteal phase of the menstrual cycle (Yonkers, O'Brien, Errikson, 2008). A more severe extension of PMS is premenstrual dysphoric disorder (PMDD). Premenstrual symptoms which occur in a cyclical pattern prior to menstruation and then wane post-menstruation include, changes to mood, behaviour, and physical impairments including visual sensitivity (Eisner, Burke and Toomey, 2004). Most females have symptoms which do not interfere with their daily life but 5% to 8% of females experience symptoms which lead to significant distress and functional impairment with symptoms disappearing within a few days of the onset of menstruation (Yesildere and Orsal, 2020). These functional impairments may be due to changes in sensory and perceptual processes (Lanfair and Smith, 1974).

2.7.1.10 Central nervous system (CNS) changes

There is evidence suggesting that physical changes occur to brain morphology, mediated by SHH, with peak grey matter volume coinciding with ovulation. Hormonal therapies have been explored as a potential treatment for many neurological diseases with varying degrees of evidence and success (Roeder and Leira, 2021). The morphological changes affect memory and learning along with pain and perception.

Haggard and Gaston (1978) found auditory perceptual variations during menstruation but not all of these effects show menstrual cycle dependent fluctuations (Pletzer *et al.*, 2019; Sherwin, 2006). These physical changes to the brain could explain the subjective fluctuations in vision during the menstrual cycle as reported by Bergin (1952), which have been found with visual field assessments (Akar *et al.*, 2005).

2.7.2 Pregnancy findings

2.7.2.1 The eye and sex steroid hormones

Gupta *et al.* (2005) and Wickham *et al.* (2000) have identified SSH receptors in ocular and adnexal tissues, suggesting these structures have the potential to be sensitive to circulating hormones and could have a possible role in ocular homeostasis. During pregnancy, oestrogen levels start to increase from week 9 to a zenith around 31-35 weeks gestation, resulting in a 20-fold increase in the normal levels of oestrogen as noted Section 1.12 (Spoerl *et al.*, 2007; Yaron *et al.*, 1999). This increase gives rise to the study hypothesis that oestrogen sensitive ocular tissues could undergo functional changes, some of which could be found during routine optometric assessments.

2.7.2.2 Effect of sex steroid hormones on visual acuity

The definition and explanation of visual acuity along with measurements was outlined in Section 1.9.

Speroff and Vande Wiele (1971) demonstrated that hormone levels vary during the human menstrual cycle. Estradiol, the most potent form of oestrogen (Section 1.7.4) ranges from 36- 380µg, reaching a sharp peak around the time of ovulation. Gandelman (1983) and Parlee (1983) showed that fluctuations in sensory thresholds occur across the menstrual cycle and as visual acuity is a sensory function, there is the potential for this fluctuate across the menstrual cycle. Kopell *et al.* (1969) found that there was an increase in visual performance around the time of ovulation and related this to the raised oestrogen level. The author suggested that from an evolutionary perspective, this enhanced sensitivity or visual improvement could have increased a female's chances of successfully mating. However, the author did not provide any evidence supporting this assertion, which is therefore speculative. These findings are not supported by Howarth and Clemes (2006) who found no significant difference in visual acuity measurements throughout the menstrual cycle.

If oestrogen has the potential to mediate increased visual performance during the menstrual cycle, the hypothesis is that this would also occur during pregnancy. Oestrogen levels peak around weeks 31-35 during pregnancy (Yaron *et al.*, 1999) but Mehdizadehkashi *et al.* (2014) did not find any observable improvements in visual acuity measurements around this time. A weakness with Mehdizadehkashi *et al.* (2014) study design was that refractive error was not measured or corrected prior to any visual acuity measurements being taken. Had this occurred, improved levels visual acuity could have been recorded, resulting in a different outcome.

2.7.2.3 Effects of oestrogen on the retina

The retina is the light receptive layer of the eye (Millodot, 2009). There is some evidence to suggest that oestrogen has a role in normal retinal function. Variations in oestrogen have been found in some retinal disorders, such as glaucoma and ischemic optic neuropathy, but this is inconclusive (Bajwa, Singh and Bajwa, 2012; Akar *et al.*, 2004). However, oestrogen deficiency is associated with increased prevalence of macular degeneration in post-menopausal women (The Eye Disease Case-Control Study Group, 1993). The mechanisms by which oestrogen exerts a protective role in the prevention of retinal changes is not completely known but thought to be related to both to genomic and nongenomic effects, such as environmental and lifestyle (Evans *et al.*, 1998).

2.7.2.4 Refractive error

Over the last six decades investigators have reviewed the effect of pregnancy on refractive error, using various methodologies, with varying outcomes. Manges *et al.* (1987) performed a study on refractive changes with a cohort of 93 pregnant participants and 38 control participants. Each of the participants had two subjective refractions 90 days apart in either trimester 1 & trimester 2, trimester 2 & trimester 3 or trimester 3 & post-partum; but the refractive error was not measured in all trimesters for each subject.

Data analysis of the refractive error used the vector method (Section 1.11.3) and a weakness in the data analysis was that data from both eyes of participants was used. There is a correlation between data from each eye of the same participant and therefore data from each eye should not be pooled for analysis because this violates the statistical principle that measurements should be independent (Armstrong, 2013). The authors stated that if a clinically significant threshold of 0.25D was used, then only 1.34% of the eyes of the pregnant women experienced a change greater than this.

Pizzarello (2003) is a frequently cited study in the literature discussing the eye and pregnancy; however, the limitations of the study along with the results are worth exploring. The paper has a headline cohort figure of 240 participants, which is often quoted, but this number represents the pregnant women invited to complete a questionnaire regarding their vision. Out of these 240 women, 83 (35%) completed the questionnaire and from this group, visual changes during pregnancy were noted by 21 women (25%). Of these 21 women, 13 agreed to take part in the study and the refractive errors of only 12 participants were reviewed and compared to matched controls. The refractive error was measured in the 3rd trimester and then within 5 months post-partum (15 weeks +/- 5 weeks).

The results show a statistically significant increase in myopia (or decrease in hyperopia) in the pregnant group but not within the control group; the mean myopic shift in refractive error, based on measurements of MSE, were 0.87D & 0.98D in the right and left eyes respectively.

Post-partum data showed that there was reduction in the amount of myopic shift but the myopic shift was still present when compared with the base line pre-partum levels. This finding could possibly arise from generalised myopic changes to refractive error over time but would not necessarily occur in non-myopic participants. The mean change in myopia was statistically significant, with all 12 subjects in the pregnant group having a myopic shift in refractive error during pregnancy, which represents 14% of the 83 who completed the questionnaire. Subsequent authors have quoted this as the percentage of pregnant women who are likely to experience changes in their refractive error (Makensen *et al.*, 2014; Sharma, 2006).

There are several sources of error with the Pizzarello (2003) study methodology and methods. There is sampling bias as only those who were experiencing visual changes were invited to participate. A participant whose myopia had changed is more likely to experience visual changes than one whose hyperopia had changed, due to accommodative levels within this age group. The small sample size limits the generalisations that can be made from the results. Measurements were completed by one examiner who was not masked to whether participants where pregnant or non-pregnant. A further limitation is that participants' existing spectacle prescription was taken as the pre-pregnancy baseline; pragmatically this is the most appropriate choice to make as the pre-pregnancy refractive error would be impossible to measure, but the refractive correction could have been out of date before pregnancy.

Lastly, in contrast to Manges *et al.* (1987), the statistical analysis was performed using only the MSE (Section 1.11.3) with the consequent loss of data on astigmatism associated with this measure. Chawla *et al.* (2013) did not measure refractive error but suggest that the refractive error could alter during pregnancy due to possible changes to the structure of the main refracting component and advocated that prescribing of glasses should be done two months post-partum. There was no data to evidence this statement.

Atas *et al.* (2014) reviewed 54 pregnant women and compared the refractive error, using a Nidek Pentacam auto-refractor, in the third trimester to the third month post-partum. There was no statistically significant difference in refractive error between the two time points and from this the authors assumed no change occurs with refractive error during pregnancy.

Nkiru *et al.* (2018) carried out a longitudinal study on a cohort of 100 pregnant women and measured their refractive error during the 2nd and 3rd trimester and 6 weeks postpartum. The study reports a myopic change in the third trimester, resolving postpartum. The authors assume that the post-partum change was a reversal to pre-pregnancy levels, but this is an unknown as pre-pregnancy or existing spectacle prescriptions were not measured. The stated myopic change is not evidenced with numerical data but rather indicates that the changes are between refractive error group and does not provide any statistical analysis to support the conclusions.

Wu, Schallhorn and Lowry (2019) carried out a cross-sectional study using two cohorts of women who used spectacles; 60 pregnant women and 60 non pregnant women and compared their refractions, measured by an auto-refractor, to their existing spectacle prescriptions. The study found that there was no statistically significant difference in the auto-refractor measurements, based on the MSE (Section 1.11.3) between the two cohorts and that there was no association of MSE with any trimester; the MSE was reported as -2.67D and -2.52D in the pregnant and non- pregnant groups respectively. Analysis of the refractive error and spectacle prescriptions used power vectors (Thibos, Wheeler and Horner, 1997) which showed, within the pregnant cohort, there was a significant association between change and trimester but not in any specific direction, which opposes the findings from Pizzarello (2003), who found a myopic trend through the trimesters.

Ali *et al.* (2022) carried out a longitudinal study on a cohort of 25 pregnant women and measured their refractive error during each trimester but not postpartum. There was a small sample which the authors acknowledge as a limitation. The methods use the mean spherical equivalent (MSE) method for recording refractive error and the limitations have been discussed in Section 1.11.3. The MSE for the cohort in the first trimester was RE -0.13D and LE 0.96D with a myopic change towards the 3rd trimester of RE -0.23D and LE -0.35D; these values are below the lower limits frequently used define the presence of a refractive error (Saw et al., 2004)

2.7.2.5 Visual acuity in pregnancy

The literature is sparse on the effects of pregnancy on visual acuity, a study by Mehdizadehkashi *et al.* (2014) being frequently cited. This study was indirectly attempting to determine the presence of refractive change during pregnancy by assessment of visual acuity levels. The study followed 112 pregnant women and measured their distance and near visual acuity, monocularly and binocularly, throughout each trimester and within the first three months post-partum. The investigators found there was a statistically significant reduction in all measurements, from the first to third trimester, with them returning near to baseline measurement soon after delivery.

The assumption made was that refractive changes had occurred based on differing visual acuity levels and that both hyperopic and myopic refractive changes had occurred. There was no consideration of the effects of accommodation on any potential hyperopic refractive change and the outcomes could have been more meaningful if the refraction along with visual acuity had been recorded.

Nikiru *et al*. (2018) in a longitudinal study investigating refractive error, measured visual acuity levels in the 2nd and 3rd trimesters along with at 6 weeks postpartum. The authors suggest that there was a worsening of visual acuity levels towards the 3rd trimester but this is not evidenced with numerical data and does not provide any statistical analysis to support the conclusions. Ali *et al*. (2022) in a longitudinal study investigating refractive error, measured the best corrected visual acuity levels (BCVA), using LogMAR acuities in each trimester but not postpartum. A reduction in BCVA was found between the first and second trimester: RE -0.13 to 0 and LE -0.14 to 0; clinically these changes are around the threshold of confidence that a real change in visual acuity has occurred (Siderov and Tiu, 1999).

2.7.2.6 Ocular structures involved in refractive error

The refractive components of the eye have been discussed in Section 1.10 and each component is discussed in more detail in the following sections.

2.7.2.7 The cornea

The human cornea is a transparent tissue with three main layers and provides the greatest refractive component of the eye's optical system; the refracting power is achieved from the curvature of the layers, the central thickness and refractive index. During pregnancy the corneal thickness and topography have been studied by various methods.

Comparison of these studies requires consideration of the instruments used for data collection; i.e. the data obtained from the best instrument in one decade may be different compared to that collected in another decade, from an instrument using improved technology. Interestingly many papers cite studies and base assumptions on results produced from instrumentation which has been superseded. SSH receptors have been located in specific organs throughout the body including the eye (Section 1.7.5). Ocular endocrinology has located oestrogen, progesterone and androgen receptors in the human cornea, iris, ciliary body, lacrimal gland, meibomian gland and conjunctiva; with oestrogen and progesterone receptors predominantly found in females and androgen receptors in males (Gupta *et al.*, 2005).

There are 3 types of oestrogen receptor: ERα, Erβ and ERg protein coupled receptors. Alpha receptors have been located within the nuclei of corneal epithelial, stromal, and endothelial cells (Suzuki *et al.*, 2001), suggesting that oestrogen may influence these tissues (Gupta *et al.*, 2005; Suzuki *et al.*, 2001; Wickham *et al.*, 2000) and it is reasonable to speculate that the biological function of the cornea could be affected by the hormonal variations which occur during pregnancy.

2.7.2.8 Corneal thickness

Corneal thickness, typically central corneal thickness (CCT) is measured using a pachymeter. This measurement is taken for a variety of clinical reasons, such as management of corneal disease and glaucoma, which are outside the scope of this study (Rashid and Farhood, 2016).

Weinreb (1988) is a frequently cited study, with no statistically significant difference found between the CCT of pregnant and non-pregnant women; however, the methods for this study used unequal subject and control groups and measurement was by optical pachymetry. There are two design principles for the instruments, based on either an optical or ultrasound measurement process; more recent instruments provide increased measurement accuracy and reliability. Early studies used optical pachymeters, which have been superseded by ultrasonic devices and more recently by the optical low-coherence reflectometer (OLCR) and the Pentacam Scheimpflug imaging system (Barkana *et al.*, 2005).

Patel and Stevenson (1994) found that optical pachymeters overestimated the central corneal thickness (CCT) and were less accurate than ultrasound devices. Barkana *et al*. (2005) looked at ultrasound, OLCR and Pentacam methods and found there to be good agreement between the three instruments. Sen *et al.* (2014) using an ultrasound pachymeter found no statistically significant difference in CCT between a group of 32 pregnant women and an age-matched female control group. Although this study measured the CCT of the pregnant group in each trimester it only reports measuring the CCT of the control group at one point.

Efe *et al.* (2012) using a small cohort of 25 pregnant women, found an increase in CCT in the 2nd and 3rd trimesters which returned to baseline measurements during the third month post-partum. The CCT measurements were 561.41µm, 566.64 µm, 573.68 µm, for the 1st, 2nd and 3rd trimesters respectively. This study used ultrasound pachymetry and there were no age-matched controls.

Atas *et al.* (2014) measured the CCT of a cohort of 54 participants, using a Scheimpflug imaging system, and found a statistically significant difference in CCT between the third trimester and third month post-partum. This study used narrow refractive error inclusion criteria and the first and second trimester results were not included; however, the statement was made that CCT in the third month post-partum was the same as pre-pregnancy levels. These outcomes were similar to those from a study by Goldich *et al.* (2014) which used a cohort of 120 participants, but the outcomes from Goldich *et al.* (2014) have been questioned due to assumptions and methodology.

2.7.2.9 Diurnal variation in corneal thickness

Harper *et al.* (1996) demonstrated a diurnal variation in CCT using optical pachymetry; the study found the only pattern to the variation was an increase during sleep. Although optical pachymetry is less accurate, it was used for practical reasons and the study was looking for relative changes rather than absolute values.

In humans, greater corneal thickness is observed in the morning, possibly due to the corneal hypoxia during sleep, which produces an osmotic gradient, attracting water into the corneal stroma. If the CCT increases due to hydration then this could affect the refractive index of the cornea, resulting in a change to the refractive error. Meek, Dennis and Khan (2003) found little change in the refractive index of the cornea if the CCT increases. Young *et al.* (2004) found that the corneal refractive index decreases in a nonlinear way as the corneal thickness increases.

Handa *et al.* (2002) and Kycle (1981) investigated the diurnal corneal thickness of a small cohort of males and females. They suggest that there is significant diurnal variation in CCT of the female cohort, which they related to hormone levels; however, the CCT was only measured on two occasions and the paper did not state at which point during the menstrual cycle the measurements were taken.

2.7.2.10 Possible role of sex hormones in corneal thickness

Receptors for both male and female sex hormones are present in human corneas of both sexes. ERα receptors have been located within the nuclei of corneal epithelial, stromal, and endothelial cells, leading to the possibility that SSH could influence the biological function of the corneal cells (Gupta *et al.*, 2005; Suzuki *et al.*, 2001). Corneal keratocytes located within the stromal layer have a role in corneal stability and biochemically, oestrogen is known to initiate changes within these cells (Suzuki *et al.*, 2005). The extra-cellular matrix, within the corneal stroma, is composed of collagens, proteoglycans and glycosaminoglycans (GAGs). Oestrogen is responsible for the synthesis of GAGs (Suzuki *et al.*, 2005).

This group of carbohydrates has a multifunctional role in the maintenance of the corneal structure by supporting collagen and elastin fibrils, maintaining the cellular spaces and the turgidity of the cornea while keeping a balance and proportion between the protein fibres (Suzuki *et al.*, 2005). GAGs also promote the ability of the collagen and elastin fibres to retain moisture, therefore remaining soluble, and so GAGs have the ability to affect the thickness of the cornea (Huang and Meek, 1999).

An increase in corneal thickness has been suggested as a result of oestrogen and progesterone levels increasing the collagenolytic activity (Sato *et al.*, 1991). Oestrogen receptors are located within the endothelial cells and it is possible that oestrogen could influence the endothelial pump mechanism, resulting in an increase in corneal thickness, but this has not been demonstrated in other endothelial tissues, such as blood vessels (Sporel *et al.*, 2007).

2.7.2.11 Corneal topography and curvature

The curvature of the cornea is measured using either a keratometer or a corneal topographer (Millodot, 2009); there are different designs of each instrument, which can either be in manual or automatic form. Several studies have looked at the effects of hormonal changes on the curvature of the cornea.

As with pachymetry measurements (Section 2.7.2.8) the outcomes of the studies are dependent on the technology used, with newer instruments having increased accuracy and reliability, while providing a greater level of detail about the corneal topography. For example, this needs to be considered when comparing outcomes from studies using a manual keratometer to the Pentacam instrument. Various investigators have evaluated the corneal curvature during pregnancy. Leach *et al.* (1971) used a manual keratometer and found there was no statistically significant difference in corneal measurements taken throughout the menstrual cycle. However, Kiely *et al.* (1983) evaluated the corneal topography and found the corneal curvature steepens in both meridians towards ovulation and then flattens post-ovulation, towards the end of the cycle. The differences in study design and detection of ovulation may account for the discrepancies.

Manges *et al.* (1986) using a manual keratometer with a cohort group of 93 pregnant women and 38 non pregnant women as a control group, found no statistically significant change in corneal curvature. In contrast, a frequently cited study by Park *et al.* (1992) evaluated the corneal curvature during pregnancy and found corneal steeping to occur in the 2nd and 3rd trimesters, which returned to normal after birth or on cessation of breastfeeding.

Erdem *et al.* (2007) found no statistical difference in corneal curvature with pre- and post-HRT use, deducing that hormones may not play a part in any corneal curvature changes. In this study the corneal measurements were taken using a Nidek optical path difference scan, which has the ability to assess the refractive power of the eye and determine the refractive power of each individual optical component in the eye.

Atas *et al.* (2014) found statistically significant changes in corneal curvature and CCT during pregnancy using the Pentacam instrument, but no significant change in the refractive error. This suggests that the increase in corneal curvature was neutralised by changes in either the refractive index of the cornea, the posterior corneal surface or the crystalline lens. No data were provided on any posterior corneal surface changes, nor was this mentioned in the paper's discussion.

2.7.2.12 Crystalline lens

The human crystalline lens has a bi-convex shape with a gradient refractive index. The crystalline lens provides approximately +20D of refractive power and provides the eyes' accommodative ability. It is an established physiological process that with age the eye loses its ability to accommodate; this is termed presbyopia (Millodot, 2009). This occurs from structural changes to the lens capsule, nucleus and cortex, with a resultant effect on the curvature and the refractive index gradient of the lens, producing a myopic shift in refractive error. Sunness (1994) reported that the curvature of the crystalline lens increases during pregnancy which could be responsible for the myopic shift as found by Pizzarello (2003).

2.7.2.13 Hormone receptors

Gupta *et al.* (2005) found oestrogen receptors within the crystalline lens and oestrogen has been implicated in the maintenance of its health and transparency (Hutchinson, Walker and Davidson, 2014; Hales *et al.*, 1997). A lower incidence of cataracts has also been found in women taking HRT (Worzala *et al.*, 2001; Cumming and Mitchell, 1997) their hypothesis was that oestrogen could have a protective effect against the formation of cataract and also have a role in the normal homeostasis of the crystalline lens. However, the mechanism by which this could occur remains unclear. A weak protective association was found between the use of an oral contraceptive pill and the development of cortical cataract (Kanthan *et al.*, 2010). Further supporting this, patients who were taking tamoxifen, a selective oestrogen antagonist, for the treatment of breast cancer are more likely to develop cataracts (Lee *et al.*, 2004; Paganini-Hill and Li, 2000).

2.7.2.14 Effects of hormones on the crystalline lens

The crystalline lens is approximately 65% water; the capsule being 80% water, the cortex 70% water and the nucleus 60% water (Van Heyningen, 1972). Lambert (1971) found that during pregnancy changes to the crystalline lens were due to an increased permeability of the lens capsule. The mechanism through which an increased water uptake may occur, could be related to the oestrogen receptors on the crystalline lens epithelium (Gupta *et al.*, 2005). This agrees with previous studies suggesting an increase in curvature and also a myopic shift in refractive error (Pizzarello, 2003; Dinn, Harris and Marcus, 2003; Manges *et al.*, 1987).

Beneyto and Perez (2006) investigated crystalline lens auto-fluorescence, during the last trimester of pregnancy. Auto-fluorescence originates from an accumulation of fluorescent, tryptophan-derived residues and protein aggregations within the structure. The paper noted that there was a decrease in the auto-fluorescence values, arising from changes to the osmotic gradient; this is caused by dilution of substances brought about by an increased water uptake of the lens.

Wang *et al.* (2003) and Hales *et al.* (1997) demonstrated that oestrogen may have antioxidant properties which could confer protection on the crystalline lens from oxidative damage, by preserving cellular mitochondrial function and maintaining cellular adenosine triphosphate (ATP) through periods of oxidative stress. Oestrogen is also considered to affect maintenance of normal cell membrane function (Zhang *et al.*, 1994).

2.7.2.15 Transient loss of accommodation and increase in myopia

Many papers refer to the possibility of a transient loss of accommodation during pregnancy combined with an increase in myopia (Mehdizadhkashi *et al.*, 2014; Chawla *et al*, 2013; Pizzarello, 2003; Manges *et al.*, 1986). These authors cite a reference by Weinstock (1971) which was a single case history of a pregnant woman who experienced the onset of severe myopia, which coincided with use of thiazide diuretic; these drugs have been associated with myopic shifts (Muchnick, 1998). In the literature there have been no other cases reported of transient loss of accommodation or a severe increase in myopia.

2.7.2.16 Intraocular pressure (IOP)

The IOP is maintained by a balance between the production and outflow of aqueous humour (Acott *et al.*, 2014). The ocular structures involved in this process are ciliary body, trabecular meshwork and conjunctival vasculature. Gupta *et al.* (2005) and Wickham *et al. (*2000) have found ERα receptors located within these structures.

The influence of hormonal levels on IOP has been observed by various studies, highlighting fluctuations in IOP measurements during the menstrual cycle. Some studies have demonstrated successful lowering of IOP, in glaucoma patients, with the use of topical oestrogen drops (Wagner, Fink and Zadnik, 2008; Gupta *et al.*, 2005; Mitchell *et al.*, 1996). Dewundara *et al*. (2016) have suggested that oestrogen may have neuroprotective effect on the progression of primary open angle glaucoma. Vajaranan *et al*. (2016) found a small reduction in IOP measurement of 0.5mmHg, in post-menopausal women, using topical hormone eye drops. Clinically this does not represent a significant reduction in IOP values compared to the standard treatments which can provide a 25% reduction in IOP (NICE CG85).

2.7.3 Summary

2.7.3.1 Vision in menstrual cycle

Hormonal variations underpin the physiological changes which occur during the menstrual cycle and these variations have an effect on the eye and its refractive components. However, studies are equivocal on the effects that these hormone variations have on refractive error but limitations of the study methodologies could explain this. There is evidence that changes to the corneal thickness occur throughout the menstrual cycle, which peak around the time of ovulation; this potential could influence the refractive status of the eye. Hormone receptors have been located in the crystalline lens, suggesting a possible role in any refractive change during the menstrual cycle. Sensory impairments and fluctuations are known to occur during the menstrual cycle and there is the potential for vision, as a sense, to be affected.

2.7.3.2 Pregnancy and refractive error

The literature is unequivocal that the cornea and crystalline lens are oestrogen sensitive tissues and how physiological changes could manifest clinically should be investigated. Studies have demonstrated that increases in the CCT and corneal curvature occur in the later stages of pregnancy and the sequel of these transient changes could result in differences in refractive error.

Pizzarello (2003) found a myopic shift in refractive error during pregnancy which partially resolved post-partum, but the study design had weaknesses, notably making it unlikely that hyperopic shifts in refraction would be detected. However, this finding was not confirmed by Atas *et al*. (2014), using a more sophisticated method of measurement compared to Pizzarello (2003).

Atas *et al.* (2014) did not find any difference in CCT but only in corneal curvature; if the anterior corneal curvature changes, any resulting refractive changes could be negated by corresponding changes to the corneal refractive index, posterior corneal surface or crystalline lens.

No comment was made about any of these variables and the study used a narrow refractive error inclusion criterion which could have influenced the results. Many of the studies had small cohorts and did not make any reference to sample size calculations. Pizzarello (2003) used a very small cohort from which subsequent authors have made generalisations which have been incorporated into clinical practice. To avoid taking measurements during each trimester of pregnancy, some authors used measurements from only the second or third trimester. Manges *et al.* (1986) used a more complex approach and separated the cohort into three groups and took measurements in different trimesters.

Some studies used either measurements in the first trimester as baseline measurements or participants' existing refractive errors as pre-pregnancy measurements; both of these have limitations but obtaining pre-pregnancy measurements is practically not possible. The ideal would be to take measurements during each trimester, from both pregnant and age-matched control groups.

The literature reviewed spans many decades and the studies use a variety of different instrument technologies, and the results need to be considered within this context. This occurred with some studies measuring CCT with optical pachymeters and others with ultrasound or a Pentacam instrument, making comparison difficult due to the varying accuracy of each instrument. This also occurred with refraction measurements as Pizzarello (2003) used subjective measurement techniques compared to Atas *et al.* (2014) who used objective automated Pentacam measurements.

In the analysis of the measurements, all the studies referred to statistically significant changes with the exception of Manges *et al.* (1986) who referred to the clinical significance of small refractive changes and related these to acuity levels. The study by Mehdizadhkashi *et al.* (2014) looking at visual acuity in pregnancy was interesting but it did not reflect the theory of the improvement of the senses by Kopell *et al.* (1969); this may have been due to study design, as best corrected visual acuity was not measured but this would be an interesting area for further research.

The outcomes of the study by Erdem *et al.* (2007) investigating possible refractive changes from HRT, provides optometrists with reassurance that any refractive changes due to HRT are not clinically significant; however, the type of HRT and whether mono or biphasic, was not stated, as different types could have the potential to affect outcomes and this is also a possible area for future study.

2.7.3.3 Unanswered question

The literature provides insights into the effects of oestrogen on the refractive components of the eye but the combined effect of oestrogen on visual acuity and refractive error is equivocal. This study aims to contribute further data about the effect of hormonal variations on refractive error and visual acuity.

2.7.4 Chapter summary

The literature shows the eye to be an oestrogen sensitive structure, with receptors being located in the structures which are involved in the eye's refractive status. The oestrogen levels involved in the menstrual cycle and pregnancy are known to fluctuate and have been shown to have effects on various aspects of ocular physiology and function; however, the effects on refractive error and visual acuity remain equivocal and the research will investigate whether this occurs.

Chapter 3 Methodologies and effects of the COVID-19 pandemic

3.1 Chapter overview

The literature review in Chapter 2 found that the eye is an oestrogen sensitive structure; however, the effects of oestrogen on refractive error and visual acuity remain equivocal. This chapter introduces the three different research studies created as part of this thesis to investigate the effects of female sex hormones on refractive error, visual acuity and dry eye symptoms. Each study is discussed in sequential order, considering the aims and design, starting with the original study plan, leading onto the amendments in response to the effects of the COVID-19 pandemic and then in response to challenging recruitment issues.

3.2 Epistemology - research philosophy

In the experience of the author, the relevance of the eye being oestrogen sensitive is not emphasised on undergraduate optometry courses, which suggests an implicit theory that this is not relevant to eyecare professionals. As the eye is oestrogen sensitive, it could be argued that this implicit theory is really an assumption and that research is required to assess whether this assumption or implicit theory is correct.

Each of the research studies assumes a positivist approach as the design is independent of the researcher and uses observational data and data analysis techniques to provide insights into the research question (Ryan, 2018). Creswell (2003) states that “positivist research designs, use methodologies which maintain the assumption of an empiricist paradigm”; that is using empirical evidence from well designed and controlled studies to provide knowledge (Webb, 2018).

3.3 Research type

Each study has a hypothesis which the design aims to address by generating empirical data for statistical analysis; quantitative research designs create meaning through objectivity (Creswell, 2003). Leedy and Ormrod (2001) state that ”quantitative research is specific in its surveying and experimentation, building on existing theories”.

Each study uses observational techniques to provide empirical data for analysis on the effects of vision in pregnancy and the menstrual cycle, by using inductive methods, which aim to derive generalisations from individual facts (Kim, 2021).

A quantitative research approach would allow the study hypotheses (Section 1.6) to be answered. However, this approach assumes that the correct research questions are being considered to provide insights into visual changes associated with the menstrual cycle and pregnancy. To empower participants to offer insights into their vision during these physiological processes and to provide confidence that the correct research questions have been asked, participants were asked to complete an open comment question. The use of open questions has been discussed by O'Cathain and Thomas (2004) who suggest that although open questions can present difficulties for analysis, they have the potential to provide further information which closed questions may not capture.

3.4 The research plans

The COVID-19 impact statement outlines the challenges created by the COVID-19 pandemic and how the restrictions imposed affected the study. The timeline of the COVID-19 pandemic, produced by the Department of Health, can be found in Appendix 1. The researcher adapted the original study design to align with the landscape during that period, which was then further adapted due to recruitment challenges.

The three research plans discussed in this chapter are

Plan A (VIP-F2F)	Vision in pregnancy with face-to-face data collection
Plan B (VIP-online)	Vision in pregnancy with online data collection
Plan C (VIMC)	Vision in the menstrual cycle with online data entry

3.5 Plan A - Vision in pregnancy with face-to-face data collection (VIP- F2F)

3.5.1 Section overview

To outline the aims and design of the study and to describe how it was planned to use a handheld portable auto-refractor and VA chart to take measurements at points throughout pregnancy and post-partum.

3.5.2 Aims of the Section

To describe the rationale for the study along with its aims and the design of each arm of the study.

3.5.3 Research hypothesis

Are there any statistically significant and/or clinically significant differences in refractive error and VA during pregnancy and into post-partum, and can any conclusions be drawn from the data to support how optometrists and healthcare practitioners manage their patients? To consider this, it was planned that the study would use serial measurements taken by an auto-refractor and LogMAR VA charts in each trimester and postpartum.

3.5.4 Justification

As discussed in Section 2.7.4, the research literature is inconclusive regarding any changes in refractive error during pregnancy and with an absence of clinical guidelines from professional bodies, the study was designed to aid healthcare professionals in management of refractive error during pregnancy.

3.5.5 Study design

The study type is observational and longitudinal, involving within-participants repeated measurements. For each participant the measurements would be taken once in each trimester and within three months post-partum, with each visit approximately 90 days apart. The inclusion and exclusion criteria are listed in Table 3-1.

Table 3-1 Plan A (VIP) inclusion and exclusion criteria

Inclusion
Between 18 and 40 years old
In first trimester
Exclusion
Diabetes
Any mucopolysaccharide disease
Systemic medications known to affect vision
Pregnancy has been facilitated by IVF
Drug or alcohol dependency
Vulnerable adult
Any ocular disease known to affect vision

3.5.6 Sample size

A pragmatic approach to sample size for research of this type is to aim for the maximum number of participants that it is feasible to test within the time available. The greater the number of participants, the narrower the confidence intervals following statistical analysis. However, it is also important to determine the minimum number of participants required for a clinically significant change in refractive error to reach statistical significance. To answer this question, a sample size calculation was carried out with G Power version 3.1.9.2. (Prajapati, Dunne and Armstrong, 2010).

The number of participants required was nine (Appendix 2), using an alpha value of 0.05, beta value of 0.95, effect size of 0.2 and a correlation between measurements of 0.9. Allowing for an attrition rate of 50%, 18 participants are required.

As the participant attrition rate is expected to be high and to provide greater internal validity, the plan was for recruitment to continue for a six-month period from commencement or until a maximum of 80 participants had been reached.

3.5.7 Consent

In line with the principles of the Declaration of Helsinki (2013), participants were asked to consent to participation prior to entering into the study. The consent process was developed to ensure that the Declaration of Helsinki principles were adhered to (Section 26) ensuring no coercion and providing participants with the ability to actively or passively withdraw from the study.

3.5.8 Publicising the research and recruitment

The process could be initiated by the pregnant woman's healthcare professional (Midwife or GP), who would introduce the study during the first routine antenatal appointment, and provide a participant information sheet (Appendix 3). If the potential participant expressed an interest during their healthcare appointment, then with their consent, details were passed on to the researcher to make contact and explain the study in more detail, provide further information and the opportunity to ask questions.

The participant information sheet (Appendix 3) was to be sent to potential participants via their preferred method of contact; the contact options were email or post. If participants expressed a wish participate during the phone conversation, a first data collection date would have been arranged to coincide with their antenatal visit or an appointment would be made at the researcher's optometry practice. The consenting process would have occurred at the first face-to-face visit, prior to any data collection.

3.5.9 Data collection venues

The plan was for data collection venues to be located within a hospital trust obstetrics department or at the researcher's optometry practice. All measurements were to be taken in a room which was appropriate for the auto-refractor and visual acuity measurements; this would have been in a room with appropriate seating, lighting and dimensions.

3.5.10 Data collection points

During pregnancy the plan was for the data collection points to coincide with the pregnant women's scheduled antenatal visits; as outlined by NICE, and the schedule of visits can be found in Figure 3-1. The post-partum data collection point was to be arranged between the researcher and the new mother, at a mutually convenient time.

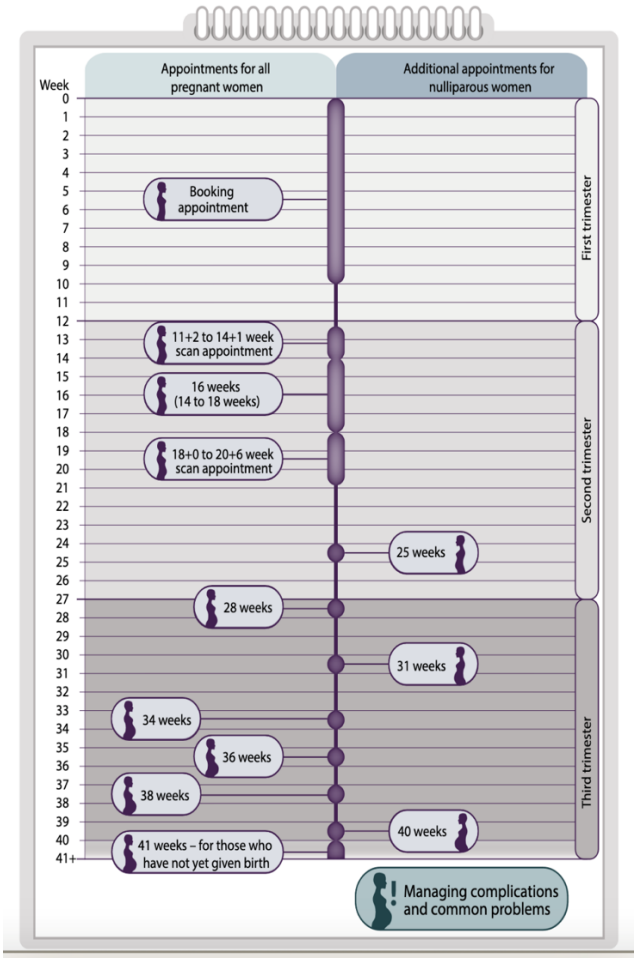

Figure 3-1 Schedule of antenatal appointments (NICE, August 2021)

3.5.10.1 Recall invitations

Prior to the data collection visit, the researcher was to contact each participant, using their choice of contact method (Section 3.5.8) to arrange the data collection visit to coincide with their antenatal visit.

3.5.10.2 Recall reminders

In the event of no response to a recall invitation, a further attempt would be made to contact the participant two weeks later. If there was no response to the second invitation, the participant would have been removed from the study and no further invitations made. If the participant contacted the researcher at a later point during their pregnancy they would have been added back into the study and invitations sent out at the next appropriate data collection point; this could result in a data collection point being missed.

3.5.10.3 Withdrawal from the study

Participants were able to actively withdraw from the study at any time by contacting the researcher directly by phone, SMS or email or passively withdraw by not responding to the recall invitations.

3.5.11 Section summary

This study did not take place because of the onset of COVID-19 pandemic and the subsequent moratorium on face-to-face data collection by LSBU (Appendix 4). When the national pandemic was declared it was unclear how long research would be disrupted and after a pause of some months, it became clear that a "Plan B" was necessary.

3.6 Plan B – Vision in pregnancy with online data collection (VIP-online)

3.6.1 Section overview

The primary research question was to investigate refractive error during pregnancy, with an inference on whether known fluctuations in oestrogen and progesterone levels (Section 1.8), during pregnancy, has any effect on refractive error. The moratorium on face-to-face research (Appendix 4) due to the COVID-19 pandemic necessitated a deviation from the original study methods; an alternative approach was adopted and is outlined in the following sections.

3.6.2 Aims of the Section

To outline the rationale for designing an additional study arm and describe its relevance and association to the original study, along with its design.

3.6.3 Research hypothesis

Are there any statistically significant and/or clinically significant differences in vision during pregnancy and into post-partum and can any conclusions be drawn from the data to support how eye care practitioners manage their patients? To consider this, the study used two self-administered validated vision tools.

3.6.4 Vision tools

1. Are there changes to vision during pregnancy, which can be detected by the NEI VQL 42 validated vision questionnaire (Appendix 10)?
2. Are there changes to vision during pregnancy, which can be detected using the online FrACT VA measurement tool Bach, (2023)?.

3.6.5 Justification

This study was designed in response to the moratorium on face-to-face data collection as a result of the COVID-19 pandemic (Appendix 4). The direction of the research changed focus onto participants' experience of vision during pregnancy. This would be achieved through the completion of a validated questionnaire in each trimester, and optionally using an online vision tool to measure the VA in each eye. It was noted in Section 2.7.1.10 that biological functions and senses can be altered during the menstrual cycle due to the fluctuation in circulating SSH levels (Soma-Pillay *et al.*, 2016; Cameron, 2014). These alterations include several ocular and optometric characteristics but the existing evidence base is unclear about the magnitude of these effects (Mehdizadehkashi *et al.*, 2014; Manges *et al.*, 2005; Pizzarello, 2003).

3.6.6 Study design

The study type is longitudinal which involves within-subjects repeated measurements, with the participants completing an online validated vision questionnaire and a self-administered online VA measurement. The VA test can be completed in normal room illumination using a personal computer, laptop or tablet device. The tests are self-administered via a study WebApp and data collection is performed at three points during the pregnancy and once post-partum. The inclusion and criteria are listed in Table 3-2.

Table 3-2 Plan B (VIP-online) inclusion and exclusion criteria

Inclusion
Between 18 and 40 years old
In first trimester
Exclusion
Diabetes
Any mucopolysaccharide disease
Systemic medications known to affect vision
Pregnancy has been facilitated by IVF
Drug or alcohol dependency
Vulnerable adult
Any ocular disease known to affect vision

3.6.7 Sample size

A simple approach to sample size determination for research of this type is to aim for the maximum number of participants that it is feasible to test, within the time available, as more participants result in narrower confidence intervals. However, it is also important to ask what is the minimum number of participants that would be required for a clinically significant change in visual acuity to reach statistical significance. A sample size calculation was carried out with GPower version 3.1.9.2, following the method and recommendations of Prajapati, Dunne and Armstrong, (2010) for repeated measures ANOVA.

The calculation was based on an effect size of 0.20, alpha 0.05, power 0.80, and correlation among repeated measures of 0.5. This gives a sample size of 36 (Appendix 5). As the participant attrition rate is expected to be high, and to provide greater internal validity, recruitment will continue for a six-month period from commencement or until a maximum of 72 participants has been reached, whichever is reached sooner.

3.6.8 Consent

The rationale for consent is outlined in Section 3.5.7. The established method of obtaining consent from participants occurs with face-to-face interaction between the researcher or their representative and the participant. This process provides the opportunity for participants to be informed about the implications of the research, ensures that the research satisfies regulatory requirements and helps mitigate any liability to the research institutions. This tried and tested process results in the participant providing a 'wet' signature on a paper consent form and providing participant and researcher with a hard copy. There are practical challenges to the consent process around organising face-to-face meetings (Welch *et al.*, 2016); however, the consent process is a vital part of any research as it is designed to inform any potential participant of the risk and benefits of taking part in the study and affords them opportunity for reflection prior to signing, avoiding coercion.

3.6.8.1 eConsenting

Although the COVID-19 pandemic accelerated changes to the consenting process, this was already occurring prior to the pandemic for low-risk studies, but concerns have been raised around adherence to those protocols which afford participant protection (Stevens *et al.*, 2016). The use of remote, digital or online consenting has been termed 'eConsenting' (Skelton *et al*., 2020) However, the convenience and practicality for participants of being able to consent remotely, from telephone / verbal or by electronic online processes, provides advantages for the researcher and any potential participants. Multiple authors have commented on these benefits and outline that eConsenting gives an opportunity to provide information which participants can digest at their own pace and helps to establish a relationship between the participant and the researcher (McGowan *et al.*, 2018; Wood *et al.*, 2011).

However, there is research suggesting that people read and process information differently between hard and digital copies; skimming over detail and searching for key words with digital text, which is further compounded by the cultural context of tech users being conditioned to accept all conditions in order to access the software, without fully reading and understanding the detail (Weinreich *et al.*, 2008). This creates a challenge for the eConsenting process and Geier *et al.* (2021) focused on whether eConsenting processes could be supported with combined measures such as conversations with the researcher. The suggestion has been made around introducing the concept of designed friction within the software. Users expect any software process to be seamless, without the challenge of clicking or moving webpages, but it has been suggested that deliberately introducing friction points into a process makes the user take time to think and this is something which could be introduced within the informed consent process (Wilbanks, 2018).

Skelton *et al.* (2020) performed a literature review on e-consenting in clinical studies and found that this approach was well received by participants and has the facility to support remotely conducted research. Gesualdo *et al.* (2021) carried out a systematic review of the use of digital tools during the consent process and also yielded positive conclusions around the benefits of digital tools during patient consent.

3.6.8.2 eConsenting in vision studies

A PubMed search using the terms: vision and ophthalmology and studies and research and eConsenting was carried out (June 2021) and did not return any results. With the effects of COVID-19 the expectation is that studies will be using eConsenting and this will be reflected in the literature over the next few years.

3.6.8.3 Consenting process for the VIP online study

The study was promoted via multiple routes and participants were required to actively reach the study WebApp page and complete the eConsent to participate. Information about the study was available on the WebApp, in multiple languages (Hindi and Gujarati), and to meet accessibility requirements the information was available in large print format.

The WebApp also provided potential participants with the opportunity to ask the researcher questions using a dedicated study email address. The consent process involved participants actively having to tick a series of boxes to acknowledge that they had read and understood what is involved in participation; there was no option to multi check with a single click. This eConsenting process was approved by the IoO, LSBU and HRA RECs. Participants were able to actively withdraw by emailing the researcher and passively withdraw by not completing any of the data collection events.

3.6.9 Plan B (VIP-online) enrolment questions

In conjunction to the consenting and assertion questions (Table 3-3) participants were also asked a series of questions to provide contextual information to supplement data from the vision tools (Table 3-4).

Table 3-3 Plan B (VIP-online) consenting and assertion questions

I have read and understand the information sheet and have had the opportunity to ask questions.
From the information sheet, I understand the nature and purpose of the research and I believe I understand what is being proposed.
I have read the “Can I take part?” Section of the website and I am suitable to take part.
I understand that my personal involvement and my particular data from this study will remain confidential.
I understand that relevant Sections of the data collected during the study may be included in academic publications and presentations and used to develop educational resources if appropriate.
I understand that the results from the data collected during the study, where it is relevant to my taking part in this research, may be looked at by individuals from the research team or from regulatory authorities. I give permission for these individuals to have access to my data.
I understand that my participation is voluntary and that I am free to withdraw from the study any time, without giving any reason, without my medical care or legal rights being affected.
I understand that once the data which has been collected, has been analysed, this will remain in the study, even if I do not participate any further in the study.
I understand that all my information will be stored securely, on a password protected computer in an environment which is locked when not in use, with only the researcher having access to any identifiable data, and destroyed after the results have been published in accordance with university policy.
I hereby fully and freely consent to participate in this study.

Table 3-4 Plan B (VIP-online) supplementary participant question

How do you prefer to be contacted: Text, Email, Both
Do you wear glasses or contact lenses: Y/N
Do you wear them all the time or selectively?
Which do you use – glasses, contact lenses or both?
When do you wear them?
Do you drive? Y/N
Do you drive with glasses? Y/N
How many weeks pregnant are you? (1-12)
Do you have any other children? (1,2,3,>4)
When is you baby due? Month, Year
Are you taking folic acid? Y/N
Approximately, how many weeks have you been taking folic acid? (1-18)

3.6.10 Data collection points

There was a total of four questionnaires to be completed throughout the study and these were completed once in each trimester during pregnancy and once during the first trimester post-partum. The first data collection point was used as the reference point from which the other data collection dates were calculated.

3.6.11 Calculations for data points

- 1st questionnaire

  Within the first trimester and used as baseline for all subsequent data collection events
- 2nd questionnaire date

  Baseline date + 91 days (13 weeks)
- 3rd questionnaire date

  Baseline date + 182 days (26 weeks)
- Post-partum questionnaire date

  Baseline date plus + 280 days (40 weeks)

This process is outlined in Figure 3-2.

3.6.11.1 Invitation timings

During the consenting process participants were asked for their contact method preference and this was used to send out invitations; the options were by email, SMS or both (Table 3-4). The first invitation was sent 10 days prior to the data collection point. A second invitation was sent on the date on which data collection was due. If there was no response a further invitation was sent 10 days after the data collection point.

3.6.11.2 Pre-term and overdue dates

The duration of pregnancy has been outlined in Section 1.8.3 and the timeframes for pre-term and overdue births have been incorporated into the schedule for invitations. The invitation date for the 3rd questionnaire allowed for the possibility of a pre-term birth and the invitation date for the 4th questionnaire allowed for the possibility of an overdue birth.

3.6.12 Reminders

The reminder process was robust enough to ensure that participants were prompted to engage, being aware that emails and SMS can often be overlooked or missed. It also provided participants with the opportunity to passively withdraw. The researcher was cognisant that complications with the pregnancy and birth could potentially occur which may be distressing for the participant and that they may wish to withdraw, but not to take steps to actively withdraw from the study. Frew *et al.* (2014) carried out a review of the barriers to retention of pregnant women in clinical studies; however, this did not cover physical complications of pregnancy.

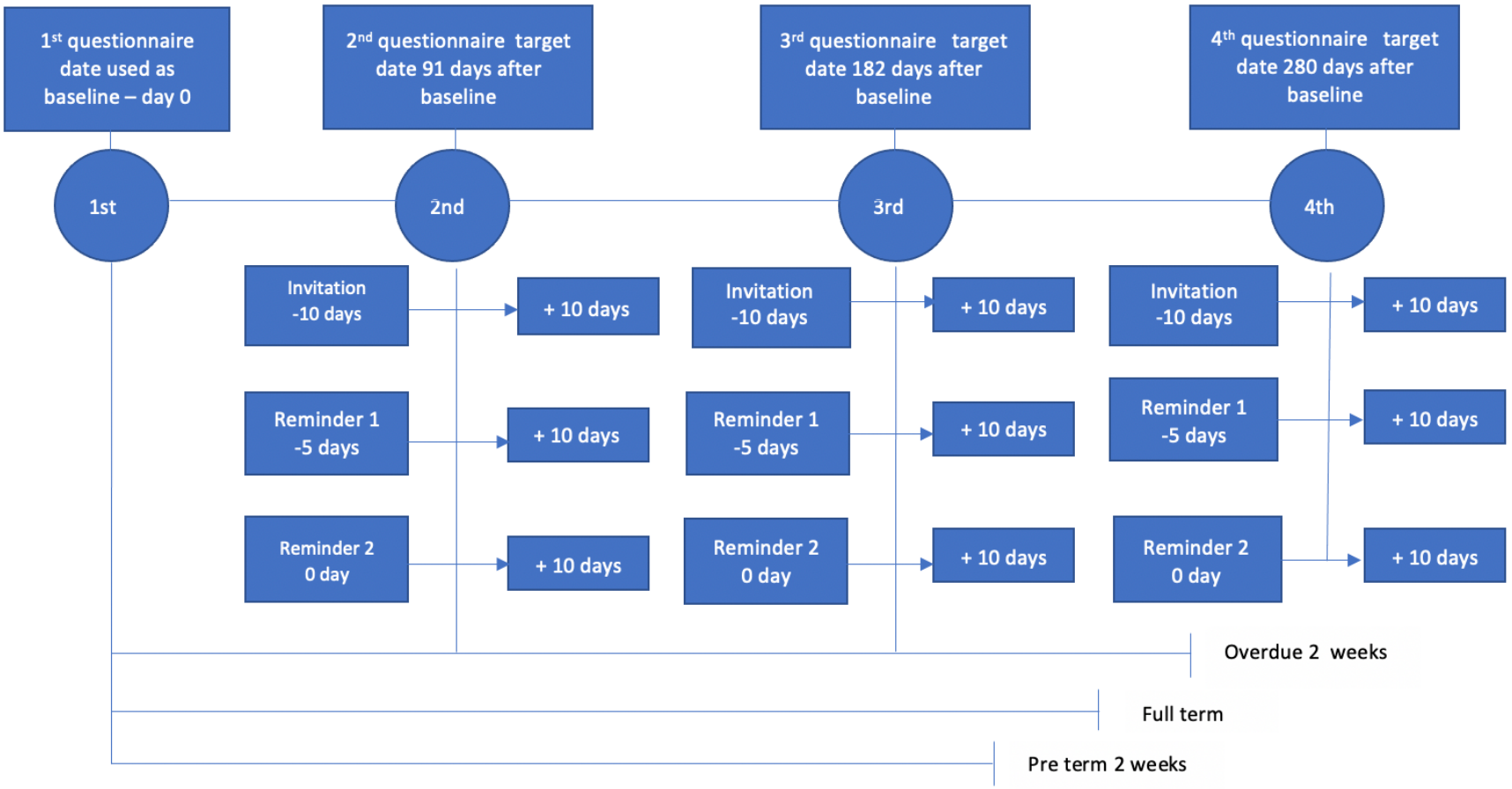

Figure 3-2 Plan B (VIP-online) data collection point

3.7 Plan C – Vision in the menstrual cycle (VIMC) with online data entry

3.7.1 Section overview

The research question was to investigate whether variations in SSH hormones have any effect on vision and dry eye during the menstrual cycle. The COVID-19 pandemic necessitated a deviation from the original study methods and an alternative approach was designed but, due to poor recruitment, the study was widened to consider whether the SSH variations during the normal menstrual cycle had any effect on vision and dry eye.

3.7.2 Aims of section

To outline the rationale of designing an additional study arm and describe its relevance and association to the original study, along with its design.

3.7.3 Research question

Are there any statistically significant and/or clinically significant differences in vision during the menstrual cycle and can any conclusions be drawn from the data to support how healthcare practitioners manage their patients? To help consider this question, a validated vision questionnaire and a self-administered online visual acuity measurement tool were employed; these tools were used to answer the below sub-questions below:

1. Are there changes to vision during the menstrual cycle which can be detected by the NEI VQL 42 validated vision questionnaire?
2. Are there changes to vision during the menstrual cycle which can be detected using the online FrACT VA tool?
3. What is the effect of the menstrual cycle on dry eye symptoms, assessed using the SANDE (Copyright © 2000. Massachusetts Eye and Ear Infirmary. All rights reserved) dry eye questionnaire?

3.7.4 Permissions for vision tools

- NEI RQL-42 is open source and did not require any specific permissions; there are caveats to its use (Appendix 6).
- Permission to use the FrACT online vision measurement tool was sought from the developer, Prof M Bach, and granted (Appendix 7).
- Permission to use the Sande dry eye questionnaire was sought from the developers and granted (Appendix 8).

3.7.5 Justification

A physiological fluctuation of SSH (Section 1.7.3) occurs during the menstrual cycle (Speroff and Vande Wiele, 1971) and SSH receptors are present in ocular structures (Gupta *et al.*, 2005) and have a direct role in ocular surface disease (Murube, 2010); however, their role, if any, in the refractive status of the eye is unclear. Increased corneal sensitivity occurs around the time of ovulation (Guttridge, 1994; Riss *et al.*, 1982; Millodot and Lamont, 1974) and may occur as a direct result of the fluctuation in SSH levels or as a result of changes to the tear film structure (Versura, Fresina and Campos, 2007) or a combination of both.

3.7.6 Study design

The study type is longitudinal, involving within-participant repeated measurements, with the participants completing an online validated vision questionnaire and a self-administered online VA measurement. The VA test can be completed in normal room illumination using a personal computer, laptop or tablet device. The tests are self-administered via a study webapp and data collection is performed at three points during the menstrual cycle.

3.7.7 Inclusion & exclusion criteria

The rationale for the inclusion criteria was that participants should be able to consent and have a predictable menstrual cycle, as this will help with the understanding of the relevant key hormonal points within the study timeframe.

The rationale for the exclusion criteria is any medical condition which could compromise the ability to consent to participate in the study or any medical / physiological condition which causes disruption to the normal menstrual cycle or any pre-existing ocular or medical pathology which could directly or indirectly affect VA. Women taking the 'mini pill' have been excluded, as progestogen- only hormone contraception affects regular menstruation (Kovacs, 1996). Table 3-5 lists the inclusion and exclusion criteria which are made available for participants to review.

3.7.8 Sample size

The same approach as Plan B (VIP-online) was adopted (Section 3.6.7). A sample size calculation was carried out with GPower *version 3.1.9.2* following the method and recommendations for repeated measures ANOVA (Prajapati, Dunne and Armstrong, 2010). The calculation was based on an effect size of 0.20, alpha 0.05, power 0.80, and correlation among repeated measures of 0.5. This gives a sample size of 36 (Appendix 9). As the participant attrition rate is expected to be high, and to provide greater internal validity, recruitment will continue for a six-month period from commencement or until a maximum of 72 participants has been reached, whichever is reached sooner.

Table 3-5 Inclusion and exclusion criteria

Inclusion criteria
Females 18 yrs. and older
Regular menstrual cycle
Exclusion criteria
Pregnant
Breast feeding
Amenorrhea (having no periods)
Progestogen based contraception
Menopause: peri/during/post
No existing ocular pathology
Mucopolysaccharide diseases
Diabetes
Drug or alcohol addiction
Vulnerable adult
Medications which are known to affect vision

3.7.9 Consent to participation

The rationale for consent is outlined in Section 3.5.7.

3.7.10 Consenting process for the VIMC online study

The process for the study is the same as that described in Section 3.6.8. for Plan B (VIP-online).

Table 3-6 Information obtained following consent

What is the name you would like us to use when communicating with you?
Select a username.
Enter your email address.
How do you prefer to be contacted? SMS or email
Please enter your mobile phone number
How old are you? 18-55
Do you wear glasses or contact lenses? Y/N
Do you wear them all waking hours or just for some activities? All waking hours or just for some activities
Which do you use – glasses, contact lenses or both? Glasses, contact lenses, both
When do they help you see better? For distance, for reading, for both
Do you drive? Y/N
Do you wear glasses or contact lenses when you drive? Y/N/Sometimes
Approximately how old were you when you started having periods? 11-17
Approximately, what was the date when your last period started? Day: Month: Year
Please estimate, as best as you can from memory, the average length of your menstrual cycles over the last 6 months? 21-35 days
Are you taking any medication? Y/N, please list if any.

3.7.11 Contact at sign up

On signing up to participate in the study a welcome email is sent to the participant, thanking them for participating in the study. Using the information provided during the sign up, the dates of data collection are calculated and these are included within the welcome email to provide the participant with the dates in advance.

3.7.12 Data collection points

Data collection points were chosen to coincide with key points during the normal menstrual cycle: the first day of the period, point of ovulation and the peak progesterone levels (Figure 3.3). These dates were calculated from the participant data, on their menstrual cycle duration and the approximate date of last period.

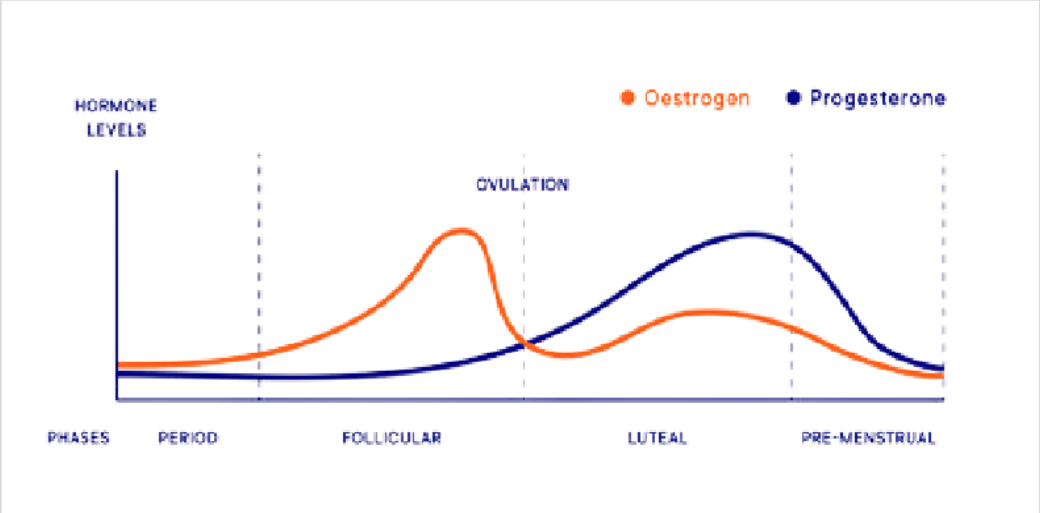

Figure 3-3 Phases of the menstrual cycle

3.7.13 Normal menstrual cycle duration

The normal menstrual cycle is 28 days +/- 4 days (Franz, 1988). During the consent and sign-up process women were asked to estimate, as best as they could from memory, the average length of their menstrual cycles over the last 6 months. These were grouped into whether their menstrual cycle was routinely < 28 days, 28 days or > 28 days.

Although there are some fluctuations around the peak levels of oestrogen and progesterone (Figure 3-4), these points were chosen as data collection points (Howarth and Clemes, 1971; Speroff and Vande Wiele, 1971).

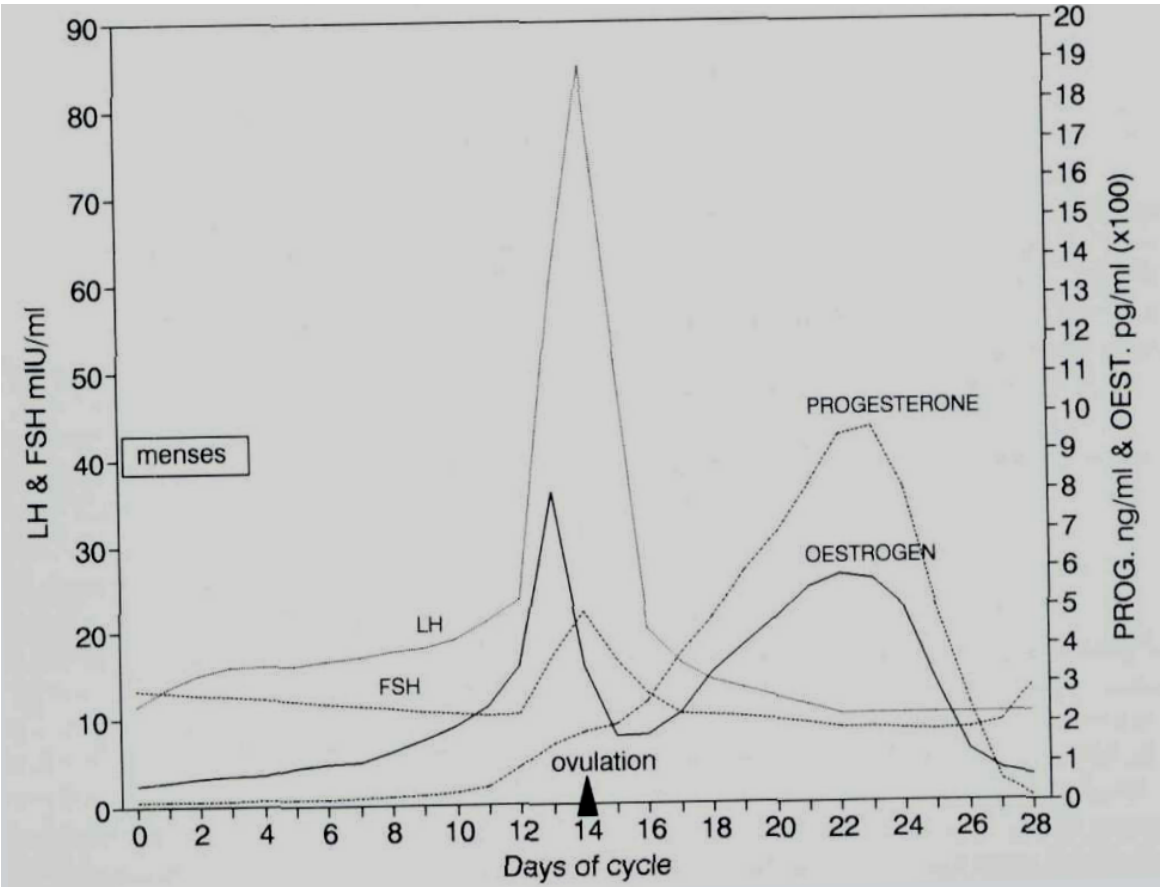

Figure 3-4 Plasma levels of female sex hormones during the menstrual cycle. Taken from: Speroff, L. and Vande Wiele, R.L. (1971)

3.7.14 Rationale for the data collection points

The planned data collection points are based around the key hormonal stages throughout the menstrual cycle. The study aimed to collect three data samples from each participant: one on the first day of their period, a second when oestrogen reaches a maximum, around ovulation on days 12-14, and a third when progesterone reaches a maximum around day 20-23 (Speroff and Vande Wiele, 1971). When participants consent and sign up to the study, they are asked for the date of the start of their last period and this date acts as a reference point for sending reminders to complete further data collection (Figure 3-5). Wegienka and Baird (2005) found that women were fairly accurate in recalling the day of the of LMP.

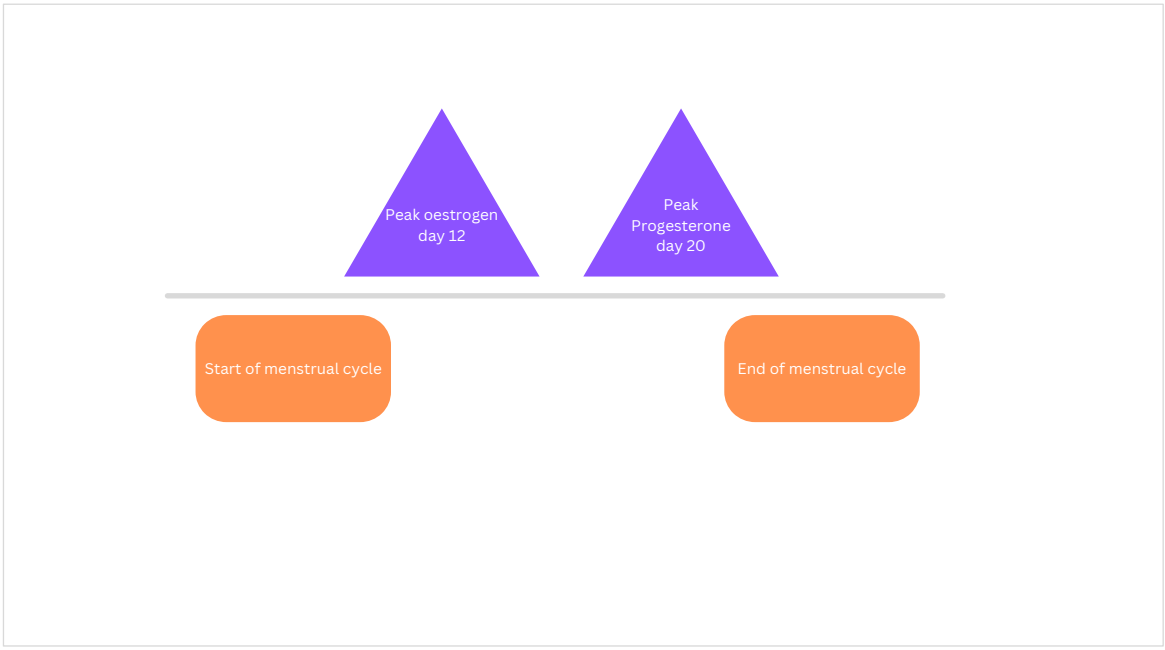

Figure 3-5 Plan V (VIMC) overview of data collection points

3.7.15 Cycle duration amended data collection dates

The algorithm used to determine the point of ovulation, peak progesterone and first day of the menstrual cycle uses the participants' reported average cycle length; recorded during the sign-up questionnaire (Table 3-6). The difference between the actual and average menstrual cycle length produces a correction factor (CF).

3.7.15.1 Correction factor versus aggregate calculation

Section 3.7.12 outlines the data collection points during the menstrual cycle; the luteal phase of the menstrual cycle is approximately constant around 12 days with the average time between ovulation and peak progesterone being 8 days (Thiyagarajan, Bashit and Jeanmonod, 2022). If an aggregate approach to different cycle lengths was used, this would produce errors in calculating the three data points with the potential to affect the study outcome.

3.7.15.2 Correction factor examples

For cycle lengths less than 28 days a negative CF is applied to the point of ovulation and for cycle lengths greater than 28 days a positive CF is applied.

Table 3-7 Examples of correction factor for different menstrual cycle duration

Cycle length	Correction factor	Ovulation	Progesterone peak	Start of period
28	0	12	20	28
32	+4	16	24	32
24	-4	8	16	22

3.7.16 Recall invitations

For each participant, on the date of data collection an email is sent with a web link to the relevant questionnaire. All the reminders are sent on the same email thread for continuity and the emails were written in a professional but friendly manner to build working relationships to promote engagement with the study.

If a participant misses less than three data collection events, then new dates are calculated for the data points which have been missed. If all three data collection events are missed, a new set of dates is calculated and sent to the participant. After completion of the third data collection event, a thank you email was sent to participants and asking them if they would kindly forward details of the study to friends and colleagues.

3.8 Section summary

Including this arm in the research creates an interesting dimension and provides further detailed information on the subject of whether variations in SSH cause clinically significant changes in vision. Amendments to the WebApp design were undertaken and promotion of the study used many of the existing networks established for the original plan but with a potentially wider audience to facilitate recruitment.

3.9 Chapter summary

This chapter has outlined the research philosophy and design of the three sequential study plans which were developed, in response to the effects of the COVID-19 pandemic.

Chapter 4 Methods

4.1 Chapter overview

Chapter 3 outlined the iterative study designs which were created in response to the COVID-19 pandemic. The original research Plan A (VIP), was designed prior to the pandemic and approaching recruitment the LSBU moratorium on face-to-face research was implemented. This resulted in the design of Plan B (VIP-online); however, limited recruitment due to the continued effects of the pandemic, necessitated the development of Plan C (VIMC). This chapter will outline and discuss the following topics for each of the three study plans outlined in Section 3.4.

- Data collection methods
- Ethics approval
- Recruitment process
- Data analysis

4.2 Plan A (VIP)

4.2.1 Section overview

This plan for this study was to measure the refractive error and visual acuity of participants using an auto-refractor and a LogMAR letter chart. Both these instruments are portable and provide measurements within a short time frame. The data collection methods combined with the choice of instruments and the rationale for use will be outlined.

4.2.2 Auto-refractor

An auto-refractor is a non-invasive instrument used to determine the objective refractive status of the eye (Millodot, 2009). The types of refractive error have been outlined in Table 1-1.

Auto-refractors can be handheld or table mounted, with the measurement process being completed in under one minute for each eye. Objective measurements can also be obtained using a clinical technique called retinoscopy (Eskridge, 1991). In clinical practice, subjective refraction is taken to be the reference standard. During clinical examination, objective measurements can be used as a starting point when determining subjective measurements and can also be used for non-communicative subjects. However, intra-optometrist variation with subjective refraction measurement has been researched, demonstrating that there can be clinically significant variations between optometrists (Garcia-Lozada, 2011).

4.2.3 Literature search

4.2.3.1 Aims

To review the current primary research literature in order to evaluate whether auto-refractors are an accurate and reliable method of measuring objective refraction and whether this method of measurement could be used in future research studies.

4.2.3.2 Objectives and methodology of literature search

A literature search was performed (search last updated April 2023) using the Cochrane library, Pubmed and Visioncite databases using the following keywords: “autorefractor and objective refraction”, “autorefractor and subjective refraction”, “autorefractor and autorefractor and accuracy”, “autorefractor and true”, “autorefractor and reliability”, “autorefractor and repeatability”, “autorefractor and duplication”, “autorefractor and portability”, “autorefractor and moveable”, “autorefractor and handheld”, “autorefractor and adult population”, “autorefractor and cycloplegic refraction”, “autorefractor and sensitivity & specificity”. Using the inclusion and exclusion criteria in Table 4-1, ten relevant papers were identified with other publications being identified from the bibliographies of these papers and included where relevant. All additional articles were included if they made an original or significant contribution to the literature.

Table 4-1 Auto-refractor literature review inclusion and exclusion criteria

Inclusion criteria
Studies looking at commercially available instruments
Studies which explore the accuracy, reliability, repeatability of auto-refractors in the adult population, (adult population used for the management of accommodation) or cycloplegic vs non cycloplegic
Comparison of refraction by auto-refractor and subjective refraction in adult population
Exclusion criteria
Studies which explore other aspects of auto-refractors
Studies which explore accuracy in children but do not use cycloplegia
Use of auto-refractors in specific ocular conditions
Use of auto-refractors in vision screening

4.2.3.3 Themes

There were several common themes within the studies and an understanding of the relevance and comparison of these enables the studies to be assessed and their outcomes placed into context.

4.2.4 Study design

Commercially there are multiple manufacturers supplying auto-refractors, each having different design features to achieve the objective measurement. The design principles are beyond the scope of this review.

The study designs either use the same instrument on all participants (de Juan *et al.*, 2012; Farrok *et al.*, 2005; Harvey *et al.*, 1997; Adams, *et al.*, 1994) or use different instruments on the participants, which has the potential to introduce instrument errors (Hashemi *et al.*, 2016; Strang *et al*.,1998). The instruments used in these studies are listed in Table 4-2.

Table 4-2 Auto-refractor Instrument types and studies

Instrument type	Studies used
Hoya AR 570	Adams *et al.*, (1998)
Nidek ARK 30	de Juan *et al.*, (2012)
Shin Nippon SRW 5000	Mallen *et al.*, (2001)
Nidek 530-A	Bennett *et al.*, (2015)
Nikon Retinomax	Farook *et al.*, (2005) Harvey *et al.*, (1997)
Topcon RM 8000	Farook *et al.*, (2005)
Topcon KR 8000	Hashemi *et al.*, (2015)

4.2.4.1 Refractive error range

The ideal outcome of a study would be for the findings to have clinical relevance across the general population; for this to occur the participant cohort should have a range of refractive errors reflecting those found in the general population or within a specialist clinics. Several studies did not state the range of the refractive errors of the participant cohort. Hashemi *et al.* (2016) had a large cohort but a limited refractive error range, which did not appear to be reflective of the general population (Williams *et al.*, 2015). Mallen *et al.* (2001) gave a refractive error range of -15.00D to +6.50D, but then went on to state that participants with a refractive error of greater than -10.00D or +2.50D were outliers and removed from the analysis. However, excluding participants with greater than +2.50D of hyperopia is not representative of the upper limit of hyperopia found in the general population and this could affect the positive outcome of the study (Williams *et al.*, 2015). Strang *et al.* (1998) was the only study in which participants' refractive error was moderately representative of the general population (Williams *et al.*, 2015).

4.2.4.2 Accommodation & cycloplegia

Accommodation is the functional ability of the eye to increase the focusing power, through a shape change in the crystalline lens (Millodot, 2009). This function primarily occurs when viewing near objects and caused by different stimuli. However, this focusing ability can also be used to overcome hyperopic refractive errors and auto-refractors require a mechanism to control this accommodative ability, as it has the potential to affect the measurements. An active accommodation creates a more myopic / less hypermetropic refractive error measurement; this can also occur during subjective refraction but clinical techniques are used to overcome this.

The eye's accommodative ability reduces with age, with the reduction becoming functionally noticeable in the 4th decade with little functional accommodation remaining in the 6th decade (Charman, 2008). An understanding of the participants' age demographics allows assessment of whether any accommodative controls are required and if appropriate controls have been employed. Accommodation is greatest in young children and can be controlled by a pharmaceutical agent which induces cycloplegia; this process is commonplace when assessing paediatric subjects but has the disadvantage of causing discomfort and resultant transient visual blurring. Harvey *et al.* (1997) described measuring subjective refraction after cycloplegia has been induced in young children; clinically, this is inappropriate as subjective refractions with young children can be challenging without overcoming the visual blurring from cycloplegia.

4.2.4.3 Participant demographics

Prevalence of refractive error in adults is known to vary with ethnicity; South-East Asian ethnicities have a greater prevalence of myopia and astigmatism (Pan *et al.*, 2013) suggesting that participant demographics could potentially influence the outcomes of the study. The outcome of the study could be affected if accommodative controls are not used for those subjects with active accommodation; this can lead to auto-refractors giving greater myopic refractive error. As mentioned in Section 4.2.4.2, accommodation is greatest in young children; if the participant cohort consists of adults the outcomes may not be applicable to children.

Harvey *et al.* (1997) investigated the validity of the instrument in assessing children's refractive errors compared to de Juan *et al.* (2012) which focuses on an older population who have undergone cataract surgery. The significance is that an auto-refractor that has a poor control over accommodation is unlikely to be suitable for use with a paediatric population but may be appropriate for use with adults.

4.2.4.4 Analysis of refractive errors

The analysis of refractive errors has been discussed in Section 1.11. Hashemi *et al.* (2015) used the MSE method in the data analysis, with the remainder using the vector notation method (Thibos, Wheeler and Horner, 1997).

4.2.4.5 Study methodology and methods

Research reviewing the validity of auto-refractors can be broadly placed into three categories:

1. Those comparing auto-refractor measurements to manual objective refractions; these occur when young children are the subject group (Harvey *et al.*, 1997)
2. Those comparing cycloplegic auto-refractor and subjective measurements (Hashemi *et al.*, 2015)
3. Those comparing eyes without cycloplegia and subjective measurements (Bennett *et al.*, 2014; Farook *et al.*, 2005; Mallen *et al.*, 2001; Strang *et al.*, 1998)

A typical research design for studies considered in this review is that data about refractive error were collected by recording measurements directly from the instruments. Strang *et al.* (1998) used a mixed methods study, with the remaining studies being quantitative. Sample sizes varied between the studies. Hashemi *et al.* (2015) used a large participant cohort, with the remainder of the studies using small cohort groups. The age range of the cohorts used in all the papers were stated but there was little detail about the age groupings. Several studies did comment on the percentages of myopia and hypermetropia within the cohort (Mallen *et al.*, 2001; Strang *et al.*, 1997).

Mallen *et al.'s* (2001) study was well designed and compared subjective and auto-refractive measurements. However, the small cohort and limited range of hypermetropia reduces its influence for routine clinical practice. The findings from Mallen *et al.* (2001) demonstrated good correlation between the two measurement methods which is supported by Farook *et al.* (2015) and Adams *et al.* (1998). Farook *et al.* (2015) suggest that handheld instruments were less accurate than table-mounted instruments; with a mean increase in myopia of 0.63D. Research by de Juan *et al.* (2012) demonstrates that although there are statistically significant differences between measurements from subjective and auto-refractor methods these are not clinically significant, and auto-refractors can be used successfully in post cataract surgical settings.

Strang *et al.* (1998) adopted a different approach and assessed the visual comfort of the participants when they wear glasses prescribed based on auto-refractor measurements compared to subjective refraction. Although there were marginal differences in participant responses, the authors felt that it was inappropriate to prescribe from auto-refractors. This would be an interesting piece of research to replicate with newer instruments and possibly an improved questionnaire. Harvey *et al.* (1997) studied a cohort of children and demonstrated that the accuracy of cycloplegic refraction is comparable with manual retinoscopy. Hashemi *et al.* (2016) used the results from an auto-refractor as the reference standard and this paradigm shift could have potential uses for future research.

4.2.4.6 Instrument selected for Plan A (VIP)

After reviewing the available literature, the Nidek Retinomax instrument was chosen for the study. The instrument is portable and provides both the refraction and corneal curvature.

4.2.5 Conclusion

There continues to be interest in developing an auto-refractor which could provide objective refractions equivalent to subjective refractions, as this could be exploited commercially. However, there are inherent difficulties which need to be overcome such as controlling the accommodative mechanism and obtaining reliable readings in the presence of lens opacities.

The idea of an automated instrument, which could produce accurate and reliable refractions, would be received with equal amounts of welcome and dismay by different stakeholders in the optical sector. Research has shown that auto-refractors have better repeatability compared to subjective refractions (Bullimore, Fusara and Adams, 1998) and the research suggests that auto-refractors are accurate and repeatable where cycloplegia has been used (Harvey *et al.*, 1997) and also for pseudophakic patients (de Juan *et al.*, 2012). After reviewing the literature and consideration of the themes, the Nikon Retinomax instrument was chosen for the VIP-F2F study. This instrument is portable, handheld and provided both refraction and keratometry readings.

4.2.6 Vision test chart

The principle and designs of vision test charts have been discussed in Section 1.9.2 The study would use a LogMAR vision test chart presented on a Tablet (iPad). This would enable the vision test chart to be corrected for various testing distances. Vision measurements are then recorded in LogMAR notation.

4.3 Plan B (VIP-online) & Plan C (VIMC)

4.3.1 Section overview

These studies were both planned with the intention of using the same tools; an online vision questionnaire and an online vision measurement test. The evolution of the questionnaire format and their challenges will be considered. Online vision tests are becoming more ubiquitous and the types and testing protocols are considered.

4.3.2 Online questionnaires

4.3.2.1 Section overview

Plan B (VIP-online) and Plan C (VIMC) studies use the same data collection tools, which comprise of a validated vision questionnaire and a self-measurement visual acuity test. Both of these tools are embedded into a purpose designed and built WebApp by the researcher.

Vision questionnaires were developed at a point in time when they were designed to be completed in paper format but in the digital age there is an expectation from researchers and participants that surveys and questionnaires will be completed in an online format; the response rates and participant attrition, between paper and digital surveys and questionnaires are considered.

4.3.2.2 Surveys versus questionnaires

The term survey and questionnaire are often used synonymously; however, this is erroneous as surveys are the process of collecting data, with questionnaires being the tool to help answer the research question. The design of a questionnaire is important, to ensure that it is efficient and effective (Tsang, Royse and Terkawi, 2017) and validated questionnaires should be used where possible to achieve this (Jones, Baxter and Khanduja, 2013). Online surveys offer the advantage of fast deployment, wide reach and lower costs, combined with benefits of automation (Ball, 2019).

4.3.2.3 Participant preference

Although there is an increasing acceptance of online processes, from shopping to medical care, there is still concern around how potential participants may perceive and engage with research questionnaires. In contrast there is also concern that limiting questionnaires to online may restrict equality of access, with the potential to exclude those who do not / or choose not have internet access. Trouvier *et al.* (2010) found an overwhelming participant preference to use an online reporting process compared to a paper-based approach.

4.3.2.4 Recruitment

Singh and Sagar (2021) commented that many online surveys are conducted via email or by an online survey platform, with the survey / WebApp link being shared widely on social media platforms, websites or with eligible contacts. The term ‘snowballing’ is used when participants are recruited by other participants; this recruitment method increases the sample size but reduces the ability of the findings to be generalised with data being unknown about those who were invited but did not participate.

Ameen and Paraharaj (2020) suggest possible mitigations to snowballing by randomly selecting the required number of respondents from a defined list, with a request not to forward the questionnaire to anyone else and collecting information about those who decline to participate and sending the questionnaire only to those who consent to participation.

4.3.2.5 Response rate

The response rate is a metric used to interpretate the efficacy of a survey and is predicated on knowledge of the numbers of invitees to participate in the survey. This can create challenges with online studies and several authors have recommended that studies using online surveys / questionnaires should publish this metric to help demonstrate the rigour of the study. The CHERRIES (Checklist for Reporting Results of Internet E-Surveys) guideline has been created with the aim of improving the quality of online surveys (Sharma *et al.*, 2006; Eysenbach, 2005).

The literature offers conflicting insights into the response rates of online surveys compared to traditional paper-based surveys. Fricker *et al.* (2005) and Aquilino (1991), found that online response rates were lower than traditional response rates for telephone surveys, which in turn are lower than response rates to surveys using face-to-face methods. However, Callegaro *et al.* (2015) suggest that participants prefer electronic survey modalities, for ease and convenience but response rates do vary for a multitude of reasons such as: survey fatigue or competing demands and privacy concerns. In contrast to this, a later study suggests that there could be slightly lower response rates with online surveys, but providing a significant cost/benefit ratio (Ebert *et al.*, 2018).

Hohwü *et al.* (2013) suggest that online surveys could replace paper-based formats and Clayten *et al.* (2013) found that for a dry eye questionnaire a web-based survey yielded the same response rates as paper-based formats. Fincham (2008) found that response rates to electronic surveys are highly variable and, without the use of follow-up reminders, are in the range of 25%–30%.

4.3.2.6 Participant demographics

The demographics of participants have the potential to affect response rates which may be related to technological literacy of the participants. Fang *et al.* (2021) found this to be the case with older generations preferring a traditional mode of survey but Kusomoto *et al.* (2017) found that older generations were just as comfortable with using online surveys as younger groups; but this finding could be due to the group of participants being highly engaged with the study. In support of this, Trouvier *et al.* (2010) study has an age range between 45-75 years old and this research found that participants expressed an overwhelming preference for an online format.

4.3.2.7 Survey duration

Several authors commented that the response rate to electronic surveys is not associated with the questionnaire length, but recommend that the duration be under 20 mins (Menon and Muraleedharan, 2020; Revilla and Ochoa, 2017). It has been reported that duration to complete the survey can be linked to other factors such as familiarity with device and platform.

4.3.2.8 Reminders

McPeake, Bateson and O'Neill (2014) suggest that response rates to electronic surveys can be improved by adopting a strategic approach involving: sending up to three reminders, personalising each email, adding the updated response rate to reminder emails along with stating the average time it would take to complete the survey in the title of the email.

Sending reminders or reinforcements has been found to positively influence survey response rates (Fan and Yan, 2010), with rates appearing to improve up to a ceiling of three or four reminders, beyond which concerns about spamming or pressurising respondents start to increase (Muñoz-Leiva F *et al.*, 2010). A Cochrane review found response rates could be positively affected by pre-notifying respondents, shortening questionnaires, incentivising responses and ensuring multiple follow-up contacts (Edwards, 2009).

Multiple authors have found that personalising invitations and adopting dynamic strategies, such as changes in the wording of reminders and including quick response (QR) codes have all been found to augment response rates (Harrison *et al*., 2019; Short, Rebar and Vandelanotte, 2015; Sauerman and Roach, 2013).

A cost-effective hybrid mode has been termed as the web-push survey, where contact is made by mail, requesting participants to make a web-based response; however, it is acknowledged that this increases demands on resources (Delnevo and Singh, 2021). Myer *et al*. (2022), in a review of surveys on surgical patients, concluded that 'every survey is unique, but the main commonality between studies is response rate, which is highly dependent on type of survey, follow-up, geography, and interviewee type'.

4.3.2.9 Section summary

The Plan A (VIP) study asked participants to engage with an online study and commit to complete an online questionnaire at four different points during their pregnancy and post-partum. The VIMC asked participants to engage with an online study and commit to complete an online questionnaire at three different points during their menstrual cycle.

With both the Plan B (VIP-online) and Plan C (VIMC) study, the aim was that any findings could be generalized to the population of women who are pregnant or who have regular periods. For generalisations to be appropriate the study demographics should reflect the target population, and this would normally occur where there is a reliable sampling process, where participants could be selected using a randomized or probability sampling method.

Due to the challenges around recruitment for these studies, this ideal was not possible but as the studies have demographic data, this should permit inferences to be drawn about the representativeness of the study population.

4.3.3 Vision questionnaires

4.3.3.1 Aims of the section

To review the research literature on vision questionnaires and to consider the most appropriate questionnaire to use in a prospective study looking at pregnant women's experiential perception of their vision during pregnancy or during the menstrual cycle. The hypothesis being considered is whether pregnancy has any effect on an expectant mother's visual function, symptoms or refractive status, and whether there are any visual changes during the menstrual cycle. The questionnaire will be required to provide information which will be considered in conjunction with the results of self-administered objective vision measurements.

4.3.3.2 Background

Vision can be considered to be a perceived appreciation of differences in an external world, with perception being multifactorial, consisting not only of visual but also psychological factors (Moschos, 2014). Clinical tests have been developed to measure various aspects of vision, the most common of which is VA. These objective and subjective measurements provide an indication of the visual function but not an individual's perception of their vision.

As health is considered to be an attribute of quality of life (QoL), an individual's perception of any aspect of their health becomes an important consideration (Price *et al.*, 2016). An holistic understanding of an individual's vision can be described as their quality of vision (QoV) (McAlinden *et al.*, 2011); two individuals may have identical visual function in terms of clinical measurements but differ in their perception of QoV (Berry *et al.*, 2003).

4.3.3.3 Ophthalmic questionnaires

Questionnaires are a set of predetermined questions used to collect data (Kember and Leung, 2008). These instruments can be an effective means of measuring constructs of interest within a targeted group (Tsang, Royse and Terkawi, 2017; Kember and Leung, 2008). Generalised instruments have been developed and widely used in healthcare to assess QoL; these are culture and condition specific (Gothwal *et al.*, 2009).

The most commonly used vision questionnaires were the short form (SF) 36 & 20 (Kember and Leung, 2008). These are non-specific instruments and do not explore specific vision-related topics or ocular conditions; this has led to various QoL questionnaires being developed for use in ophthalmology. The complexity of vision, and the effect that various conditions can have on it, make the creation of an ideal instrument somewhat of a nirvana. Many instruments have been created to explore the effects on vision due to various ocular conditions, such as: diabetes or hypertension and cataract.

To gain a deeper insight into an individual's QoV, instruments in the form of questionnaires have been used. Such instruments have contributed to a deeper understanding of the effects of certain ocular diseases on an individual's QoV and QoL. This places importance on an individual's perception of their QoV as an outcome measure of treatment and management of ocular disease. For the outcome data from questionnaires to be relevant, they need to be validated for the condition which they are assessing. Many vision related instruments have been developed and validated for use with various ocular pathologies; the aim of this review is to determine if there are any suitable vision related questionnaires which consider the effects of refractive of error.

4.3.4 Literature search

4.3.4.1 Aims

To review the current primary research literature in order to evaluate whether vision questionnaires would be an appropriate tool to answer the research aim (Section 1.4).

4.3.4.2 Objectives and methodology of literature search

A literature search was performed (search last updated 08.11.23) using the Cochrane library, Pubmed and Visioncite databases using the following keywords: "Vision and questionnaire", "Vision and questionnaire and longitudinal", "Vision and questionnaire and refractive error", "Vision and questionnaire and pregnancy", "Vision & questionnaire & refractive error & pregnancy" and "Vision & questionnaire & refractive error & non presbyopia".

The search results are listed in Table 4-3. Using the inclusion and exclusion criteria in Table 4-4, seven relevant papers were identified, listed in Table 4-5, with other publications being identified from the bibliographies of these papers and included where relevant. All additional articles were included if they made an original or significant contribution to the literature.

Table 4-3 Vision questionnaire literature search outcomes

Keywords	Outputs
Vision and questionnaire	3696
Vision and questionnaire and longitudinal	168 of which 5 were relevant
Vision and questionnaire and refractive error	0
Vision and questionnaire and pregnancy	43 of which 1 was relevant
Vision & questionnaire & refractive error & pregnancy	4 of which 1 was relevant
Vision & questionnaire & refractive error & non presbyopia	0

Table 4-4 Vision questionnaire inclusion and exclusion criteria

Inclusion criteria
Refractive error
Cataracts
Laser surgery
Pregnancy
Exclusion criteria
Glaucoma
Uveitis
Visual fields
Macular degeneration
Low vision
Corneal disease

Table 4-5 Vision questionnaires highlighted from literature review.

Name of questionnaire	Year	Studies
SF 20	1982	Stewart, Ware, and Brook (1978); Stewart, Ware, and Brook (1982.)
SF36	1992	Ware and Sherbourne (1992)
VAQ (Visual acuities questionnaire)	1992	Slone *et al.* (1992)
VF - 14	1992	Mangione, *et al.* (1992)
NEI VF 11 R (Rasch)	1994	Steinberg, E.P. *et al.* (1994)
NEI VQL 25	2001	Mangione, *et al.* (2001)
NEI VQF -25 + 14 optional items)	2001	Mangione, *et al.* (1998)
NEI RQL-42	2002	McDonnell *et al.* (2003); Hays *et al*. (2003); Berry *et al*. (2003)
NEI GQL 15	2003	Nelson *et al.* (2003)

4.3.4.3 Themes

There were several common themes within the studies and an understanding of the relevance and comparison of these enables the studies to be assessed and their outcomes placed into context.

4.3.4.4 Validation

There are multiple measures which can contribute towards assessment of an instrument's efficacy. The validity of an instrument assesses its ability to measure the intended construct, with reliability demonstrating its ability to be replicated (Chen *et al.*, 2017; Wong, Ong and Kuek 2012). An assessment of the instruments construct validity can be made from a review of the nature and grouping of the questions. This includes the convergent and discriminant validity of the questionnaire, which considers the positive and negative correlations, respectively, between the questions and subscales of the questionnaire. The internal consistency (IC) of the instrument is measured using Cronbach's alpha with multi-trait analysis assessing the correlation of items (or questions) within subscales; this process allows questions to be disregarded or moved into another subscale. Discriminant analysis then compares the correlation with subscales versus other subscales (Barry *et al.*, 2017).

4.3.4.5 Rasch analysis

Psychometric modelling analyses the categorical data produced by the questionnaire and is a function between (a) the respondent's abilities, attitudes, or personality traits and (b) the item difficulty (McNeeley *et al.*, 2018; Rasch, 1980). These attributes can lead to nonlinear outcome data, resulting in errors when linear statistical analysis methods are applied. To remedy this issue, Rasch mathematical modelling is applied to the questions during the development of the instrument. Questionnaires developed without Rasch analysis give equal weighting to each item which assumes that each item contributes equally (i.e. has the same difficulty) to the overall assessment of the construct being measured.

Rasch analysis helps define the subscale structure of the items within questionnaires (McAlinden *et al.*, 2011; Gothwal *et al.*, 2009; Lamoureux *et al.*, 2008; Lamoureux *et al.*, 2007; Pesudovs, Elliott and Coster, 2005) giving equal weighting to the questions; this provides linear output data and is referred to as "linear person measurements"(Boone, 2016). Over the last decade the use of Rasch analysis has become the standard means of assessing the validity of a questionnaire (Mönestam, 2016). As well as being used in the design of questionnaires, to define subscale structure, it is also used to dismiss questionnaires on statistical grounds alone (Agramunt *et al.*, 2018; Finger *et al.*, 2012; McAlinden *et al.*, 2012; Gothwal *et al.*, 2010; Gothwal *et al.*, 2009).

However, a major shortcoming of Rasch analysis is the assumption of homogeneity of the questionnaire and the test population (McNeeley *et al.*, 2018). Rasch termed this 'invariant objectivity' (Rasch, 1980; Rasch, 1977; Rasch, 1961). However, these conditions are unlikely to be met as the questionnaire may function differently in participant subgroups or the responses may depend upon more than one underlying construct. An example could be a young participant who undergoes cataract surgery, who may have a different lived experience compared to an older participant who has had the same procedure and yet Rasch analysis assumes this would be viewed in exactly the same manner.

Of the vision instruments in Table 4-6 three have undergone a Rasch assessment but the outcome of each process suggests that each instrument has shortcomings and improvements to the questionnaire could be made. However, Nichols et al., 2003, found that the NEI-RQL-42 and RSVP generally had a good reliability and validity in a sample of patients with a refractive error. McNeely *et al.* (2018) support the suggestion made by Nichols *et al.* (2003), that other factors, such as question content, should be considered in choosing one of these instruments for studies of refractive error correction.

Table 4-6 Vision questionnaires for consideration

Questionnaire name	Use	Relevance to the project	Rasch weighted scoring or validated
VAQ	Everyday visual task	Yes	Gothwal *et al.*,(2009)
NEI VF-14, NEI VF-11 NEI VF-9	Cataracts- but modified & validated?	No	Lamoureux E L *et al.* (2009)
NEI RQL-42	Refractive error	Yes	McAlinden, Skiadaresi and Pesudovs (2011) Outcome: suggest to use alternative vision tool Nichols *et al*. (2003) McNeely *et al*. (2018)
QIRC	Refractive error	No	Pseudovs *et al*. (2004)
RSVP	Refractive error	Yes	Garamendi *et al*. (2006) Outcome: suggests that improvements should be made
SUN	Single question on refractive error & single on pregnancy	No	Fernandez-Montero, (2017)

4.3.4.6 Condition specific

QoL instruments have been developed to be used with participants having specific ocular pathologies, visual deficits or surgical procedures; validation forms part of the development, making the instrument specific for a particular set of conditions. If the conditions are changed, this has the potential to adversely affect the outcome as the instrument may not be as effective or sensitive (Toit *et al.*, 2008). As an example, the EORTC questionnaire was designed and validated for participants who were undergoing treatment for uveal melanoma; existing ocular questionnaires did not explore any issues that the patient group were encountering. Using this questionnaire to explore the experiences of a participant after cataract surgery would not yield relevant information. From the literature search, 11 questionnaires were excluded based on the ocular condition, the remaining six instruments are listed in the Table 4-6. The VF-14 instrument was developed by Mangione in 1992 and was found to be a reliable and valid measure of visual function in patients with retinal disease (Linder *et al.*, 1999). Although specific to certain ophthalmic conditions it remains a popular questionnaire in ophthalmology, particularly in the assessment of the impact of cataract surgery.

4.3.4.7 Participant attrition and retention

Response rates and participant attrition are considerations in surveys and over recent years a range of methods to assess response rates has been used (McCambridge *et al.*, 2011). Attrition during self-administered online trials is known to be a complex phenomenon compared to conventional trials; compliance during trials is closely related to the loss to follow-up rates for research purposes (Fenwick *et al.*, 2016; Eysenbach, 2005). Prevention of attrition may involve issues that are different from those concerned with maximizing survey response rates; compliance with being interviewed or providing questionnaire data at some time after study entry is likely to be influenced by the length of involvement and the demands it makes upon the participant. However, there is not a clear evidence base on the effective methods to prevent loss to follow-up specifically, in the contexts of online cohort studies and trials (McCambridge *et al.*, 2011). Participant retention has been considered but this appears to be mainly in weight loss and nutritional programmes (Leonard *et al.*, 2014). A PubMed search of attrition and vision questionnaires did not find any results, and this is an area which may need further research.

4.3.4.8 Number of questions and relevance to the proposed study

Of the six questionnaires in Table 4-6, there were three which had questions relevant to the proposed study, these were: The visual activities questionnaire, NEI RQL-42, and RSVP. The SUN project did consider pregnancy and myopia but this questionnaire only had two questions relating to vision. All three questionnaires covered different areas of visual function and the questionnaire most suited to the proposed study was the RSVP. With the exception of the SUN study the questionnaires identified had the number of questions ranging from 20 – 42 (Ferandez-Montero *et al.*, 2017). The RSVP was not used in the studies, as it was not possible to gain permission from the authors.

4.3.4.9 Previous studies attempting to detect small changes over time

Many of the questionnaires have been used to assess the difference in patient-perceived visual outcomes, pre- and post-operatively, in cataract and refractive surgery. With these scenarios there is likely to be a significant refractive change and one which will be easily perceived by the participant. Such large changes are unlikely to occur in the proposed study, which is looking at visual changes in pregnancy, therefore any instrument will need to be sensitive enough to detect small changes. The RSVP and the group of NEI VQL instruments have been found to have good discriminant abilities with refractive error (Nichols *et al.*, 2001).

There are examples of general questionnaires being used in longitudinal studies looking at the long-term effects of cataract surgery (Keel *et al.*, 2017; Mönestam, 2016) and refractive surgery outcomes (Price *et al.*, 2016) but the literature search did not reveal any research investigating the outcomes of studies where the changes in refraction are likely to be small.

4.3.4.10 Changes to the questionnaire

For the vision in pregnancy study, the NEI RQL-42 validated vision questionnaire was used with several additional questions specifically related to the pregnancy included at the end. For the VIMC study, these pregnancy questions were removed and replaced with two short questions from the SANDE© dry eye questionnaire (Amparo, Schaumberg and Dana, 2015).

4.3.4.11 Section summary

From the review there are two questionnaire instruments which could be suitable for the study, both have undergone Rasch analysis. The NEI RQL-42 had a positive outcome from the Rasch analysis but the RSVP outcome raised some concerns about robustness. Rasch analysis itself does have some limitations and weaknesses. The literature suggests that instruments should be considered holistically and on this basis NEI RQL-42 instrument is the preferred choice (Appendix 10).

4.3.5 Online vision tests

4.3.5.1 Aims

To review the current online vision tests and explain the rationale for the selected choice of test for use in the Plan B (VIP-online) and Plan C (VIMC) studies. The pertinent features and important considerations will be discussed along with how these can influence the testing process and importantly the outcomes.

4.3.5.2 Background

As discussed in Section 1.9, uncorrected vision and corrected visual acuity are common clinical measurements used as indicators of visual function (Kniestedt and Stamper, 2003). The tests are usually performed by an eye care professional and commonly during an eye examination. Traditional models of health care delivery have been challenged by the effects of the COVID-19 pandemic, leading towards patient centred models of care (Gupta *et al.*, 2021).

This has led to an evaluation and reassessment of how care could be provided and the tentacles of these changes have extended into eye-care. Although it is acknowledged that some clinical assessments require specialist non-portable equipment, there is now significant interest in having patient centred care models, which utilise modern mobile device technology to enable assessment at the patient's convenience (Ventola, 2014). VA is a clinical measurement which has the potential to be self-measured by an appropriate App, using a mobile device/ tablet or home computer.

4.3.5.3 Visual acuity charts

The different types of vision test chart have been outlined in Section 1.9.2. However, it is worth placing these in the context of electronic devices.

The Snellen chart (Rewri, Kakkar and Raghav, 2013; Snellen, 1862) is the most common method for the measurement of vision in ophthalmic and general practice, but has limitations due to the non-geometric progression in letter sizing and the inconsistent number of letters per line (Tousignant *et al.*, 2020 and Lovie-Kitchen, 2015). These limitations have been overcome by the use of LogMAR charts (Bailey and Lovie, 1976) which are now frequently employed in general practice and clinical research. However, the Snellen chart remains popular due to the familiarity and the well-known scoring system.

Mobile phone technology has evolved rapidly in recent years and a simple Google search estimates that in July 2022, 7.26 billion mobile phones were being used globally, equating to 91.54% of the world population. In the UK, there are an estimated 62.3 million mobile phones being used.

The data are constantly changing and accurate data are difficult to attain. In 2013 an estimated 280 million (20%) of the 1.4 billion mobile phones sold were smartphones and this proportion will increase, particularly in low-income settings (Hempel, 2010), where fixed-line technology has been "leapfrogged" straight to mobile technology (Goldemberg, 1998). The huge uptake in use of mobile devices provides opportunities for users to access health provision without the previously required infrastructure.

4.3.5.4 Considerations for self-administered tests

VA measurement is a standardised process (Bennett & Rabbetts, 1991) and there are features which need to be in place to ensure that any online vision tests produce measurements which are comparable to the standardised measurements obtained from a vision chart used in a clinical setting.

4.3.5.5 Calibration

Vision charts are designed to be presented at certain distances from the participant to ensure that the letter size is standardised. An online vision test should have a form a calibration process which ensures that the measurement distance is recorded enabling letters / shapes sizes to be shown at the correct size.

4.3.5.6 Self-administered or assistance needed

The ideal test is one which the user can administer themselves and all of the apps / WebApps were assessed for this feature.

4.3.5.7 Free / payable

To encourage uptake of participation, a requirement for any online vision tool to be used in the studies was that it was open source and available at no charge to participants.

4.3.5.8 Type of device

To facilitate participation and avoid discrimination, the vision tool chosen for the study should be available on all devices: Apple, Android and WebApp.

4.3.5.9 Overview of literature review

4.3.5.10 Objectives and methodology of literature review

A search was undertaken using the Google search engine to identify online tools for assessing visual acuity; this search engine was chosen as it is one of the most commonly used search engines. Google play and the Apple store were also used to identify smartphone / tablet vision tool applications.

4.3.5.11 Search terms

The following keywords and phrases were used: “visual acuity and free”, “visual acuity and online”, “visual acuity and internet based”, “vison”, “visual acuity and eye test”, “visual acuity and screen”, “visual acuity and eye check”, “visual acuity and eye chart”, “visual acuity and vision chart”, “ visual acuity and prescription”.

4.3.5.12 Search outputs

Google search returned 1,680,000 results and the first 100 hits were reviewed (10/10/2020). The inclusion criteria for the review are listed in Table 4-7 and the charts chosen for review are listed in Table 4-8.

Table 4-7 Vision test review inclusion criteria

Inclusion
Free
Suitable for laptops / desk top computers
Suitable for tablets; Android and Apple
Suitable for smartphones; Android and Apple

Table 4-8 Online vision tests

Name of tool	Cost	Phone type	Device	Web based / app	Self-administered	Calibration	Optotype
Verana	Free	Android & IOS	Tablet / Phone	Both	Yes	No	Letters
Open-source test chart	Free	Android & IOS	Tablet / Phone	Web	Yes	Yes	Letters
Ocular check	Free	Unknown	Unknown	Unknown	No	Yes	Letters
Professional VA test	Free	Android & IOS	Tablet / Phone	Unknown	Yes	Yes	Tumbling E
E-Y-E-Check	Free	IOS	Tablet / Phone	App	Yes	Yes	Tumbling E
Peek acuity chart	Free	Andriod	Tablet / Phone	App	No	Yes	Letters
Esee online	Free	Andriod	Tablet / phone	Web	Yes	Yes	Letters
FrACT	Free	No	Computer / Tablet	Web	Yes	Yes	Single letter

4.3.5.13 Findings

Only free online vision tools were reviewed as free access was an essential feature to facilitate recruitment to and participation in the study. The ideal self-administered test should be accurate, quick, easy to use and not require assistance from another person.

The following tests were considered: The Peek acuity chart, Esee Acuity Chart, FrACT Chart and the Open-Source test chart. The Peek acuity chart appears to be a very versatile tool but has a significant disadvantage of only being available on Android products. Devices using Android applications have approximately 71% market share but this would exclude the 29% of Apple IOS users (Statista, 2023).

The Esee Acuity Tool has the advantage that it is web based but there are concerns around the validity of the tool and the precision of the measurements. The FrACT chart has been used widely in vision research and has a large number of citations, but the concern around this chart is the ability to self-administer and the user friendliness. The open-source chart does not appear to have been used in vision research but has anecdotally been used extensively during the SARS-COV2 lockdown period by clinicians. It is functional but in order to self-administer correctly, good instructions will need to be provided.

4.3.5.14 FrACT

As the Freiburg FrACT chart has been used in previous vision research, it was chosen as the preferred online self-assessment VA chart. The chart employs the use of the Landolt C test, with the subject having to indicate the direction of the gap in the letter C. Visual acuities from LogMAR 1.22 to LogMAR -0.3 can be tested at various distances.

4.3.5.15 Chart design features

Vision charts are traditionally printed as high contrast charts and presenting this image on a computer poses challenges due to the pixilated nature of images which are presented on the screen. The quality of the computer screen will determine the quality of the image and affect the level of vision measured. To improve the quality of the presented image, the FrACT test employs two commonly used graphic design techniques: anti-aliasing and dithering.

"Anti-aliasing (AA) is a technique for improving spatial resolution at the cost of luminance resolution" Bach, (1997). This technique involves smoothing the rough edges created by individual pixels. There are different AA techniques and a review of these techniques is outside the scope of this thesis. Although the process of AA improves the spatial resolution it can have the effect of reducing the luminance of the image, which in turn can affect the detection of the image by the participant.

"Dithering is a technique for improving luminance resolution at the cost of spatial resolution" Bach, (1997). This technique involves the addition of pixels to a digital image and complements AA by simulating colours or shading. This is useful where there is a limited colour palette available, as it extends the colour palette by creating the illusion of more colours. The technique allows subthreshold contrast stimuli to be generated on a conventional display having standard 8-bit video resolution. The difference between 8-and-10 bit video resolution is highlighted in Figure 4-1.

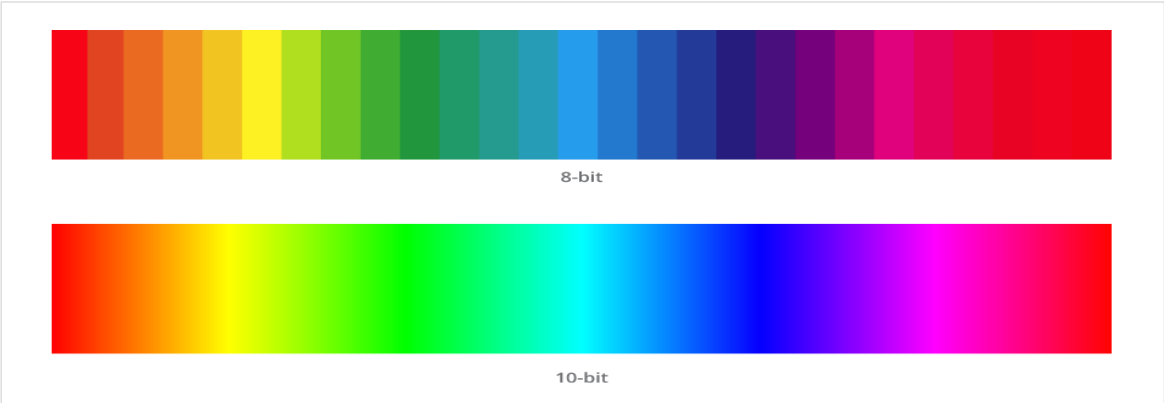

Figure 4-1 Dithering example

4.3.5.16 Image contrast and device brightness levels

Clinical vision test charts use black letters / pictures on a white background which provides a level of image contrast; contrast is the difference in luminance or colour which makes an object distinguishable and British Standard 4272 recommends that the contrast level should be ≥ 90%. Test charts are illuminated to a certain level; with illumination being measured in cd/m2 with a recommended level of 150 cd/m^2 (Bennett and Rabbetts, 1991).

Test charts used on electronic devices are internally illuminated and controlled by the brightness function; brightness is the subjective correlate or impression of luminance (Tunnacliffe and Hirst, 1983). Luminance is measured in candelas per meter squared cd/m^2 but the display screen industry use the unit NIT; which is derived from the Latin Nitere, "to shine", with 1 cd/m^2 being equivalent to 1 Nit. A typical Apple MacBook has a screen brightness of 500 Nits and an Apple iPhone 825 Nits; Android products are around 700 Nits which ensures that any test chart presented on an electronic screen would meet the recommended levels of illumination.

4.3.6 Conclusion

The healthcare community is embracing mobile technologies with their potential in healthcare information delivery, real-time patient monitoring, research data collection and mobile telemedicine for the provision of expertise to remote locations (Bastawrous and Armstrong, 2013). Regulation of these technologies is provided in the UK by the MHRA and in the USA by the FDA. Rules and guidance around the regulation of online health tools are complex but can be reduced to whether or not they provide a clinical diagnosis. Software developers can circumvent the regulatory processes, with changes to the classifications of the tool and this brings challenges for the end users. Yeung *et al.* (2019) carried out a scoping review of e-VA tools during 2017. Their findings suggested there was a wide range and easy availability of such tests, but they raised concerns around the validation of the tests and the very important issue of calibration was often overlooked. Tools which have considered calibration and validation are often chargeable to the end user and these are less likely to be used by the public.

The potential for measuring VA and refractive error using handheld electronic devices is a growing area of research (Bastawrous *et al.*, 2015; Bastawrous and Armstrong, 2013). Most studies have employed a healthcare worker to assist in taking measurements. Nevertheless, early evidence for unassisted VA testing and subjective refraction is emerging (Tousignant *et al.*, 2020; Rewri, Kakkar and Raghav, 2013; Srinivasan *et al.*, 2012). A significant consideration with self-administered assessment is the calibration of the chart; acuity charts are calibrated to use at a certain distance and failure to do this will result in an erroneous score, which could lead to an inappropriate management and outcome.

Research into self-administered vision measurements remains limited (Nagra, Vianya-Estopa and Wolffsohn, 2020). Other healthcare professions, such as medicine, are guided by a growing evidence base for conducting telephone and video consultations (Mohr *et al.*, 2019) but there are comparatively few studies specific to primary care optometry.

After consideration of the features, the FrACT open-source instrument was chosen to be the vision measurement tool for the VIP and VIMC studies. To support this decision, a group of the researchers' friends and colleagues were asked to trial the FrACT tool; their feedback was constructive and suggested improvements to the instructions, which were incorporated into the study (Appendix 11).

4.3.7 WebApp

4.3.7.1 Section overview

To support Plan B (VIP-online) and Plan C (VIMC) online studies a web-based application was created to allow potential participants to read about the study, capture sign up and consent information and to facilitate data capture (Appendix 27).

4.3.7.2 Website versus Web application (WebApp)

A website is a collection of publicly accessible and interlinked web pages which share a single domain name. They are uni-directional, allowing the viewer to access information but without any interaction. WebApps are web-based software applications which allow interaction between the user and the software programme.

4.3.7.3 WebApp design

The WebApp was created using the WordPress open-source software, which provided the structure for the webpages and the software programme. A database was created and integrated into the WebApp, facilitating participant data input; reminder algorithms were created to provide the dates for the reminders to be sent.

4.3.7.4 Requirements for WebApp

There were multiple requirements which the WebApp needed to incorporate and were considerations in its design and build.

4.3.7.5 Participant confidentiality

During the sign-up process participants are asked to create a username and after registration a weblink is sent via email and/or SMS message, allowing them to create a password. The WebApp has the facility for participants to reset their passwords.

4.3.7.6 Consent and participant information

The consent process occurs through the WebApp and the documents are stored securely. The consent questions for Plan B (VIP-online) are in Table 3-3, with additional information questions in Table 3-4, and Table 3-6 for Plan C (VIMC).

4.3.7.7 Data security

Consent and questionnaire data are stored in a database, which is stored securely on an Amazon Web Server (AWS); AWS are ISO 27001 accredited.

4.3.7.8 Access to review

The researcher is able to download participant identifiable data but this is anonymised when data sharing with the research team.

4.3.7.9 Questionnaire and vision test instructions

As part of the participant information, there is a small sample of the questions found in the questionnaire along with user friendly instructions for the FrACT online visual acuity test. The existing instructions found on the FrACT website were thought to be too complex for members of the public to understand. A set of user-friendly instructions was developed, by an iterative process, with input from clinicians and potential participants. The written instructions placed on the study website, contain useful screen shots which participants can easily follow.

4.3.8 Domain names

The WebApp was initially developed for the Plan B (VIP-online) study but then modified for the Plan C (VIMC) study; all the design features were retained but the branding for the study was changed. Consideration was given to domain names for both the Plan B (VIP-online) and Plan C (VIMC) studies. The Plan B (VIP-online) domain name was chosen and registered as www.visioninpregnancy.com. To provide consistency for the study an email address was created for the researcher, adam@visioninpregnancy.com, which would allow participants to communicate directly with the researcher and from which the researcher could send participant notifications.

The Plan C (VIMC) vision in menstrual cycle domain name was chosen after informal discussions with a cross section of women of different ages. The aim was for the domain name to be short and eye catching. It became clear that different age groups of women, used various euphemisms for the menstrual cycle and after considerable discussion, the study name '28dayvision' was chosen.

The domain name was chosen and registered as www.28dayvision.com. To provide consistency for the study an email address was created for the researcher, adam@28dayvision.com, which would allow participants to communicate directly with the researcher and from which the researcher could send participant notifications.

4.3.9 Quick response (QR) codes

The use of QR codes is widespread and helps potential viewers to reach a website easily and quickly. To facilitate potential participants reaching both study WebApps, QR codes were developed and placed on the participant posters and sheets (Appendix 12).

4.3.10 Ethics

4.3.10.1 Section overview

As the study was being conducted as part of a professional doctorate programme from LSBU, with support from the IoO, approval from each institution's research ethics committee (REC) was required in conjunction with approval from the Health Research Authority (HRA) REC. The order of submission to each REC, for each study plan was: IoO, LSBU and HRA. This section outlines the ethics approval process.

4.3.10.2 Repeated ethics submissions

As there were changes to the original study design, each research ethics committee (IoO, LSBU and the HRA) were contacted to obtain approval for each significant change.

4.3.10.3 Challenges with ethics approvals

During the COVID-19 period the timeframe for the approval process was delayed, due to challenges with staffing resources and an influx of COVID-19 research applications, which took priority.

4.3.10.4 Summary of ethics approvals

Multiple ethics applications were made for each of the three studies. These are summarised in Table 4-9.

Table 4-9 Summary of ethics approval

Institution	VIP F2F	VIP – online	VIMC
IoO	Approved 12/10/19 Appendix 13	Approved 23/4/21 Appendix 15	Approved 3/1/22 Appendix 18
LSBU	COVID-19 moratorium Appendix 14	Approved 24/3/22 Appendix 16	Approved 24/3/22 Appendix 19
HRA	Not submitted	Not required 13/7/21 Appendix 17	Not submitted Not required

4.3.11 Recruitment

4.3.11.1 Section overview

To describe the recruitment strategy and processes for each of the three study plans

Plan A Vision in pregnancy
Plan B Vision in pregnancy online
Plan C Vision in the menstrual cycle

4.3.12 Plan A (VIP)

4.3.12.1 Strategy

The recruitment strategy was developed as part of the preparatory work for the study, with the aim of building professional relationships that might subsequently be useful for recruitment. During mid-2019 to early 2020, this involved discussing the study and its aims with a range of identified healthcare professionals: midwives, GPs, optometrists and mothers. It was emphasized that recruitment could not be started before full ethical approval had been received.

4.3.12.2 Local GPs

The researcher's optometry practice is based in a suburb of Nottingham and has good working relationships with three local medical practices and the incumbent GPs. The GPs were contacted personally for their support and input to the study and possible recruitment opportunities. Their feedback was positive with suggestions on recruitment strategies involving local midwifery teams (Appendix 20).

4.3.12.3 Midwives

The researcher is an employee of a local secondary care trust, Sherwood Forest Hospital Trust (SFHT) and contact was made with the Trust hospital midwifery team as they organise and deliver support for both hospital and community midwifery for the North Nottinghamshire region. There was on an ongoing dialogue with the midwifery team.

4.3.12.4 Feedback

The local medical practices agreed to support and promote the study, with flyers and posters within the practices but commented that pregnant women are normally managed by midwifery. The midwifery team at SFHT were contacted and after several meetings said they were happy to provide support and for the researcher to attend antenatal clinics to recruit pregnant women and also to take measurements within the clinic environment.

4.3.12.5 Effects of COVID-19 on recruitment

The COVID-19 national pandemic forced all non-essential healthcare to be suspended, which included the possibility of the researcher attending antenatal clinics. In conjunction with this, LSBU issued a moratorium on all face-to-face data collection (Appendix 4).

4.3.13 Plan B (VIP-online)

4.3.13.1 Strategy

Although the COVID-19 period created significant challenges, the change in direction to an online study created potential opportunities for recruitment. Healthcare professional groups were contacted with a view to them circulating study details to their membership. The midwifery team at SFHT were contacted and extensive discussions took place to ask the midwives to promote the study directly to all newly pregnant women. Other online avenues were considered and used to promote the study (Table 4-10).

Table 4-10 Plan B (VIP-online) - summary of contacts to promote the study

Healthcare organisations
Local optical committees (LOC)
Local pharmacy committees (LPC)
Local medical committees (LMC)
Midwifery department
Royal college of midwives
Non healthcare organisations / forums
Mumsnet online group
Local neighbourhood online forum groups
Friends and family contacts
Facebook
Social media influencer (with 35,000 followers)

Healthcare professional groups

These were an obvious starting point to promote the study. Research was carried out to determine and locate first points of contact within these groups (Appendix 22).

Local optical committees (LOCs)

The LOCs are statutory bodies, which support optometrists and practices within defined geographical areas in relation to ophthalmic NHS services; some LOCs widen their scope of activity to become involved in training events and other areas which may interest their membership. Membership of the LOC is voluntary and therefore they may not have details of all the optometrists in an area. There are approximately 75 LOCs in the UK (https://www.loc-online.co.uk/) and they have a national overarching company called Local optical committee support unit (LOCSU). The researcher contacted LOCSU to ask if they would circulate details of the study to the membership distribution list. There are approximately 15,000 optometrists and 6,000 dispensing opticians in the UK. Details of the study were sent to the officers/point of contact for each LOC, with the request that they forward it by email to their membership.

Local pharmacy committees (LPC)

The LPCs are statutory bodies, which support pharmacists within defined geographical areas in relation to NHS services; some LPCs widen their scope of activity to become involved in training events and other areas which may interest their membership. There are approximately 52 LPCs in the UK. Contact details for each of the LPCs were found from internet searches. An email was sent to each of the LPCs promoting the study and asking them to forward details to their membership. There are approximately 11,826 pharmacy practices in the UK with 42,990 registered pharmacists.

Local medical committees (LMC)

The LMCs are statutory bodies which represent general practitioners' interests to local NHS authorities. There are 89 LMCs in the UK with approximately 27,985 registered GPs (https://www.bma.org.uk/what-we-do/local-medical-committees). Contact details for each of the LMCs were found from internet searches and email sent to each of the LMC points of contact asking them to promote the study to their membership.

Snowballing

Following the blanket email to the LMCs, the secretary of the Highlands LMC reached out and provided a contact for the Divisional General Manager of Women and Children Health at Raigmore Hospital, Inverness. After email discussions with them, they facilitated contact with the speciality doctor in charge of obstetrics for the Highlands. This individual was very supportive of the study and expressed an interest in promoting it with their team and patients. Posters and leaflets were sent for distribution and follow up emails were sent.

Midwifery departments

Local midwifery departments within Nottinghamshire were contacted to seek support for the study. There are two main midwifery departments; City Hospital Trust and Sherwood Forest Hospital Trust (SFHT). The team leaders for each department were informed of the study and its aims and asked to promote the study to their patients. The team from SFHT were receptive and supportive of the study aims and posters and leaflets were provided for them to distribute (Appendix 21).

Non-healthcare organisations / forums

Having an online study provided other opportunities and avenues to promote the study, to increase the reach and the number of potential participants. These are outlined below.

Mumsnet

This is an online forum which was initially started to support parents but has since grown into an online presence with a much wider scope. It offers support and guidance for all areas related to parenting, consumer related topics, personal support forums and current events. They do not directly support research of any kind but do allow details of research projects to posted on a specific section within the forum. This requires viewers to actively look at this page. The project was reviewed by a member of their team and approval was given to post on their forum.

Neighbourhood forums

The research team posted details of the study on their local neighbourhood forums. This was in an attempt to use as many free online avenues as possible to promote the study.

Personal contacts / family and friends

The research team promoted the study within their colleague groups, Twitter, and their family and friends. Everyone was asked if they would share the details with their contact groups. This was a continuous process throughout the recruitment period.

Facebook (FB)

Information about the study was shared on the researchers FB page and asked contacts to post on their FB pages. The research team had contacts with the wider optometry community who have significant FB followings and they kindly posted details about the study.

Social media influencer

The researcher engaged the support from a young female social media influencer, who has approximately 35,000 followers. Details of the study were posted on multiple occasions. The rationale for using this route was that her followers were predominantly female and within the appropriate age grouping for participation.

Leaflets

A leaflet was designed based on the branding from the study WebApp home page (Appendix 25), which included a QR code (Appendix 12). With consent from the intended recipient, the leaflets were sent to the obstetrics department in Scotland and also to the SFHT midwifery team.

Royal College of Midwives (RCM)

The RCM were approached for support and kindly emailed their members about the study and how to contact the researcher. The study was also placed on their research web pages (Appendix 23). The RCM was keen to promote and engage with the study as they considered this a good example of multi-disciplinary research and was an area which they had not previously been involved with.

Feedback

All of the groups contacted offered verbal support. The professional organisations circulated the study details to their membership. There was direct feedback from some of the members, in particular a common theme from LMC groups was that the study was unlikely to be promoted due to the lack of incentives for GPs (Appendix 24).

4.3.13.2 Section summary

Time and consideration were given to explore all the possible avenues which could practically be used to promote the study and facilitate recruitment. Putting the strategy into place required considerable time and commitment from the research team. During the process there was some very positive and supportive feedback; the research team were surprised by some of the feedback from the LMC suggesting that GPs would require to be incentivised to promote the study.

4.3.14 Plan C (VIMC)

A diverse approach was taken to promote and recruit into the study (Table 4-11) which included many of the methods used in the previous studies and some new approaches. It was started with personal networks; using family and friends and asking them to share the study with their networks. Eye care colleagues were asked to consider participating and to share the study with friends and family networks. The study was promoted on social media, with the support from a social media influencer on their Instagram account. The study was also promoted passively by including details on email signatures and by leaflets in the researcher's optometric practices.

Table 4-11 Plan C (VIMC) – summary of contacts to promote the study

Healthcare organisations
Local optical committees (LOC)
Non healthcare organisations / forums
Mumsnet online group
Local neighbourhood online forum groups
Friends and family contacts
Facebook
Social influencer
Professional publications
Universities
Posters

LOC: See Section 4.3.13.1

Neighbourhood forums: See Section 4.3.13.1

Personal contacts / family and friends: See Section 4.3.13.1

Facebook (FB): See Section 4.3.13.1

Social media influencer: See Section 4.3.13.1

Professional publications

The study was promoted in the two main professional magazines; The Optician and Optometry Today.

https://www.aop.org.uk/ot/science-and-vision/research/2022/06/16/study-examines-vision-changes-during-menstrual-cycle

Posters

A poster was designed based on the branding from the study WebApp home page; this included the QR code. The poster was displayed within the researcher's practice. The poster was also displayed on SFHT staff notice boards, after permission was given from the internal research team (Appendix 25).

Universities

A LSBU staff member, who is a member of the research team, kindly emailed details of the study to all the students within their department and another research team member who is an Emeritus professor at City, University of London, obtained permission for details of the study to be promoted to the new intake of students in September 2022. The contents of the email circulated to students of both universities is in Appendix 26. Another member of the research team emailed detailed to a large number of personal contacts and tweeted information to over 940 followers who are mostly eye care professionals.

4.3.14.1 Section summary

Time and consideration were given to explore all the possible avenues which could practically be used to promote the study and facilitate recruitment. Putting the strategy into place required considerable time and commitment from the research team.

4.4 Data analysis

4.4.1 Section overview

To outline and discuss the data analysis process for Plan B (VIP-online) and Plan C (VIMC) study. At the point of sign up to the Plan B (VIP-online) and Plan C (VIMC) studies, participants will be asked to complete a series of questions designed to provide descriptive information about their vision during their pregnancy and menstrual cycle. Participants will then complete a series of vision questionnaires and acuity measurements, at specific points during their menstrual cycle. The data analysis plan was amended post data collection events due to the attrition rate during the Plan B (VIP online).

4.4.2 Aims of data analysis

- To describe the cohort characteristics
- To perform inferential assessment of inter participant data
- To assess if data collection dates are aligned with those provided to the participants.

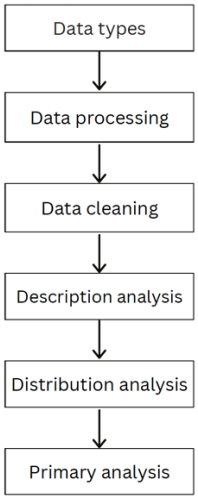

Figure 4-2 Data analysis flowchart

4.4.3 Data types

1. Demographic data, will be stored in Microsoft Excel.
2. NEI RQL 42 questionnaire ordinal data will be stored in Microsoft Excel.

4.4.4 Data processing

1. Nominal NEI RQL 42 questionnaire data will be transformed to ordinal data using Microsoft Excel.
2. Data will then be used to create the NEI RQL subscales (Appendix 10).

4.4.4.1 NEI RQL-42 scoring system

The NEI RQL-42 questionnaire has a marking schedule to convert questionnaire responses into ordinal data for analysis (Appendix 10). Microsoft Excel was used to complete this process and the 13 outcome measures of the NEI RQL-42 are formed from grouping question responses. For example, the Far vision outcome measure, is determined from grouping data from questions 5, 6, 9, and 10 (Appendix 10).

Of the NEI RQL 42 13 subscales, five were considered to be pertinent to the research aims (Sections 1.4) and were used with Plan B (VIP-online) and Plan C (VIMC). The subscales used were: far vision, near vision, glare, diurnal variation, and clarity of vision.

4.4.5 Data collection event dates

Using information which the participants provided at the point of sign up, data collection events were calculated to coincide with ovulation, peak progesterone levels and the first day of a period. The dates were compared to the actual dates the participants completed the questionnaire, with the findings being displayed in a box and whisker plot. This information helps to place the generalised findings from the inferential analysis into context around what happens during these key points in the menstrual cycle.

4.4.6 Data cleaning

1. Rounding of numbers

Within excel, numbers were rounded to one decimal place. The rationale was to provide a balance between facilitating interpretation and the loss of accuracy.

2. Blank question responses

This situation arises from sub-questions not being required to be completed. These blank responses will remain with the dataset and used in the analysis.

3. Missing data

There are various approaches to managing missing data and a decision on the approach requires consideration of whether bias or distortion are introduced into the conclusions (Kang, 2013). The process of imputation was considered; single line imputation, such as last observation brought forward, requires missing data to be less than 5% and multiple data imputation, requires the missing data to be less than 40% (Dettori, Norvell and Chapman, 2018).

The approach adopted for Plan B (VIP-online) was to delete participants from inferential statistical analysis if they only complete one data event. The approach adopted for Plan C (VIMC) was to delete participants from inferential statistical analysis if they completed fewer than two questionnaires. The rationale for this approach was that including the data for one questionnaire only, had the potential to distort the findings. The data for participants who completed fewer than 2 questionnaires were included separately within the descriptive statistics (Section 5.4).

4.4.7 Descriptive analysis

The descriptive analysis will be undertaken on both the total cohort of participants who signed up to the Plan B (VIP-online) and Plan C (VIMC) studies (Section 5.5, 5.6 respectively) Descriptive data for vision correction will be presented for Plan B (VIP-online) and Plan C (VIMC) in Section 5.7.

4.4.8 Participant medication

Descriptive data for medications declared by participants will be presented for Plan B (VIP-online) and Plan C (VIMC) in Section 5.8.

4.4.9 Distribution analysis

Prior to inferential data analysis, the data were assessed to determine if they were normally distributed. This can be achieved from a visual plot or by numerical testing. An immediate impression can be provided by a graphical display of the data, such as histograms, box plots, P–P Plots, Q–Q Plots, which can be supported with analytical tests such as the Shapiro–Wilk test, Kolmogorov–Smirnov test, skewness, kurtosis. With a symmetric distribution the mean, median and mode of a distribution coincide; that is, skewness = 0, kurtosis (excess) = 0. Skewness is a measure of symmetry, or more precisely, the lack of symmetry of the normal distribution; Kurtosis is a measure of how peaked the distribution curve (Mishra *et al*., 2019). A distribution is called approximately normal if skewness or kurtosis (excess) of the data are between − 1 and + 1 but for small sample sizes a Z test is applied using skewness and kurtosis (Ghasemi and Zahediasl, 2012).

The Shapiro–Wilk test is an appropriate method for testing the normality of small sample sizes (<50 samples) although it can also be used for larger sample sizes, while Kolmogorov–Smirnov test is used for n ≥50. If the data are normally distributed then parametric tests are applied and if not normally distributed, non-parametric testing is applied. Each subscale data will be tested for normality and the choice of inferential test was based on the outcome. SPSS software was used to analyse the data in the 13 outcome measures of the NEI RQL-42, for intra and inter subject analyses, at specified points with the menstrual cycle.

4.4.10 Primary analysis

Statistical analysis was used to confirm the null hypotheses, for Plan B (VIP-online) and Plan C (VIMC), found in Section 1.6.

Statistical significance is a measure of the probability of the null hypothesis being true compared to the acceptable level of uncertainty regarding the true answer (Tenny and Abdelgwad, 2022). The alpha significance level is classically set at 5%, indicating a 95% probability that the outcome is not attributable to chance. The beta significance level is directly related to the power of the study and whether it fails to reject the null hypothesis, which would be a Type II error. A beta level of 0.8 gives an 20% probability of making a Type II error.

4.4.10.1 Intra and inter participant data analysis

Assessment of data will be performed to determine the presence of any statistically significant differences in each of the five NEI RQL 42 subscales, Sande dry eye assessment and visual acuity measurements.

Data collection points for Plan B (VIP-online) were outlined in Section 3.6.10 and Plan C (VIMC) were outlined in Section 3.7.12. these dates were determined by the researcher from information provided by the participant. The actual date on which participants entered their results will be compared to the date provided for the participants to do this.

4.4.10.2 Testing mean differences

To determine if any statistically significant differences occur within the participants, for each of the key points during pregnancy and within the menstrual cycle, tests are applied to the data.

The Wilcoxon signed rank test is the non-parametric equivalent of the paired t test, which compares the medians of dependent groups two groups (Kim, 2014; Divine *et al*., 2013). The assumptions for using this test are

1. Dependent sample: These are paired measurements to assess for differences between a before and after measurement.
2. Independence: Paired observations are randomly and independently drawn.
3. Continuous dependent variable: Variables are measured on a continuous scale
4. Ordinal level of measurement: This is necessary to ensure that the two paired values can be compared.

4.4.10.3 Section summary

This Section outlines the data analysis plan and the descriptive and inferential tests which are applied to data from Plan B (VIP-online) and Plan C (VIMC) study.

4.5 Chapter summary

This chapter has outlined the rationale for the choice of autorefractor instrument and letter chart design, with the Nidek Retinomax and LogMAR chart design being selected for the Plan A (VIP) study. A review of the different types of vision questionnaire was carried out to determine the most suitable choice of questionnaire, with the NEI RQL-42 selected for Plan B (VIP-online) and Plan C (VIMC).The different ethics committee reviews and timelines were discussed along with the data analysis Plan B (VIP-online) and Plan C (VIMC) were outlined.

Chapter 5 Results

5.1 Chapter overview

The previous chapter discussed the choice of instruments selected for each of the study plans and outlined the data analysis process. This chapter will describe the results for Plan B (VIP-online) and Plan C (VIMC). It will start with describing the study populations, sample size and attrition rates, followed by descriptive statistics with the emphasis on Plan C (VIMC). The results from Plan C (VIMC) NEI RQL-42 questionnaire, Sande dry eye questions one and two, and FrACT vision test will be presented and then followed by a summary of the findings.

5.2 Participants and sample size

5.2.1 Plan B: (VIP-online)

There were four participants who enrolled into the study by completing the online sign-up questionnaire and consent forms; the list of enrolment questions can be found in Section 3.6.9. All participants were within the first trimester of pregnancy, with three participants being prima gravida and one multigravida.

5.2.2 Plan C: (VIMC)

There were 44 participants who enrolled into the study by completing the online sign-up questionnaire and consent forms. The list of enrolment questions can be found in Table 3-6. On enrolment participants were sent the three dates for data collection and also an email was sent on the day of data collection (Section 3.7.12).

Twenty-two participants did not complete any questionnaire or visual acuity test. Of the remaining 22 participants, six participants completed a single questionnaire, seven participants completed two questionnaires and nine participants completed all three questionnaire (Figure 5-1). Thirty-six participants did not complete any visual acuity tests. Five participants completed one visual acuity test and three participants completed all three visual acuity tests.

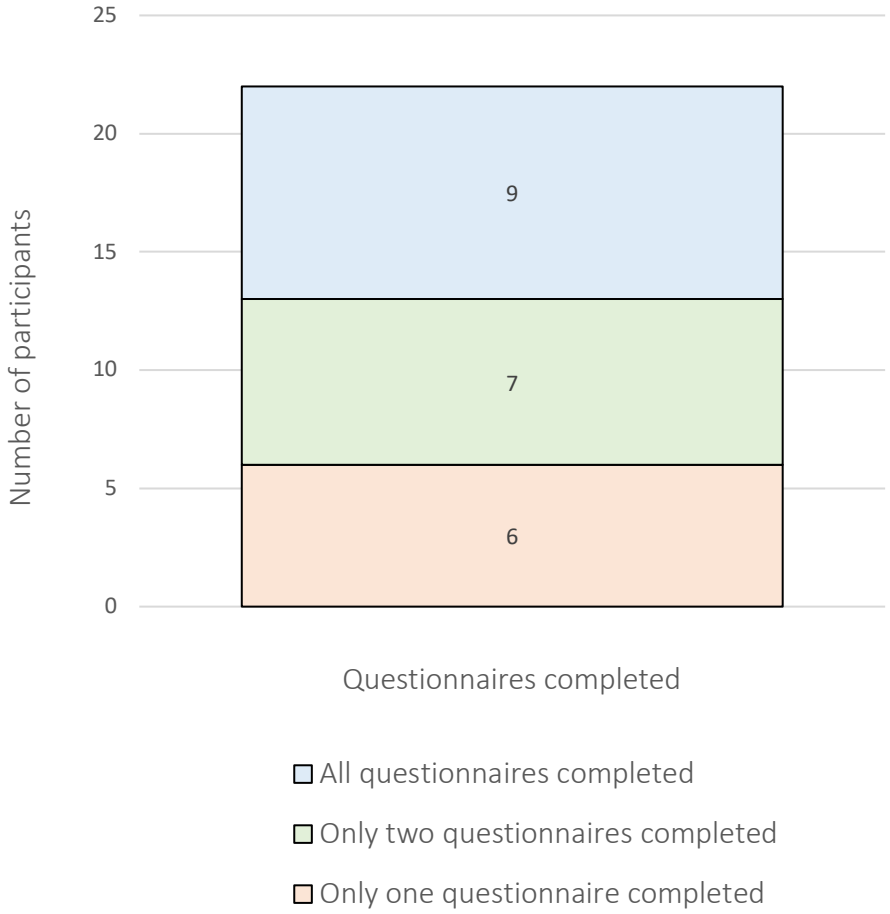

Figure 5-1 Number of questionnaires completed by participant

5.3 Participant identification

At the point of enrolment into the study, participants were assigned a code. All codes start with the letter P and are in numerical order. Each participant was also assigned a colour, which is used to distinguish their data in the figures presented throughout this chapter.

5.3.1 Plan B: (VIP-online)

Table 5-1 Assigned colours for VIP-online participants

P1		P3	
P2		P4	

5.3.2 Plan C: (VIMC)

The assigned colours to VIMC participants are shown in Figure 5-2. Participants: P1, P20, P21, P26-P44, did not complete any questionnaires and were not assigned a colour. Participants: P14-P19, completed only one questionnaire and were excluded from the data analysis (Section 5.12).

Table 5-2 Assigned colours for VIMC participants

P2		P13	
P3		P14	
P4		P15	
P5		P16	
P6		P17	
P7		P18	
P8		P19	
P9		P22	
P10		P23	
P11		P24	
P12		P25	

5.4 Data collection points

5.4.1 Plan B (VIP-online)

The four participants who completed a single questionnaire at the point of enrolment into the study, were within their first trimester of pregnancy and were 11, 10, 10, and 8 weeks pregnant respectively.

5.4.2 Plan C (VIMC)

A total of 47 participant questionnaire data collection events were carried out. Figure 5-2 shows the breakdown for all data points. There were six data points for participants who completed only a single questionnaire, 14 data collection points for participants who completed only two questionnaires and 27 data points for those participants who completed all three questionnaires.

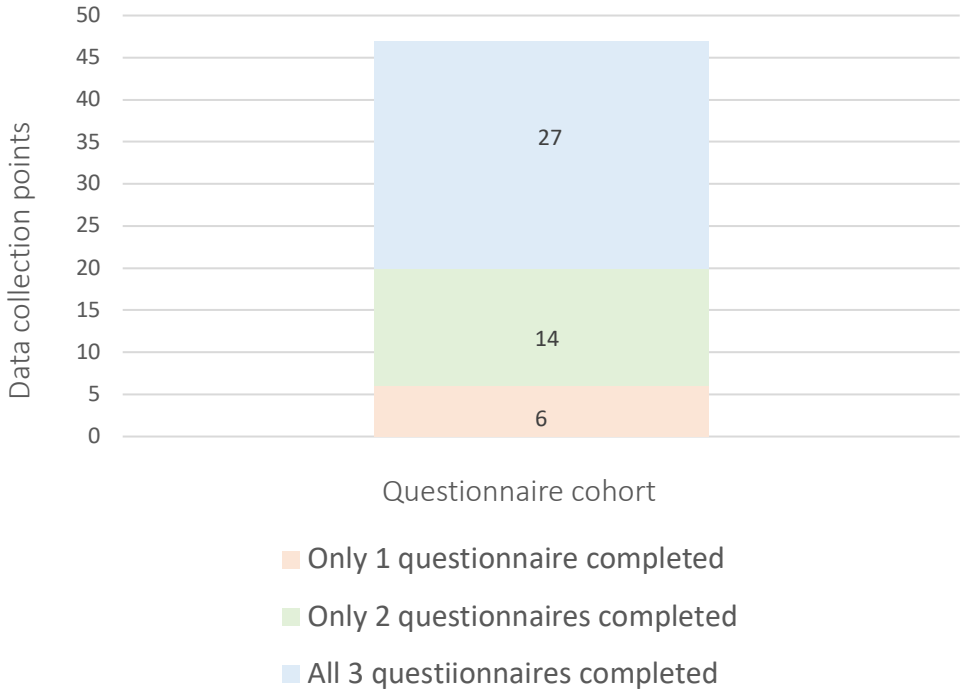

Figure 5-2 Completed data collection points for each questionnaire cohort

For each participant who completed the study, there were three data collection points which were planned to coincide with key points during the menstrual cycle: M - menstruation, P – peak progesterone level, O – peak oestrogen level. The timings of when participants were invited to provide these data were calculated based on the information provided at the point of enrolment into the study; this information can be found in Section 3.7.12.

For all completed questionnaires and vision tests, the calculated dates were compared to the actual dates of completion and are listed in Table 5-3, Table 5-4 and Table 5-5. Within the tables a positive sign denotes that questionnaires were completed early and a negative sign, denotes that questionnaires were completed after the calculated questionnaire date. The data highlight that three questionnaires were completed prior to the participant being requested to complete them. There were 6.4% of questionnaires completed early, 66.0% of questionnaires were completed on the calculated date and 27.6% of questionnaires were completed late.

Table 5-3 Difference in completion dates, for the cohort which completed only 1 questionnaire.

Participant	O data point	P data point	M data point
P14	0	-	-
P15	+16	-	-
P16	0	-	-
P17	-	-	0
P18	0	-	-
P19	0	-	-

0=Data collected on time
O=Ovulation point, P=Peak progesterone level, M=First day of menstruation
Positive values = Questionnaires were completed before the calculated date
Negative values = Questionnaires were completed after the calculated date

Table 5-4 Difference in completion dates, for the cohort which completed only 2 questionnaires.

Participant	O data point	P data point	M data point
P2	0	-	-8
P3	-3	-	0
P4	0	0	-
P5	-	-8	0
P22	-1	0	-
P23	0	0	-
P24	0	0	-

0=Data collected on time
O=Ovulation point, P=Peak progesterone level, M=First day of menstruation
Positive values = Questionnaires were completed before the calculated date
Negative values = Questionnaires were completed after the calculated date

Table 5-5 Difference in completion dates for the cohort which completed all three questionnaires

Participant	O data point	P data point	M data point
P6	-2	-1	-2
P7	-4	0	0
P8	0	0	0
P9	-4	0	0
P10	0	-1	-1
P11	+5	0	0
P12	-2	0	0
P13	0	0	0
P25	+3	0	-17

0=Data collected on time
O=Ovulation point, P=Peak progesterone level, M=First day of menstruation
Positive values = Questionnaires were completed before the calculated date
Negative values = Questionnaires were completed after the calculated date

The accuracy of participants' recollection of the date of their last period, with a worked example, is considered further in the discussion.

5.4.3 Early completion of questionnaires

Early completion of questionnaires was possible as the WebApp questionnaires were open and not locked, allowing participants to complete them early. Participant P15 completed a questionnaire 16 days early and it appears that this was completed at the point of enrolment into the study. However, this participant only completed one questionnaire and their data have not been analysed.

5.4.4 Late completion of questionnaires

There were 13 questionnaires which were completed after the calculated date (Table 5-6). The late completed data have the potential to skew the outcome analysis; however, the decision was made to retain the data, with the rationale that the calculated dates were based on self-reported information on the date of the last period, which could be inaccurate. Table 5-6 highlights that 69% of late questionnaires were completed no more than 4 days from the calculated dates (highlighted in grey).

Table 5-7 and Table 5-8 show the descriptive data for the number of days compared to the calculated dates that the questionnaires and vision tests were completed; within the tables, negative values relate to days after the calculated data collection day positive values relate to days before the calculated day. The late O data point questionnaires would be completed prior to the peak progesterone level and the P data point questionnaires would be completed within the luteal phase, prior to the start of the menstrual period.

There were four participants who completed the M data point questionnaire late; a likely explanation is that their menstrual cycles started late. Participant P25 completed the M data event questionnaire 17 days late. This participant is over 50 years old and a speculation for late completion is an irregular cycle duration due to the participant being perimenopausal.

Table 5-6 Number of questionnaires completed late

Day(s) late	Number of questionnaires
1	4
2	2
3	1
4	2
8	3
17	1

Table 5-7 Descriptive statistics for the variable describing the difference between the date of questionnaire completion and the calculated date in days

	O	P	M
Mean	-0.4	-1.6	-1.7
Standard Error	1.0	0.8	1.1
Median	0.0	0.0	0.0
Mode	0.0	0.0	0.0
Standard Deviation	4.3	2.8	4.5
Sample Variance	18.7	7.7	20.6
Kurtosis	9.8	1.3	9.4
Skewness	-2.8	-1.6	-3.0
Range	20.0	8.0	17.0
Minimum	-16.0	-8.0	-17.0
Maximum	4.0	0.0	0.0
Count	18.0	12.0	17.0

0=Data collected on time
O=Ovulation point, P=Peak progesterone level, M=First day of menstruation
Positive values = Questionnaires were completed before the calculated date
Negative values = Questionnaires were completed after the calculated date

Table 5-8 Descriptive statistics for the variable describing the difference between the date of vision test and the calculated date in days

	O	P	M
Mean	-1.6	-1.7	0.0
Standard Error	1.6	1.1	0.0
Median	0.0	0.0	0.0
Mode	0.0	0.0	0.0
Standard Deviation	3.6	2.6	0.0
Sample Variance	12.8	6.7	0.0
Kurtosis	5.0	-1.9	-
Skewness	-2.2	-0.9	-
Range	8.0	5.0	0.0
Minimum	-8.0	-5.0	0.0
Maximum	0.0	0.0	0.0
Count	5.0	6.0	3.0

0=Data collected on time
O=Ovulation point, P=Peak progesterone level, M=First day of menstruation
Positive values = Questionnaires were completed before the calculated date
Negative values = Questionnaires were completed after the calculated date

5.5 Demographic data

5.5.1 Plan B (VIP online)

These data were not collected from participants at the point of enrolment, as the study protocol did not require this information.

5.6 Plan C (VIMC)

5.6.1 Age demographics

The age demographics of the study participants can be found in Table 5-9. The age range for participants who signed up to the study was between 18–55 years, with the mean age of the cohort who completed all three questionnaires being 30.5 years. Participants have been grouped into four age ranges demonstrating which age groups completed questionnaires (Table 5-10).

Table 5-9 Age demographics all participants (years).

	Only 1 questionnaire completed	Only 2 questionnaires completed	All 3 questionnaires completed
Mean	36.0	38.0	35.3
Standard Error	4.9	3.4	3.3
Median	37.0	38.0	32.0
Mode	#N/A	#N/A	#N/A
Standard Deviation	11.9	8.8	9.9
Sample Variance	142.4	78.0	99.0
Kurtosis	-1.2	-2.2	-0.7
Skewness	0.2	-0.1	1.0
Range	31.0	21.0	26.0
Minimum	22.0	27.0	26.0
Maximum	53.0	48.0	52.0
Count	6	7	9

Table 5-10 Age distribution of participants (years) who completed questionnaires.

Age (years)	Only 1 questionnaire completed	Only 2 questionnaires completed	All 3 questionnaires completed
≤ 20	0	0	0
21 -30	2	2	4
31-50	3	5	4
>51	1	0	1

5.6.2 Menarche and menstrual cycle data

The participants' reported menarche age, for each cohort are found in Table 5-11. The mean participant reported menarche age of those which enrolled into the VIMC study was 13 years old, with a range of 11-17 years.

The reported duration of the menstrual cycle for each cohort are found Table 5-12. The median duration of the menstrual cycle for all participants, who signed up to the study, was 28 days with a range of 21 – 35 days. With age, the duration of the menstrual cycle is known to vary and Table 5-13 shows the duration of the menstrual cycle for those study participants who were 50 years and older.

Table 5-11 Reported age of menarche (years).

	Only 1 questionnaire completed	Only 2 questionnaires completed	All 3 questionnaires completed
Mean	13.5	13.3	12.9
Standard Error	0.9	0.5	0.4
Median	14.0	13.5	13.0
Mode	14.0	14.0	13.0
Standard Deviation	2.3	1.3	1.0
Sample Variance	5.1	1.6	1.0
Kurtosis	-0.1	-0.0	0.8
Skewness	0.3	-0.6	-0.9
Range	6.0	4.0	3.0
Minimum	11.0	11.0	11.0
Maximum	17.0	15.0	14.0
Count	6.0	7.0	9.0

Table 5-12 Reported duration of menstrual cycle (days).

	Only 1 questionnaire completed	Only 2 questionnaires completed	All 3 questionnaires completed
Mean	29.1	26.4	26.9
Standard Error	0.9	1.3	0.9
Median	29.0	28.0	28.0
Mode	28.0	28.0	28.0
Standard Deviation	2.2	3.6	2.6
Sample Variance	5.0	12.8	7.0
Kurtosis	-1.1	-1.2	3.8
Skewness	-0.2	-0.5	-1.9
Range	6.0	10.0	8.0
Minimum	26.0	21.0	21.0
Maximum	32.0	31.0	29.0
Count	6.0	7.0	9.0

Table 5-13 Duration of menstrual cycle for all those participants who enrolled ≥ 50 yrs old.

Age	Duration of menses
50	21 days
52	22 days
53	28 days
55	28 days

5.7 Vision correction

5.7.1 Plan B (VIP online)

Vision correction was used by three participants. One participant used both spectacles and contact lenses with two only using spectacles. Of those who used vision correction, two used them constantly and one used them selectively. One participant used vision correction for distance vision only tasks and two used them both for distance and near vision tasks. All participants indicated that they were drivers and two indicated that they used glasses for driving.

5.7.2 Plan C (VIMC)

The 44 participants who enrolled into the study were asked whether they required any form of vision correction. Twenty-nine participants reported that they required some form of vision correction and 15 participants reported no vision correction was required. Of those that reported using vision correction, 18 participants used glasses, two used contact lenses and nine participants used both glasses and contact lenses. Sixteen participants reported using vision correction all waking hours and thirteen participants reported using them selectively. Eleven participants used them for distance vision, five participants used them for near vision and 13 participants used them for both distance and near vision tasks.

5.7.3 Driving & vision correction

Thirty-six participants indicated that they drive and eight reported that they did not drive. Of the drivers, 19 participants reported using vision correction, 12 participants reported not using correction and five participants did not respond.

5.8 Medications taken by participants

5.8.1 Plan B (VIP-online)

All four participants reported taking folic acid. At the point of consent and sign up, they had been taking folic acid for 7, 4, 18, and 8 weeks respectively. One participant reported taking folic acid prior to pregnancy. No participants reported taking any other medication.

5.8.2 Plan C (VIMC)

Of the 22 participants who completed at least one questionnaire, 13 listed taking at least one medication. The age range for those taking medications was between, 18 and 53 years Two participants indicated medical conditions for which they were being treated; poly cystic ovary syndrome (PCOS) and atrial fibrillation (AF). The list of medications and recognised possible, ocular adverse reactions are listed in Table 5-14.

.

Table 5-14 Types of medications and associated ocular adverse reactions

Drug name	Condition	Ocular adverse reactions *	Frequency
Amlodipine	Hypertension	Visual disturbance / visual impairment	Rare
Gederal	Contraception	Eye irritation for contact lens wearers	Rare
Semaglutide	Anti diabetic	None	
Ferrous sulphate	Anaemia	None	
Yaltormin	Anti-diabetic	None	
Lamotrigine	Epilepsy	Diplopia, Blurred vision, Conjunctivitis	Rare
Combined pill	Contraception	Eye irritation for contact lens wearers	Rare
Desloratadine	Anti allergic	Eye dryness	Rare
Verapamil	Hypertension	None	
Rigevidon	Contraception	Eye irritation for contact lens wearers	Rare

Drug name	Condition	Ocular adverse reactions *	Frequency
Levothyroxine	Hypothyroidism	None	
Sertraline	Antidepressant	Mydriasis, Scotoma, Glaucoma, Diplopia, Photophobia, Hyphaema, Anisocoria, Lacrimal disorder, Maculopathy	Rare
Naproxen	Inflammatory	None	
Metformin	Anti-diabetic	Visual disturbance, Macular oedema	Common
Pantoprazole	PPI	Disturbances in vision / blurred vision	Unknown
Lanzoprazole	GORD	Visual disturbances	Rare
Ramapril	Hypertension	None	
Clopidogrel	Antiplatelet	Eye bleeding (conjunctival, ocular, retinal)	Unknown

*www.medicines.org.uk

5.9 NEI RQL-42 and vision test results

The NEI RQL-42 has 13 subscales, but for this chapter the analysis has been carried out on the data from subscales which are considered pertinent to assessing visual changes during pregnancy and the menstrual cycle. The chosen subscales are clarity of vision, far vision, near vision, glare, and diurnal variation. In addition, the results of the two questions in the Sande dry eye questionnaire and the vision test data obtained from the FrACT vision test were also analysed.

5.9.1 Subscale values

Each of the 13 subscales are formed from a group of questions; the number of questions in the groups range from two to five. Using the NEI RQL-42 scoring key (Appendix 10) the answer to each question is assigned a numerical value and the mean of the total of the values for each subscale is used as the overall score for the subscale. As an example, for the subscale “far vision” and participant number four, the values for each of the five questions in this subscale when the questionnaire was first completed were: 100, 100, 66.67, 75 and 75 respectively, giving a mean value of 83.3 which is used as the subscale score for that participant. This process is applied across subscales for each participant data collection event.

5.10 Plan B (VIP-online)

With a single data point for each participant, the subscale values have been incorporated into a single scatter plot (Figure 5-3) Diurnal variation data points for P2, P3 and P4 have been jittered by 2.5 points to facilitate observation, with the full dataset (without jittering) in Table 5-15.

5.11 Jittering

In the profile plots, the data have been jittered to facilitate observation of identical data points. This involved changing the data values by the minimum to provide a visible difference in the data points. This process creates observable differences in the numerical values between the graphs and the tabular data.

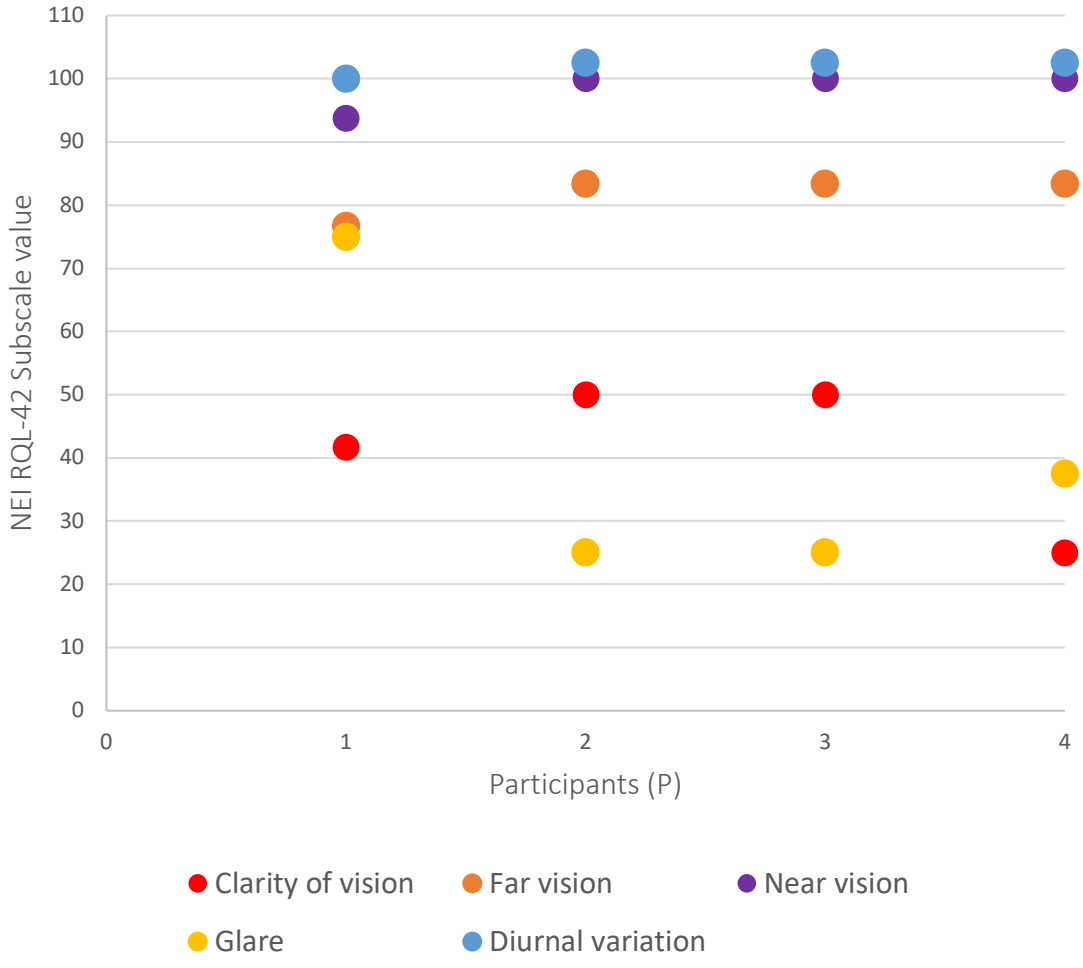

Figure 5-3 Plan B (VIP –online) participant subscale plot

Table 5-15 VIP-online, subscale dataset

Subscale	P1	P2	P3	P4
Clarity of vision	41.7	50.0	50.0	25.0
Far vision	76.7	83.3	83.3	83.3
Near vision	93.7	100.0	100.0	100.0
Glare	75.0	25.0	25.0	37.5
Diurnal variation	100.0	100.0	100.0	100.0

(Higher values indicate greater refractive error-related quality of life)

5.12 Plan C (VIMC)

There was a total of 47 vision questionnaire data events (Figure 5-1); of these, there were six single event questionnaires generated by participants who only completed one questionnaire, representing 13% of the total number of data points. Given the potential for these data to distort the study findings, these participants and their data were excluded from further analysis. The remaining participants were separated into two cohorts; those who completed two and three questionnaires respectively. For each NEI RQL-42 subscale, vision test and Sande dry eye questions one and two, profile plots were generated to illustrate participant responses.

Box and whisker plots were generated to provide further indication of the data variation for the three data collection points; O, P and M. The vertical box height, indicating the inter quartile range (IQR), from the first to the third quartile, with upper and lower whiskers representing most data and the respective upper and lower data values; dots above or below the whiskers representing outliers.

The horizontal line within the box represents the median value of the data; an off-centre line indicates skewed data and if absent then the median value coincides with either the upper or lower quartile value. The cross (X) within either the box or on the vertical whisker line, represents the mean value of the data.

The small sample size has the potential to influence the normality of the data, by an inadequate estimation of the dispersion of the data which results in a non-normal frequency distribution curve. For each NEI RQL-42 subscale and Sande dry eye question one and two, normality was assessed using the Shapiro-Wilk test, which is suitable for small sample sizes (Yap & Sim, 2011).

Table 5-16 Normality distribution for subscales

Subscale	Only 2 questionnaires completed cohort	All 3 questionnaires completed cohort
Clarity of vision	No	No
Far vision	No	No
Near vision	No	No
Glare	No	No
Diurnal variation	Yes	Yes
Sande dry eye 1	No	Yes
Sande dry eye 2	Yes	Yes

More than half of the datasets are not normally distributed (Table 5-16) and as a result the Wilcoxon signed rank test was used for comparative analyses. The Wilcoxon signed rank test is based on the difference in scoring between the repeated measures; in addition to analysing the signs of the differences, it also takes into account the magnitude of the observed differences between pairs of measurements. There are two test outputs used to describe differences between the two groups. The Z score is calculated from the ranks of the groups and can be compared to a normal distribution; a Z value of +/- 1.96 = 2SD, which equates to a confidence interval of 95% (Curtis *et al.*, 2016; Hazra, 2016). The P value or asymptotic significance (Asymp.Sig) value indicates whether the null hypothesis (H_0) can be accepted or rejected in favour of the alternative hypothesis (H_1).

The data events chosen for further analysis are those having the greatest difference in IQR and, where the IQRs are similar, those having the greatest observable differences in the box and whisker plots. Table 5-17 outlines the data collection events which were used to determine if any statistically significant difference was present and the table numbers where the corresponding SPSS Wilcoxon signed rank test output is presented.

Table 5-17 Choice of data events for analysis

Subscale	Only 2 questionnaires completed cohort	All 3 questionnaires completed cohort
Clarity of vision	O-M	M-P
Far vision	O-M	O-M
Near vision	O-M	O-M
Glare	P-M	P-O
Diurnal variation	O-M	O-M
Sande dry eye Qu1	P-M	O-P
Sande dry eye Qu2	O-M	P-M

5.12.1 Subscale - Clarity of vision

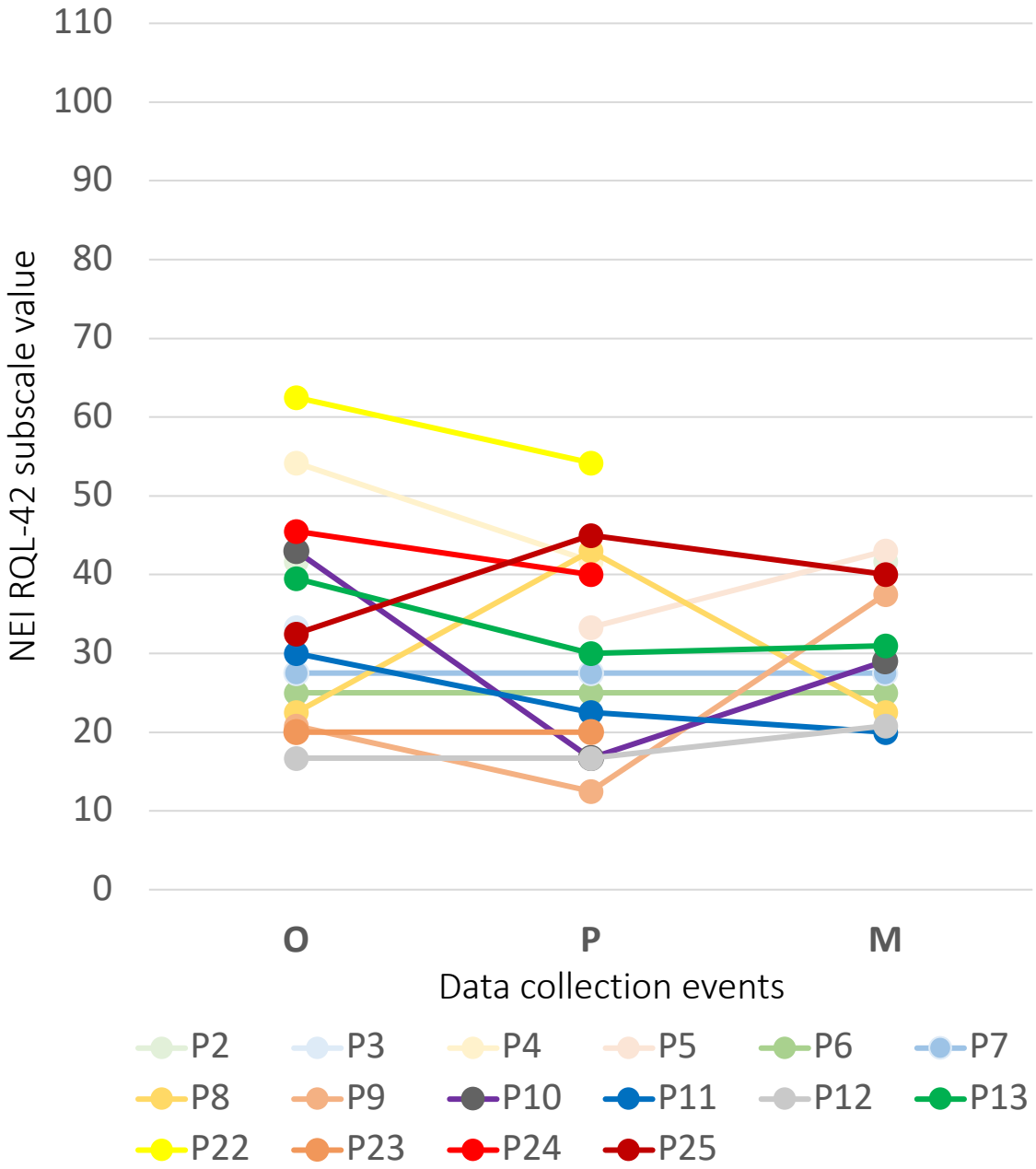

Figure 5-4 Clarity of vision, profile plot for participants who completed at least two questionnaires.

M data points for participants P3, P6, P7 and P10 are similar values with points being close together.

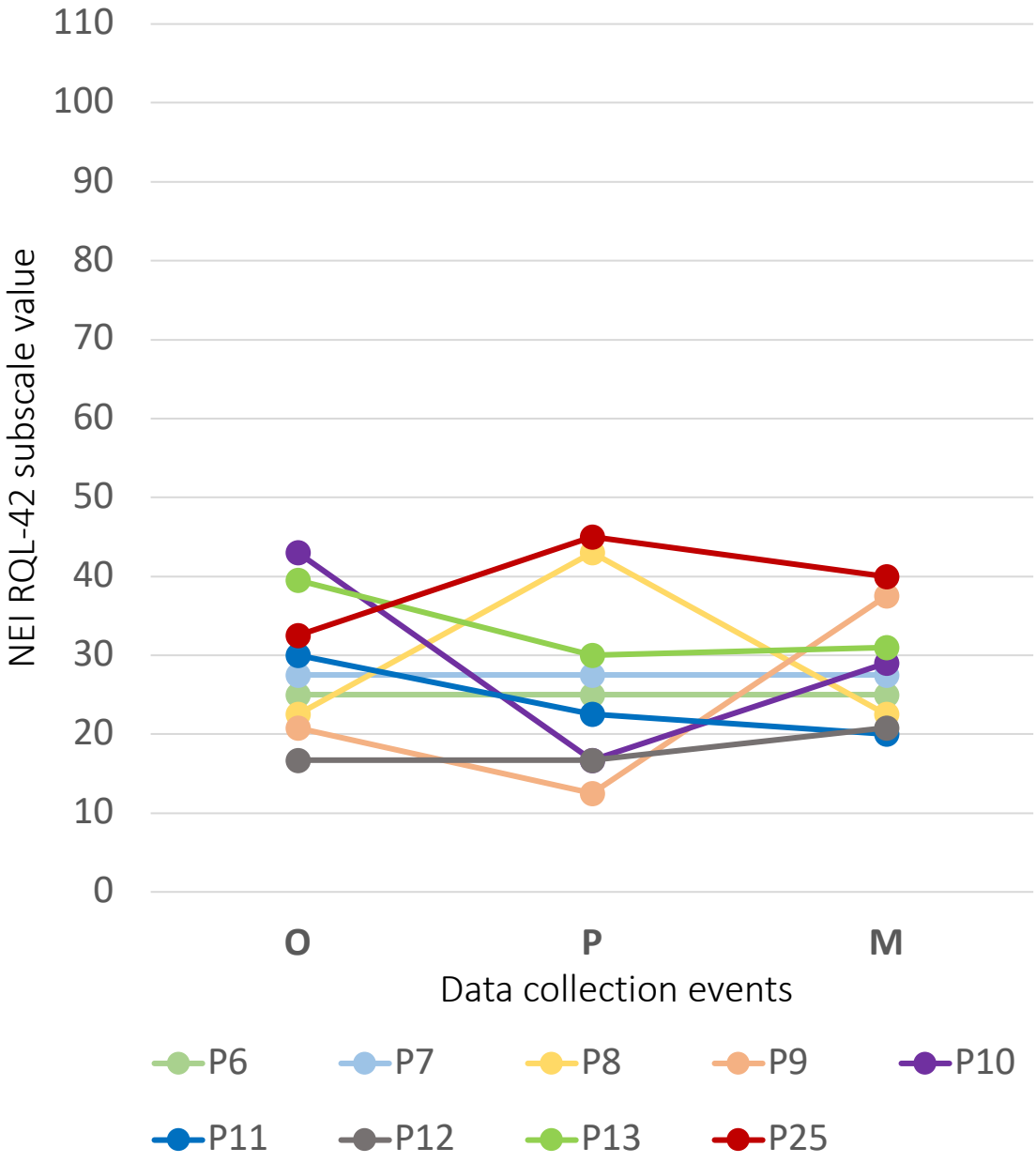

Figure 5-5 Clarity of vision, profile plot for participants who completed three questionnaires

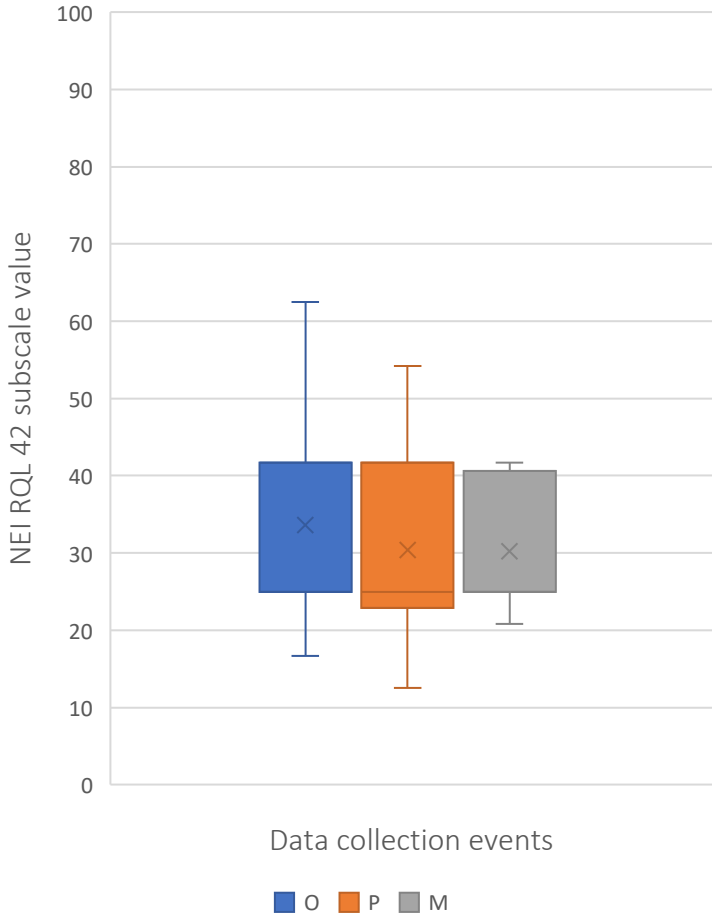

Figure 5-6 Clarity of vision, box & whisker plot for participants who completed at least two questionnaires

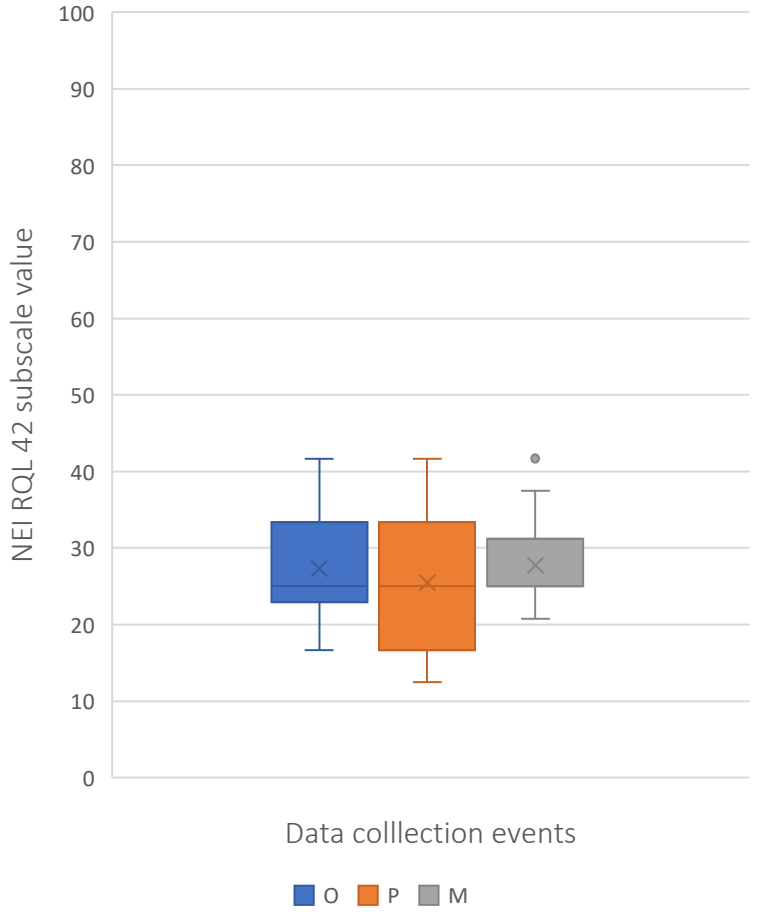

Figure 5-7 Clarity of vision, box & whisker plot for those participants who completed three questionnaire

Table 5-18 Clarity of vision, dataset for all participants who completed at least two questionnaires

	O	P	M
P2	41.7	-	41.7
P3	33.3	-	29.1
P4	54.2	41.7	-
P5	-	33.3	41.7
P6	25.0	25.0	25.0
P7	25.0	25.0	25.0
P8	25.0	41.7	25.0
P9	20.8	12.5	37.5
P10	41.7	16.7	25.0
P11	25.0	25.0	25.0
P12	16.7	16.7	20.8
P13	41.7	25.0	25.0
P22	62.5	54.2	-
P23	25.0	25.0	-
P24	41.7	41.7	-
P25	25.0	41.7	41.7

Table 5-19 Clarity of vision, dataset for all participants who completed three questionnaires

	O	P	M
P6	25.0	25.0	25.0
P7	25.0	25.0	25.0
P8	25.0	41.7	25.0
P9	20.8	12.5	37.5
P10	41.7	16.7	25.0
P11	25.0	25.0	25.0
P12	16.7	16.7	20.8
P13	41.7	25.0	25.0
P25	25.0	41.7	41.7

Table 5-20 Clarity of vision, SPSS output of descriptive data for participants who completed at least two questionnaires

Descriptives

			Statistic	Std. Error
Data_event_O	Mean		33.6200	3.39138
	95% Confidence Interval for Mean	Lower Bound	26.3462	
		Upper Bound	40.8938	
	5% Trimmed Mean		32.9556	
	Median		25.0000	
	Variance		172.522	
	Std. Deviation		13.13475	
	Minimum		16.70	
	Maximum		62.50	
	Range		45.80	
	Interquartile Range		16.70	
	Skewness		.877	.580
	Kurtosis		.049	1.121
Data_event_P	Mean		30.3714	3.25407
	95% Confidence Interval for Mean	Lower Bound	23.3414	
		Upper Bound	37.4014	
	5% Trimmed Mean		30.0405	
	Median		25.0000	
	Variance		148.245	
	Std. Deviation		12.17560	
	Minimum		12.50	
	Maximum		54.20	
	Range		41.70	
	Interquartile Range		18.78	
	Skewness		.387	.597
	Kurtosis		-.698	1.154
Data_event_M	Mean		30.2083	2.30587
	95% Confidence Interval for Mean	Lower Bound	25.1331	
		Upper Bound	35.2835	
	5% Trimmed Mean		30.0926	
	Median		25.0000	
	Variance		63.804	
	Std. Deviation		7.98777	
	Minimum		20.80	
	Maximum		41.70	
	Range		20.90	
	Interquartile Range		15.65	
	Skewness		.697	.637
	Kurtosis		-1.425	1.232

Table 5-21 Clarity of vision, SPSS output of descriptive data for participants who completed three questionnaires

Descriptives

			Statistic	Std. Error
Data_event_O	Mean		27.3222	2.87657
	95% Confidence Interval for Mean	Lower Bound	20.6888	
		Upper Bound	33.9556	
	5% Trimmed Mean		27.1136	
	Median		25.0000	
	Variance		74.472	
	Std. Deviation		8.62971	
	Minimum		16.70	
	Maximum		41.70	
	Range		25.00	
	Interquartile Range		10.45	
	Skewness		1.102	.717
	Kurtosis		.266	1.400
Data_event_P	Mean		25.4778	3.43543
	95% Confidence Interval for Mean	Lower Bound	17.5557	
		Upper Bound	33.3999	
	5% Trimmed Mean		25.2975	
	Median		25.0000	
	Variance		106.219	
	Std. Deviation		10.30628	
	Minimum		12.50	
	Maximum		41.70	
	Range		29.20	
	Interquartile Range		16.65	
	Skewness		.734	.717
	Kurtosis		-.328	1.400
Data_event_M	Mean		27.7778	2.30740
	95% Confidence Interval for Mean	Lower Bound	22.4569	
		Upper Bound	33.0987	
	5% Trimmed Mean		27.3920	
	Median		25.0000	
	Variance		47.917	
	Std. Deviation		6.92221	
	Minimum		20.80	
	Maximum		41.70	
	Range		20.90	
	Interquartile Range		6.25	
	Skewness		1.526	.717
	Kurtosis		1.172	1.400

Table 5-22 Clarity of vision, SPPS output for participants who completed at least two questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data_collection_O	.384	9	.000	.776	9	.011
Data_collection_P	.296	9	.022	.854	9	.083
Data_collection_M	.434	9	.000	.697	9	.001

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_collection_M - Data_collection_O	Negative Ranks	3[a]	3.67	11.00
	Positive Ranks	3[b]	3.33	10.00
	Ties	5[c]		
	Total	11		

a. Data_collection_M < Data_collection_O

b. Data_collection_M > Data_collection_O

c. Data_collection_M = Data_collection_O

Test Statistics[a]

	Data_collection_M - Data_collection_O
Z	-.108[b]
Asymp. Sig. (2-tailed)	.914

a. Wilcoxon Signed Ranks Test

b. Based on positive ranks.

Table 5-23 Clarity of vision, SPPS output for participants who completed three questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data_event_O	.384	9	.000	.775	9	.011
Data_event_P	.296	9	.022	.854	9	.083
Data_event_M	.434	9	.000	.698	9	.001

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_collection_M - Data_collection_P	Negative Ranks	1[a]	3.00	3.00
	Positive Ranks	3[b]	2.33	7.00
	Ties	5[c]		
	Total	9		

a. Data_collection_M < Data_collection_P

b. Data_collection_M > Data_collection_P

c. Data_collection_M = Data_collection_P

Test Statistics[a]

	Data_collection_M - Data_collection_P
Z	-.730[b]
Asymp. Sig. (2-tailed)	.465

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

5.12.2 Subscale – Far vision

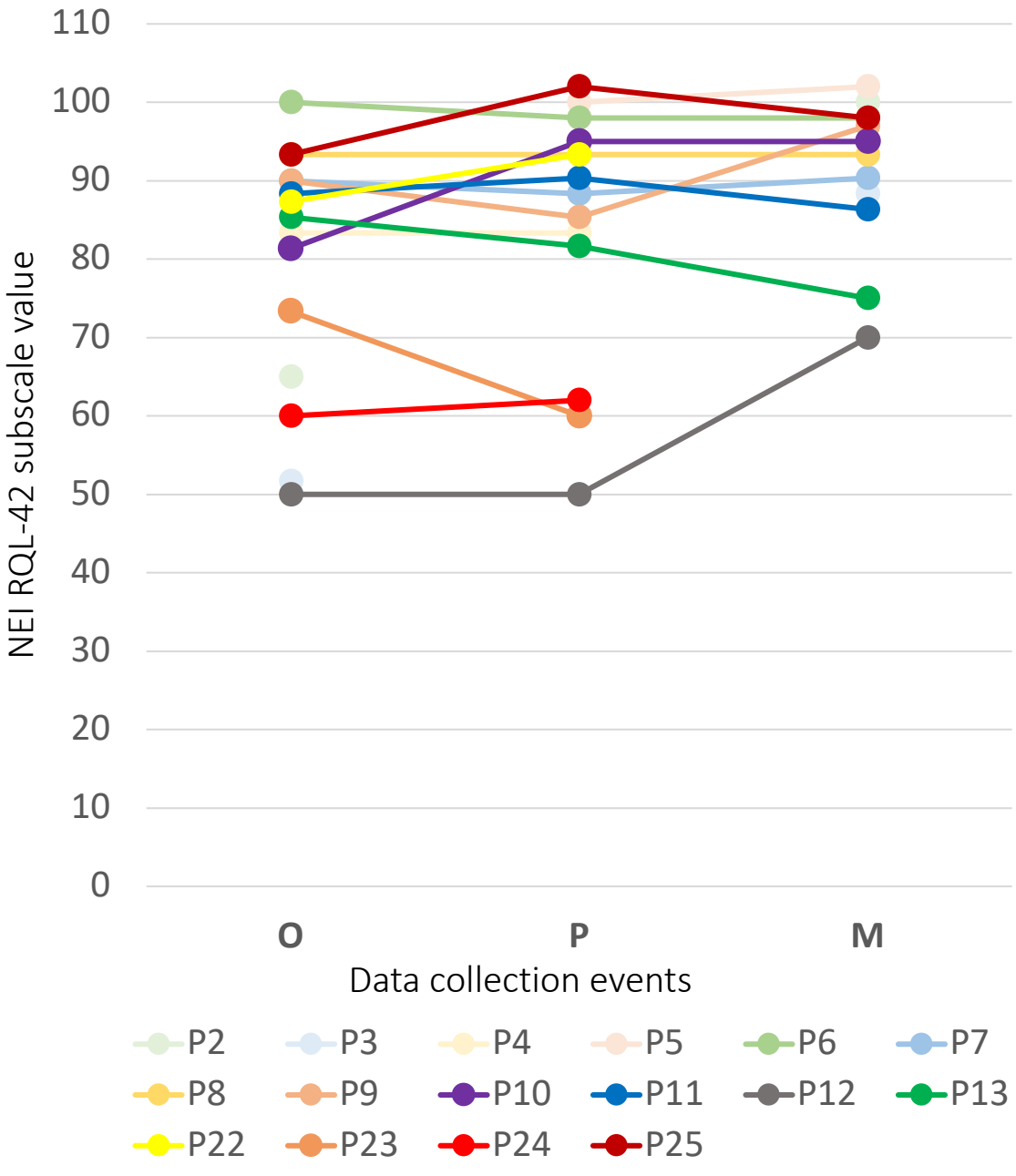

Figure 5-8 Far vision, profile plots for participants who completed at least two questionnaires

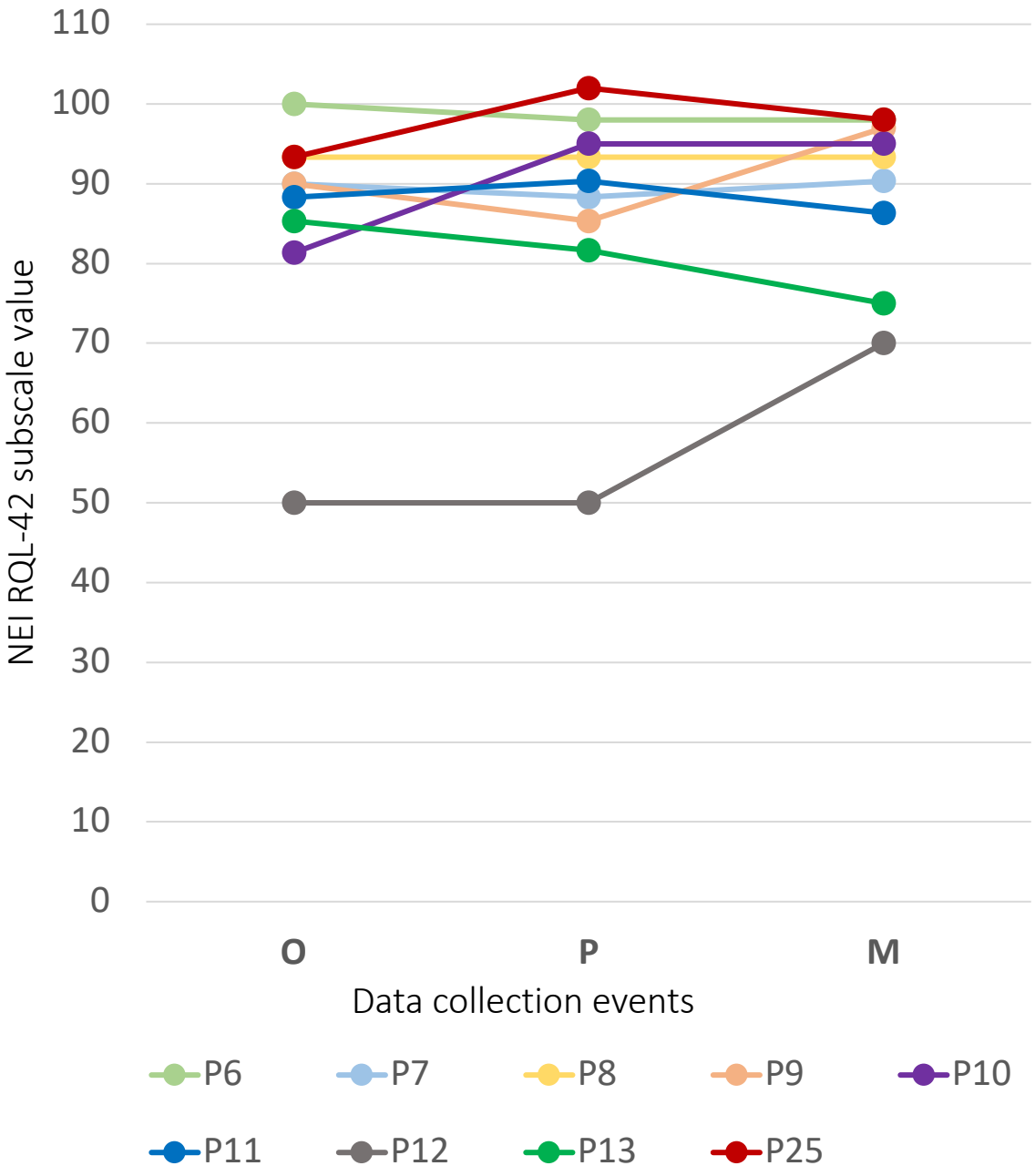

Figure 5-9 Far vision, profile plots for participants who completed three questionnaire

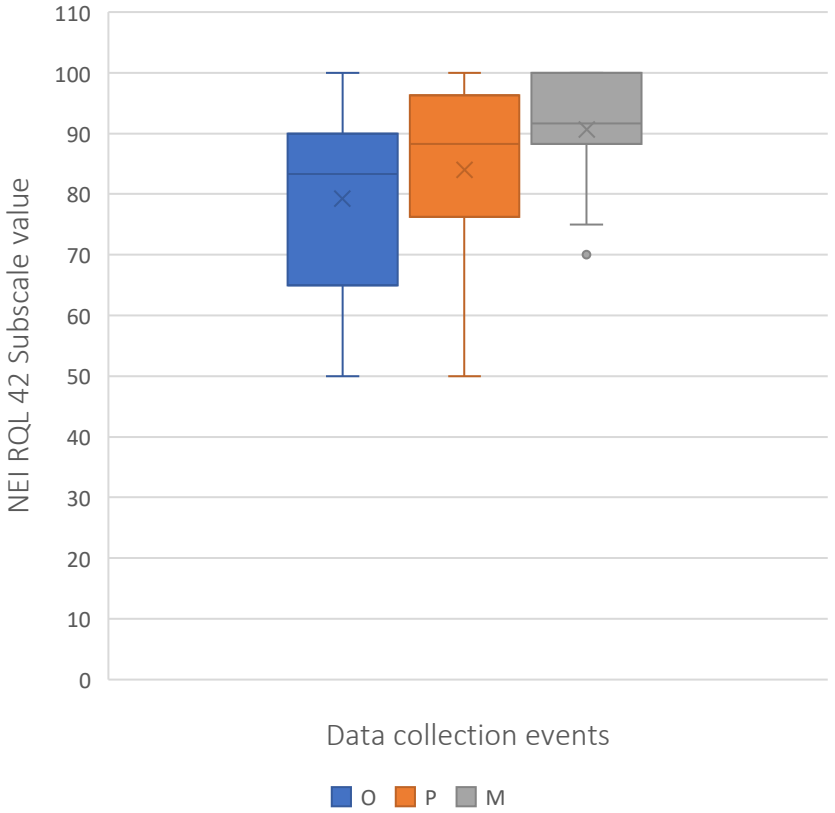

Figure 5-10 Far vision, box & whisker plots for those participants who completed at least two questionnaires

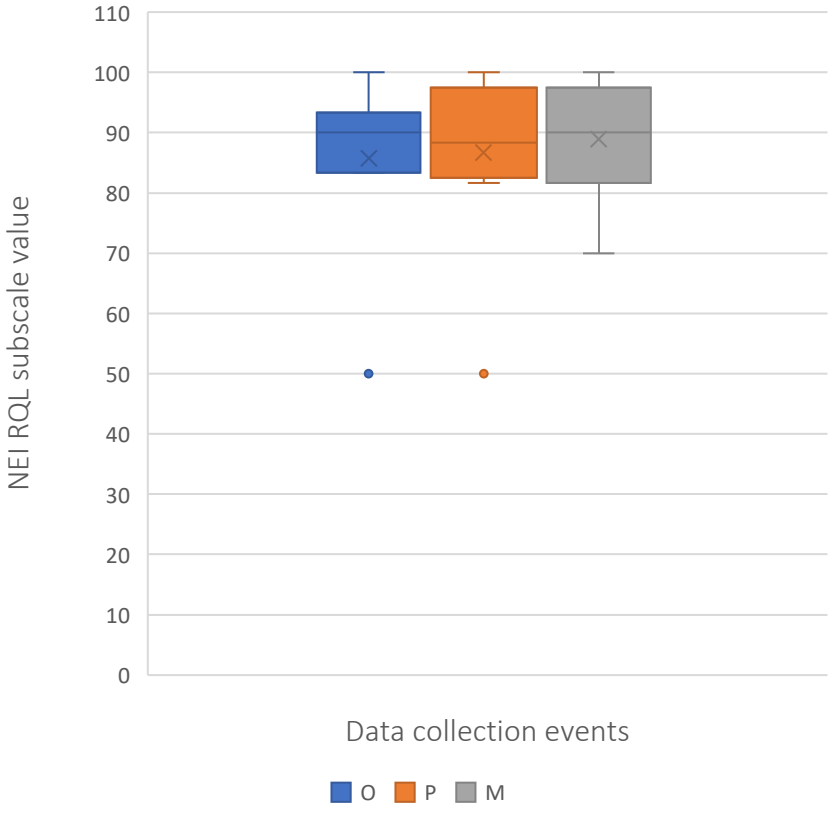

Figure 5-11 Far vision, box & whisker plots for those participants who completed three questionnaires

Table 5-24 Far vision, dataset for all those participants who completed at least two questionnaires

	O	P	M
P2	65.0	-	100.0
P3	51.7	-	88.3
P4	83.3	83.3	-
P5	-	100.0	100.0
P6	100.0	100.0	100.0
P7	90.0	88.3	88.3
P8	93.3	93.3	93.3
P9	90.0	83.3	90.0
P10	83.3	95.0	95.0
P11	88.3	88.3	88.3
P12	50.0	50.0	70.0
P13	83.3	81.7	75.0
P22	83.3	93.3	-
P23	73.3	60.0	-
P24	60.0	60.0	-
P25	93.3	100.0	100.0

Table 5-25 Far vision, dataset for all those participants who completed three questionnaires

	O	P	M
P6	100.0	100.0	100.0
P7	90.0	88.3	88.3
P8	93.3	93.3	93.3
P9	90.0	83.3	90.0
P10	83.3	95.0	95.0
P11	88.3	88.3	88.3
P12	50.0	50.0	70.0
P13	83.3	81.7	75.0
P25	93.3	100.0	100.0

Table 5-26 Far vision, SPSS output of descriptive data for those participants who completed at least two questionnaires

Descriptives

			Statistic	Std. Error
Data_event_O	Mean		79.2067	4.04002
	95% Confidence Interval for Mean	Lower Bound	70.5417	
		Upper Bound	87.8716	
	5% Trimmed Mean		79.6741	
	Median		83.3000	
	Variance		244.826	
	Std. Deviation		15.64693	
	Minimum		50.00	
	Maximum		100.00	
	Range		50.00	
	Interquartile Range		25.00	
	Skewness		-.812	.580
	Kurtosis		-.508	1.121
Data_event_P	Mean		84.0379	4.33055
	95% Confidence Interval for Mean	Lower Bound	74.6823	
		Upper Bound	93.3934	
	5% Trimmed Mean		85.0421	
	Median		88.3000	
	Variance		262.551	
	Std. Deviation		16.20344	
	Minimum		50.00	
	Maximum		100.00	
	Range		50.00	
	Interquartile Range		19.97	
	Skewness		-1.096	.597
	Kurtosis		.126	1.154
Data_event_M	Mean		90.6833	2.83906
	95% Confidence Interval for Mean	Lower Bound	84.4346	
		Upper Bound	96.9321	
	5% Trimmed Mean		91.3148	
	Median		91.6500	
	Variance		96.723	
	Std. Deviation		9.83480	
	Minimum		70.00	
	Maximum		100.00	
	Range		30.00	
	Interquartile Range		11.70	
	Skewness		-1.080	.637
	Kurtosis		.584	1.232

Table 5-27 Far vision, SPSS output of descriptive data for those participants who completed three questionnaires

Descriptives

			Statistic	Std. Error
Data_event_O	Mean		85.7222	4.78678
	95% Confidence Interval for Mean	Lower Bound	74.6839	
		Upper Bound	96.7606	
	5% Trimmed Mean		86.9136	
	Median		90.0000	
	Variance		206.219	
	Std. Deviation		14.36034	
	Minimum		50.00	
	Maximum		100.00	
	Range		50.00	
	Interquartile Range		10.00	
	Skewness		-2.261	.717
	Kurtosis		5.993	1.400
Data_event_P	Mean		86.6556	5.07552
	95% Confidence Interval for Mean	Lower Bound	74.9514	
		Upper Bound	98.3597	
	5% Trimmed Mean		87.9506	
	Median		88.3000	
	Variance		231.848	
	Std. Deviation		15.22655	
	Minimum		50.00	
	Maximum		100.00	
	Range		50.00	
	Interquartile Range		15.00	
	Skewness		-1.993	.717
	Kurtosis		4.778	1.400
Data_event_M	Mean		88.8778	3.44669
	95% Confidence Interval for Mean	Lower Bound	80.9297	
		Upper Bound	96.8259	
	5% Trimmed Mean		89.3086	
	Median		90.0000	
	Variance		106.917	
	Std. Deviation		10.34007	
	Minimum		70.00	
	Maximum		100.00	
	Range		30.00	
	Interquartile Range		15.85	
	Skewness		-.920	.717
	Kurtosis		.033	1.400

Table 5-28 Far vision, SPPS output for those participants who completed at least two questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data_event_O	.312	13	.001	.825	13	.014
Data_event_P	.325	13	.001	.754	13	.002
Data_event_M	.321	13	.001	.694	13	.000

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_event_M - Data_event_O	Negative Ranks	2[a]	2.00	4.00
	Positive Ranks	5[b]	4.80	24.00
	Ties	4[c]		
	Total	11		

a. Data_event_M < Data_event_O

b. Data_event_M > Data_event_O

c. Data_event_M = Data_event_O

Test Statistics[a]

	Data_event_M - Data_event_P	Data_event_M - Data_event_O
Z	-.535[b]	-1.690[b]
Asymp. Sig. (2-tailed)	.593	.091

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

Table 5-29 Far vision, SPPS output for those participants who completed three questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data_event_O	.322	9	.008	.735	9	.004
Data_event_P	.261	9	.077	.785	9	.014
Data_event_M	.255	9	.093	.889	9	.193

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_event_M - Data_event_O	Negative Ranks	2[a]	2.00	4.00
	Positive Ranks	3[b]	3.67	11.00
	Ties	4[c]		
	Total	9		

a. Data_event_M < Data_event_O

b. Data_event_M > Data_event_O

c. Data_event_M = Data_event_O

Test Statistics[a]

	Data_event_M - Data_event_O
Z	-.944[b]
Asymp. Sig. (2-tailed)	.345

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

5.12.3 Subscale – Near vision

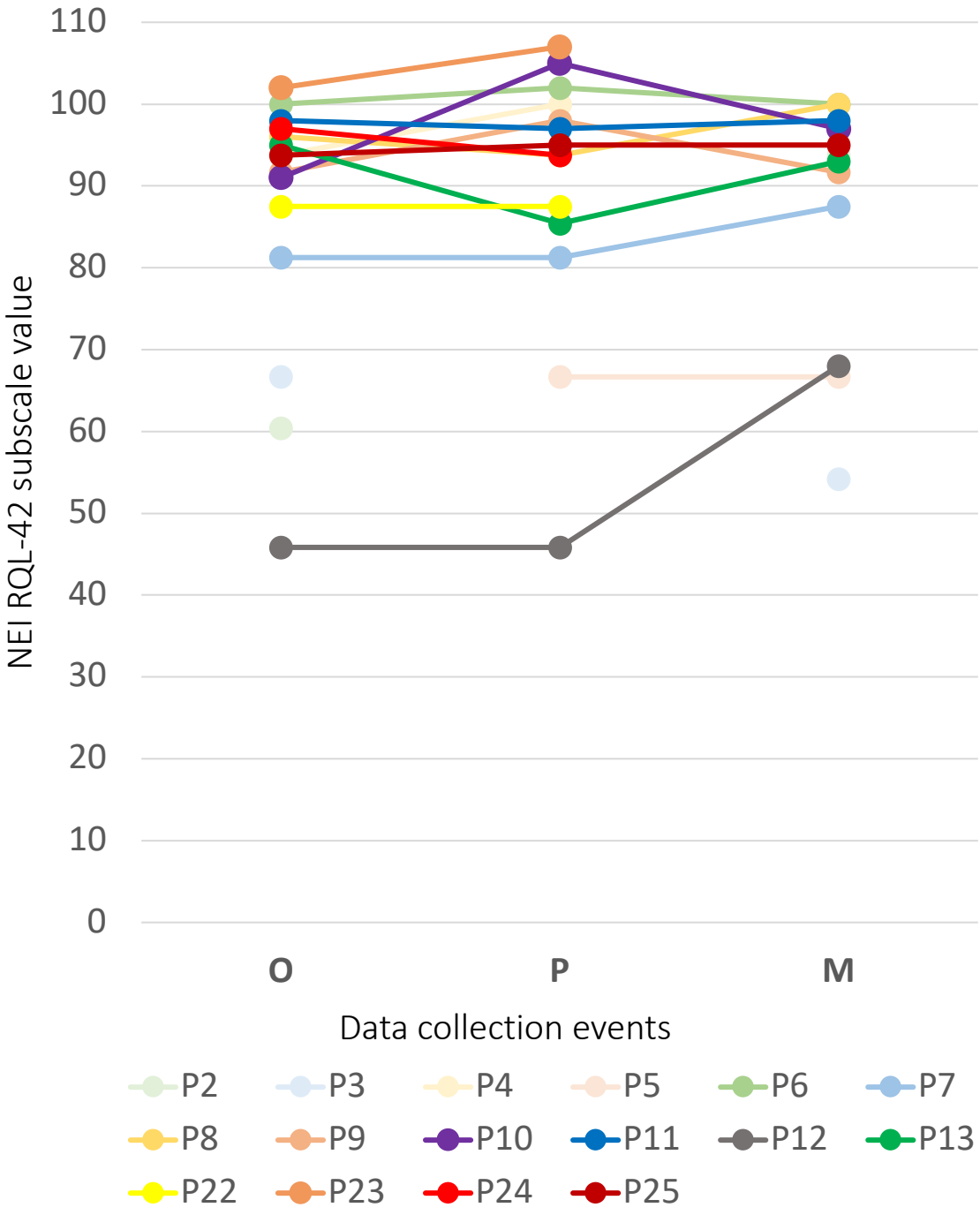

Figure 5-12 Near vision, profile plots for participants who completed at least two questionnaires

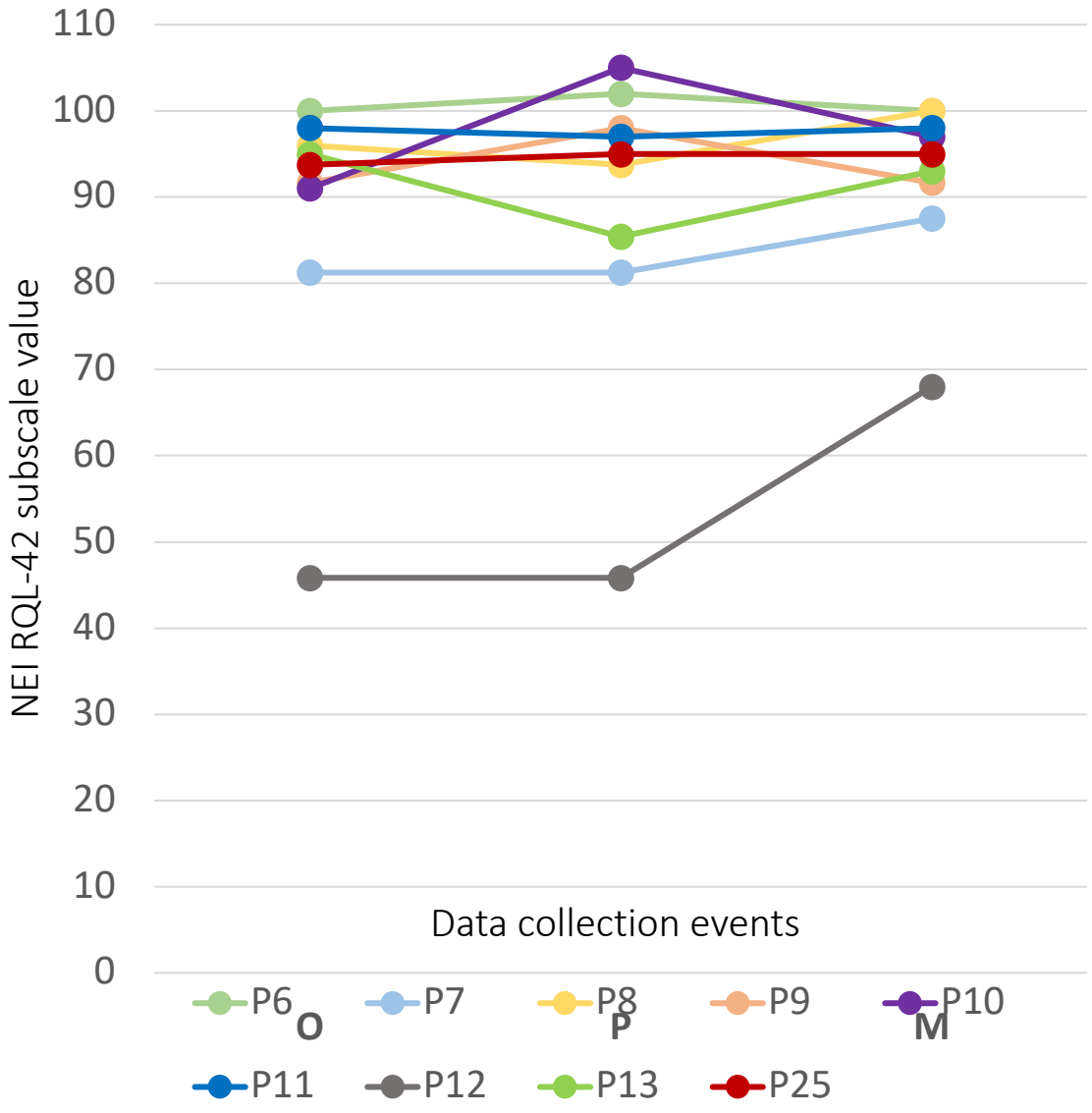

Figure 5-13 Near vision, profile plots for participants who completed three questionnaires

Figure 5-14 Near vision, box & whisker plots for those participants who completed at least two questionnaires

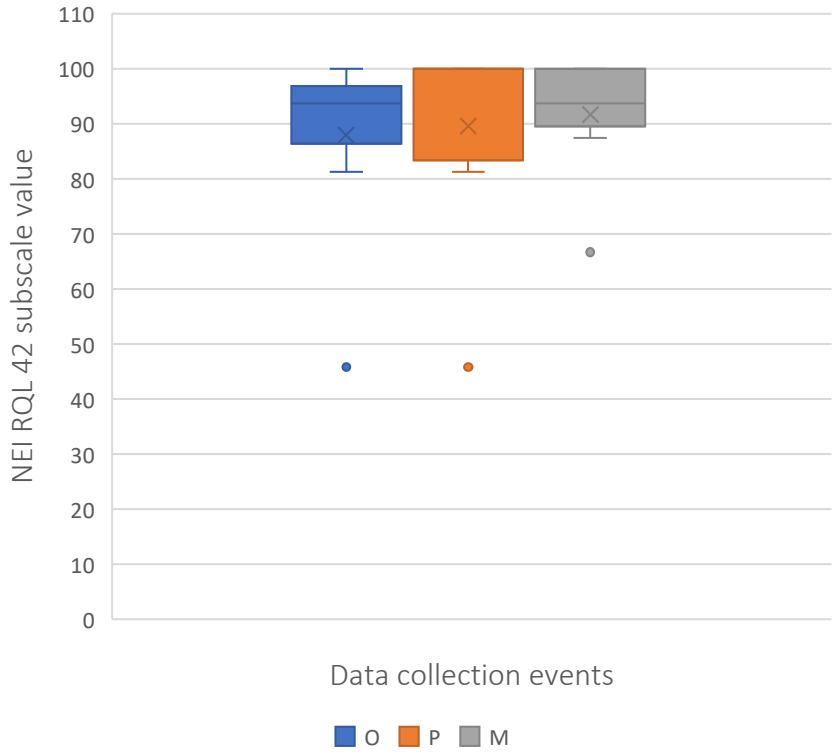

Figure 5-15 Near vision, box & whisker plots for those participants who completed three questionnaires

Table 5-30 Near vision, dataset for all those participants who completed at least two questionnaires

	O	P	M
P2	60.4	-	93.8
P3	66.7	-	54.2
P4	93.7	100.0	-
P5	-	66.7	66.7
P6	100.0	100.0	100.0
P7	81.2	81.3	87.5
P8	93.8	93.8	100.0
P9	91.7	100.0	91.7
P10	93.8	100.0	93.8
P11	100.0	100.0	100.0
P12	45.8	45.8	66.7
P13	91.7	85.4	91.7
P22	87.5	87.5	-
P23	100.0	100.0	-
P24	100.0	93.8	-
P25	93.8	100.0	93.8

Table 5-31 Near vision, dataset for all those participants who completed three questionnaires

	O	P	M
P6	100.0	100.0	100.0
P7	81.2	81.3	87.5
P8	93.8	93.8	100.0
P9	91.7	100.0	91.7
P10	93.8	100.0	93.8
P11	100.0	100.0	100.0
P12	45.8	45.8	66.7
P13	91.7	85.4	91.7
P25	93.8	100.0	93.8

Table 5-32 Near vision, SPSS output of descriptive data for those participants who completed at least 2 questionnaires

Descriptives

			Statistic	Std. Error
Data_collection_O	Mean		86.6733	4.22756
	95% Confidence Interval for Mean	Lower Bound	77.6061	
		Upper Bound	95.7405	
	5% Trimmed Mean		88.2037	
	Median		93.7000	
	Variance		268.084	
	Std. Deviation		16.37326	
	Minimum		45.80	
	Maximum		100.00	
	Range		54.20	
	Interquartile Range		18.80	
	Skewness		-1.566	.580
	Kurtosis		1.682	1.121
Data_collection_P	Mean		89.5929	4.27502
	95% Confidence Interval for Mean	Lower Bound	80.3572	
		Upper Bound	98.8285	
	5% Trimmed Mean		91.4476	
	Median		96.9000	
	Variance		255.861	
	Std. Deviation		15.99565	
	Minimum		45.80	
	Maximum		100.00	
	Range		54.20	
	Interquartile Range		15.63	
	Skewness		-1.943	.597
	Kurtosis		3.712	1.154
Datra_collection_M	Mean		86.6583	4.42853
	95% Confidence Interval for Mean	Lower Bound	76.9112	
		Upper Bound	96.4055	
	5% Trimmed Mean		87.7204	
	Median		92.7500	
	Variance		235.343	
	Std. Deviation		15.34088	
	Minimum		54.20	
	Maximum		100.00	
	Range		45.80	
	Interquartile Range		26.55	
	Skewness		-1.258	.637
	Kurtosis		.324	1.232

Table 5-33 Near vision, SPSS output of descriptive data for those participants who completed 3 questionnaires

Descriptives

			Statistic	Std. Error
Data_event_O	Mean		87.9778	5.58193
	95% Confidence Interval for Mean	Lower Bound	75.1058	
		Upper Bound	100.8497	
	5% Trimmed Mean		89.6531	
	Median		93.8000	
	Variance		280.422	
	Std. Deviation		16.74580	
	Minimum		45.80	
	Maximum		100.00	
	Range		54.20	
	Interquartile Range		10.45	
	Skewness		-2.436	.717
	Kurtosis		6.371	1.400
Data_event_P	Mean		89.59	5.967
	95% Confidence Interval for Mean	Lower Bound	75.83	
		Upper Bound	103.35	
	5% Trimmed Mean		91.44	
	Median		100.00	
	Variance		320.426	
	Std. Deviation		17.900	
	Minimum		46	
	Maximum		100	
	Range		54	
	Interquartile Range		17	
	Skewness		-2.210	.717
	Kurtosis		5.188	1.400
Data_event_M	Mean		91.6889	3.45231
	95% Confidence Interval for Mean	Lower Bound	83.7278	
		Upper Bound	99.6499	
	5% Trimmed Mean		92.6154	
	Median		93.8000	
	Variance		107.266	
	Std. Deviation		10.35694	
	Minimum		66.70	
	Maximum		100.00	
	Range		33.30	
	Interquartile Range		10.40	
	Skewness		-2.016	.717
	Kurtosis		4.847	1.400

Table 5-34 Near vision, SPPS output for those participants who completed at least 2 questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data_event_O	.366	9	.001	.665	9	.001
Data_event_P	.280	9	.040	.670	9	.001
Data_event_M	.278	9	.043	.758	9	.007

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_event_M - Data_event_P	Negative Ranks	3[a]	3.67	11.00
	Positive Ranks	4[b]	4.25	17.00
	Ties	3[c]		
	Total	10		

a. Data_event_M < Data_event_P

b. Data_event_M > Data_event_P

c. Data_event_M = Data_event_P

Test Statistics[a]

	Data_event_M - Data_event_P
Z	-.516[b]
Asymp. Sig. (2-tailed)	.606

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

Table 5-35 Near vision, SPPS output for those participants who completed 3 questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data_event_O	.366	9	.001	.665	9	.001
Data_event_P	.280	9	.040	.670	9	.001
Data_event_M	.278	9	.043	.758	9	.007

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_event_M - Data_event_O	Negative Ranks	0[a]	.00	.00
	Positive Ranks	3[b]	2.00	6.00
	Ties	6[c]		
	Total	9		

a. Data_event_M < Data_event_O

b. Data_event_M > Data_event_O

c. Data_event_M = Data_event_O

Test Statistics[a]

	Data_event_M - Data_event_O
Z	-1.604[b]
Asymp. Sig. (2-tailed)	.109

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

5.12.4 Subscale – Glare

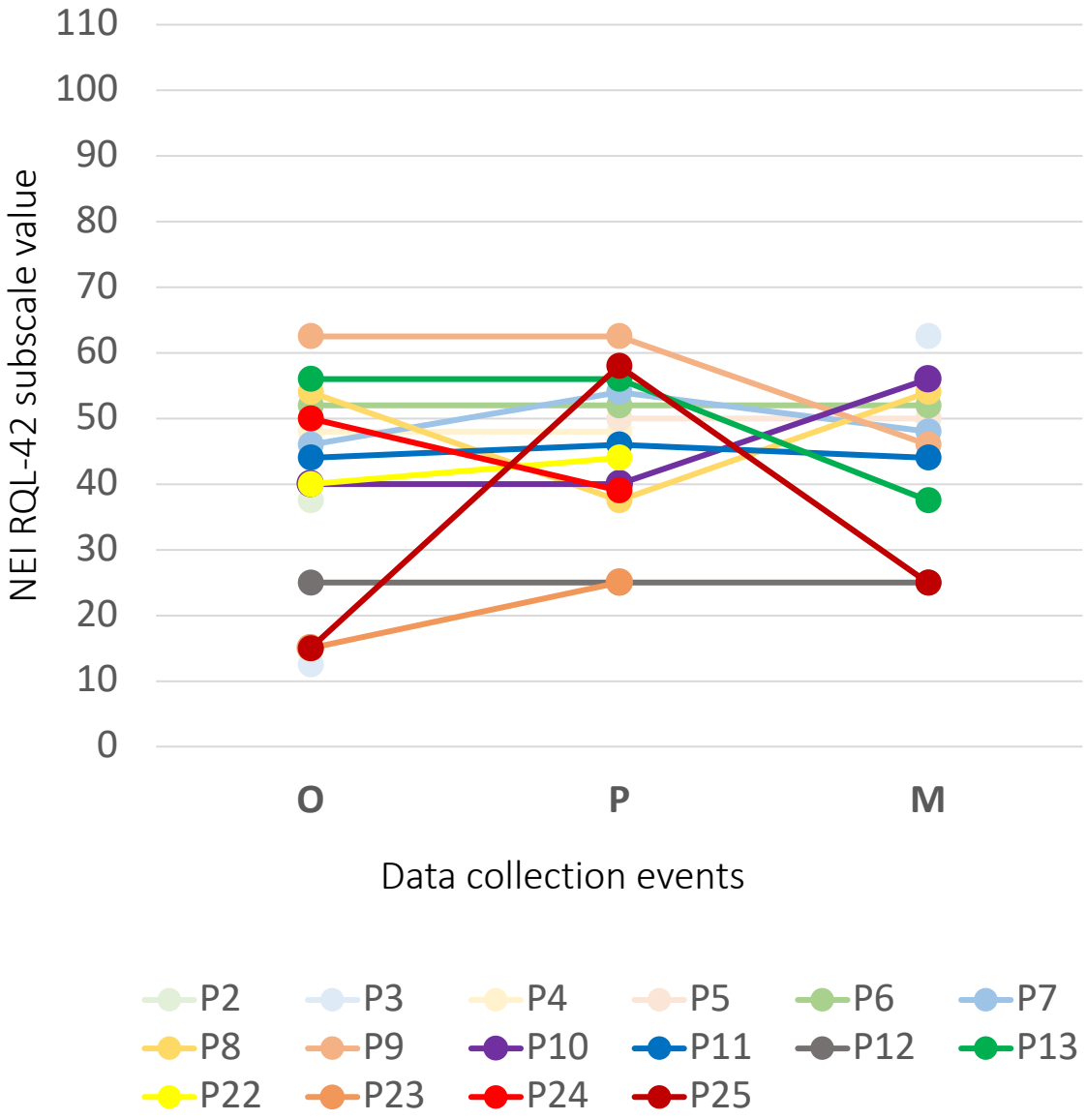

Figure 5-16 Glare, profile plots for participants who completed at least two questionnaires

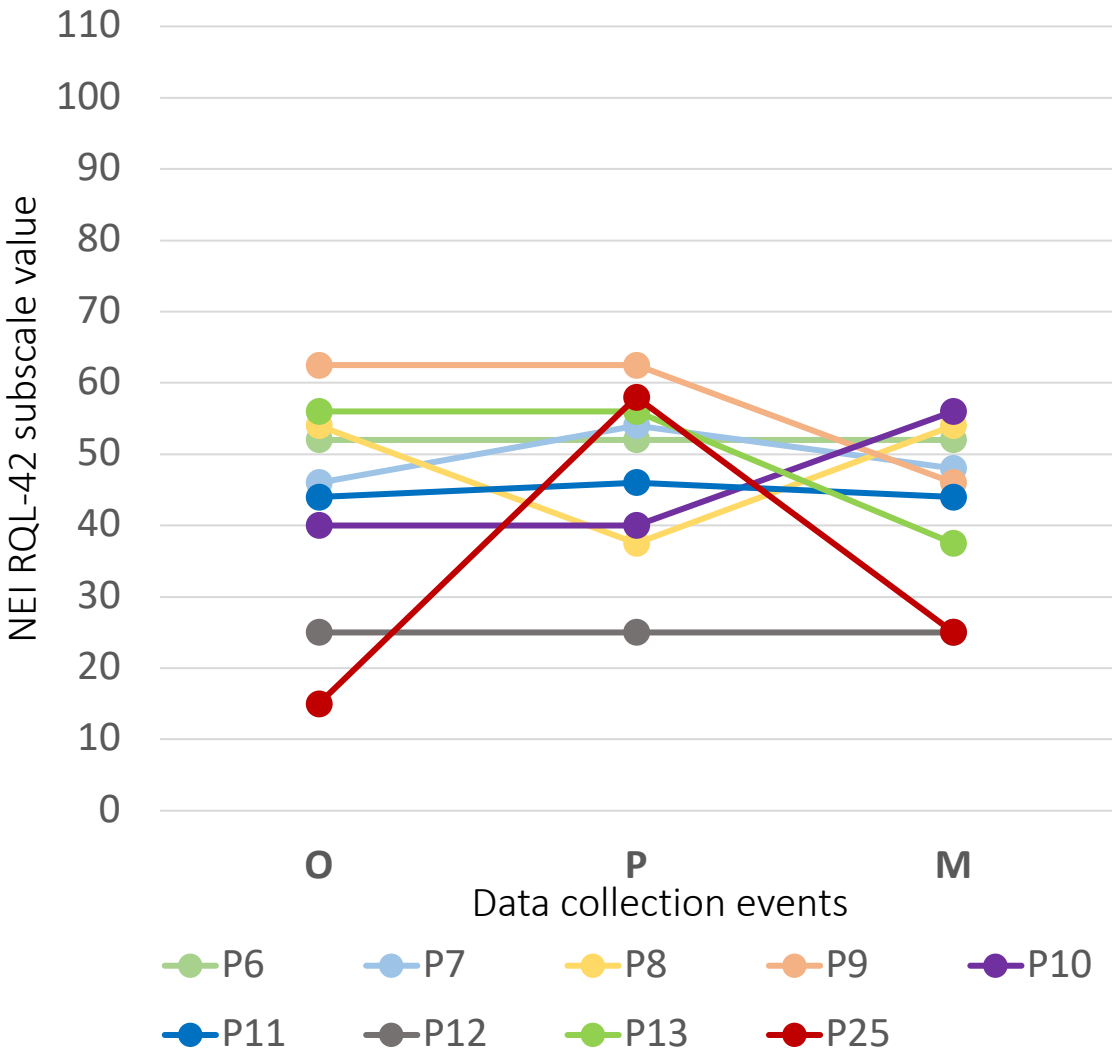

Figure 5-17 Glare, profile plots for participants who completed three questionnaires

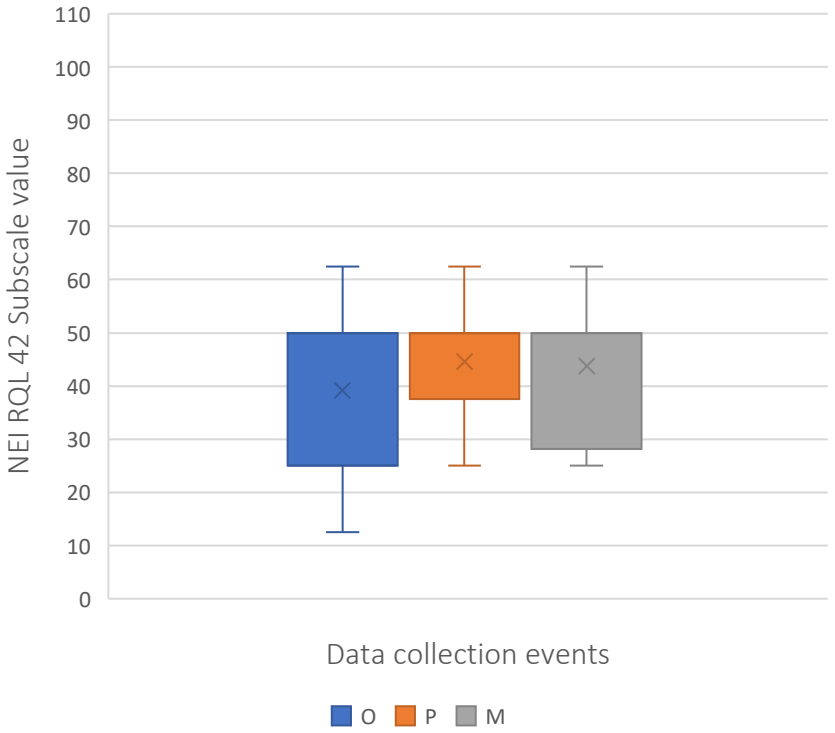

Figure 5-18 Glare, box & whisker plots for those participants who completed at least two questionnaires

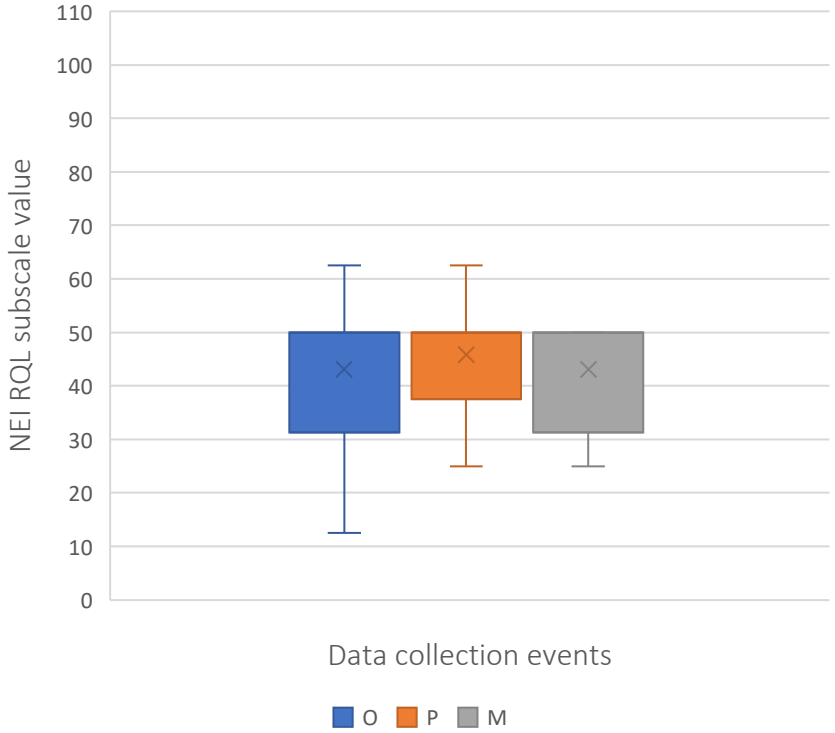

Figure 5-19 Glare, box & whisker plots for those participants who completed three questionnaires

Table 5-36 Glare, dataset for all those participants who completed at least two questionnaires

	O	P	M
P2	37.5	-	25.0
P3	12.5	-	62.5
P4	50.0	50.0	-
P5	-	50.0	50.0
P6	50.0	50.0	50.0
P7	50.0	50.0	50.0
P8	50.0	37.5	50.0
P9	62.5	62.5	50.0
P10	37.5	37.5	50.0
P11	50.0	50.0	50.0
P12	25.0	25.0	25.0
P13	50.0	50.0	37.5
P22	37.5	50.0	-
P23	12.5	25.0	-
P24	50.0	37.5	-
P25	12.5	50.0	25.0

Table 5-37 Glare, dataset for all those participants who completed three questionnaires

	O	P	M
P6	50.0	50.0	50.0
P7	50.0	50.0	50.0
P8	50.0	37.5	50.0
P9	62.5	62.5	50.0
P10	37.5	37.5	50.0
P11	50.0	50.0	50.0
P12	25.0	25.0	25.0
P13	50.0	50.0	37.5
P25	12.5	50.0	25.0

Table 5-38 Glare, SPSS output of descriptive data for those participants who completed at least two questionnaires

Descriptives

			Statistic	Std. Error
Data_collection_O	Mean		39.1667	4.20223
	95% Confidence Interval for Mean	Lower Bound	30.1538	
		Upper Bound	48.1796	
	5% Trimmed Mean		39.3519	
	Median		50.0000	
	Variance		264.881	
	Std. Deviation		16.27516	
	Minimum		12.50	
	Maximum		62.50	
	Range		50.00	
	Interquartile Range		25.00	
	Skewness		-.729	.580
	Kurtosis		-.715	1.121
Data_collection_P	Mean		44.6429	2.84510
	95% Confidence Interval for Mean	Lower Bound	38.4964	
		Upper Bound	50.7893	
	5% Trimmed Mean		44.7421	
	Median		50.0000	
	Variance		113.324	
	Std. Deviation		10.64538	
	Minimum		25.00	
	Maximum		62.50	
	Range		37.50	
	Interquartile Range		12.50	
	Skewness		-.694	.597
	Kurtosis		.103	1.154
Datra_collection_M	Mean		43.7500	3.60844
	95% Confidence Interval for Mean	Lower Bound	35.8079	
		Upper Bound	51.6921	
	5% Trimmed Mean		43.7500	
	Median		50.0000	
	Variance		156.250	
	Std. Deviation		12.50000	
	Minimum		25.00	
	Maximum		62.50	
	Range		37.50	
	Interquartile Range		21.88	
	Skewness		-.655	.637
	Kurtosis		-.764	1.232

Table 5-39 Glare, SPSS output of descriptive data for those participants who completed three questionnaires

Descriptives

			Statistic	Std. Error
Data_collection_O	Mean		43.0556	5.15014
	95% Confidence Interval for Mean	Lower Bound	31.1793	
		Upper Bound	54.9318	
	5% Trimmed Mean		43.6728	
	Median		50.0000	
	Variance		238.715	
	Std. Deviation		15.45041	
	Minimum		12.50	
	Maximum		62.50	
	Range		50.00	
	Interquartile Range		18.75	
	Skewness		-1.114	.717
	Kurtosis		.757	1.400
Data_collection_P	Mean		45.8333	3.60844
	95% Confidence Interval for Mean	Lower Bound	37.5123	
		Upper Bound	54.1544	
	5% Trimmed Mean		46.0648	
	Median		50.0000	
	Variance		117.188	
	Std. Deviation		10.82532	
	Minimum		25.00	
	Maximum		62.50	
	Range		37.50	
	Interquartile Range		12.50	
	Skewness		-.660	.717
	Kurtosis		.825	1.400
Datra_collection_M	Mean		43.0556	3.67465
	95% Confidence Interval for Mean	Lower Bound	34.5818	
		Upper Bound	51.5293	
	5% Trimmed Mean		43.6728	
	Median		50.0000	
	Variance		121.528	
	Std. Deviation		11.02396	
	Minimum		25.00	
	Maximum		50.00	
	Range		25.00	
	Interquartile Range		18.75	
	Skewness		-1.192	.717
	Kurtosis		-.446	1.400

Table 5-40 Glare, SPPS output for those participants who completed at least two questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data_event_O	.281	15	.002	.832	15	.010
Data_event_P	.335	14	.000	.825	14	.010
Data_event_M	.358	12	.000	.783	12	.006

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_event_P - Data_event_O	Negative Ranks	2[a]	2.50	5.00
	Positive Ranks	3[b]	3.33	10.00
	Ties	8[c]		
	Total	13		

a. Data_event_P < Data_event_O

b. Data_event_P > Data_event_O

c. Data_event_P = Data_event_O

Test Statistics[a]

	Data_event_P - Data_event_O
Z	-.707[b]
Asymp. Sig. (2-tailed)	.480

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

Table 5-41 Glare, SPPS output for those participants who completed three questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data_collection_O	.340	9	.003	.839	9	.056
Data_collection_P	.317	9	.010	.873	9	.132
Data_collection_M	.402	9	.000	.658	9	.000

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_collection_P - Data_collection_O	Negative Ranks	1[a]	1.00	1.00
	Positive Ranks	1[b]	2.00	2.00
	Ties	7[c]		
	Total	9		

a. Data_collection_P < Data_collection_O

b. Data_collection_P > Data_collection_O

c. Data_collection_P = Data_collection_O

Test Statistics[a]

	Data_collection_P - Data_collection_O
Z	-.447[b]
Asymp. Sig. (2-tailed)	.655

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

5.12.5 Subscale - Diurnal variation

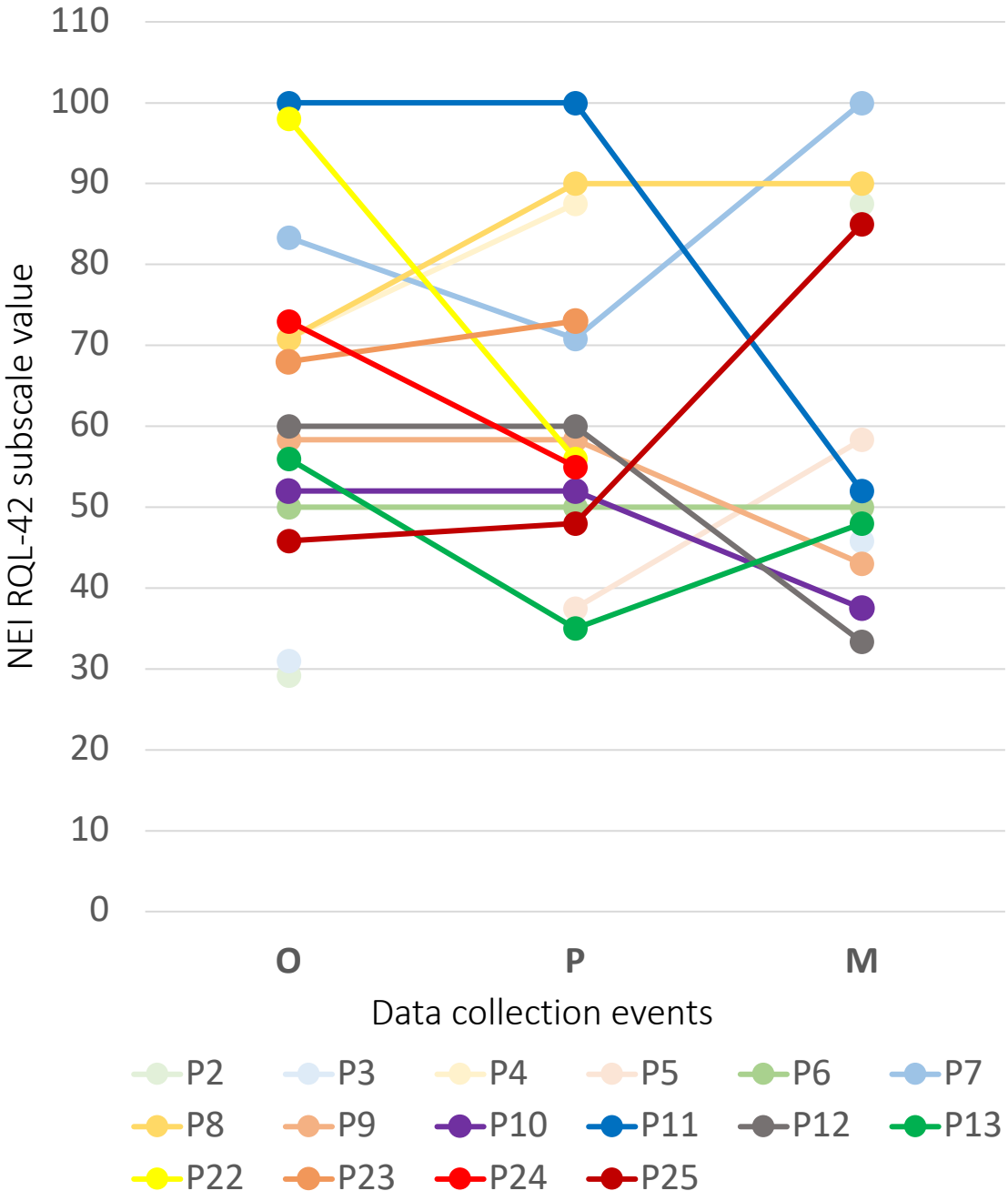

Figure 5-20Diurnal variation, profile plots for participants who completed at least two questionnaires

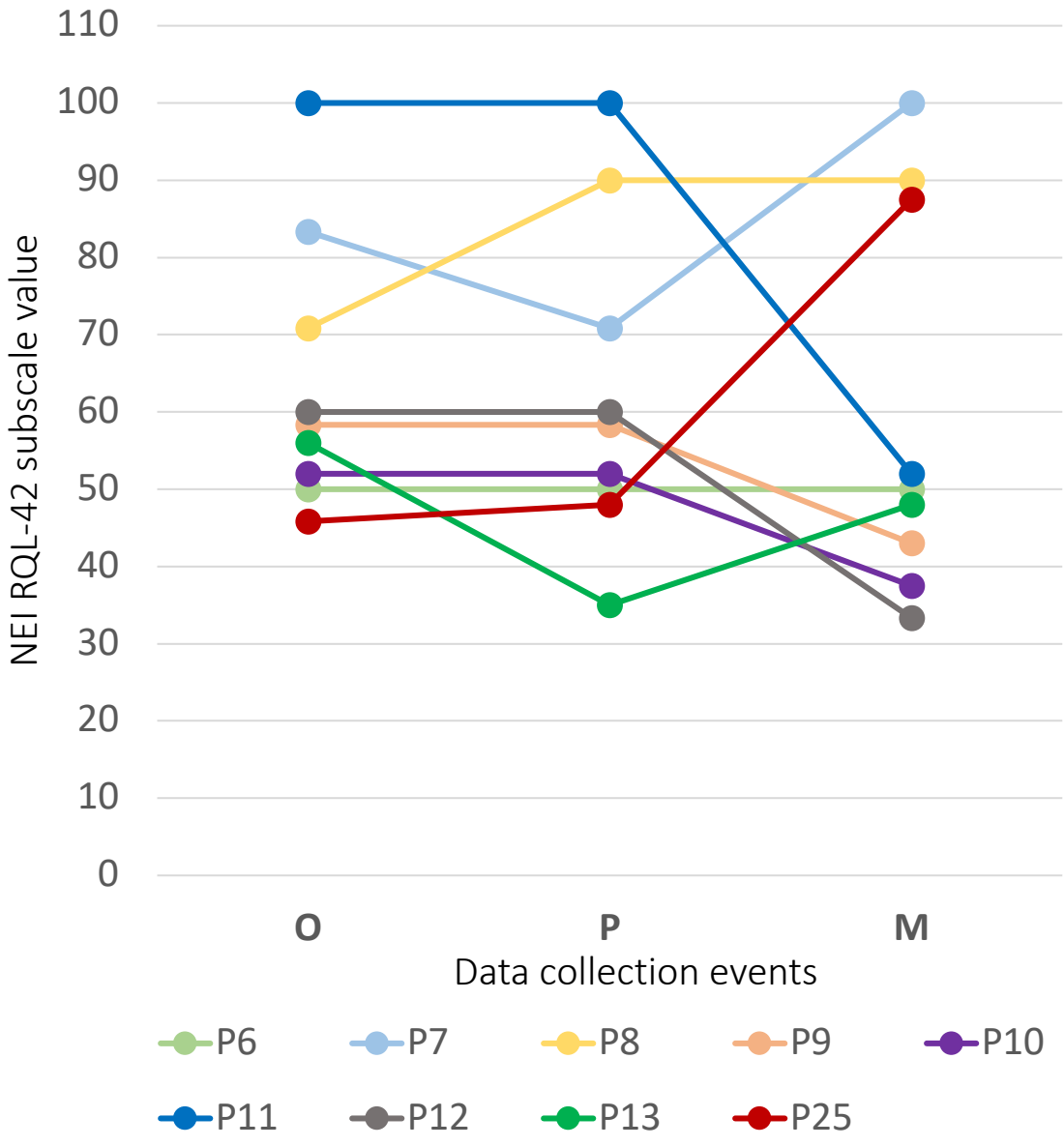

Figure 5-21 Diurnal variation, Profile plots for participants who completed three questionnaires

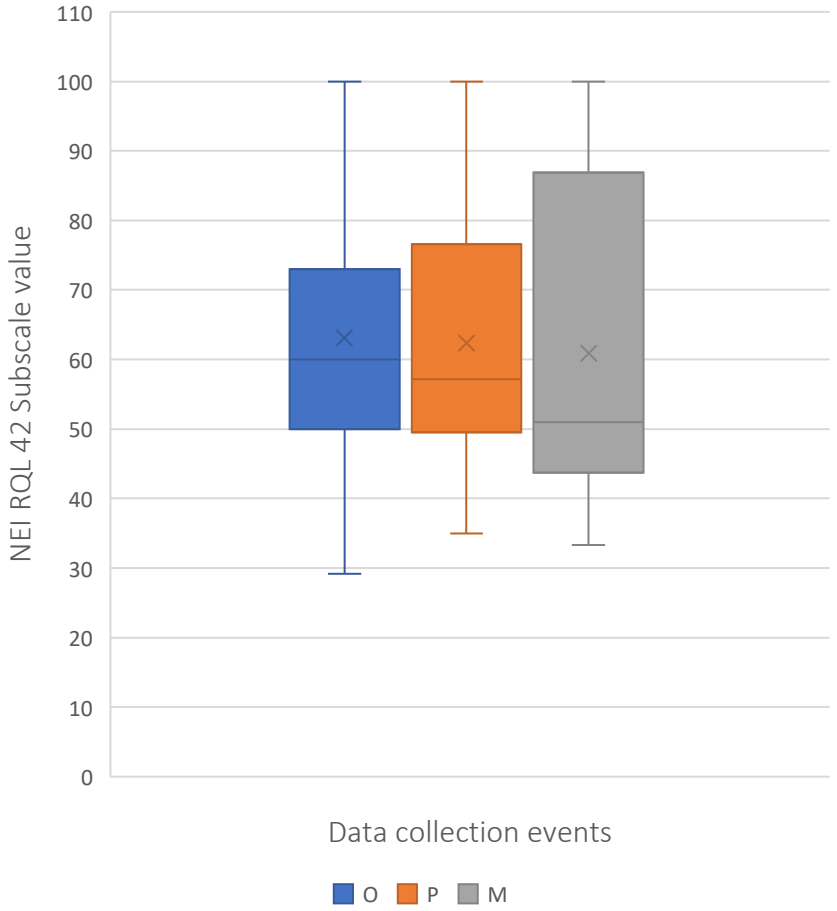

Figure 5-22 Diurnal variation, box & whisker plots for those participants who completed at least two questionnaires

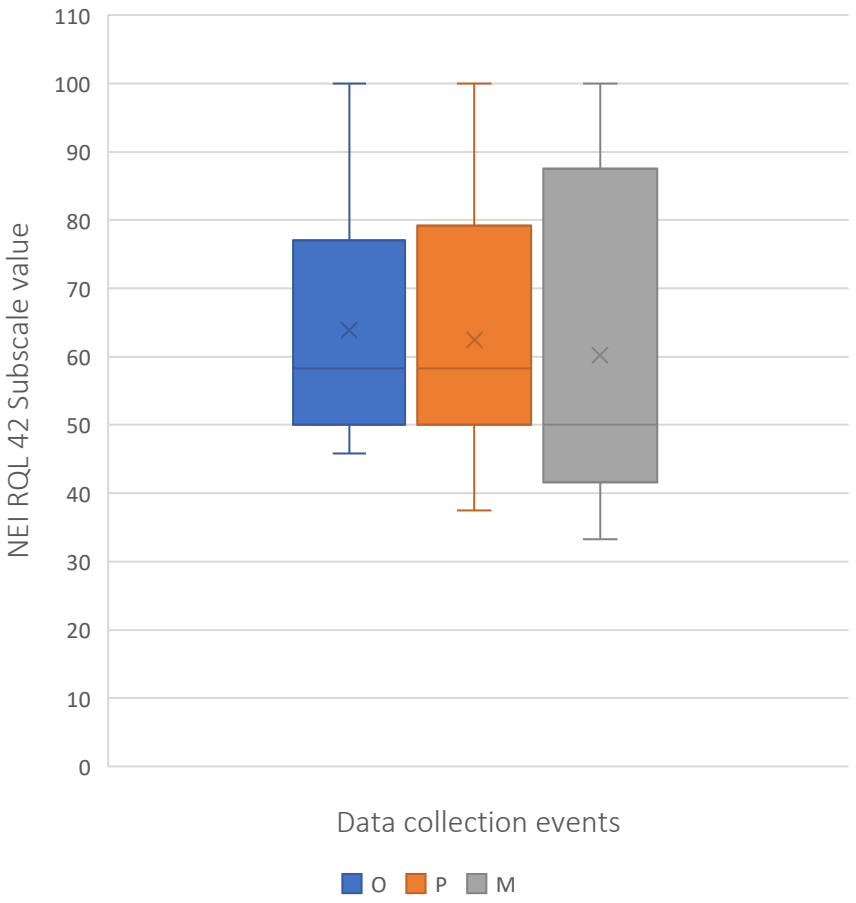

Figure 5-23 Diurnal variation, box & whisker plots for those participants who completed three questionnaires

Table 5-42 Diurnal variation, dataset for all those participants who completed at least two questionnaires

	O	P	M
P2	29.2	-	87.5
P3	29.1	-	45.8
P4	70.8	87.5	-
P5	-	37.5	58.3
P6	50.0	50.0	50.0
P7	83.3	70.8	100.0
P8	70.8	87.5	87.5
P9	58.3	58.3	45.8
P10	50.0	50.0	37.5
P11	100.0	100.0	50.0
P12	58.3	58.3	33.3
P13	58.3	37.5	50.0
P22	100.0	58.3	-
P23	70.8	70.8	-
P24	70.8	58.3	-
P25	45.8	50	87.5

Table 5-43 Diurnal variation, dataset for all those participants who completed three questionnaires

	O	P	M
P6	50.0	50.0	50.0
P7	83.3	70.8	100.0
P8	70.8	87.5	87.5
P9	58.3	58.3	45.8
P10	50.0	50.0	37.5
P11	100.0	100.0	50.0
P12	58.3	58.3	33.3
P13	58.3	37.5	50.0
P25	45.8	50	87.5

Table 5-44 Diurnal variation, SPSS output of descriptive data for those participants who completed at least two questionnaires

Descriptives

			Statistic	Std. Error
Data_collection_O	Mean		63.0333	5.51413
	95% Confidence Interval for Mean	Lower Bound	51.2067	
		Upper Bound	74.8600	
	5% Trimmed Mean		62.8648	
	Median		58.3000	
	Variance		456.085	
	Std. Deviation		21.35615	
	Minimum		29.10	
	Maximum		100.00	
	Range		70.90	
	Interquartile Range		20.80	
	Skewness		.199	.580
	Kurtosis		-.229	1.121
Data_collection_P	Mean		62.4857	5.01828
	95% Confidence Interval for Mean	Lower Bound	51.6444	
		Upper Bound	73.3271	
	5% Trimmed Mean		61.7897	
	Median		58.3000	
	Variance		352.564	
	Std. Deviation		18.77670	
	Minimum		37.50	
	Maximum		100.00	
	Range		62.50	
	Interquartile Range		24.97	
	Skewness		.650	.597
	Kurtosis		-.270	1.154
Datra_collection_M	Mean		61.1000	6.61698
	95% Confidence Interval for Mean	Lower Bound	46.5361	
		Upper Bound	75.6639	
	5% Trimmed Mean		60.4833	
	Median		50.0000	
	Variance		525.413	
	Std. Deviation		22.92188	
	Minimum		33.30	
	Maximum		100.00	
	Range		66.70	
	Interquartile Range		41.70	
	Skewness		.617	.637
	Kurtosis		-1.288	1.232

Table 5-45 Diurnal variation, SPSS output of descriptive data for those participants who completed three questionnaires

Descriptives

			Statistic	Std. Error
Data_collection_O	Mean		63.8667	5.93399
	95% Confidence Interval for Mean	Lower Bound	50.1829	
		Upper Bound	77.5505	
	5% Trimmed Mean		62.8630	
	Median		58.3000	
	Variance		316.910	
	Std. Deviation		17.80197	
	Minimum		45.80	
	Maximum		100.00	
	Range		54.20	
	Interquartile Range		27.05	
	Skewness		1.228	.717
	Kurtosis		.851	1.400
Data_collection_P	Mean		62.4889	6.69698
	95% Confidence Interval for Mean	Lower Bound	47.0456	
		Upper Bound	77.9322	
	5% Trimmed Mean		61.7932	
	Median		58.3000	
	Variance		403.646	
	Std. Deviation		20.09095	
	Minimum		37.50	
	Maximum		100.00	
	Range		62.50	
	Interquartile Range		29.15	
	Skewness		.939	.717
	Kurtosis		.097	1.400
Datra_collection_M	Mean		60.1778	8.19298
	95% Confidence Interval for Mean	Lower Bound	41.2847	
		Upper Bound	79.0708	
	5% Trimmed Mean		59.4586	
	Median		50.0000	
	Variance		604.124	
	Std. Deviation		24.57894	
	Minimum		33.30	
	Maximum		100.00	
	Range		66.70	
	Interquartile Range		45.85	
	Skewness		.722	.717
	Kurtosis		-1.276	1.400

Table 5-46 Diurnal variation, SPPS output for those participants who completed at least two questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data_event_O	.289	9	.029	.865	9	.108
Data_event_P	.249	9	.113	.898	9	.243
Data_event_M	.327	9	.006	.841	9	.059

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_event_M - Data_event_O	Negative Ranks	5[a]	4.40	22.00
	Positive Ranks	5[b]	6.60	33.00
	Ties	1[c]		
	Total	11		

a. Data_event_M < Data_event_O

b. Data_event_M > Data_event_O

c. Data_event_M = Data_event_O

Test Statistics[a]

	Data_event_M - Data_event_O
Z	-.562[b]
Asymp. Sig. (2-tailed)	.574

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

Table 5-47 Diurnal variation, SPPS output for those participants who completed three questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data event O	.366	9	.001	.665	9	.001
Data event P	.280	9	.040	.670	9	.001
Data event M	.278	9	.043	.758	9	.007

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_event_M - Data_event_O	Negative Ranks	5[a]	4.00	20.00
	Positive Ranks	3[b]	5.33	16.00
	Ties	1[c]		
	Total	9		

a. Data_event_M < Data_event_O

b. Data_event_M > Data_event_O

c. Data_event_M = Data_event_O

Test Statistics[a]

	Data_event_M - Data_event_O
Z	-.281[b]
Asymp. Sig. (2-tailed)	.779

a. Wilcoxon Signed Ranks Test

b. Based on positive ranks.

5.12.6 Sande dry eye question 1

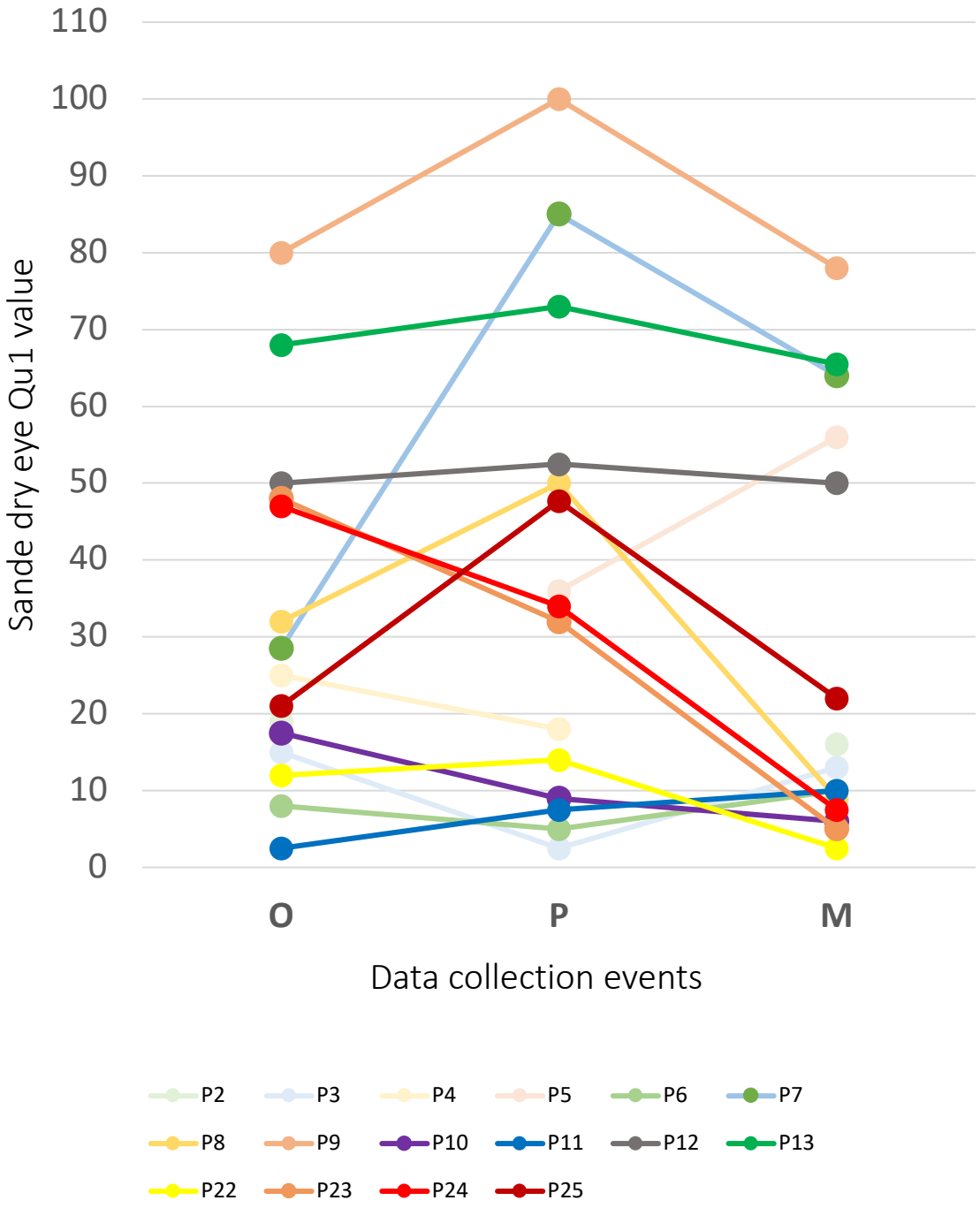

Figure 5-24 Sande dry eye question 1, profile plots for participants who completed at least two questionnaires

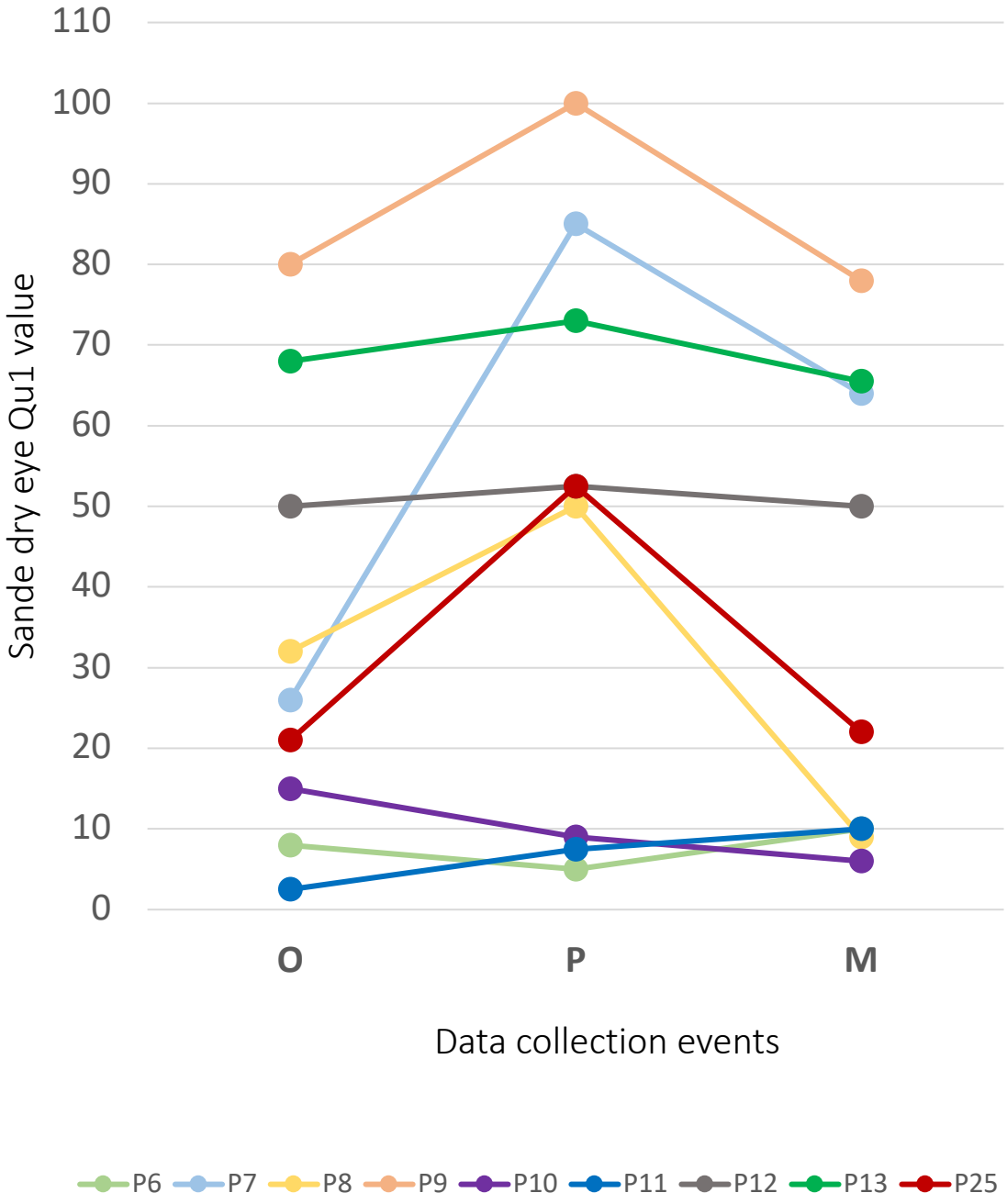

Figure 5-25 Sande dry eye question 1, profile plots for participants who completed three questionnaires

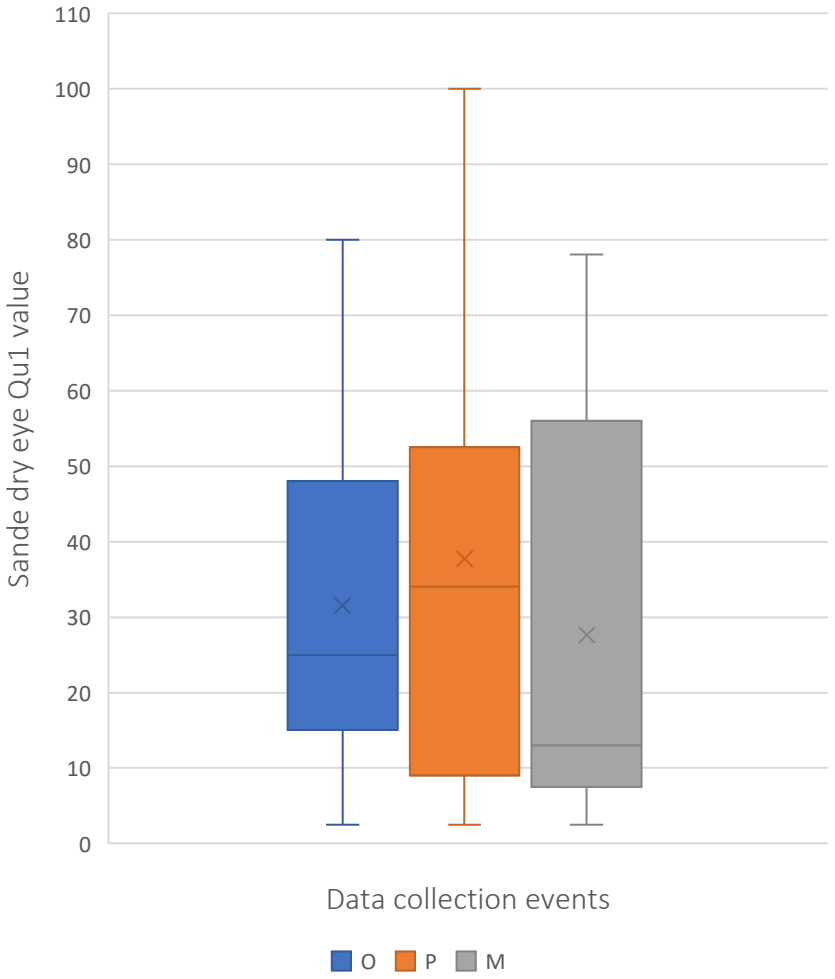

Figure 5-26 Sande dry eye question 1, box & whisker plots for those participants who completed at least two questionnaires

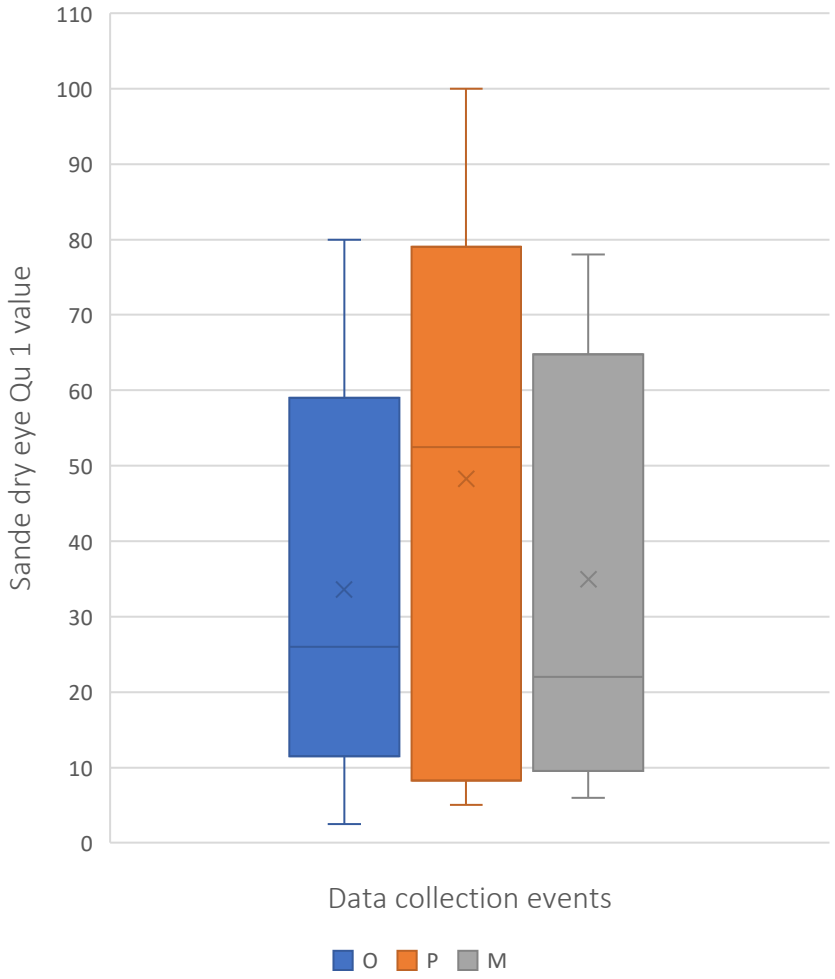

Figure 5-27 Sande dry eye question 1, box & whisker plots for those participants who completed three questionnaires

Table 5-48 Sande dry eye question 1, dataset for all those participants who completed at least two questionnaires

	O	P	M
P2	19.0	-	16.0
P3	15.0	-	13.0
P4	25.0	18.0	-
P5	-	36.0	56.0
P6	8.0	5.0	10.0
P7	28.5	85.0	64.0
P8	32.0	50.0	9.0
P9	80.0	100.0	78.0
P10	17.5	9.0	6.0
P11	2.5	7.5	10.0
P12	50.0	52.5	50.0
P13	68.0	73.0	65.5
P22	12.0	14.0	-
P23	48.0	32.0	-
P24	47.0	34.0	-
P25	21.0	47.7	22.0

Table 5-49 Sande dry eye question 1, dataset for all those participants who completed at least three questionnaires

	O	P	M
P6	8.0	5.0	10.0
P7	26.0	85.0	64.0
P8	32.0	50.0	9.0
P9	80.0	100.0	78.0
P10	15.0	9.0	6.0
P11	2.5	7.5	10.0
P12	50.0	52.5	50.0
P13	68.0	73.0	65.5
P25	21.0	52.5	22.0

Table 5-50 Sande dry eye question 1, SPSS output of descriptive data for those participants who completed at least two questionnaires

Descriptives

			Statistic	Std. Error
Data_collection_O	Mean		33.0385	6.63602
	95% Confidence Interval for Mean	Lower Bound	18.5798	
		Upper Bound	47.4971	
	5% Trimmed Mean		32.1261	
	Median		28.5000	
	Variance		572.478	
	Std. Deviation		23.92650	
	Minimum		2.50	
	Maximum		80.00	
	Range		77.50	
	Interquartile Range		35.50	
	Skewness		.664	.616
	Kurtosis		-.489	1.191
Data_collection_P	Mean		39.4000	8.93329
	95% Confidence Interval for Mean	Lower Bound	19.9360	
		Upper Bound	58.8640	
	5% Trimmed Mean		38.0833	
	Median		34.0000	
	Variance		1037.447	
	Std. Deviation		32.20942	
	Minimum		2.50	
	Maximum		100.00	
	Range		97.50	
	Interquartile Range		54.50	
	Skewness		.562	.616
	Kurtosis		-.764	1.191
Datra_collection_M	Mean		26.3462	7.59731
	95% Confidence Interval for Mean	Lower Bound	9.7930	
		Upper Bound	42.8993	
	5% Trimmed Mean		24.8013	
	Median		10.0000	
	Variance		750.349	
	Std. Deviation		27.39251	
	Minimum		2.50	
	Maximum		78.00	
	Range		75.50	
	Interquartile Range		50.25	
	Skewness		1.005	.616
	Kurtosis		-.772	1.191

Table 5-51 Sande dry eye question 1, SPSS output of descriptive data for those participants who completed three questionnaires

Descriptives

			Statistic	Std. Error
Data_event_O	Mean		33.6111	8.96977
	95% Confidence Interval for Mean	Lower Bound	12.9268	
		Upper Bound	54.2954	
	5% Trimmed Mean		32.7623	
	Median		26.0000	
	Variance		724.111	
	Std. Deviation		26.90931	
	Minimum		2.50	
	Maximum		80.00	
	Range		77.50	
	Interquartile Range		47.50	
	Skewness		.735	.717
	Kurtosis		-.680	1.400
Data_event_P	Mean		48.28	11.638
	95% Confidence Interval for Mean	Lower Bound	21.44	
		Upper Bound	75.12	
	5% Trimmed Mean		47.81	
	Median		52.50	
	Variance		1219.007	
	Std. Deviation		34.914	
	Minimum		5	
	Maximum		100	
	Range		95	
	Interquartile Range		71	
	Skewness		-.024	.717
	Kurtosis		-1.326	1.400
Data_event_M	Mean		34.9444	9.70483
	95% Confidence Interval for Mean	Lower Bound	12.5651	
		Upper Bound	57.3238	
	5% Trimmed Mean		34.1605	
	Median		22.0000	
	Variance		847.653	
	Std. Deviation		29.11448	
	Minimum		6.00	
	Maximum		78.00	
	Range		72.00	
	Interquartile Range		55.25	
	Skewness		.400	.717
	Kurtosis		-1.951	1.400

Table 5-52 Sande dry eye question 1, SPPS output for those participants who completed at least two questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data event O	.178	16	.187	.922	16	.184
Data event P	.139	16	.200*	.908	16	.106
Data event M	.231	16	.023	.794	16	.002

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_collection_P - Data_collection_O	Negative Ranks	6[a]	7.17	43.00
	Positive Ranks	8[b]	7.75	62.00
	Ties	0[c]		
	Total	14		

a. Data_collection_P < Data_collection_O

b. Data_collection_P > Data_collection_O

c. Data_collection_P = Data_collection_O

Test Statistics[a]

	Data_collection_P - Data_collection_O
Z	-.597[b]
Asymp. Sig. (2-tailed)	.551

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

Table 5-53 Sande dry eye question 1, SPPS output for those participants who completed three questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data event O	.186	9	.200*	.933	9	.510
Data event P	.206	9	.200*	.908	9	.305
Data event M	.218	9	.200*	.862	9	.100

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_collection_P - Data_collection_O	Negative Ranks	2[a]	3.50	7.00
	Positive Ranks	7[b]	5.43	38.00
	Ties	0[c]		
	Total	9		

a. Data_collection_P < Data_collection_O

b. Data_collection_P > Data_collection_O

c. Data_collection_P = Data_collection_O

Test Statistics[a]

	Data_collection_P - Data_collection_O
Z	-1.838[b]
Asymp. Sig. (2-tailed)	.066

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

5.12.7 Sande dry eye question 2

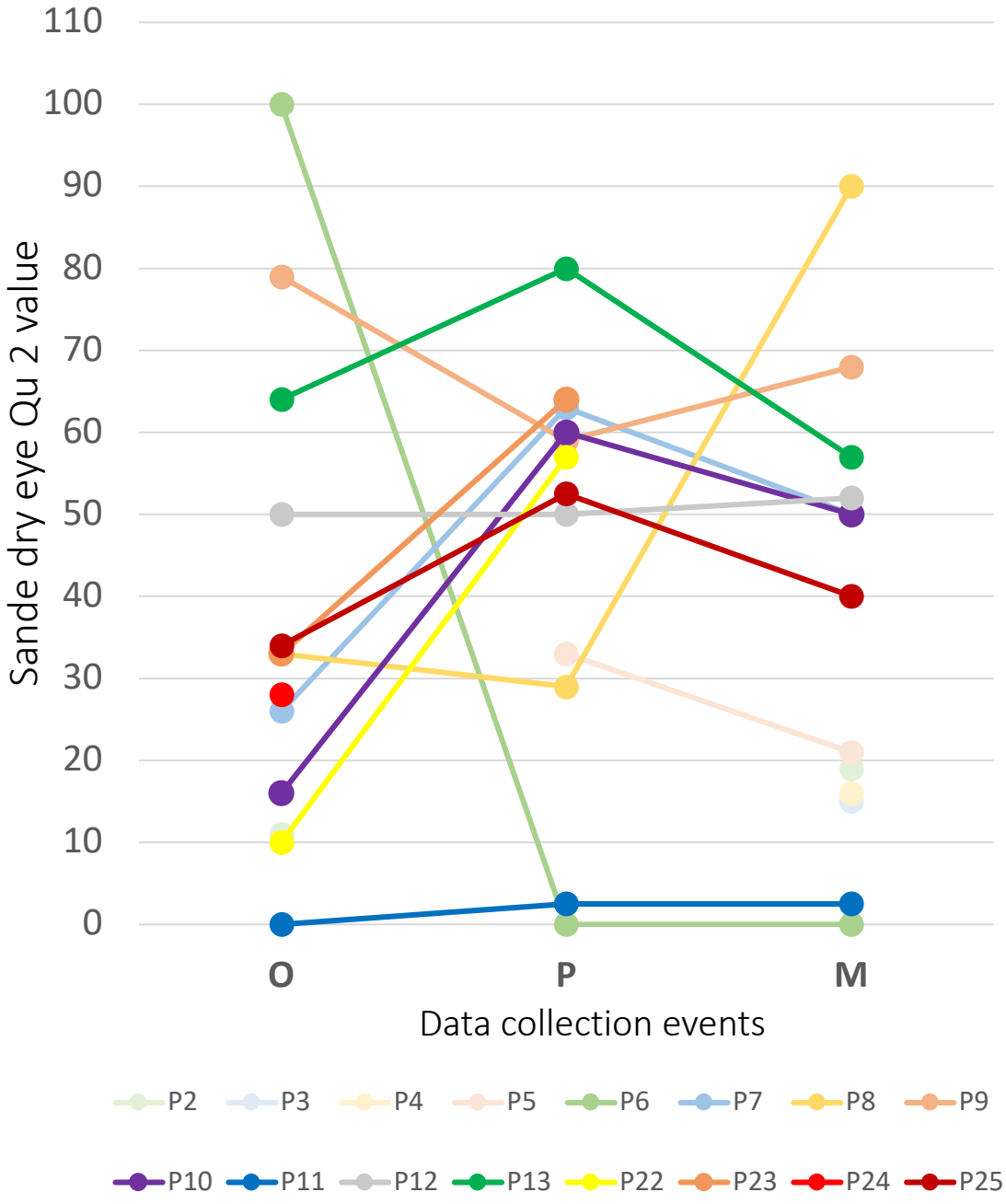

Figure 5-28 Sande dry eye question 2, profile plots for participants who completed at least two questionnaires

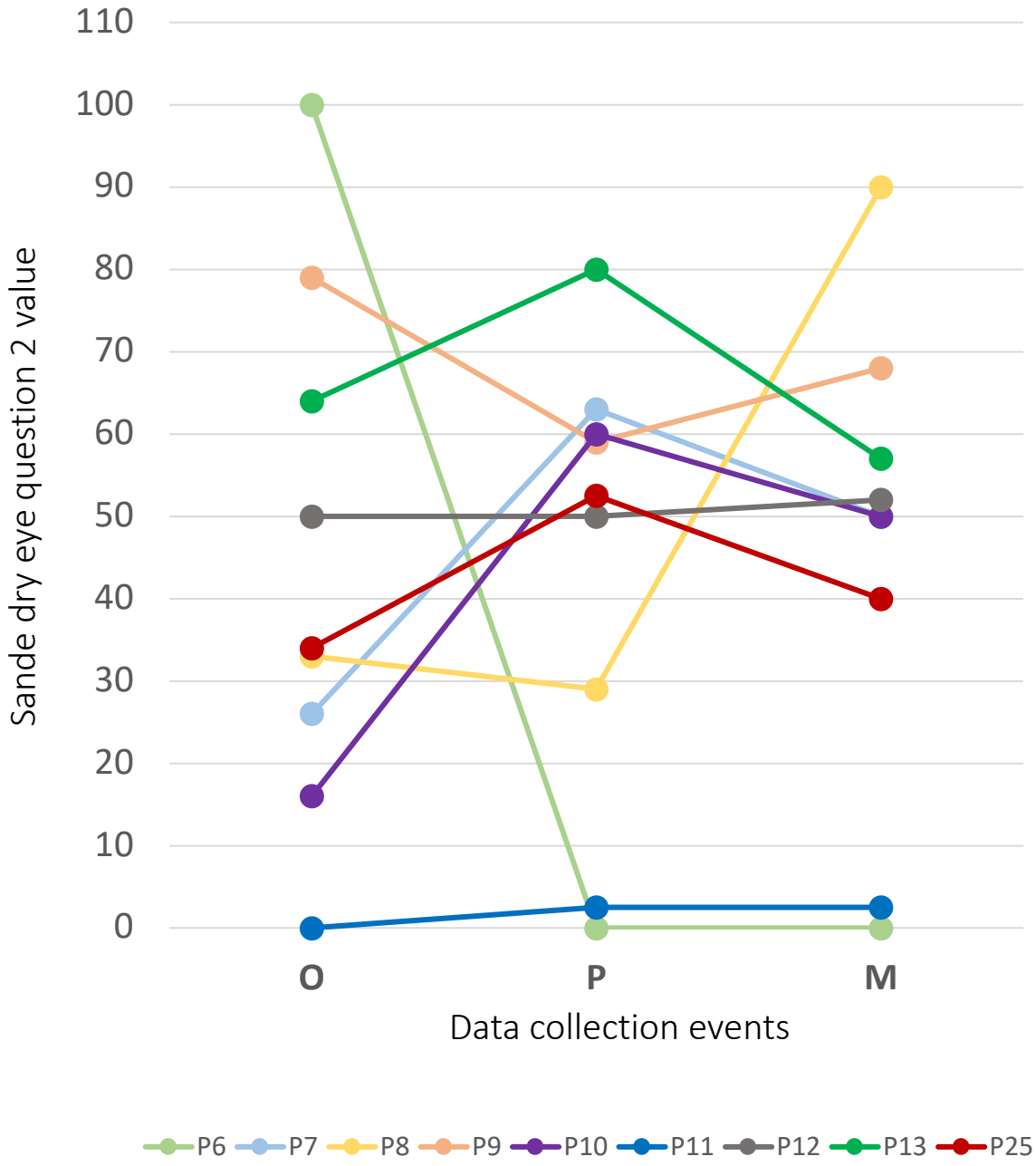

Figure 5-29 Sande dry eye question 2, profile plots for participants who completed three questionnaires

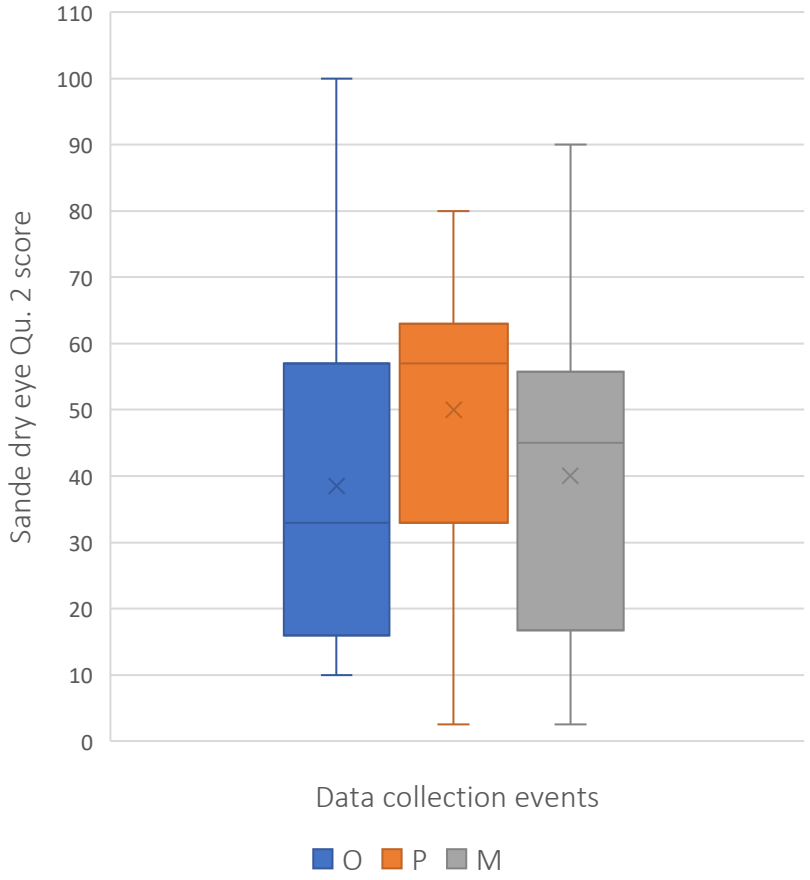

Figure 5-30 Sande dry eye question 2, box & whisker plots for those participants who completed at least two questionnaires

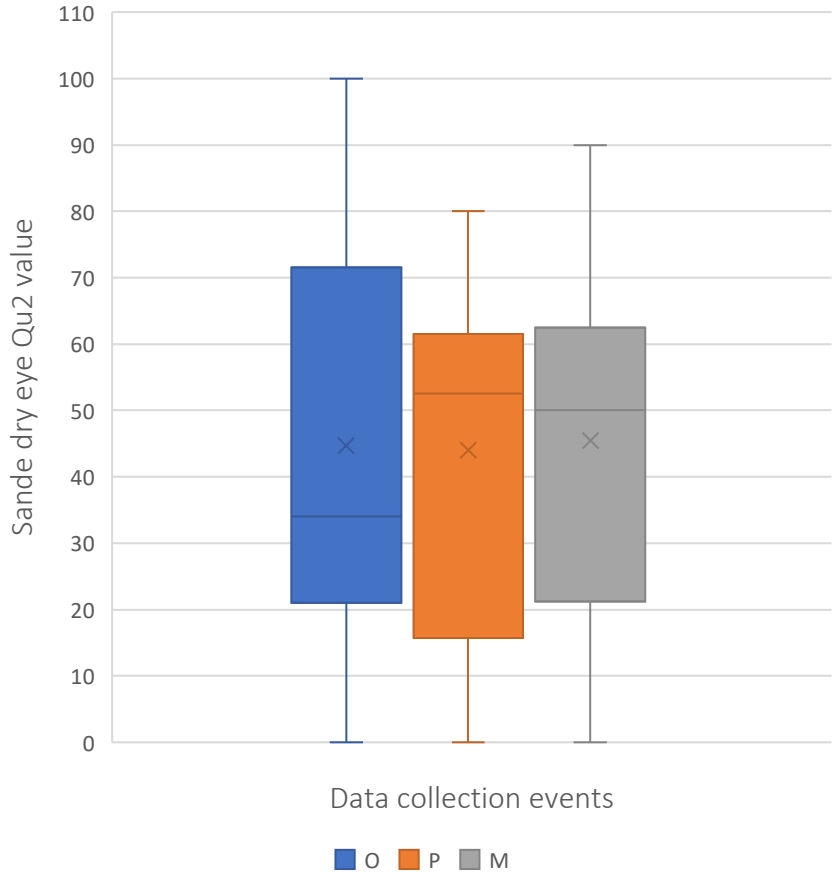

Figure 5-31 Sande dry eye question 2, box & whisker plots for those participants who completed three questionnaires

Table 5-54 Sande dry eye question 2, dataset for all those participants who completed at least two questionnaires

	O	P	M
P2	11.0	-	19.0
P3	-	-	15.0
P4	16.0	16.0	-
P5	-	33.0	21.0
P6	100.0	-	-
P7	26.0	63.0	50.0
P8	33.0	29.0	90.0
P9	79.0	59.0	68.0
P10	16.0	60.0	50.0
P11	0.0	2.5	2.5
P12	50.0	50.0	52.0
P13	64.0	80.0	57.0
P22	10.0	57.0	-
P23	33.0	64.0	-
P24	28.0	-	-
P25	34.0	52.5	40.0

Table 5-55 Sande dry eye question 2, dataset for all those participants who completed at least three questionnaires

	O	P	M
P6	100.0	0.0	0.0
P7	26.0	63.0	50.0
P8	33.0	29.0	90.0
P9	79.0	59.0	68.0
P10	16.0	60.0	50.0
P11	0.0	2.5	2.5
P12	50.0	50.0	52.0
P13	64.0	80.0	57.0
P25	34.0	52.5	40.0

Table 5-56 Sande dry eye question 2, SPSS output of descriptive data for those participants who completed at least two questionnaires

Descriptives

			Statistic	Std. Error
Data_collection_O	Mean		43.1429	8.43019
	95% Confidence Interval for Mean	Lower Bound	22.5149	
		Upper Bound	63.7708	
	5% Trimmed Mean		42.6587	
	Median		34.0000	
	Variance		497.476	
	Std. Deviation		22.30417	
	Minimum		16.00	
	Maximum		79.00	
	Range		63.00	
	Interquartile Range		38.00	
	Skewness		.603	.794
	Kurtosis		-.702	1.587
Data_collection_P	Mean		56.2143	5.82876
	95% Confidence Interval for Mean	Lower Bound	41.9518	
		Upper Bound	70.4768	
	5% Trimmed Mean		56.4048	
	Median		59.0000	
	Variance		237.821	
	Std. Deviation		15.42146	
	Minimum		29.00	
	Maximum		80.00	
	Range		51.00	
	Interquartile Range		13.00	
	Skewness		-.420	.794
	Kurtosis		1.800	1.587
Data_collection_M	Mean		58.1429	6.19688
	95% Confidence Interval for Mean	Lower Bound	42.9796	
		Upper Bound	73.3061	
	5% Trimmed Mean		57.3810	
	Median		52.0000	
	Variance		268.810	
	Std. Deviation		16.39541	
	Minimum		40.00	
	Maximum		90.00	
	Range		50.00	
	Interquartile Range		18.00	
	Skewness		1.377	.794
	Kurtosis		2.079	1.587

Table 5-57 Sande dry eye question 2, SPSS output of descriptive data for those participants who completed three questionnaires

Descriptives

			Statistic	Std. Error
Data_collection_O	Mean		44.6667	10.57907
	95% Confidence Interval for Mean	Lower Bound	20.2713	
		Upper Bound	69.0620	
	5% Trimmed Mean		44.0741	
	Median		34.0000	
	Variance		1007.250	
	Std. Deviation		31.73720	
	Minimum		.00	
	Maximum		100.00	
	Range		100.00	
	Interquartile Range		50.50	
	Skewness		.479	.717
	Kurtosis		-.423	1.400
Data_collection_P	Mean		44.0000	9.22670
	95% Confidence Interval for Mean	Lower Bound	22.7232	
		Upper Bound	65.2768	
	5% Trimmed Mean		44.4444	
	Median		52.5000	
	Variance		766.188	
	Std. Deviation		27.68009	
	Minimum		.00	
	Maximum		80.00	
	Range		80.00	
	Interquartile Range		45.75	
	Skewness		-.744	.717
	Kurtosis		-.603	1.400
Data_collection_M	Mean		45.5000	9.61119
	95% Confidence Interval for Mean	Lower Bound	23.3366	
		Upper Bound	67.6634	
	5% Trimmed Mean		45.5556	
	Median		50.0000	
	Variance		831.375	
	Std. Deviation		28.83357	
	Minimum		.00	
	Maximum		90.00	
	Range		90.00	
	Interquartile Range		41.25	
	Skewness		-.485	.717
	Kurtosis		.042	1.400

Table 5-58 Sande dry eye question 2, SPSS output for those participants who completed at least two questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data event O	.230	7	.200*	.947	7	.703
Data event P	.201	7	.200*	.948	7	.710
Data event M	.242	7	.200*	.876	7	.211

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_collection_M - Data_collection_O	Negative Ranks	2[a]	4.00	8.00
	Positive Ranks	6[b]	4.67	28.00
	Ties	1[c]		
	Total	9		

a. Data_collection_M < Data_collection_O

b. Data_collection_M > Data_collection_O

c. Data_collection_M = Data_collection_O

Test Statistics[a]

	Data_collection_M - Data_collection_O
Z	-1.400[b]
Asymp. Sig. (2-tailed)	.161

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

Table 5-59 Sande dry eye question 2, SPPS output those participants who completed three questionnaires

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data event O	.187	9	.200*	.971	9	.901
Data event P	.252	9	.102	.886	9	.183
Data event M	.229	9	.192	.910	9	.313

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_collection_M - Data_collection_P	Negative Ranks	4[a]	4.50	18.00
	Positive Ranks	3[b]	3.33	10.00
	Ties	2[c]		
	Total	9		

a. Data_collection_M < Data_collection_P

b. Data_collection_M > Data_collection_P

c. Data_collection_M = Data_collection_P

Test Statistics[a]

	Data_collection_M - Data_collection_P
Z	-.676[b]
Asymp. Sig. (2-tailed)	.499

a. Wilcoxon Signed Ranks Test

b. Based on positive ranks.

5.12.8 Visual acuity

Profile graph

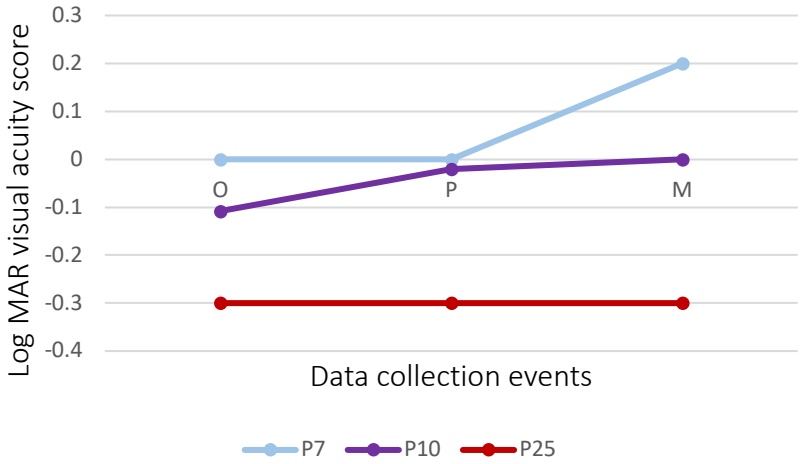

Figure 5-32 Visual acuity, profile plots for participants who completed one or more acuity measurements

Table 5-60 Visual acuity, dataset for all those participants who completed all three visual acuity measurements

	O	P	M
P7	0.0	0.0	0.2
P10	-0.1	0.0	0.0
P25	-0.3	-0.3	-0.3

Table 5-61 Visual acuity, SPSS output of descriptive data for those participants who completed three acuity measurements

Descriptives

			Statistic	Std. Error
Data_collection_O	Mean		-.1360	.08773
	95% Confidence Interval for Mean	Lower Bound	-.5135	
		Upper Bound	.2415	
	5% Trimmed Mean		.	
	Median		-.1080	
	Variance		.023	
	Std. Deviation		.15195	
	Minimum		-.30	
	Maximum		.00	
	Range		.30	
	Interquartile Range		.	
	Skewness		-.801	1.225
	Kurtosis		.	.
Data_collection_P	Mean		-.1067	.09684
	95% Confidence Interval for Mean	Lower Bound	-.5233	
		Upper Bound	.3100	
	5% Trimmed Mean		.	
	Median		-.0200	
	Variance		.028	
	Std. Deviation		.16773	
	Minimum		-.30	
	Maximum		.00	
	Range		.30	
	Interquartile Range		.	
	Skewness		-1.704	1.225
	Kurtosis		.	.
Datra_collection_M	Mean		-.0333	.14530
	95% Confidence Interval for Mean	Lower Bound	-.6585	
		Upper Bound	.5918	
	5% Trimmed Mean		.	
	Median		.0000	
	Variance		.063	
	Std. Deviation		.25166	
	Minimum		-.30	
	Maximum		.20	
	Range		.50	
	Interquartile Range		.	
	Skewness		-.586	1.225
	Kurtosis		.	.

Table 5-62 Visual acuity, SPPS output for those participants who completed three acuity measurements

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Data_collection_O	.240	3	.	.975	3	.694
Data_collection_P	.364	3	.	.800	3	.114
Datra_collection_M	.219	3	.	.987	3	.780

a. Lilliefors Significance Correction

Ranks

		N	Mean Rank	Sum of Ranks
Data_collection_P - Data_collection_O	Negative Ranks	0[a]	.00	.00
	Positive Ranks	1[b]	1.00	1.00
	Ties	2[c]		
	Total	3		

a. Data_collection_P < Data_collection_O

b. Data_collection_P > Data_collection_O

c. Data_collection_P = Data_collection_O

Test Statistics[a]

	Data_collection_P - Data_collection_O
Z	-1.000[b]
Asymp. Sig. (2-tailed)	.317

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

5.12.9 Summary of study NEI RQL-42 results

Table 5-63 shows subscale scores for the NEI RQL-42 questionnaire derived during its validation process. The data were from a cross-sectional study consisting of 665 myopes, 375 hyperopes, and 114 emmetropes. The cohort size for the VIMC study is considerably smaller. The table also shows the scoring from the Plan C (VIMC) study for both cohorts (only completed two questionnaires and the completed all three questionnaires), and for the three data collection points (O,P,M). The Sande dry eye 1 and 2 questions have not been included as these do not form part of the NEI RQL-42 validated questionnaire.

Table 5-63 NEI RAL-42 results summary

RAND= scores obtained during NEI RQL-42 validation

Clarity of vision	Mean	SD	N	CI (+/-)	Value	SD	N	CI (+/-)
RAND	83.9	18.4	1154	1.1	83.9	18.4	1154	1.1
VIMC (O)	33.6	13.1	15	6.6	27.3	8.6	9	5.6
VIMC (P)	30.4	12.2	14	6.4	25.5	10.3	9	6.7
VIMC (M)	30.2	8.0	12	4.5	27.8	6.9	9	4.5
Far vison	Mean	SD	N	CI (+/-)	Value	SD	N	CI (+/-)
RAND	83.5	15.9	1154	0.9	83.5	15.9	1154	0.9
VIMC (O)	79.2	15.6	15	7.9	85.7	14.3	9	9.3
VIMC (P)	84.0	16.2	14	8.5	86.7	15.2	9	9.9
VIMC (M)	90.7	9.3	12	5.3	88.9	10.3	9	6.7
Near vision	Mean	SD	N	CI (+/-)	Value	SD	N	CI (+/-)
RAND	83.9	18.0	1154	1.0	83.9	18.0	1154	1.0
VIMC (O)	86.7	16.7	15	8.5	88.0	16.7	9	10.9
VIMC (P)	89.6	16.0	14	8.4	89.6	18.0	9	11.8
VIMC (M)	86.7	15.3	12	8.7	91.7	10.3	9	6.7

Glare	Mean	SD	N	CI (+/-)	Value	SD	N	CI (+/-
RAND	76.4	26.4	1154	1.5	76.4	26.4	1154	1.5
VIMC (O)	39.2	16.2	15	8.2	43.1	15.5	9	10.1
VIMC (P)	44.6	10.6	14	5.6	45.8	10.8	9	7.1
VIMC (M)	43.7	12.5	12	7.1	43.1	11.0	9	7.2
Diurnal variation	Mean	SD	N	CI (+/-)	Value	SD	N	CI (+/-
RAND	74.6	23.1	1154	1.3	74.6	23.1	1154	1.3
VIMC (O)	63.0	21.4	15	10.8	63.9	17.8	9	11.6
VIMC (P)	62.5	18.8	14	9.8	62.5	20.1	9	13.1
VIMC (M)	61.1	22.9	12	13.0	60.2	24.5	9	16.0

NEI RQL-42 values

Only 2 questionnaires completed cohort

All 3 questionnaires completed cohort

Large differences between NEI RQL-42 and VIMC study values

5.13 Summary of main statistical analysis

Section 5.4.2 outlines the number of data events for the Plan C (VIMC) study and that those participants who only completed one questionnaire were excluded from the analysis, leaving 41 data events for analysis. For each NEI RQL-42 subscale, vision test and Sande dry eye question one and two, profile graphs were generated for both cohorts providing a visual illustration of variations within the data. The box and whisker plots provide a further indication of the data variation and are shown for the three data collection points; O, P and M.

Table 5-64 outlines the SPSS outputs for each of the NEI RQL-42 subscales and Sande dry eye questions one and two. All the subscales in both cohort groups have an asymptotic significance value greater than 0.05, confirming the null hypothesis and indicating an absence of any statistically significant difference between any of the data events for each of the subscales.

Table 5-64 Wilcoxon signed rank test outputs for each subscale

Subscale	Only 2 questionnaires completed cohort	All 3 questionnaires completed cohort
	Asym Sig	Asym Sig
Clarity of vision	0.108	0.465
Far vision	0.091	0.345
Near vision	0.606	0.109
Glare	0.480	0.655
Diurnal variation	0.574	0.779
Sande dry eye 1	0.551	0.660
Sande dry eye 2	0.161	0.499

5.14 Effect size

To provide additional insights into any differences between two cohorts or how meaningful any differences are, an effect size (ES) can be calculated which illustrates the magnitude of any differences; this is in contrast to statistical significance analysis, which only examines whether findings are likely to be due to chance. Both of these analysis methods provide information which can be used to inform the study conclusions.

The ES values can support the practical implications of the research findings, with a large ES indicating a greater practical significance, while a small ES indicates a more limited practical application. Cohen (1990) and Glass *et al*. (1981) suggest that the primary outcome of research should be concerned with the ES, rather than statistical significance, as it provides useful descriptive data. Cohen, (1990) classified effect sizes as small (d= 0.2), medium (d=0.5), and large (d=0.8).

Using normally distributed data from two independent groups, the ES can be measured by the standardized difference between two means, using the following formula for Cohen's d (Sullivan and Feinn, 2012).

$$ES = \frac{Mean\ cohort1 - Mean\ cohort2}{\sqrt{(\mathrm{N1} - 1) * SD1^2 + (N2 - 1) * SD2^2)/(N1 + N2 - 2)}}$$

Where:

ES=effect size

N_1=participant number of first cohort

N_2=participant number of second cohort

SD_1=Standard deviation of the first participant cohort

SD_2=Standard deviation of the second participant cohort

Although the formula is based on the data being normally distributed, there was a greater number of subscales with non-normally distributed data; however, the decision was taken to use the formula to calculate the ES, but noting the lack the accuracy with the non-normally distributed subscales.

Table 5-65 Calculated effect sizes for both cohorts

	Only 2 questionnaires completed	All 3 questionnaires completed
Clarity of vision	0.3	0.3
Far vision	0.9	0.3
Near vision	0.2	0.3
Glare	0.4	0.2
Diurnal variation	0.1	0.2
Sande dry eye 1	0.2	0.5
Sande dry eye 2	0.8	0.1

The statistical test results from the Wilcoxon signed rank test, for each cohort and subscale, show there was no statistically significant difference between any of the subscales (Table 5-64). However, a large ES was achieved for the far vision and Sande dry eye 2 questionnaire subscales for the 2 only completed questionnaires cohort. Table 5-16 indicates that the far vision subscale data for the only 2 completed questionnaires was not normally distributed and this could have influenced the ES value. A medium ES was found for the Sande dry eye 1 questionnaire for the all 3 questionnaires completed. These ES suggests that although statistical hypothesis testing did not indicate any statistically significant differences, measurable differences were present between the two groups.

5.15 Participants' comments during the process

During completion of the questionnaires, participants were invited to leave any comments about their eyes or vision which they have noticed around that point in the menstrual cycle. Although there were 47 data collection events (Section 5.4.2) only five comments were made (Table 5-66) and these are considered further in the discussion chapter (Section 6.4.6).

Table 5-66 Participant comments.

Participant	Data event	Comments
P2	O	Today my vision has shifted and is somewhat blurry and I feel disorientated
P9	O	I use Hycosan extra for my dry eyes. 2 days before my period starts I use it every 1-2 hours.
P16	O	I very occasionally get severe dry eye symptoms that last about an hour
P17	M	I have worn glasses since I was 3 and contact lenses since I was 13. I continuously look at laser eye surgery but as I am long sighted it's not as effective.
P22	O	Definitely changes over the course of the month, my vision deteriorates and I am much more reliant on my glasses (ie blurry vision, headaches etc) for couple of weeks and then it starts to clear and settle again.

5.16 Effect of medications

During the sign-up process to the study, participants were asked to report any medications which were being taken and these have been listed in Table 5-67. Lightly shaded cells are those participants who either did not complete any or only one questionnaire.

Table 5-67 Participation medication list.

Participant	Age	Medication 1	Medication 2	Medication 3	Medication 4	Medication 5
P2	32	Ridgevidon				
P6	27	Gederal				
P7	52	Amlodipine				
P12	28	Sertraline				
P23	29	Desloratadine	Pantoprazol			
P19	53	Amlodipine				
Excluded	38	Semaglutide				
Excluded	42	Ferrous sulphate				
Excluded	34	Yaltormin XR	Metformin	Naproxen	Sertaline	
Excluded	34	Lamotrigine				
Excluded	18	Combined Pill				
Excluded	55	Verapamil	Lansoprazole	Ramipril	Clopidogrel	Metformin
Excluded	46	Levothyroxine				

The class of medications which have reported potential ocular side effects of dryness or blurred vision, as listed at www.medicines.org.uk, are listed in Table 5-68.

Table 5-68 Class of medications and ocular side effects

Class of medication	Type of medication 1	Type of medication 2	Side effects
Contraceptive	Ridgevidon	Gederal	Dryness
Hypertension	Amlodapine,		Blurred vison
Anti-histamine	Desloratadine		Dryness
PPI	Pantoprazol		Blurred vison
Anti-depressant	Sertraline		Blurred vision

To determine whether the responses provided by the participants taking medication influenced the overall cohort responses, the individual participants were reviewed and compared to the cohorts; these were placed in quartiles.

Quartile 1: The set of data points between the minimum value and the first quartile.
Quartile 2: set of data points between the lower quartile and the median.
Quartile 3: The set of data between the median and the upper quartile.
Quartile 4:The set of data points between the upper quartile and the maximum value of the data set.

Table 5-69 considers those participants taking medications with listed side effects of blurred vision and Table 5-70 considers those participants taking medications with listed side effects of ocular dryness.

Table 5-69 Subscales involved with blurred vision.

(Q=quartile)

Participant	Subscale	O	P	M
P7	Clarity of vision	Q2	Q2	Q2
	Far vision	Q3	Q2	Q2
	Near Vision	Q1	Q1	Q1
	Glare	Q2	Q2	Q2
	Diurnal variation	Q4	Q4	Q4
P12	Clarity of vision	Q1	Q1	Q1
	Far vision	Q1	Q1	Q1
	Near Vision	Q1	Q1	Q1
	Glare	Q1	Q1	Q1
	Diurnal variation	Q2	Q3	Q1
P23	Clarity of vision	Q1	Q1	-
	Far vision	Q1	Q1	-
	Near Vision	Q4	Q3	-
	Glare	Q1	Q1	-
	Diurnal variation	Q3	Q3	-

Table 5-70 Subscales involved with ocular dryness.

Participant	Subscale	O	P	M
P2	Sande dry eye 1	Q3	-	Q4
	Sande dry eye 2	Q2	-	Q3
P6	Sande dry eye 1	Q1	Q1	Q1
	Sande dry eye 2	Q1	Q1	Q1

The low participant numbers make drawing any conclusions difficult but observations can be made from the analysis and can be seen in the profile plots in Section 5.12. The participant P12, who was taking Sertraline, has responses which are within the first quartile of the cohort, indicating that they had more difficulty compared to the rest of the cohort with those tasks outlined in the NEI RQL-42 questions and Sertraline is known to induce mydriasis, which can affect vision.

Participant P7, who was taking Amlodapine, has responses for the near vision subscale within the 1st quartile of the cohort, indicating more difficulty with those near vision tasks outlined in the NEI RQL-42 questions. This patient is 52 years old and the near vision difficulties could be attributed to presbyopia rather than the medication.

Participant P23 who was taking Pantoprazol, has responses within the first quartile of the cohort for far vision, glare and clarity of vision. These lower scores indicate increased difficulty with those tasks outlined in the NEI RQL-42 questions.

The two participants P2 and P6 both reported taking oral contraceptives. P6 completed all three questionnaires and the observations from the Sande dry questions, with responses within the first quartile of the cohort, indicating more difficulty with ocular dryness. This is consistent with the adverse effects listed for the drugs (www.medicines.org.uk).

5.17 Chapter summary

This chapter presents data from the Plan B (VIP-online) and Plan C (VIMC) studies. The descriptive data described the age of menarche and duration of the menstrual cycle which were consistent with literature. Statistical analysis of the Plan C (VIMC) data confirms the null hypothesis (Section 1.6); there were no statistically significant differences for each of the five NEI RQL 42 subscales and the Sande dry eye questions. The NEI RQL 42 subscale values were compared to those published by RAND. Participants' comments about their vision during the menstrual cycle were presented along with the potential ocular effects of medications being taken.

Chapter 6 Discussion

6.1 Chapter overview

The key research findings are presented, related to the aims and objectives (Sections 1.4 and 1.5), and compared to the literature. The study has areas of originality which are outlined, followed by the strengths and weaknesses. Suggestions for further research and recommendations are made followed by a conclusion.

6.2 Study research aims

Anecdotal evidence from optometrists indicates that changes in refractive error may occur throughout the menstrual cycle and during pregnancy, along with dry eye symptoms, but the evidence base is inconclusive. Currently no clinical guidelines exist on when it is appropriate to prescribe spectacles, either during all phases of the menstrual cycle or during pregnancy. This results in uncertainty for optometrists when considering prescribing glasses and providing advice to their patients. The research reported in this thesis investigated whether visual changes and dry eye symptoms occur during the menstrual cycle and pregnancy, and captured self-reported visual experiences. The hypotheses in Section 1.6 were tested, to address the research aims and answer the research objectives outlined in Section 1.5.

6.3 Key findings

Four participants were enrolled into the Plan B (VIP-online) study, with each participant completing a single vision questionnaire. No visual acuity data were collected for this study. Forty-four participants were enrolled into the Plan C (VIMC) study, with nine participants completing all three questionnaires, seven participants completing two questionnaires and six participants completing a single questionnaire (Section 5.2.2) Twenty-two participants did not complete any vision questionnaires. Sixty-six percent of questionnaires were completed on the calculated date. Three participants provided visual acuity data for each of the three data collection points (Section 5.4.2).

The mean age of participants enrolled into the Plan C (VIMC) was 30.5 yrs (Section 5.6.1), with mean age of menarche of 13.5 yrs and a mean menstrual cycle length of 28 days (Section 5.6.2). The datasets were analysed for distribution normality (Table 5-16), revealing that 64% of subscales contained non normally distributed data with 36% containing normally distributed data. There was insufficient data from Plan B (VIP-online) to perform inferential testing. Inferential analysis of data from Plan C (VIMC) study, did not show any statistically significant differences between the data collection events, for any of the 5 subscales and Sande dry questions. The data suggest there are no clinically significant visual changes or dry eye symptoms during the menstrual cycle.

6.4 Appraisal of results

6.4.1 Visual acuity

The possible effects of oestrogen on visual acuity are discussed in Section 2.7.2.2, with equivocal findings from several studies. Oestrogen receptors have been isolated in the cornea and retina, giving rise to the hypothesis that oestrogen may influence refractive error and retinal function. This was discussed in Section 2.7.2.7 and Ghahfarakh *et al.* (2015) found that corneal thickness was maximal around the time of ovulation, potentially inducing a myopic refractive error shift. However, Erdem *et al.* (2007) did not find any difference in refractive error with women using HRT. Parlee (1983) highlighted that sensory fluctuations occur throughout the menstrual cycle leading to the suggestion that visual acuity could be influenced by oestrogen levels. The findings (trends) of Plan C (VIMC), align with elements of previous research with participants reporting more difficulties with their vision around the time of ovulation.

6.4.2 Menstrual cycle and menarche data.

In Plan C (VIMC), the mean reported duration of the menstrual cycle was 28 days which is consistent with the literature (Reed and Carr, 2018). The literature suggests that the upper age limit for normal menstruation is around 50 years of age.

The menstrual cycle duration changes with age, becoming initially shorter during the transition into menopause and increasing towards the final menstrual period and the post menopause phase. (Harlow and Paramsothy, 2011). However, the study data (Table 5-13) do not align with this, but the small cohort makes drawing comparisons to Harlow and Paramsothy (2011) difficult. The literature indicates that menarche typically occurs between the ages of 10 and 16 with the mean onset being 12.4 years (Marques, Maderia and Gama, 2022). The mean participant-reported age for menarche was 13.5 years old, with a range of 11-17 years (Table 5-11) which is consistent with the literature.

6.4.3 Age

As oestrogen levels are known to fluctuate throughout the menstrual cycle (Reed and Car, 2018), the speculation is that oestrogen has a direct influence on participants' vision. As women enter the peri-menopause phase their oestrogen levels start to reduce and in the first year of the menopausal period, there is a reduction on average of 80% of pre-menopausal oestrogen levels (Horstman *et al.*, 2018). The mean ages are 34 and 32 years for the only two questionnaires completed and all three questionnaires completed cohorts respectively. Within both cohorts there were two women over the age of 50 years old (Table 5-13); as these participants self-declared that they met the inclusion criteria for enrolment into the study (Table 3-5) this suggests they have not entered the peri-menopause phase. Considering the variation of oestrogen with age, a lower or higher mean age of participants may have yielded different results.

6.4.4 NEI RQL 42 subscales

Far vision

The mean results shown in Tables 5-26 and Table 5-27 demonstrated a tendency which, although not reaching statistical significance, is suggestive that participants in both cohorts had more difficulties around the time of ovulation (Means=79.2 and 85.7 for the at least two and three questionnaires completed cohorts respectively) and fewer difficulties around the time of menstruation (Means=90.7 and 88.9 for the at least two and three questionnaires completed cohorts respectively).

The questions in the subscale relate to distance visual tasks, these include judging distances using practical examples such as parking a car, walking downstairs and driving in different lighting conditions, which can be considered to be surrogate determinants for possible changes in the distance refractive error. These perceived changes by participants could be affected by refractive changes, tear film or retinal changes. Guo *et al*. (2021) found that changes occur in the retinal vasculature during the menstrual cycle but there is no literature on the effects of retinal thickness; an increase in retinal thickness could account for a hypermetropic shift in refractive error. However, for young participants with normal ocular accommodation, it is unlikely that a hypermetropic shift in refractive error would cause noticeable difficulties in distance vision but small myopic refractive changes could impair distance vision. Any myopic changes and subsequent reductions in acuity could affect the responses to the questions around participants' experiences with driving and judging distances at night and in poor lighting conditions (Cohen *et al*., 2007).

Wood (2020) found that night time visual discomfort from road lighting and car headlights have a significant impact on vision. As 88% of participants were drivers, these visual effects could have influenced the scoring. In developing countries, nyctalopia (night blindness) can occur with pregnancy and is related to vitamin A deficiency (Pizzarello, 2003; Christian, 2002). However, there is no literature on the potential effects of vitamin A on the menstrual cycle. A literature search was undertaken with no papers found (Pubmed 05.09.23). Choung, Dawson and Smith (1990) found no involvement of vitamin A deficiency in PMS and this is unlikely to play a role in the subscale scoring.

Near vision

The mean results shown in Table 5-32 demonstrated a tendency which, although not reaching statistical significance, is suggestive that participants in the two questionnaires completed cohort had more difficulties around the time of menstruation (Mean=86.6) and fewer difficulties around the time of peak progesterone (Mean=89.5). The mean results shown in Tables 5-33 demonstrated a tendency which, although not reaching statistical significance, is suggestive that participants in the three questionnaires completed cohort had more difficulties around the time of ovulation (Mean=87.9) and fewer difficulties around the time of menstruation (Mean=91.6).

The questions in the subscale relate to near visual tasks, and include reading, using computers and practical near vision tasks such reading ingredients on food packets. Although the near vision subscale questions relate to near vision tasks, these appear to be around paper- based near vision tasks and do not reflect the current digital world; there is no mention of smartphones, tablets or visual display units in any of the subscale questions. As digital devices are ubiquitous, it is possible that participants related their visual experiences with near vision tasks to their digital device use. It is known that these devices can create ocular and visual symptoms (Issa *et al.*, 2021) but at the time when the developers created the NEI RQL42 such devices may not have been a consideration. The mean differences in the near vision subscale could be related to these symptoms.

Diurnal fluctuation

The mean results shown in Table 5-45 demonstrated a tendency which, although not reaching statistical significance, is suggestive that participants in the three questionnaires completed cohort had more difficulties around the time of menstruation (Mean=60.2) and fewer difficulties around the time of ovulation (Mean=63.9). The questions in the subscale relate to difficulties with hobbies and changes in the clarity of vision throughout the day.

Clarity of vision

The mean results shown in Table 5-20 demonstrated a tendency which, although not reaching statistical significance, is suggestive that participants in the two questionnaires completed cohort had more difficulties around the time of menstruation (Mean=30.4) and fewer difficulties around the time of ovulation (Mean=33.6). The mean results shown in Table 5-21 demonstrated a tendency which, although not reaching statistical significance, is suggestive that participants in the three questionnaires completed cohort had more difficulties around the time of peak progesterone (Mean=25.5) and fewer difficulties around the time of menstruation (Mean=27.8). The questions in the subscale relate to how bothersome the eyes and vision have been.

The clarity of vision subscale scoring was considerably lower at all three data collection points compared to the RAND normative database. This difference could be attributed to the modest sample size in the present research or the interpretation of the questions, which form the subscale, by the cohort. The retina is known to be a SSH sensitive tissue with oestrogen having a neuroprotective effect. HRT has been linked to protective effects for certain types of age-related disorders, which appear to be derived from antioxidant activity (Nuzzi *et al.*, 2018). This leads to the speculation that oestrogen is unlikely to have an adverse effect on vision at a neuronal level.

Glare

The mean results shown in Tables 5-38 and Table 5-39 demonstrated a tendency which, although not reaching statistical significance, is suggestive that participants in both cohorts had more difficulties around the time of ovulation (Means=39.2 and 43.0 for the at least two and three questionnaires completed cohorts respectively) and fewer difficulties around the time of menstruation (Means=44.6 and 45.8 for the at least two and three questionnaires completed cohorts respectively).

The questions within the glare subscale could be open to interpretation by participants because they mention starbursts and halos around light sources at night. These effects could potentially be related to uncorrected refractive error rather than to physiological changes to the eye. Glare, without being defined for participants, could be confused with photophobia (light sensitivity) and this problem could arise from multiple situations and causes.

The term glare is commonly used by drivers at night, from the discomfort encountered from the headlights of oncoming cars and for those who spend time outdoors without sunglasses. Both of these could have the potential to affect scores on this subscale. Menstrual headaches which occur just prior to menses are related to lower oestrogen levels and can also cause photophobia (Moy and Gupta, 2020). This does not agree with outcomes of the study findings as more symptoms were reported around ovulation

Sande dry eye question 1

The question attempts to determine the frequency of any dry eye symptoms. The mean results shown in Tables 5-50 and Table 5-51 demonstrated a tendency which, although not reaching statistical significance, is suggestive that participants in both cohorts had more difficulties around the time of ovulation (Means=33.0 and 33.6 for the at least two and three questionnaires completed cohorts respectively) and fewer difficulties around the time of peak progesterone (Means=39.4 and 48.3 for the at least two and three questionnaires completed cohorts respectively).

One function of a healthy tear film is to contribute to the refracting capabilities of the eye by providing a smooth anterior refracting surface and any changes to the structure or stability of the tear film can result in reported responses to changes in perceived clarity of vision (D'Souza *et al.*, 2020).

Sande dry eye question 2

The question attempts to determine the severity of any dry eye symptoms. The mean results shown in Table 5-56 demonstrated a tendency which, although not reaching statistical significance, is suggestive that participants in the two questionnaires completed cohort had more difficulties around the time of ovulation (Mean=43.1) and fewer difficulties around the time of menstruation (Mean=58.1). The mean results shown in Table 5-57 demonstrated a tendency which, although not reaching statistical significance, is suggestive that participants in the three questionnaires completed cohort had more difficulties around the time of peak progesterone (Mean=44.0) and fewer difficulties around the time of menstruation (Mean = 45.5). This could influence participants' responses for the clarity of vision subscale; however, this only occurred with participant P25.

Schematic diagrams have been created using the outcomes from NEI RQl 42 and Sande dry eye questionnaires for both cohort groups (Figure 6-1 and Figure 6-2). These show a tendency for worse symptoms around the time of ovulation; for the far vision, near vision, glare and Sande dry eye question 1, with symptoms improving towards menstruation.

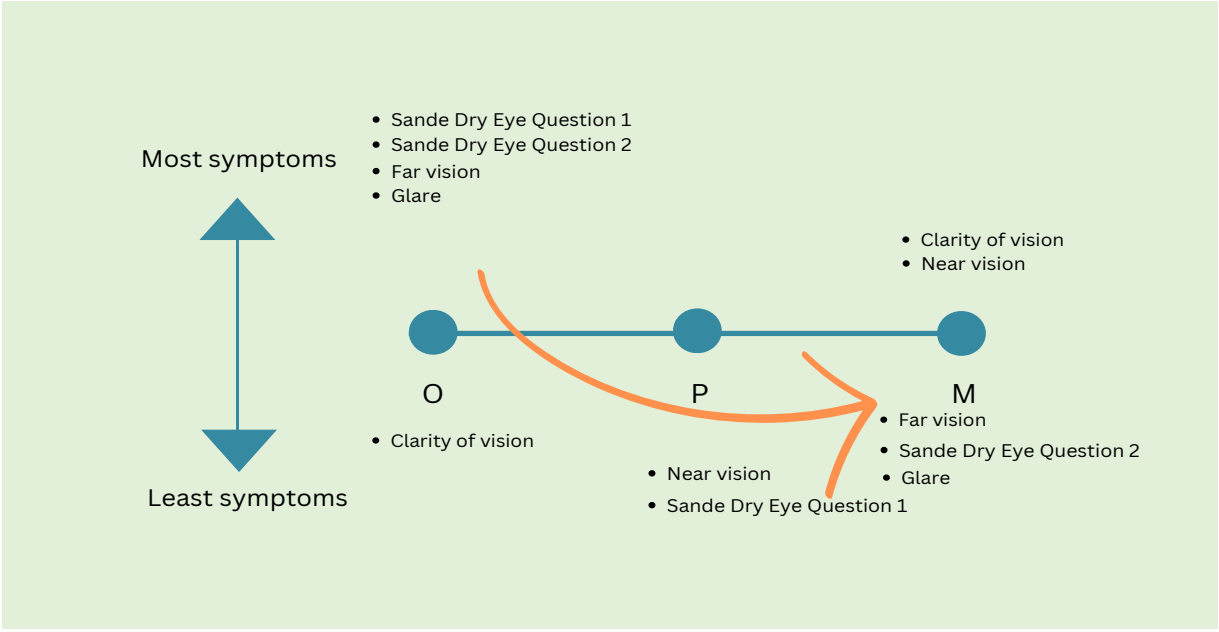

Figure 6-1 Schematic of symptoms, for only 2 completed questionnaires

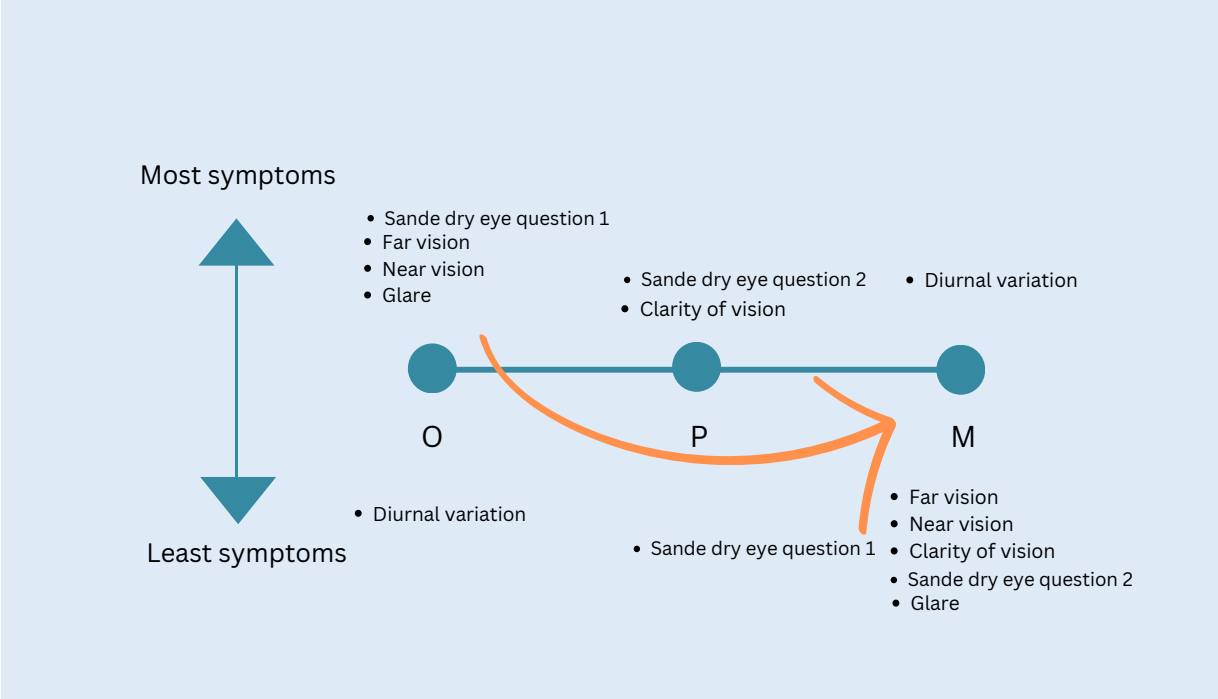

Figure 6-2 Schematic of symptoms, for all 3 completed questionnaires

6.4.5 Attrition rates

6.4.5.1 Plan B (VIP-online)

The Plan B (VIP-online) study attrition rate, after completion of the first data event during the first trimester, was 100%. This could be related to the small sample size; however, there are many other potential reasons for such a high attrition rate, ranging from loss of interest, competing time demands, illness, enrolment in other healthcare studies and pressures of family life.

6.4.5.2 Plan C (VIMC)

The Plan C (VIMC) attrition rate from those who enrolled to those who completed all 3 questionnaire data collection events was 79.5% (Section 5.2.2). From the attrition cohort, 62.8% did not complete any questionnaire data events. Eysenbach (2015) describes the phases with enrolment and non-engagement and the Plan C (VIMC) follows the pattern.

During the enrolment phase, interest and engagement were high as participants considered the study, leading to the attrition phase where participants exit at a higher rate, which then slows to the stable phase where participants are more likely to complete the study. In the Plan C (VIMC) study participants did exit during the stable phase but at a slower rate.

Some participants did not complete all three questionnaires and the reasons for missed data collection events can only be speculative. Online studies have been reported to have attrition rates of between 30-70% (Gustavson, 2012); the attrition rate of Plan C (VIMC) defined by those who enrolled but failed to complete all three questionnaires was higher than this upper limit.

A literature search on the causes of attrition in research indicates that this is multifactorial and can be associated with age, ethnicity, gender and the study design. A literature search for attrition in vision research did not yield any results and comparison of the Plan C (VIMC) to other studies has limitations because of study design and participant demographics.

Exit questionnaires for Plan B (VIP-online) or Plan C (VIMC) studies were not incorporated into the process. Although this might have provided useful information, the inclusion of an additional task would ironically be likely to further increase attrition. However, the lack of an exit questionnaire means that the reasons for participants exiting the study are unknown and purely speculative.

6.4.6 Participants' comments

The participants were invited to leave comments about any ocular changes they have previously experienced during their menstrual cycle or which occurred during the study (Section 3.7). The aim of this open question was to gather subjective data and relate these to the outcomes of statistical analysis of the study data; comments are summarised in Table 5-66. There were two themes; dry eye symptoms and blurred vision.

6.4.7 Dry eye symptoms

P16 only completed one data event questionnaire and was not included in any cohort for data analysis and no conclusions can be drawn. P9 completed all three questionnaires and complained of dry eye symptoms prior to the start of her period. However, the participant's responses for Sande dry eye question 1, which considers the frequency of symptoms, indicates greater frequency when the progesterone levels are maximal (Figure 5-24) and the Sande dry eye question 2, which considers the severity of symptoms, was lowest at the time of peak progesterone and maximal at the time of ovulation (Figure 5-28). These responses are not consistent with the participant comments at the time of enrolling into the study.

6.4.8 Blurred vision

P17 only completed one data event questionnaire and was not included into any cohort for data analysis and no conclusions can be drawn. P2 and P22 completed two data collection events. The NEI RQL subscales which could be related to blurred vision are far (Section 5.12.2) and near vision (Section 5.12.3) and clarity of vision (Section 5.12.1).

P2 had maximal responses at data collection point M and lowest at data point O for both far and near vision subscales, indicating greater difficulty around these points in the menstrual cycle._In Table 5-66, P22 commented "Definitely changes over the course of the month, my vision deteriorates and I am much more reliant on my glasses (i.e. blurry vision, headaches etc) for couple of weeks and then it starts to clear and settle again." The comment was made at the data collection point O and it indicates that the participant's vision changes throughout the menstrual cycle but they did not indicate where in the menstrual cycle that they experienced the changes. The participants' NEI RQL-42 and Sande© dry eye questionnaire responses, indicate that symptoms are greater around ovulation and at the time of peak progesterone levels.

6.4.9 Effects of medication on vision

The Plan C (VIMC) study highlighted near vision difficulties with the participant taking Amlodipine and it could be beneficial to explore this in a larger cohort. If male subjects were used, it would remove the potential confounding issues of oestrogen and progesterone variations and allow direct investigation of the impact of the drug. However, a potential issue is that Amlodipine is a calcium channel blocker (CCB) and NICE recommends angiotensin-converting enzyme (ACE) inhibitors as first treatment and CCB as adjunct treatment, introducing further potential confounding variables (NG136).

6.5 Comparison with the literature

Responsiveness of an instrument describes the ability to detect change over time and is achieved by measuring the difference in the mean construct values. For the NEI RQL-42, this is the mean subscale values for the NEI RQL-42 questionnaire (de Vet *et al*., 2011; Mokkink *et al.*, 2010). Whether any difference in the mean values represents a meaningful difference is dependent on the variable being measured and the clinical effect that the change represents. Responsiveness can be used to compare the subscale outcomes of the NEI RQL-42 questionnaire for different studies. A literature search on the responsiveness of the NEI RQL-42 questionnaire yielded one paper by Pakpour *et al*. (2013) which provided numerical values for the subscale outcomes; the authors considered these to represent meaningful differences in participants' visual experience.

The differences in the means of the subscale values, for the Plan C (VIMC) study are compared to those values given by Pakpour *et al*. (2013) in Table 6-1. All values from the Plan C (VIMC) study are below the minimum values which Pakpour *et al*. (2013) considered to represent meaningful differences, with the exception of the far vision subscale. This suggests that the Plan C (VIMC) outcomes did not reach a threshold to detect clinically meaningful differences; however, this is comparing the Plan C (VIMC) outcomes to a single research paper which may not be representative.

Queirós *et al*. (2012) found that the NEI RQL-42 instrument was sensitive enough to detect differences in the visual outcomes of post refractive surgical procedures. Colombo-Barboza *et al*. (2022) used the instrument to assess pre- and post-refractive surgical outcomes and also concluded the instrument was sensitive to detect clinical change. However, they did comment that there were no standards to identify which scores or domain increases could be considered average, above average, or excellent in the literature.

Table 6-1 Differences in the means Plan C (VIMC) study compared with Pakpour *et al*. (2013)

Subscale	Pakpour *et al*. (2013)	Only 2 questionnaires completed	All 3 questionnaires completed
Clarity of vision	4.00	3.4	2.3
Far vision	7.81	11.5	3.2
Near vision	7.26	0	3.7
Glare	9.68	5.4	2.7
Diurnal variation	6.99	2.1	3.7

(Pakpour *et al*., 2013)

6.6 Strengths and weaknesses

6.6.1 Strengths

Recruitment process

Engagement of a young female social media influencer provided the opportunity to organise repeated social media posts over a period of time and enabled information about the study to be disseminated to a number of potential participants.

Online enrolment

This process provided potential participants with the opportunity to consider the study prior to enrolment, resulting in a greater level of engagement in the study and potentially less attrition.

WebApp

Plan B (VIP-online) and Plan C (VIMC) study were accessed through a purpose designed and built WebApp; an important feature was the security of participant data. To facilitate this, each participant was issued with unique login details but the feedback from one participant suggested that the login details should be dispensed with to facilitate easier access. It is likely that such a change would have been unacceptable to the ethics committees. The way participants login to secure areas could be reviewed and improved; such as using face recognition, but this could create additional challenges for the research team around the management of participant biometric data.

e-Consenting

Plan B (VIP-online) and Plan C (VIMC) were online studies which used self-reported data collection methods; questionnaires and an online visual acuity measurement test. This presented low ethical risks to participants, with the HRA advising that the study was below their threshold for requiring approval. The Plan C (VIMC) study was conducted in accordance with the principles of the Declaration of Helsinki and an e-consenting process was used to ensure that participants were informed about the study and any potential risks. The consenting process traditionally requires a 'wet' signature, with a member of the study team being present, but the effects of the COVID-19 pandemic accelerated the use of remote or digital/eConsenting processes for low-risk studies. A literature search did not return any vision research which had used this process.

Engagement with participants

Using an online method of delivery for data collection provided the opportunity to communicate easily with participants, using their preferred method of contact, typically SMS or email. This also provided an easy opportunity for participants to contact the researcher with any questions or concerns.

Automated recall / prompts

Recall algorithms were developed for Plan B (VIP-online) and Plan C (VIMC), which were based on information provided by the participant on the stage of pregnancy, the date of last period and the average menstrual cycle duration. Invitations to complete a data event and recall prompts were calculated and automated at the time of enrolment. Participants were also sent an initial welcome email with the data collection dates included.

6.6.2 Weaknesses

Plan A (VIP) participants' pre-pregnancy refractive error

A limitation of the original research plan (Plan A, VIP) is that it assumed that the pre-pregnancy refractive error could be determined from participants' spectacle prescription, from their current spectacles, or their latest eye examination prescription if this was available. If participants do not wear glasses, the assumption was that they did not have a significant refractive error.

However, this overlooks the possibility of uncorrected refractive errors. Uncorrected myopic refractive errors frequently result in symptoms and serve as a prompt to seek attention but uncorrected hypermetropic refractive errors can be symptomless, dependent on adequate levels of accommodation being present (Sun *et al*., 1988). Although this original research plan was not possible because of the pandemic, this limitation is mentioned here in case other researchers adopt this approach.

Refraction method

Plan A (VIP) was to use an autorefractor to determine the refractive error. The reference standard for refraction would be a subjective refraction (Elliott, 2017) but an auto refractor is a compromise which balances the demands of participants' time, location, level of engagement and accuracy. The Nidek Retinomax handheld auto-refractor obtains data on the corneal curvature but does not provide information regarding CCT, which could be useful when interpreting data around change in.

Vision questionnaires

The NEI RQL 42 and Sande dry eye vision questionnaire tools were not specifically designed or validated for use to assess vision during the menstrual cycle or pregnancy. It was assumed that these questionnaire instruments would be appropriate and the relevant subscales were chosen.

Data collection points

Data collection points for Plan C (VIMC) were based on participant reported information. Although the literature finds women to be fairly accurate in recalling key menstrual cycle dates, as data collection points are not based on physiological markers but on calendar dates this has the potential for error. This type of study methodology does not permit the more accurate determination of the key menstrual cycle points that could be afforded from salivary assay or blood tests (Howarth and Clemes, 2016).

Potential sources of bias

Bias is defined as any systematic error in the design, conduct, or analysis of a study (Althubaiti, 2016) and can arise from the processes for participant enrolment and data collection methods (Hennekens, 1987). Bias can be grouped into observational, self-reporting, confirmation and measurement error types. Each of the study designs had areas of inherent bias which require consideration and mitigation.

With Plan A (VIP) there was the potential for measurement errors from incorrect use of the autorefractor instrument and standardised visual acuity chart. With this plan, these errors would have been mitigated by routine calibration of the auto-refractor and an experienced clinician measuring visual acuity. The recruitment process for Plan B (VIP-online) and Plan C (VIMC) could have introduced selection bias resulting in a sample that may not be representative of the general population, and cohorts were not grouped for age or ethnicity. This bias was minimised by the wide promotion and the use of snowballing (Section 4.3.13.1). Nonetheless, it is still possible that bias was introduced because people without access to a computer or without the skills necessary to use an online portal would be unlikely to have participated. Self-reporting bias could arise from the use of questionnaires, but this was mitigated by using validated questionnaires to reduce variability.

With Plan C (VIMC) recall bias could arise from participants incorrectly recording their date of last period. Creinin, Keverline and Meyn (2004) found that women both over- and under-estimate the number of days from the date of last period. However, Wegienka and Baird (2005) found that women are fairly good at recalling the date of their last period, with a slight tendency to underestimate the number of days. Although the literature indicates fairly good recall, small errors in recollecting these dates are inevitable.

Participant recruitment

Plan A (VIP) study did not attract any participants. During the design and development of the VIP study, several local GPs and midwifery team members were consulted for their views on how to maximize participant engagement and recruitment. Their suggestions were considered and where appropriate incorporated into the study design. Indeed, many of these healthcare professionals were strongly supportive and offered to assist with disseminating information about the study to facilitate recruitment. Although significant contributions from both health professional groups were made, the effects of the COVID-19 pandemic halted the progress of the study.

Plan B (VIP-online) study only attracted four participants (Section 5.2.1), furthermore the participants who enrolled for Plan B (VIP-online) only completed one questionnaire with no participant completing the study. During the development of the VIP-online study, midwifery teams were consulted for their input and to facilitate engagement and support. However, the direct and indirect effects of the COVID-19 pandemic adversely affected participant recruitment.

The reduction in face-to-face clinical appointments during the national lockdown(s) and recovery period(s) (Appendix 1), decreased opportunity for healthcare professionals to directly promote and discuss the study with their patients and meant that the professionals' time with pregnant women was reduced so they had to prioritise clinical work over other activities, such as promoting the study. The reduced clinical time also limited the opportunity for pregnant women to encounter study promotional material located in clinic environments. As the effects of the COVID-19 pandemic waned and face-to-face healthcare appointments resumed, feedback from healthcare professionals indicated that the combination of limited staffing resources and high appointment capacity pressures, continued to impair their opportunities to discuss the study with their patients.

For Plan C (VIMC), a diverse approach was adopted to maximize recruitment (Section 4.3.14). A young female social media influencer (with over 35,000 followers) kindly promoted the study on multiple occasions, by posting details of the study to her large number of followers; which were assumed to be young women. The study was also widely promoted within two university undergraduate populations. Although considerable time and efforts were directed towards promoting the VIMC study it achieved limited response.

Several ideas have been mooted to explain this, such as a general saturation and fatigue from constant requests to engage with online surveys/questionnaires or to provide feedback for various health and retail encounters, combined with a post COVID-19 pandemic lethargy towards participating in voluntary activities.

e-Consenting

The Plan C (VIMC) study e-consenting process provided participants with easy access to study materials and enabled enrolment at a convenient time; but this ease also facilitates passive withdrawal from the study through non engagement/participation, resulting in potentially higher attrition rates.

WebApp login features

Plan B (VIP) and Plan C (VIMC) online studies were accessed through a purpose designed and built WebApp. An important feature was the security of participant data and to facilitate this, each participant was issued with unique login details. However, feedback from one participant recommended the unique login details should be dispensed with to facilitate easier access.

NEI RQL-42 validation cohort

The participant demographics used in the validation process of the RAND NEI RQL 42 questionnaire (Section 5.12.9) includes information on the refractive status of participants but does not include information on participant gender. It is speculated that the gender demographics would not introduce any bias; having males included into the cohort could reduce the effects of fluctuating oestrogen levels during the menstrual cycle. However, the large difference in the mean values between the NEI RQL-42 normative database and Plan C (VIMC), could be more attributable to the differences in cohort size but the possibility of an effect from gender bias remains.

6.7 Originality and unique features

The study used two validated questionnaires and an online visual acuity test. The study incorporated several areas of originality, and indeed unique features, which are outlined below.

Bespoke designed and built WebApps (Section 4.3.7)

Although the use of websites to provide information to participants is becoming more commonplace, the use of WebApps to provide participant information and act as a point of data collection are less common and the researcher believes that this maybe the first time these have been used for vision sciences research. For the present research a customised WebApp was designed that met with favourable comments from participants.

e-Consenting process (Section 3.6.8.1)

This process is becoming an accepted practice but this approach has not been used widely in vision

NEI RQL 42 vision questionnaire (Section 4.4.4.1)

This is the first time that this questionnaire has been used for research into vision during the menstrual cycle and pregnancy.

Calculated data collection events (Section 3.6.11)

The research developed algorithms for calculating the data collection events for the Plan B (VIP-online) and Plan C (VIMC), using data provided from the participant in combination with the literature on pregnancy trimester duration and duration if the different stages within the menstrual cycle.

Instructions for the FrACT tool (Appendix 11)

The FrACT online vision tool has basic user instructions that are designed for vision scientists and eye care practitioners. These were expanded and improved, using non-technical language, to make the set-up process easier for participants. This instructions are available for other researchers to use (Appendix 11). The FrACT test has been used in over 520 research studies and it is hoped that user-friendly instructions will be helpful to future researchers.

6.8 Summary of findings

The limited data collected from Plan B (VIP-online) did not permit any useful analysis to be undertaken. Analysis of the data obtained from Plan C (VIMC), showed there were no statistically significant differences between different phases of the menstrual cycle based on data obtained with the NEI RQL 42 questionnaire subscales and the Sande dry eye questions. However, analysis did suggest a trend towards greater visual difficulties around the time of ovulation, which correlated with participants' comments. Also, there was no statistically significant difference in visual acuity, throughout the menstrual cycle, which suggests that although the eye is an oestrogen sensitive organ the normal fluctuating oestrogen levels during the menstrual do not adversely affect the vision.

Implications for optometrists

Optometrists can be confident that female patients should not experience large visual changes during the menstrual cycle, although there may-be reported tendencies towards certain visual difficulty and dry eye symptoms, which are greater around the time of ovulation. The findings of the research should not influence the prescribing of spectacles. However, these comments should be tempered with a note of caution given the small sample size of the study.

6.9 Future research

The original research question of Plan A (VIP) to measure the refractive error throughout pregnancy and post-partum still remains unanswered. The researcher considers to be an important area of study which needs to be completed.

Using the Plan C (VIMC) study design with a larger and more diverse cohort would enable further detailed analysis of self-reported visual difficulties during the menstrual cycle and would facilitate ethnic and age stratification.

The Plan C (VIMC) study design could also be used to investigate visual difficulties during the onset of the menopause and consider any associations with hormonal changes. Further self-reported questionnaire studies investigating the effects of oestrogen could integrate with other Apps used to predict ovulation and menstruation.

6.10 Recommendations

WebApp login

The way participants login to secure areas could be reviewed and improved; such as using face recognition but this could create additional challenges for the research team having to store participant biometric data.

e-Consenting

The increase in the use of e-consenting for low-risk studies improves convenience and uptake in enrolment but the detached nature of the enrolment process can have negative effects on participants completing the study. Placing friction points during the e-consenting process could help reduce attrition rates for those participants with a low interest in the study and help re-enforce engagement for participants who have an interest in the study. A practical example could be to include a process to ensure that participants had read all the study documents; such as having to indicate at the end of each document that it had been read and understood, possibly incorporating a timed delay to ensure that enough time has elapsed before the acknowledgment was accepted.

Online visual acuity test

The FrACT online self-measurement vision test was chosen for its standardisation because it had been used in many previous vision studies. However, the disadvantages of this test are the complexity and time taken to set up the test, plus the requirement for a companion to be present to support completion of the test. The choice for vision researchers using self-measurement visual acuity tests is the balance between ease of use and the precision gained from standardisation.

Recruitment

A recommendation from the recruitment experience would be for any researcher to adopt a more direct approach towards the target group, rather than adopting a generalized and diverse approach to promoting any study. While both Plan A (VIP) and Plan B (VIP-online) had good engagement from the healthcare professionals to promote the study, a further recommendation from the experience would be for researchers to minimize the reliance on intermediaries and where possible to promote the study directly themselves. As none of the three studies offered any form of incentive to participate, this is something which could be considered to encourage participation and reduce attrition rates.

6.11 Conclusions

Given the absence of clinical guidelines for eyecare professionals on prescribing of spectacles during pregnancy and the menstrual cycle, this thesis investigates visual changes that may occur during the menstrual cycle and pregnancy. As women of all age groups and all stages of reproductive life routinely present to community optometrists for eye examinations an understanding of the hormonal processes, either during the menstrual cycle or pregnancy, is important to contextualise symptoms of ocular and visual complaints in relation to normal hormonal variations.

The literature indicates that the eye is an oestrogen sensitive structure, with oestrogen receptors found within the refractive components of the eye. During the menstrual cycle and pregnancy, oestrogen levels are known to fluctuate and have been shown to have effects on various aspects of ocular physiology and function; however, the effects on refractive error and visual acuity remain equivocal. Although participant numbers were low and no statistically significant changes were found, the Plan C (VIMC) study detected subtle self-reported changes during the menstrual cycle, which can be related to the normal fluctuation in oestrogen and progesterone levels. The data tentatively suggest that visual symptoms may be greater around ovulation, reducing towards menstruation. Further studies with larger cohorts are required to fully investigate this preliminary finding.

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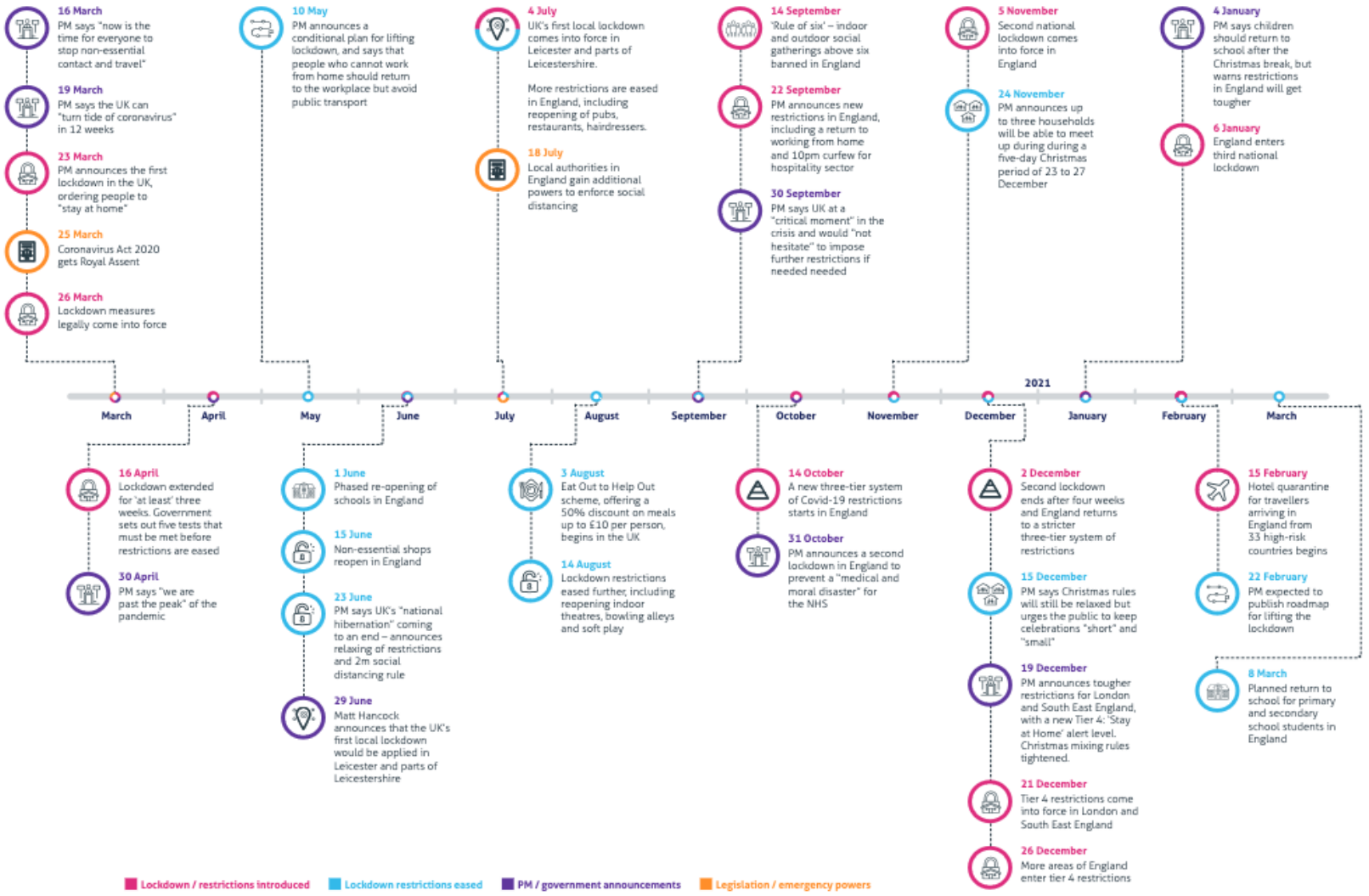
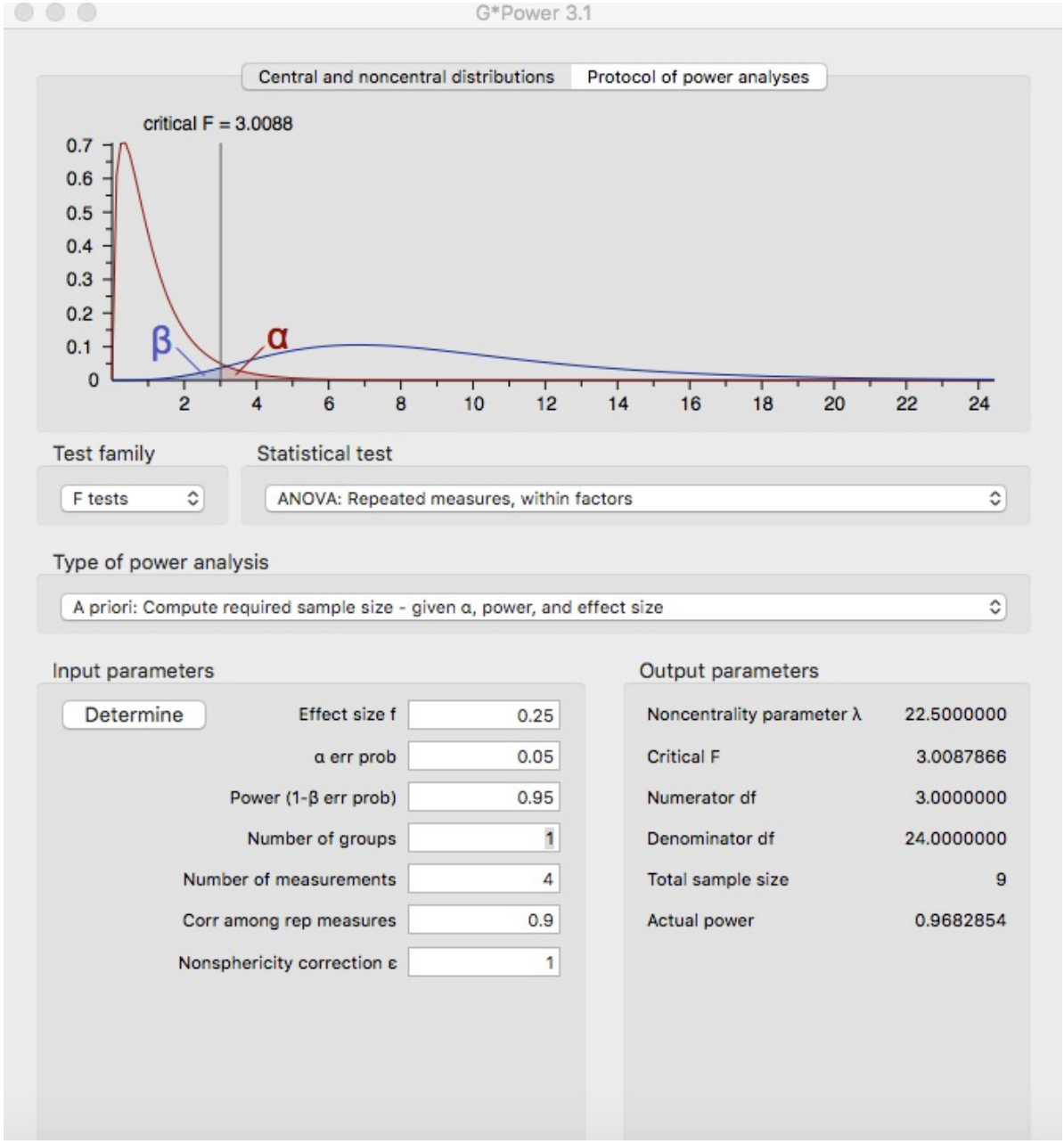
Appendix 1 COVID-19 pandemic timeline March 20 to March 21



Appendix 2 Sample size calculations Plan A VIP



Appendix 3 Plan A – VIP - Participant information Sheet

PARTICIPANT INFORMATION SHEET

Study title: Does refractive error change during pregnancy?

As you are pregnant, you have been invited to participate in a clinical study looking at whether pregnancy affects refractive error. Refractive errors are optical errors of the eye that can cause blurred vision. The most common types of refractive error are short-sightedness (myopia), long-sightedness (hypermetropia) and astigmatism.

The study is being organised by the researcher as part of a doctoral award. The study receives no external funding from any organisation and is being carried out in conjunction with London South Bank University (LSBU) and The Institute of Optometry (IoO). The research is being reviewed by NHS, LSBU and IoO ethics committees.

Before you decide to participate, it is important that you understand why the research is being done and what it will involve. Please read carefully the following information and take the time you need to speak about this with your friends, family, midwife, or GP. If you need further information regarding this study, do not hesitate to contact the study researcher.

This information sheet describes your rights and obligations as a study participant. If you agree to participate in this study, you will be given a signed copy that you should keep. Your participation in the study is entirely voluntary. If you agree to participate, you can decide at any time to stop participating, for any reason, by informing the study researcher. You are not required to justify your withdrawal, and your present or future medical and optometric care will not be affected.

Why is this study being performed?

The purpose of the study is to look at whether refractive error changes during pregnancy. The goal of the research is to help produce guidelines for eyecare practitioners about when it is appropriate to prescribe glasses for pregnant women, as there are currently no guidelines.

How and where will this clinical study be conducted?

This study will be conducted in the Nottinghamshire area. If you agree to participate in the study, the researcher will contact you to discuss the study, to ensure that you are suiTable, and to answer any questions. The study will involve simple non-invasive measurements of your eyes, rather like some of the tests in a normal eye examination (we will not be measuring eye pressure, so there will be no air puff test). We wish to take the measurement three times throughout your pregnancy and once more about three months after the baby is born. This process is very quick and harmless to you and your baby. The researcher will offer you a choice of venues and suiTable times where this can be done. We plan to make the visits coincide with your routine anti-natal checks.

What would taking part involve?

An instrument is used which automatically measures the eye's refractive error. This handheld instrument is often used during routine eye examinations and sight tests.

You will be asked to look at a picture inside the instrument; there is no discomfort and no flashes of light. The measurements take a few seconds and the whole process will take approximately 5 minutes. We would like you to commit to having 4 sets of measurements taken, as this will enable us to see if there are any patterns of change during your pregnancy and just after the birth. We may also measure your visual acuity (letter chart test) and ask you some questions about your medical history and pregnancy.

What are the possible benefits of taking part?

There are no benefits to you from taking part in the study but you will be helping us develop clinical guidelines for community optometrists about when to prescribe glasses for pregnant women.

What are the possible disadvantages and risks of taking part?

Participating in this study is safe and will have no effect on you or your baby. As the study is only taking measurements from your eyes with a simple non-invasive instrument, it is not expected that anything will go wrong. The researcher is an experienced optometrist who uses instruments like this in routine practice. Instruments of this type are used widely in research studies and also in routine eye examinations and sight tests.

Are there any additional expenses for potential participants?

There are no fees or expenses payable for participation in the study.

How will my information be kept confidential?

Your participation in the study will be recorded in a study clinical record. Your personal data collected for this trial will be anonymised using a unique participant identifier number (PIN). The collection and processing of your personal data will be limited to that necessary for contacting you during the research and this will be stored on a password-protected spreadsheet that is only accessed by the researcher. The separate spreadsheets that are used by the research team for analysing the results will not contain personal data and will only contain your PIN and data that are necessary to evaluate the results of this study. That means your name, address or telephone numbers will not be included in this spreadsheet. All data will be collected and processed with care to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Scientific publications will not mention the names of any participants and we will not take any photos of participants. All patient identifiable data will be destroyed 6 months after the results are published.

Who will have access to my data?

Only the research team will have access to your personal data. You have the right to request, through the study researcher, access to your personal data and the right to request rectification of any data that are not correct or complete.

Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

What if something goes wrong?

Should your participation in this study cause any damage to your health, insurance cover has been arranged through London South Bank University. In the event of any problems, or any questions about the research, please contact the research team:

Mr Adam Holliday
Willoughby House
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Southwell
Notts. NG25 0HQ
adam.holliday1@nhs.net
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Professor Bruce Evans
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Plan A – VIP – participant consent form

PARTICIPANT CONSENT FOR

Study title: Does refractive error change during pregnancy

Please tick

1. I confirm that I have read and understand the information sheet dated 18.08.19 (version 5) for the above study and have had the opportunity to ask questions. ☐
2. The researcher has explained the nature and purpose of the research and I believe that I understand what is being proposed. ☐
3. I understand that my personal involvement and my particular data from this study will remain confidential ☐
4. I understand that relevant Sections of the data collected during the study may be included in academic publications and presentations and used to develop educational resources if appropriate. ☐
5. I understand that relevant Sections of data collected during the study, may be looked at by individuals from the research team or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data. ☐
6. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
7. I understand that all my information will be stored securely, on a password protected computer in an environment which is locked when not in use, with only the researcher having access to any identifiable data, and destroyed after the results have been published in accordance with university policy. ☐
8. I hereby fully and freely consent to participate in this study ☐

Name of Patient	Date [DD/MMM/YYYY]	Signature
Name of Person taking consent	Date [DD/MMM/YYYY]	Signature

Appendix 4 LSBU moratorium on F2F data collection

From: Nicola Thomas (via LSBU VLE)

Sent: 17 March 2020 16:54:49 (UTC+00:00) Dublin, Edinburgh, Lisbon, London

To: Holliday, Adam

Subject: ms_CRS_HAN_006_1920: Important information about suspension of face-to-face data collection

ms_CRS_HAN_006_1920 » Forums » Announcements » Important information about suspension of face-to-face data collection

Important information about suspension of face-to-face data collection

by Nicola Thomas - Tuesday, 17 March 2020, 4:40 PM

Please see the email received this afternoon from the university ethics panel - IF THIS AFFECTS YOU, PLEASE DO NOT WORRY AS I WILL WORK WITH YOUR SUPERVISORY TEAM TO SORT OUT THE ISSUES. It would help if you could email me with your specific concerns, with intended date of data collection if appropriate.

Thank you, Nicki

nicola.thomas@lsbu.ac.uk

Dear Doctoral students,

Given current events, the University Ethics Panel (UEP) is placing a moratorium on all face-to-face research data collection for staff, MRes and PhD students, effective immediately. This includes all data collection where the data collector and participant are physically copresent. Data collection which does not involve face-to-face contact is unaffected.

If you are able to move your data collection method online, please make arrangements to do so, and request a significant amendment via haplo, which we will review and in most cases approve as soon as possible. If you cannot alter your methodology, data collection must pause immediately.

We recognise that this is likely to cause significant disruption and concerns around funded research, commercial work and PhD study. However, we must take sensible steps to protect the wellbeing of participants and researchers.

In exceptional circumstances, where there is a prima facie case that the moratorium is (i) especially disruptive, (ii) the work has significant and wide beneficence, (iii) such beneficence cannot be realised at a later date and (iv) the additional risk to participants is very low, UEP is able to review requests for exceptions. However, these will only be granted under very exceptional circumstances. To apply, please email ethics@lsbu.ac.uk; ensure you include your ethics number, school, name and email of PI (and PhD supervisor if appropriate) and a clear explanation why you meet the criteria above. PhD students considering an application for review should discuss this with their supervisor first.

The continuation of this moratorium will be reviewed on an on-going basis.

All queries around this moratorium should be directed to ethics@lsbu.ac.uk

Thanks in advance for your co-operation and understanding, and apologies for any cross posting.

Prof. Daniel Frings, Chair of University Ethics Panel
Professor of Social Psychology
Centre for Addictive Behaviours Research
Room E334
Division of Psychology (School of Applied Sciences)

London South Bank University
EST 1892

Face-to-face data collection during the COVID19 Pandemic

While the COVID19 situation persists, it is likely that research related risk to participants and staff will vary at different times. We are adapting to this by allowing face-to-face data collection to operate at one of three levels, with the level of activity dependent on risk. The level can change according to circumstance and go in either direction. The decision to make a level change is taken by the Academic Board with a recommendation from URC, based on advice from UEP, REI, H&S, Technical services and RBoS. The current levels of research activity can be found on Haplo (https://research.lsbu.ac.uk/), and changes announced by the Provost. These research levels are set by LSBU should not be confused with the UK COVID alert level. This document provides guidance on each level, and the requirements for risk assessment, participant eligibility, participant facing documentation, etc. Please note that at all levels of activity ethics proposals will likely require amendment and these should be lodged and approved via the ethics system on haplo.

LSBU research level 4: Face-to-face data collection moratorium

1. No face-to-face data collection permitted.

LSBU research level 3: Social distancing research only

1. Only face-to-face research in which social distancing can be maintained can be conducted. Research requiring close contact (i.e. in which social distancing is not possible) remains under the moratorium

2. The following should not take part in face-to-face research as participants or data collecting researchers:
   - Clinically extremely vulnerable or clinically vulnerable people
   - People who have travelled abroad in the last 14 days
   - People who are displaying COVID19 symptoms
   - People living in a household where someone else has displayed symptoms in the last 14 days.

   Consideration as to exclusion should be given to BAME status of participants over 55 or with co-morbidities.

3. A risk assessment should be conducted by the research team intending to carry out the work and confirmed with a competent member of staff someone outside the research team (usually, lab technicians) following the guidelines below.

4. No physical contact between individuals (including, for instance, handshakes etc).

5. Unless current advice contradicts this policy, PPE may be excessive outside of clinical and care environments. If face coverings (*note, these differ from respirator masks which are not recommended outside of healthcare settings*) are going to be implemented as a control measure, wearers should be instructed on safe wear, securing, removal, cleaning and hand

From: Nicola Thomas (via LSBU VLE)
Sent: 08 September 2020 10:00:55 (UTC+00:00) Dublin, Edinburgh, Lisbon, London
To: Holliday, Adam
Subject: ms_CRS_HAN_006_1920: Moratorium on face-to-face research lifted

ms_CRS_HAN_006_1920 » Forums » Announcements » Moratorium on face-to-face research lifted

Moratorium on face-to-face research lifted
by Nicola Thomas - Tuesday, 8 September 2020, 9:57 AM

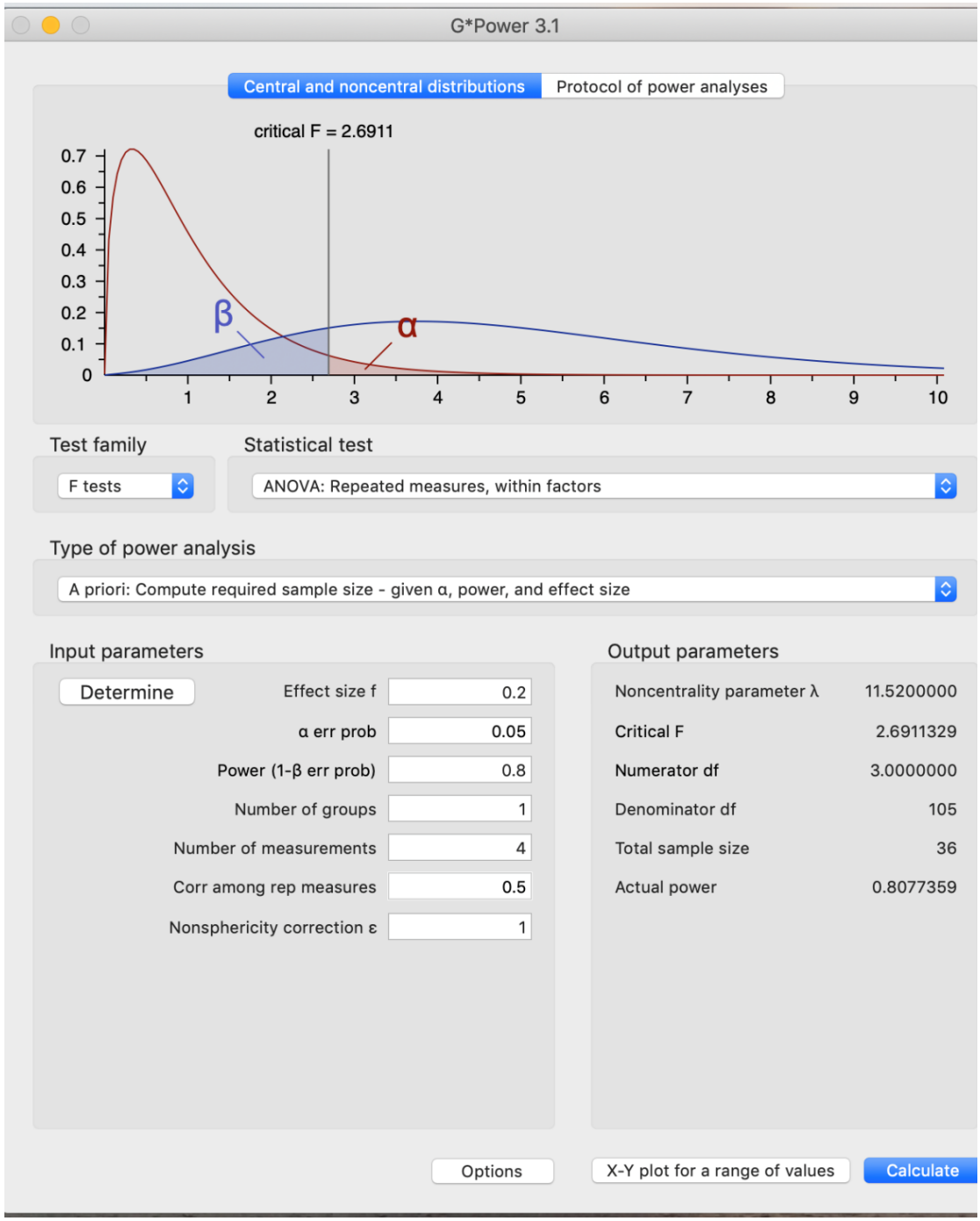
COVID research levels guidance.pdf

I have received the following communication from Dr Adele Stewart-Lord, Chair of the School Ethics Committee

I can now confirm that the moratorium on face-to-face research has been lifted. Please see the information below from the university ethics committee outlining the nec requirements for this type of research to continue / commence. Please note that, at all levels of activity, ethics proposals (including risk assessments) will likely require and these should be lodged and approved via the ethics system on HAPLO before work recommences. Full details are outlined in the attached guidance document.

Kind regards Dr. Adéle Stewart-Lord
Chair HSCSEP
School of Health and Social Care
See this post in context

Appendix 5 Sample size Plan B VIP-online



Appendix 6 Permission to use NEI RQL-42

NEI RQL-42 permission

NATIONAL EYE INSTITUTE

REFRACTIVE ERROR QUALITY OF LIFE INSTRUMENT—42

(NEI RQL-42)

(SELF-ADMINISTERED FORMAT)

August 2001; Version 1.0

RAND hereby grants permission to use the "National Eye Institute Refractive Error Quality of Life Instrument--42 (NEI RQL-42) in accordance with the following conditions which shall be assumed by all to have been agreed to as a consequence of accepting and using this document:

1. Although we do not recommend it, changes to the NEI RQL-42 may be made without the written permission of RAND. However, all such changes shall be clearly identified as having been made by the recipient.
2. The user of this NEI RQL-42 accepts full responsibility, and agrees to hold RAND harmless, for the accuracy of any translations of the NEI RQL-42 into another language and for any errors, omissions, misinterpretations, or consequences thereof.
3. The user of this NEI RQL-42 accepts full responsibility, and agrees to hold RAND harmless, for any consequences resulting from the use of the NEI RQL-42.
4. The user of the NEI RQL-42 will provide a credit line when printing and distributing this document or in publications of results or analyses based on this instrument acknowledging that it was developed at RAND under the sponsorship of the National Eye Institute. The user will also cite the appropriate development papers. Check the RAND web site (www.rand.org/health/surveysnav.html) for updates and recommended citations.
5. No further written permission is needed for use of the NEI RQL-42.

Appendix 7 Permission to use FrACT

bjwe@bruce-evans.co.uk Mon, May 24, 2021, 4:33 PM

to **Michael**, **Dave**, me

Dear Michael

Hope you and the family are well.

I mentioned last year the research study by Adam Holliday, an experienced optometrist and part-time doctorate student supervised by David Edgar and me. Adam is planning to investigate vision during and after pregnancy. He will assess perception of vision (via a questionnaire) and VA (FrACT). The plan is for the study to be completely administered online, and Adam has created a website which can be viewed at https://www.visioninpregnancy.com/

The study needs approval from 3 ethics committees, and we have received approval from the first two and are about to submit to the third. Whilst awaiting review, we thought it would be a good opportunity to invite your comments, if you have time, on the instructions we have written to assist participants in undertaking FrACT. These can be viewed on the website under Tests, 1st Trimester, 1st Vision Test; or directly via https://www.visioninpregnancy.com/vision-test-sample/

Thank you very much if you have time to look at this and no problem at all if you are too busy.

Hope you can make a visit to the UK soon and have that sail!

Prof. Michael Bach <michael.bach@uni-freiburg.de> Tue, May 25,

2021,
6:15 PM

Dear Bruce and All:

> I mentioned last year the research study by Adam Holliday, an experienced optometrist and part-time doctorate student supervised by David Edgar and me. Adam is planning to investigate vision during and after pregnancy. He will assess perception of vision (via a questionnaire) and VA (FrACT). The plan is for the study to be completely administered online, and Adam has created a website which can be viewed at
> https://www.visioninpregnancy.com/

>
> The study needs approval from 3 ethics committees, and we have received approval from the first two and are about to submit to the third. Whilst awaiting review, we thought it would be a good opportunity to invite your comments, if you have time, on the instructions we have written to assist participants in undertaking FrACT. These can be viewed on the website under Tests, 1st Trimester, 1st Vision Test; or directly via https://www.visioninpregnancy.com/vision-test-sample/
Fascinating project! All thumbs here.

Some suggestions:
* Use this URL
https://michaelbach.de/ot/FrACT10/capp2021-05/
which has several advantages: no distracting surroundings, possibly can leave out the fullscreen step, and it will stay constant ("long-term support") even if the generic version updates. Especially no need to re-calibrate with updates.

* In the Settings screenshot, I suggest:
• make the ruler-length textfield _empty_ (using a simple graphics editor).

Otherwise some might think that 130 has to be entered.

• Preset the "Observer distance" to 200 (not 40)

• Untick the "Show operating info…" because that implies a needless dialog

• Consider un-ticking "Show info (top left)" because it's not needed

• Consider ticking Settings>General>Feedback>Reward pictures at end, or is that too childish?

• Consider un-ticking Setting>Acuity>Formatting>decimal. Then there's only »one« number on the result screen.

* Very clear all-in-all. Well phrased how to deal with the obnoxious forced choice situation. Perhaps add: "If it's difficult, it just means you have good vision":).

Good luck! Don’t hesitate to contact me further.

Best, Michael

Appendix 8 Permission to use Sande dry eye questionnaire

Permissions to use the SANDE© with the Massachusetts Eye and Ear Infirmary

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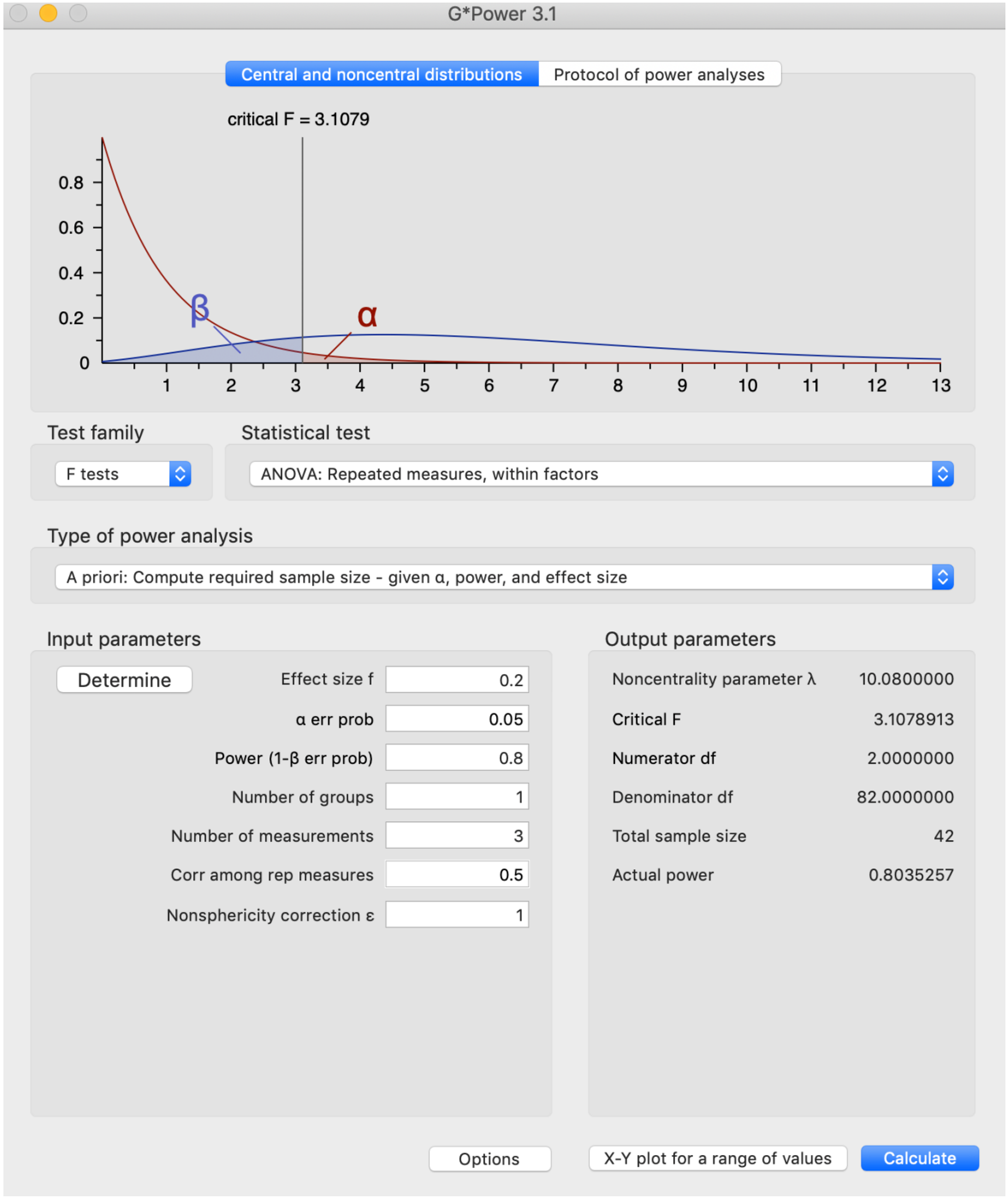
Appendix 9 Sample size Plan C VIMC



Appendix 10 NEI RQL-42 questionnaire

REFRACTIVE ERROR QUALITY OF LIFE INSTRUMENT—42 (NEI RQL-42)

(SELF-ADMINISTERED FORMAT)
August 2001; Version 1.0

INSTRUCTIONS:

The following is a survey with statements about problems that involve your vision or feelings that you have about your vision correction. After each question please choose the response that best describes your situation.

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision correction and how it affects your life, your answers must be as accurate as possible.

We would like you to fill in the answers to these questions by yourself, if possible.

Please answer every question (unless you are asked to skip questions because they don't apply to you).

Answer the questions by marking the box corresponding to your response.

If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.

Please complete the questionnaire before leaving the center and give it to a member of the project staff. Do not take it home.

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

NATIONAL EYE INSTITUTE
42-ITEM REFRACTIVE ERROR QUALITY OF LIFE INSTRUMENT

Date of Completion: ☐☐ ☐☐ ☐☐☐☐

1. If you had perfect vision without glasses, contact lenses, or any other type of vision correction, how different would your life be?

(Mark an X in the one box that best describes your answer.)

No difference 1 ☐
Small difference for the better 2 ☐
Large difference for the better 3 ☐
I have this already 4 ☐

The following questions are about the effect of your vision on your activities.

When you answer the questions, think about the vision correction you normally use for each activity, including glasses, contact lenses, a magnifier, or nothing at all.

2. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, fixing things around the house, sewing, using hand tools, or working with a computer?

(Mark One)
No difficulty at all 1 ☐
A little difficulty 2 ☐
Moderate difficulty 3 ☐
A lot of difficulty 4 ☐
Never try to do these activities because of vision 5 ☐
Never do these activities for other reasons 6 ☐

3. How much difficulty do you have seeing because of changes in the clarity of your vision over the course of theday?

(Mark One)

Don't have changes in the clarity of my vision	1	☐
No difficulty at all	2	☐
A little difficulty	3	☐
Moderate difficulty	4	☐
A lot of difficulty	5	☐

4. How much difficulty do you have judging distances, like walking downstairs or parking a car?

(Mark One)

No difficulty at all	1	☐
A little difficulty	2	☐
Moderate difficulty	3	☐
A lot of difficulty	4	☐

5. How much difficulty do you have seeing things off to the side, like cars coming out of driveways or side streets or people coming out of doorways?

(Mark One)

No difficulty at all	1	☐
A little difficulty	2	☐
Moderate difficulty	3	☐
A lot of difficulty	4	☐

6. How much difficulty do you have getting used to the dark when you move from a lighted area into a dark place, like walking into a dark movie theater?

(Mark One)

No difficulty at all	1	☐
A little difficulty	2	☐
Moderate difficulty	3	☐
A lot of difficulty	4	☐

7. How much difficulty do you have reading ordinary print in newspapers?

(Mark One)

No difficulty at all	1	☐
A little difficulty	2	☐
Moderate difficulty	3	☐
A lot of difficulty	4	☐
Never try to do this because of vision	5	☐

8. How much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms?

(Mark One)

No difficulty at all	1	☐
A little difficulty	2	☐
Moderate difficulty	3	☐
A lot of difficulty	4	☐
Never try to do this because of vision	5	☐

9. How much difficulty do you have driving at night?

(Mark One)

No difficulty at all	1	☐
A little difficulty	2	☐
Moderate difficulty	3	☐
A lot of difficulty	4	☐
Never drive at night because of vision	5	☐
Never do this for other reasons	6	☐

10. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic?

(Mark One)

No difficulty at all	1	☐
A little difficulty	2	☐
Moderate difficulty	3	☐
A lot of difficulty	4	☐
Never drive in these conditions because of vision	5	☐
Never do this for other reasons	6	☐

11. Because of your eyesight, how much difficulty do you have with your daily activities?

(Mark One)

No difficulty at all	1	☐
A little difficulty	2	☐
Moderate difficulty	3	☐
A lot of difficulty	4	☐

12. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like hiking, swimming, aerobics, team sports, or jogging)*(Mark One)*

No difficulty at all	1	☐
A little difficulty	2	☐
Moderate difficulty	3	☐
A lot of difficulty	4	☐
Never try to do these activities because of vision	5	☐
Never do these activities for other reasons	6	☐

QUESTIONS ABOUT YOUR VISION

13. Do you need to wear glasses or bi-focal lenses or use a magnifier when you are reading something brief, like directions, a menu, or a recipe?

(Mark One)

Yes, all of the time	1	☐
Yes, some of the time	2	☐
No	3	☐

14. Do you need to wear glasses or bi-focal lenses or use a magnifier when you are reading something long, like a book, a magazine article, or the newspaper?

(Mark One)

Yes, all of the time	1	☐
Yes, some of the time	2	☐
No	3	☐

15. When driving at night, do you need to wear glasses or contacts?

(Mark One)

Yes, all of the time	1	☐
Yes, some of the time	2	☐
No	3	☐
Don't drive at night because of vision	4	☐
Don't drive at night for other reasons	5	☐

16. At dusk, when it is just starting to get dark, do you need to wear glasses or contacts for driving?

(Mark One)

Yes, all of the time	1	☐
Yes, some of the time	2	☐
No	3	☐
Don't drive at dusk because of vision	4	☐
Don't drive at dusk for other reasons	5	☐

When you answer these questions, think about the vision correction you normally use, including glasses, contact lenses, a magnifier or nothing at all.

17. How often when you are around bright lights at night do you see starbursts or halos that bother you or make it difficult to see?

(Mark One)

All of the time	1	☐
Most of the time	2	☐
Some of the time	3	☐
A little of the time	4	☐
None of the time	5	☐

18. How often do you experience pain or discomfort in and around your eyes (for example, burning, itching, or aching)?

(Mark One)

All of the time	1	☐
Most of the time	2	☐
Some of the time	3	☐
A little of the time	4	☐
None of the time	5	☐

19. How much does dryness in your eyes bother you?

(Mark One)

Don't have dryness	1	☐
Not at all	2	☐
Very little	3	☐
Moderately	4	☐
Quite a bit	5	☐
A lot	6	☐

20. How often are you bothered by changes in the clarity of your vision over the course of the day?

(Mark One)

Never	1	☐
Rarely	2	☐
Occasionally	3	☐
Sometimes	4	☐
All of the time	5	☐

21. How often do you worry about your eyesight or vision?
(Mark One)

Never 1 ☐
Rarely 2 ☐
Occasionally 3 ☐
Sometimes 4 ☐
All of the time 5 ☐

22. How often do you notice or think about your eyesight or vision?
(Mark One)

Never 1 ☐
Rarely 2 ☐
Occasionally 3 ☐
Sometimes 4 ☐
All of the time 5 ☐

YOUR VISION CORRECTION

When you answer these questions, think about the vision correction that you normally use, including glasses, contact lenses, a magnifier, surgery, or nothing at all.

23. At this time, how clear is your vision using the correction you normally use, including glasses, contact lenses, a magnifier, surgery, or nothing at all?

(Mark One)

Perfectly clear 1 ☐
Pretty clear 2 ☐
Somewhat clear 3 ☐
Not clear at all 4 ☐

24. How much pain or discomfort do you have in and around your eyes (for example, burning, itching, or aching)?

(Mark One)

None 1 ☐
Mild 2 ☐
Moderate 3 ☐
Severe 4 ☐
Very severe 5 ☐

25. How often do you have headaches that you think are related to your vision or vision correction?

(Mark One)

Never 1 ☐
Rarely 2 ☐
Occasionally 3 ☐
Sometimes 4 ☐
All of the time 5 ☐

26. How satisfied are you with the glasses, contact lenses, magnifier, or other type of correction (including surgery) you have?

(Mark One)

Completely satisfied 1 ☐
Very satisfied 2 ☐
Somewhat satisfied 3 ☐
Somewhat dissatisfied 4 ☐
Very dissatisfied 5 ☐
Completely dissatisfied 6 ☐

27. In terms of your appearance, how satisfied are you with the glasses, contact lenses, magnifier, or other type of correction (including surgery) you have?

(Mark One)

Completely satisfied 1 ☐
Very satisfied 2 ☐
Somewhat satisfied 3 ☐
Somewhat dissatisfied 4 ☐
Very dissatisfied 5 ☐
Completely dissatisfied 6 ☐

28. If you had perfect vision without glasses, contacts, or any other type of vision correction, how much do you think your life would change?

(Mark One)

No change 1 ☐
Small change for the better 2 ☐
Large change for the better 3 ☐
I have this already 4 ☐

29 In terms of your appearance, is the type of vision correction you have now the best you have ever had?

(Mark One)

Yes 1 ☐
No 2 ☐

30. In terms of your appearance, is there a type of vision correction that is better than what you have now?

(Mark One)

Yes 1 ☐
No 2 ☐

31. How often did you use a type of correction or treatment that was uncomfortable in the last 4 weeks because it made you look better

(Mark One)

All of the time..... 1 ☐
Most of the time..... 2 ☐
Some of the time..... 3 ☐
A little of the time..... 4 ☐
None of the time..... 5 ☐

32. How often did you use a type of correction that did not correct your vision as well as another correction would have in the last 4 weeks because it made you look better?

(Mark One)

All of the time..... 1 ☐
Most of the time..... 2 ☐
Some of the time..... 3 ☐
A little of the time..... 4 ☐
None of the time..... 5 ☐

33. Because of your vision, do you take part less than you would like in active sports or other outdoor activities (like hiking, swimming, aerobics, team sports, or jogging)?

(Mark One)

Yes 1 ☐
No 2 ☐

34. Are there any recreational or sports activities that you don't do because of your eyesight or the type of vision correction you have?

(Mark One)

Yes, many 1 ☐
Yes, a few 2 ☐
No 3 ☐

35. Are there daily activities that you would like to do, but don't do because of your vision or the type of vision correction you have?

(Mark One)
Yes, many 1 ☐
Yes, a few 2 ☐
No 3 ☐

Have you experienced any of the following problems in the last 4 weeks? If yes, how bothersome has it been? Please respond for problems in either or both eyes.

		Mark One	If yes, how bothersome has it been? ***(Mark One)***
36.	Tearing?	**a.** Yes..... 1 ☐ → No ..... 2 ☐	**b.** Very ..... 1 ☐ Somewhat..... 2 ☐ A little..... 3 ☐ Not at all ..... 4 ☐
37.	Distorted vision?	**a.** Yes..... 1 ☐ → No ..... 2 ☐	**b.** Very ..... 1 ☐ Somewhat..... 2 ☐ A little..... 3 ☐ Not at all ..... 4 ☐
38.	Glare?	**a.** Yes..... 1 ☐ → No ..... 2 ☐	**b.** Very ..... 1 ☐ Somewhat..... 2 ☐ A little..... 3 ☐ Not at all ..... 4 ☐

Have you experienced any of the following problems in the last 4 weeks? If yes, how bothersome has it been? Please respond for problems in either or both eyes.

		Mark One	If yes, how bothersome has it been? ***(Mark One)***
39.	Blurry vision with your eyesight or the type of vision correction you use?	**a.** Yes..... 1 ☐ → No ..... 2 ☐	**b.** Very ..... 1 ☐ Somewhat..... 2 ☐ A little..... 3 ☐ Not at all ..... 4 ☐
40.	Trouble seeing?	**a.** Yes..... 1 ☐ → No ..... 2 ☐	**b.** Very ..... 1 ☐ Somewhat..... 2 ☐ A little..... 3 ☐ Not at all ..... 4 ☐
41.	Itching in or around your eyes?	**a.** Yes..... 1 ☐ → No ..... 2 ☐	**b.** Very ..... 1 ☐ Somewhat..... 2 ☐ A little..... 3 ☐ Not at all ..... 4 ☐

Have you experienced any of the following problems in the last 4 weeks? If yes, how bothersome has it been? Please respond for problems in either or both eyes.

		Mark One	If yes, how bothersome has it been? ***(Mark One)***
42.	Soreness or tiredness in your eyes?	**a.** Yes..... 1 ☐ → No.....2 ☐	**b.** Very .....1 ☐ Somewhat.....2 ☐ A little .....3 ☐ Not at all.....4 ☐

Table 1. Scoring Key: Recoding of Items (continued)

ITEM NUMBERS	Original response category	To recoded value of
26, 27	1 ---->	100
	2 ---->	80
	3 ---->	60
	4 ---->	40
	5 ---->	20
	6 ---->	0
29	1 ---->	100
	2 ---->	0
30, 33	1 ---->	0
	2 ---->	100
36b(†), 37b(†), 38b(†), 39b(†), 40b(†), 41b(†), 42b(†)	(b=1) ---->	0
	(b=2) ---->	25
	(b=3) ---->	50
	(b=4) ---->	75
	(a=2 and b=missing) ---->	100

† Items 36b-42b have four response levels, but are expanded to five levels using items 36a-42a, respectively. If a = 2, then b should have been left blank. If there is a discrepancy between a and b, the user needs to decide how to resolve the discrepancy. In many cases, going with the response to b (ignoring a) when there is a discrepancy may be reasonable.

Table 3: Central Tendency, variability (including floor and ceiling effects), and reliability of RQL-42 Scales‡

Measure	Mean	Standard Deviation	% Floor	% Ceiling	Internal Consistency Reliability
Clarity of vision	83.85	18.36	0.1	27.3	0.72
Expectations	43.57	38.22	34.6	22.2	0.90
Near vision	83.94	18.03	0.0	33.5	0.85
Far vision	83.48	15.85	0.0	20.0	0.81
Diurnal fluctuations	74.58	23.13	0.3	30.3	0.73
Activity limitations	85.28	21.92	0.1	53.5	0.76
Glare	76.40	26.41	1.6	40.1	o.75
Symptoms	79.20	16.79	0.0	12.7	0.78
Dependence on correction	42.38	34.75	28.6	15.2	0.74
Worry	61.31	26.04	3.6	10.1	0.80
Suboptimal correction	92.74	17.28	0.8	81.5	0.64
Appearance	79.31	27.00	0.7	31.8	0.66
Satisfaction with correction	74.85	22.55	1.5	28.4	NA

‡ Data is from a cross-sectional study consisting of 665 myopes, 375 hyperopes, and 114 emmetropes recruited from the practices of six medical centers.

NA – Not applicable for a single-item measure.

Table 2: Averaging Items to Generate RQL-42 Scales

Scale	Number of Items	After Recoding Per Table 1, Average the Following Items
Clarity of vision	4	23, 37b, 39b, 40b
Expectations	2	1, 28
Near vision	4	2, 7, 8, 11
Far vision	5	4, 5, 6, 9, 10
Diurnal fluctuations	2	3, 20
Activity limitations	4	12, 33, 34, 35
Glare	2	17, 38b
Symptoms	7	18, 19, 24, 25, 36b, 41b, 42b
Dependence on correction	4	13, 14, 15, 16
Worry	2	21, 22
Suboptimal correction	2	31, 32
Appearance	3	27, 29, 30
Satisfaction with correction	1	26

Appendix 11 FrACT user instructions

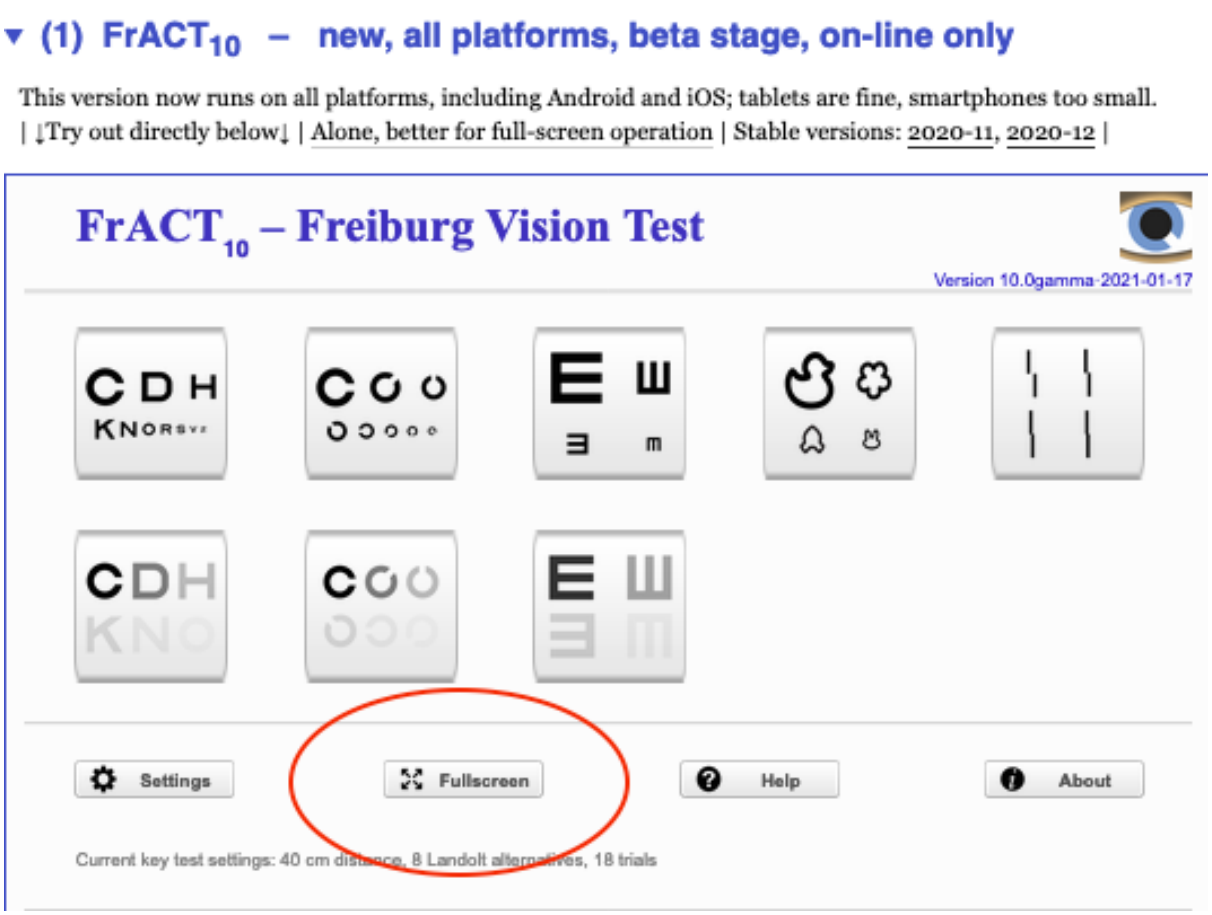
The website details – Freiburg Vision Test

The above link will take you to the test. The test was developed by Professor Michael Bach and we are grateful for his permission to use the test.

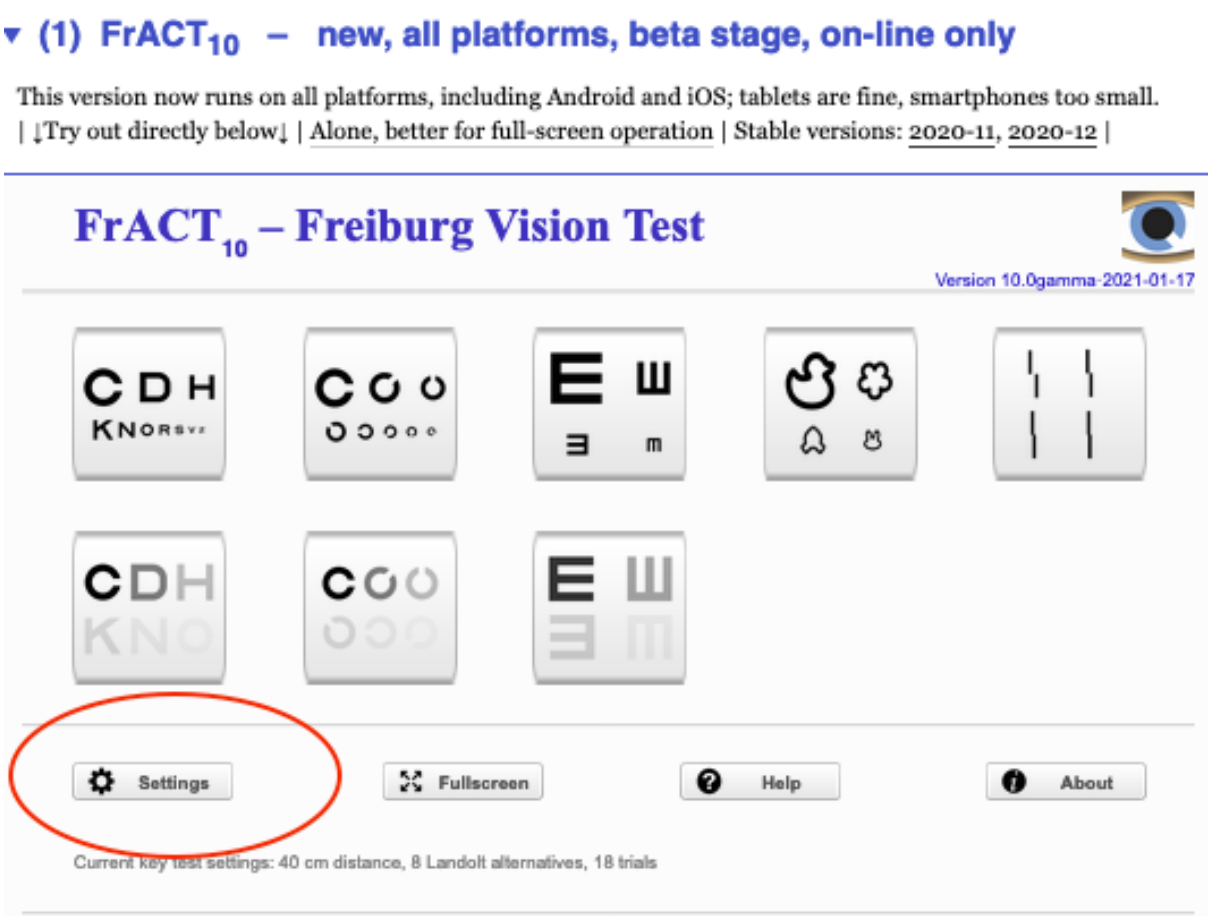
Setting up

You will need someone to help, both when setting up and when doing the test.

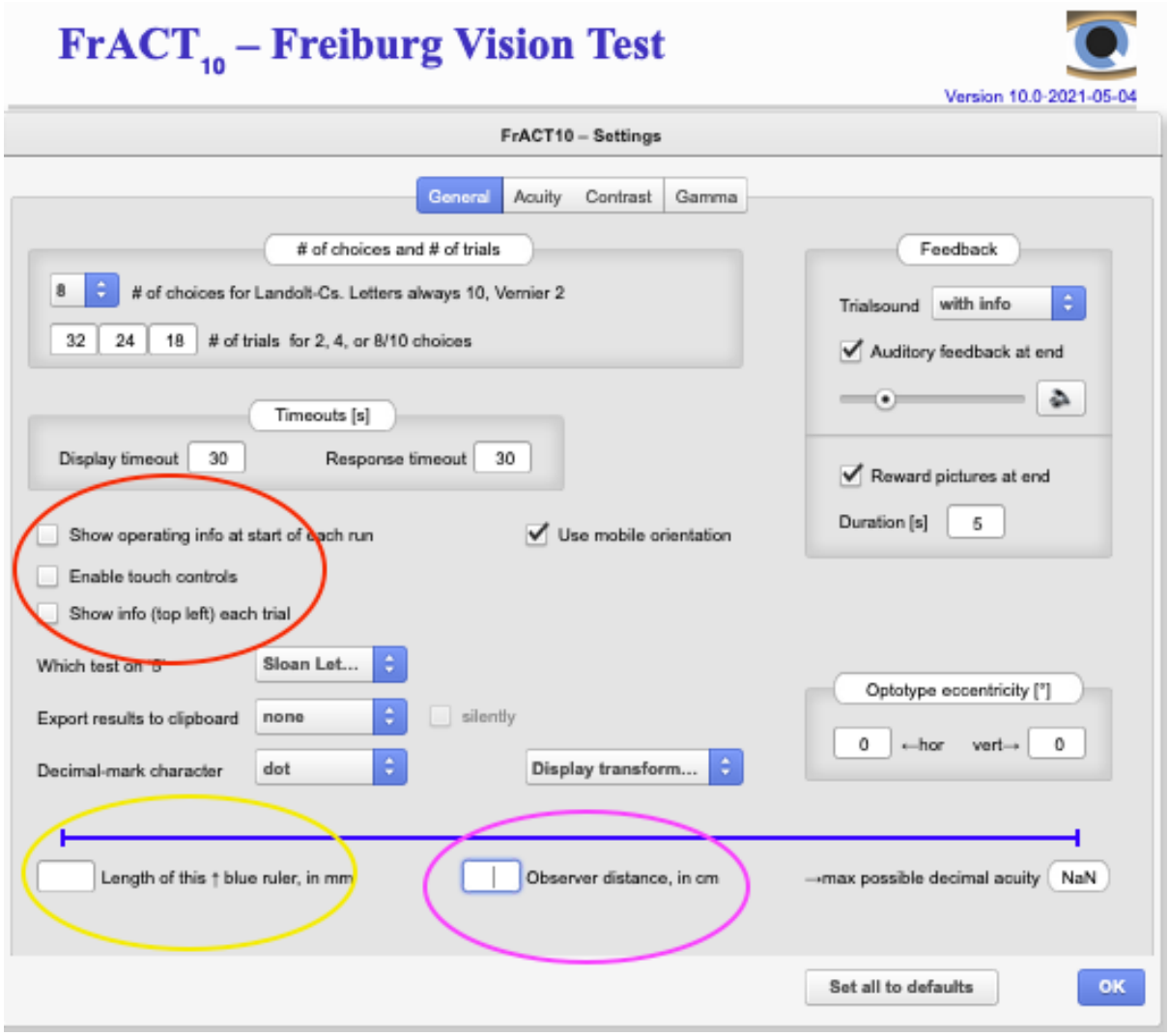
2. At this stage, you need to decide where you will stand or sit (whichever you prefer) when you are doing the test. This should be a minimum of 200 centimetres and a maximum of 600 centimetres from the screen. You don't need to measure the distance accurately yet. If you are going to sit, please now place a chair where you will be sitting for the test. If you are going to stand, please place something on the floor to roughly mark where your feet will be.
3. When you go to the website, below is the page which you will see.



4. Press the button circled above to go to full screen mode.



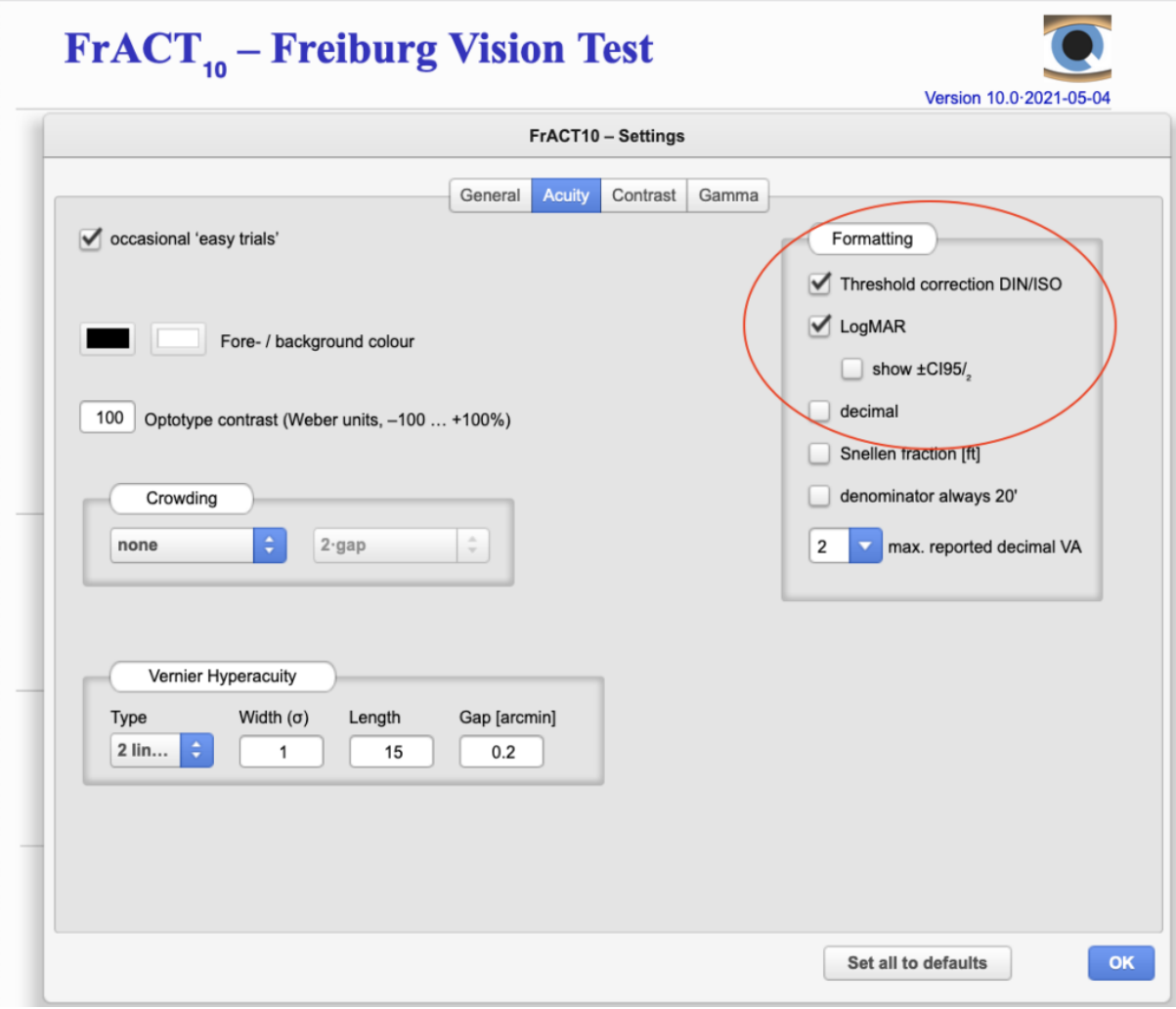
5. Please select the Settings button, circled above. (You might be presented with this message, "All settings were set to their default values". If you see this message then click OK.) This takes you to the page below:



6. Make sure you have the same boxes unticked as those in the red ellipse above.

7. Measure the length of the blue line and enter it in **mm**. (within the yellow ellipse)

8. Now sit on the chair or stand at the distance from the screen you have chosen. With the assistance of your helper measure in centimetres how far away you are sitting or standing from the screen and your helper enters this distance in the box in the pink ellipse. The best way to measure this distance is to use a tape measure from your forehead to the screen. Please stay sitting or standing at this distance until the test is finished.



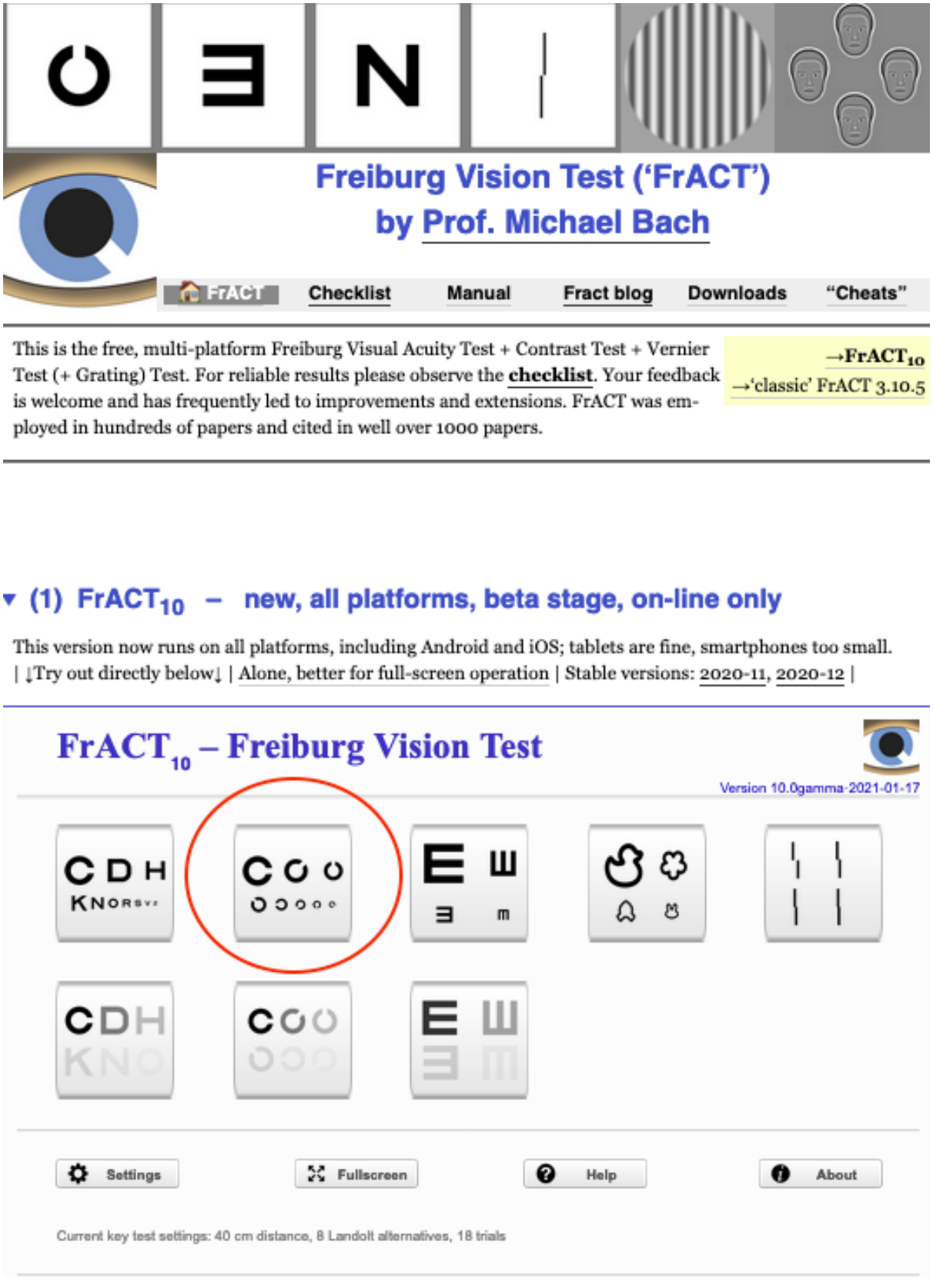
9. On the acuity tab, ensure that only the boxes in the red circle are ticked.

10. After you have done this, your helper should press or click on OK and you will go back to the main screen.

Test procedure

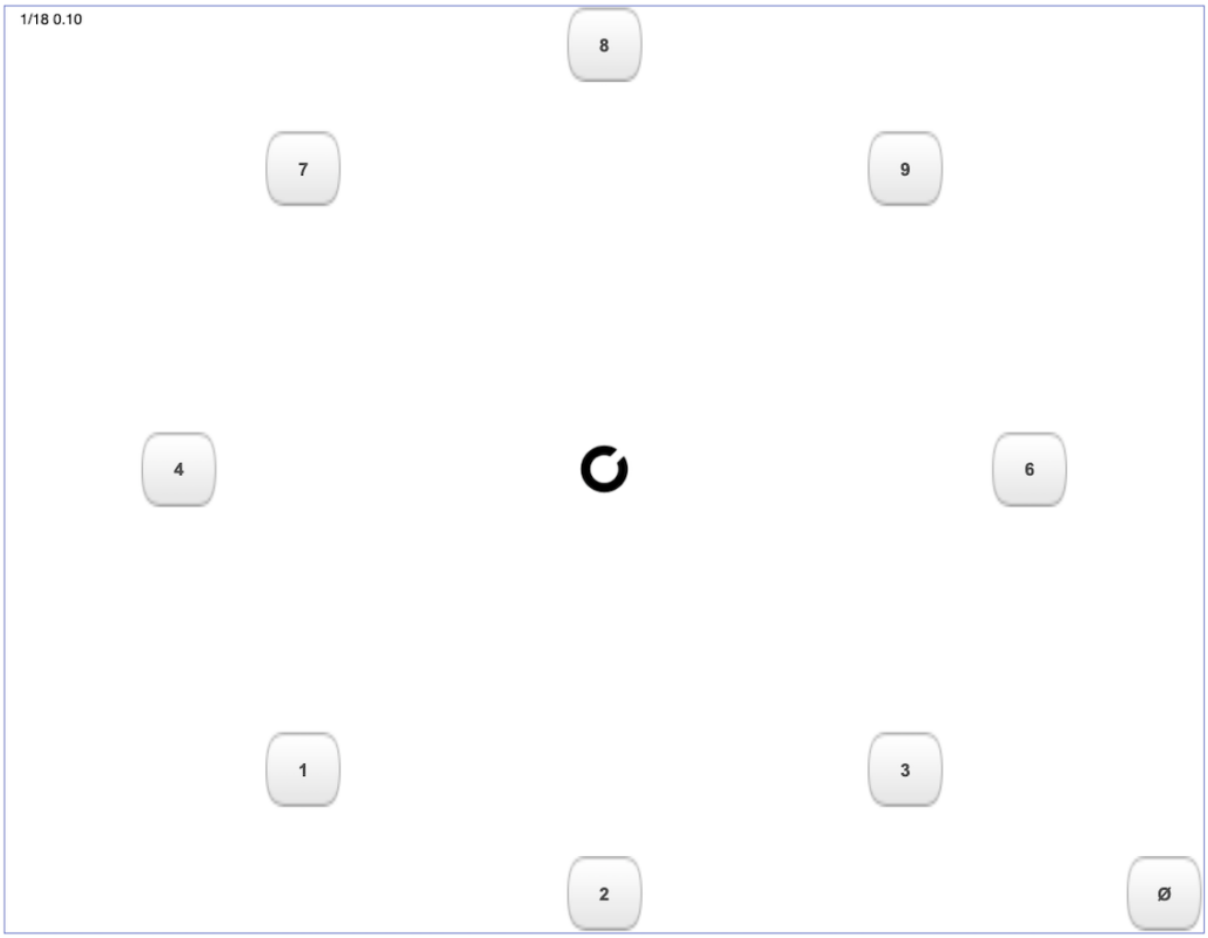
11. Please stay at the correct distance from the screen, as measured and recorded above. Please keep both eyes open and do not close or cover one eye. Please do not “squint” your eyelids together and please do not lean forwards. It is important for your head to stay at the measured distance from the computer screen.

12. When the test starts your helper will need to be near the keyboard to type in your responses using the number keys or to click on your responses using the mouse. To start the test your helper should select the option circled below:



13. The program will present a test window, like that below. Your job from where you are standing or sitting at the measured distance from the screen, is to indicate to your helper at the keyboard where you think the position of the gap in the letter **C** is. So, in the example

below you might indicate by saying “top right”, or two o’clock, or by pointing with your hand. Your helper will then type in the number indicated on screen (in this example, 9), or click on the number.



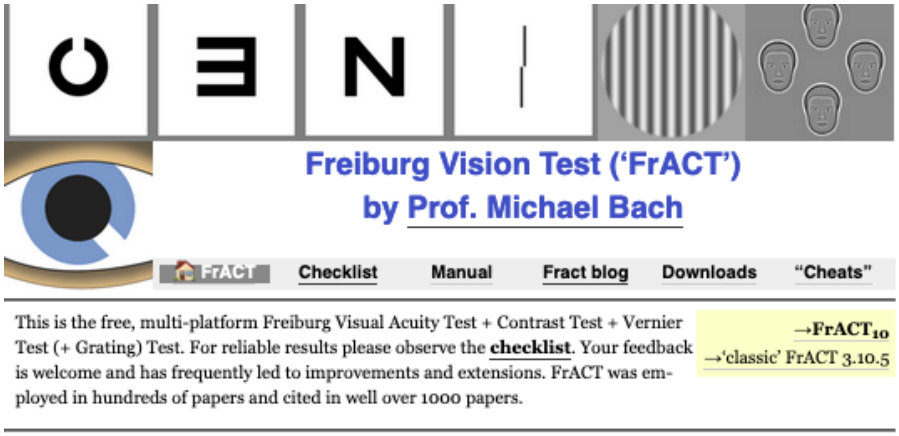
14. As soon as your helper types in the response the program will present another C at a different orientation. You must not move any closer. Again tell your helper where you think the gap in the C is positioned so they can select the appropriate number.

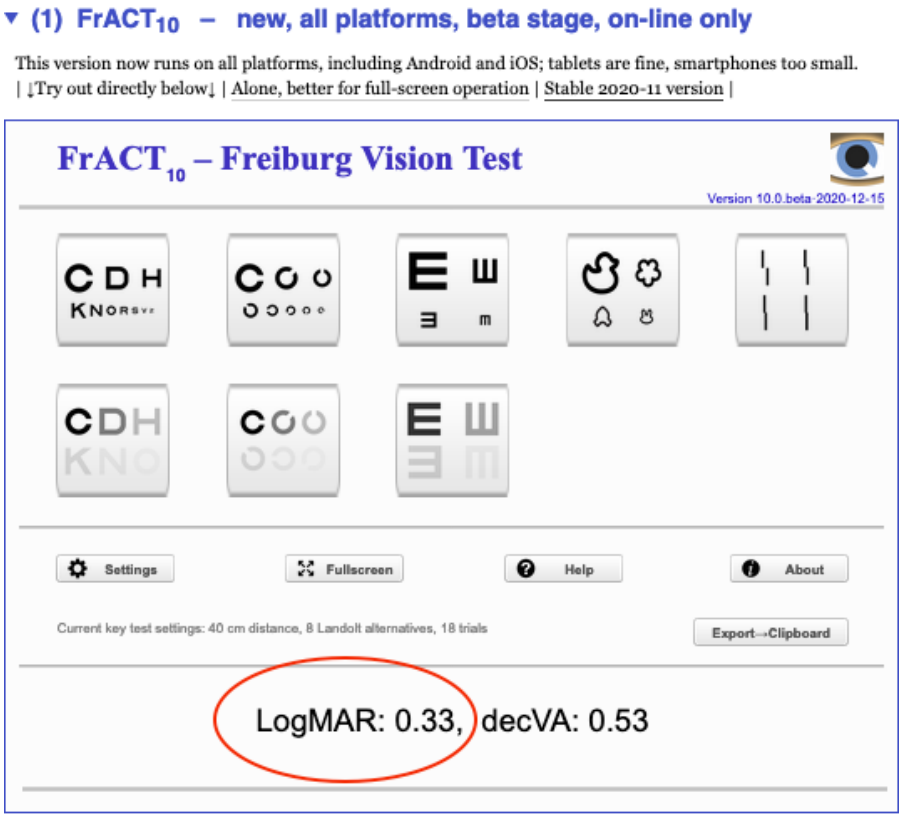
15. Everyone is tempted to “cheat”, by moving closer, but please be careful not to. Similarly, your helper may be tempted to give you a clue, but please avoid this.

16. If you have the sound enabled on your computer, it will play you a pleasant tone when you answer correctly and a less pleasant tone when you answer incorrectly. These sounds are to encourage you. Please continue even if you get several answers wrong, infact some wrong entries are neccessary for the best measurement.

17. As you progress, the program will make the C smaller and occasionally larger. At times, the C will be so small that you will think you are guessing. It is important to continue, even at this point where you are sure you are guessing. The computer takes the probability of guessing into account.

18. When the test is complete, the **C** disappears and you will see a screen like that below:





19. Please write down the first number. In the example above, this is 0.33 as circled above.

Please do not record the second number.

20. Then return to the Vision Test page on the website and enter your results where indicated.

Appendix 12 QR CODES

Plan B - VIP online www.visioninpregnancy.com

Plan C - VIMC online www.28dayvision.com

Appendix 13 IoO Ethics VIP F2F

INSTITUTE OF OPTOMETRY

Application for approval of research studies

(modified October 2019 after REC comments)

Is this project part of a degree? □no □BSc □MSc □MPhil □PhD √. Dr Optom.

A. Brief details of project

1. **Title of project:** Does refractive error change during pregnancy?

2. Principal investigator: Adam Holliday

3. Other investigators involved: Bruce Evans, David Edgar

4. Source of financial support (if any): self-funding

5. Likely duration of project and where will it be carried out (if not all at IoO):

This is an observational longitudinal study and will take approximately 18 months. Data collection from participants will potentially be carried out in a variety of locations including: NHS hospital facilities, GP surgeries, optometry practices and children's Sure Start centres.

6. Abstract outlining proposed research (not more than 200 words - include the aim of the project and the principal methods to be used)

The aim is to determine whether changes in refractive error occur during any trimester of pregnancy or within the first trimester postpartum. This will be achieved by measuring the refractive error of a cohort of pregnant women, using an autorefractor, during each trimester and within the first trimester postpartum; then performing statistical analysis of the results. At each visit corneal curvature will be measured with the autorefractor and LogMAR visual acuity recorded using computerised charts. Optometrists are encouraged to make evidence-based clinical decisions, which extend to prescribing correction for refractive error. However, there is little research evidence to inform decisions about optometric prescribing during pregnancy and these decisions are often based on received wisdom. Office for National Statistics (ONS) data states there were 696,271 live births in 2016. There are no research data to inform how many women attend community optometrists during pregnancy, but on the balance of probabilities many pregnant women are likely attend for eye examinations. Since the stability of refractive error during pregnancy is unknown, this raises questions about the appropriateness of prescribing new spectacles during pregnancy. There are no clinical guidelines for optometrists, nationally or internationally, on management of refractive errors during pregnancy and this research aims to provide guidance.

B. Other institutions

6. Is any other institution (e.g. University, hospital etc.) involved in this work?
(if no proceed to Section C.)

Yes

7. Institution(s) involved:London South Bank University

8. Contact at institution(s):

Professor Nicola Thomas
Professor of Kidney Care, School of Health and Social Care, London South Bank University, 103 Borough Road, London, SE1 0AA
+44 (0)20 7815 8045 e: nicola.thomas@lsbu.ac.uk @nicolamthomas

9. Role of institution:

Awarding institution for Dr Optometry.

10. Has ethical approval been sought/granted at other institution?

Ethical approval will be sought from LSBU and IRAS after the IoO REC

C. Commercial sponsorship

11. Is this study being performed with commercial sponsorship?

No

12. If this project involves participation or sponsorship by the manufacturer or distributor, confirm that indemnification or no fault liability has been obtained:

N/A

NOTE: Where product trials are undertaken at the Institute of Optometry, this fact must NOT be used in any form of advertising, sales promotion or publicity without the express permission of the Research and Ethical Committee. It should be explicitly stated in the agreement with the funding body whether the study will be published in the public domain or not, and this decision should be followed regardless of the outcome. It is recommended that the person(s) responsible for writing the paper(s) is/are also specified in the agreement.

D. Outline of project

Research aims.

To determine whether changes in refractive error occur during any trimester of pregnancy or within the first trimester postpartum. It is hoped that the outcomes of this study will inform the development of professional guidelines for optometrists on prescribing for refractive errors during pregnancy.

Research objectives.

To measure the refractive error, corneal curvature, and visual acuity (VA) of a cohort of pregnant women, during each trimester and also postpartum. Analysis of the data will determine any statistically or clinically significant differences in refractive error. Any significant correlations between refractive error change and changes in VA or corneal curvature will be identified. The outcomes of data analysis will be used to create clinical guidelines for community optometrists on the management of refractive error in pregnancy.

Inclusion and exclusion criteria

Inclusion criteria
Pregnant women, primigravida & multigravida

Exclusion criterion
Individuals who have diabetes
Individuals who have Mucopolysaccharide Diseases
Individuals taking systemic medications known to affect refractive error
Individuals having a multiple pregnancy
Pregnancies facilitated by IVF
Individuals with pre-existing ocular pathology, known to affect refractive error.
RGP (rigid / hard) contact lens wearers

Sample size

A pragmatic approach to sample size for research of this type is to aim for the maximum number of participants that it is feasible to test within the time available. The greater the number of participants, the narrower the confidence intervals following statistical analysis. However, it is also important to determine the minimum number of participants required for a clinically significant change in refractive error to reach statistical significance. To answer this question, a sample size calculation was carried out with G Power version 3.1.9.2.

The number of participants required was 9, using an alpha value of 0.05, beta value of 0.95, effect size of 0.25D and a correlation between measurements of 0.95. Allowing for an attrition rate of 50%, 18 participants are required. As the participant attrition rate is expected to be high and to provide greater internal validity, recruitment will continue for a six-month period from commencement or until a maximum of 80 participants has been reached.

Data collection venues

As no special experimental conditions are required, a choice of convenient locations will be offered, which will include local optometry practices, GP buildings, and locations of parent and toddler groups.

Proposed data to be collected

Refractive error measurements will be taken using a portable non-invasive auto-refractor (Righton Retinomax 3), which takes less than one minute per eye to measure refractive error. The autorefractor will be calibrated at the start of each data collection session. The instrument will measure the refractive error and corneal curvature of each eye. A literature search has found that the instrument has been widely used in research, with no adverse effects. The instrument is also used in optometric practice for measuring refractive error in children and adults, including pregnant women, and does not emit any harmful radiation.

LogMAR Visual acuity will be measured using an electronic acuity chart. This will be calibrated for the testing distance. The illumination of the chart & environment will be measured prior to each data collection session, with a light meter.

Medical information will be obtained from the participants about ocular health, general health, medications being taken and information relating to the pregnancy.

Statistical analysis

Post data collection, both individual and group changes in refractive error will be analysed. It will not be possible to measure participants' baseline pre-pregnancy refractive errors. In the absence of this pre-pregnancy measurement, an average refractive error for each participant across the four trimesters (pregnancy and post-partum) will be calculated using astigmatic decompensation and the expression for total sphero-cylindrical power (Bennett, 1984). This allows the calculation of the 'change in refractive error' from this average value for each participant for each of the four measurement time points (i.e. each trimester and post-partum). Initially, graphs of the change in refractive error across trimesters and post-partum for each participant will be inspected to identify any clinically significant trends and to determine any idiosyncratic effects which might be lost by using averaged data.

Group data of changes in refractive error for each trimester will be tested for normality, and parametric or non-parametric tests used as appropriate. Analysis of variance (or a non-parametric equivalent) will be used to test for any statistically significant differences in the mean change in refractive error across the four measurement time points and post hoc analysis will be used to investigate these.

To remove any violation of independence the measurements from one eye only will be used. However, as measurements from both eyes have been taken, inter-eye correlations will be assessed at each trimester. A high inter eye correlation, in the presence of a change in refractive error would support the argument that this change is due to the pregnancy; poor inter-eye correlation weakens the argument that change is due to pregnancy. Possible correlations between refractive error change and VA or corneal curvature will be assessed using Pearson's or Spearman's test as appropriate. Statistical analysis will be carried out using SPSS.

13. On an additional page, using separate headings, give:

Background to the project that highlights why it is being performed.

A recent literature search on this topic identified 786 articles and from inspection of the titles and abstracts, 37 were suitable for inclusion; other relevant publications were identified from the bibliographies of these papers and included. Much of the research literature is based on studies with small sample sizes, from which generalizations are made. Over the last six decades several investigators have researched the effects of pregnancy on refractive error, using various methodologies, with varyingw outcomes.

The most frequently cited research, by Pizzarello, (2003) showed a statistically significant increase in myopia during pregnancy, continuing postpartum. However, the limitations of this study along with the results need to be considered. The study mentions a sample size of 240 participants, which is frequently cited, but the refractive error of only 13 participants was measured and compared to matched controls. From this cohort of 13 only two participants had a statistically significant change in their refractive error. Erroneously, subsequent authors have cited this as the percentage of pregnant women who are likely to experience changes in their refractive error. The internal validity of this study is questionable owing to sources of error which could influence study outcomes: the participants' existing spectacle prescription was taken as the pre-pregnancy baseline refractive error. Pragmatically this is the most appropriate choice as the pre-conception refractive error would be impossible to obtain; but the spectacle prescription could have been incorrect or outdated before pregnancy. The participants' refractive error was measured by retinoscopy, a clinical technique which can yield varying results even for the most skilled clinician. An alternative method would have been to use an auto-refractor, providing greater accuracy and reliability; these are automated instruments used to provide objective refraction measurements. Statistical analysis of these data used the 'mean spherical error' approach, which is an aggregation of the spherical and astigmatic refractive error and can result in a loss of useful data.

Changes in refractive error within an adult eye are largely determined by: the curvature, thickness and refractive index of the cornea and the crystalline lens. During pregnancy, hormonal levels are known to vary; there are oestrogen, progesterone and androgen receptors in the human cornea, with oestrogen and progesterone receptors predominantly found in females and androgen receptors in males (Gupta *et al*., 2005).

Therefore, hormones have the potential to influence these tissues (Gupta *et al*., 2005, Suzuki, *et al*., 2001, Wickham *et al*., 2000). As the cornea is the major refracting component of the eye, it is reasonable to assume that it could be influenced by hormonal variations during pregnancy, resulting in changes to the refractive error. There have been several studies investigating the effects of hormonal changes (including during pregnancy) on the curvature of the cornea, with equivocal results (Leach *et al*., 1971; Kiely, Carney, Smith, 1983; Manger *et al*., 1987l; Park *et al*., 1992). Atas *et al*., 2014 found statistically significant changes in the anterior corneal curvature and central corneal thickness during pregnancy but with no significant change in refractive error. It seems likely that the increase in corneal curvature was neutralised by other elements which contribute to the refractive status (e.g., refractive index of the cornea, posterior corneal surface or crystalline lens). Sunness & Santos, (1994) reported that the curvature of the crystalline lens increases during pregnancy and this increase could be responsible for the myopic shift found by Pizzarello (2003).

As hormonal levels change at times other than during pregnancy, investigators have considered whether any change in refractive error occurs during the normal menstrual cycle or during hormone replacement therapy. The hormonal change during the menstrual cycle is well documented (Speroff & Vande Wiele, 1971) and the effects of this on refractive error have been investigated by Bergin (1952) and Gong *et al*., (2015), with small refractive changes occurring. Erdem *et al*. (2007) found no statistically significant change occurring with women undergoing hormone replacement therapy (HRT); however, no information on the type of HRT was provided in these studies. Optometrists are encouraged to make evidence-based clinical decisions, which extend to prescribing refractive corrections. However, the literature review indicates a weak evidence-base to inform decisions about optometric prescribing during pregnancy. The Office for National Statistics (ONS) data, states there were 696,271 live births in 2016.

There are no research data to inform how many women attend for sight tests during pregnancy, but many pregnant women must attend for eye examinations. Since the stability

of refractive error during pregnancy is unknown, it raises questions about the appropriateness of prescribing new spectacles during pregnancy. There are no clinical guidelines for optometrists, nationally or internationally, on the management of refractive errors during pregnancy and this research aims to inform guidance.

Detailed description of the experimental protocol describing the methods to be used and outlining why specific methods were chosen.

The study design will use an observational method and take repeated measurements of refractive error, corneal curvature and VA from within a cohort. The methodology of the study will adopt a positivist approach; there will be an objective outcome, based on an objective, rational and logical approach to the research, which is independent from the researcher.

Preliminary enquiries have been made to discover the most feasible approach to take. Contacts and introductions have been made with the community midwifery team within Nottinghamshire, the midwifery team at Sherwood Forest Hospital Trust, the research team within the trust and multiple GP practices within the Nottinghamshire area.

Collaboration with health care professionals is important for this research, to facilitate participant recruitment and in the development of operational plans; these relationships continue to be nurtured and strengthened. Repeated objective measurements of the refractive error of both eyes will be taken using the Righton Retinomax 3 autorefractor, from participants during each trimester and the first trimester postpartum. At each visit corneal curvature will be measured with the autorefractor and LogMAR visual acuity recorded using computerised charts. All participants will be identified through their GP or midwife, during the first trimester. They will be provided with a PIS (attached), with the researcher contacting those who express an interest in participating, to answer any questions and seek consent.

E. Participants

14. Approximate number of participants:

There will be a minimum of 18 and a maximum of 80 participants.

15. Estimated age range of participants:

18 – 40years

16. How will participants be recruited?

Recruitment will be initiated by the participants' GP / midwife.

17. How will participant consent be obtained (it is recommended that you modify the form in the Appendix)?

The recruiter will provide the potential participant with the attached PIS (ver 5). Participants will be consented on a different day, by the researcher to allow time for reflection and consideration.

18. Are your procedures potentially harmful to the participant or are participants likely to feel any pain, distress or discomfort.?

No

19. What steps, if any, will be taken to safeguard the confidentiality of the results of the investigation?

All personal data collected for this trial will be anonymised using a unique participant identifier number (PIN). The collection and processing of personal data will be limited to that necessary for contacting participants during the research and will be stored on a password-protected spreadsheet that is only accessed by the researcher (AH).
Separate spreadsheets will be used by the research team for analysing the results which will not contain personal data. Participants will only be referred to by the PIN in any correspondence between members of the research team. All data will be collected and

processed with care to ensure confidentiality and compliance with applicable data protection laws and regulations. Scientific publications will not mention the names of any participants and we will not take any images of participants. All patient identifiable data will be destroyed 6 months after the results are published.

20. How will participants be kept informed of progress?

This will be done by direct communication with them, by using their preferred method; SMS, email, phone

F. Declaration

I certify that to the best of my knowledge the information given above, together with any supporting material, is complete and correct.

Principal Investigator

Name Adam Holliday Signature [submitted electronically]

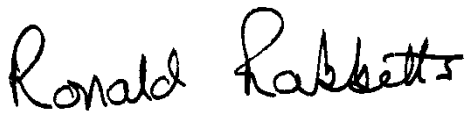
Date 12 October 2019

G. Approval

The above application has/has not been approved by the Departmental Research & Ethical Committee

Chairman of Research & Ethical Committee

Name Ronald Rabbetts Signature



Appendix 14 LSBU ethics VIP F2F

EST 1892 LSBU

Institute of Health and Social Care

Dr. Adéle Stewart-Lord
Chair HSCSEP Ethics Panel
Institute of Health and Social Care
London South Bank University | 103 Borough Road, London, SE1 0AA
t: +44 (0)20 7815 7931|
e: stewara2@lsbu.ac.uk

20 July 2021

Dear Adam Holiday

Ethics approval **ETH2021-0114**

Study title: Vision in pregnancy

Thank you for submitting your proposal for ethical review.

I am writing to inform you that your application has now been approved.

Your project has received ethical approval from the date of this notification until 20 July 2024.

Yours sincerely,

Dr. Adéle Stewart-Lord

Chair HSC School Ethics Panel

Appendix 15 IoO ethics VIP online

Please note: the Amendment is at the end of the

INSTITUTE OF OPTOMETRY

Application for approval of research studies

(the Institute does not have facilities for research involving animal subjects)

please submit a printed (and signed) copy of this form to Bruce Evans at the Institute and also by e-mail to bjwe@bruce-evans.co.uk, from whom it can be obtained

Is this project part of a degree? ☐no ☐BSc ☐MSc ☐MPhil ☐PhD ☒ Dr Optom.

A. Brief details of project

1. **Title of project:** Vision in pregnancy

2. Principal investigator: Adam Holliday

3. Other investigators involved: Bruce Evans, David Edgar

4. Source of financial support (if any): self-funding

5. Likely duration of project and where will it be carried out (if not all at IoO):

This is an observational longitudinal study and will take approximately 10 months. Data collection will be carried out by self-assessment tests via a purpose-built website (details below).

6. Abstract outlining proposed research (not more than 200 words - include the aim of the project and the principal methods to be used)

Reproduction of IRAS draft form Section A6-1: Summary of study:

Little research has been undertaken on the effects of pregnancy on vision and there remains a gap in the evidence base. Although there is some literature on the physiological changes which can occur to the eye during pregnancy, the paucity of literature on possible effects on vision presents a challenge to community optometrists when providing advice and guidance to pregnant women, for example, on whether a change in spectacles should be recommended. The study will recruit a cohort of pregnant women and ask all participants, once in each trimester and once after the birth, to complete an online validated questionnaire about their vision. As an additional optional element, participants will be invited to complete at each stage an online visual acuity test. A widely used validated automated online visual acuity test will be used for those participating in this element of the research. The data will be analysed to investigate any changes in visual symptoms and function during and after pregnancy. The study outcomes will be used to inform community optometrists about the effects of pregnancy on vision.

Reproduction of IRAS draft form Section A6-2: Summary of main issues:

The study uses self-administered data collection tests, avoiding face-to-face encounters. Participation and data entry is via a purpose-built website, www.visioninpregnancy.com. The website is currently locked to general access, but the following login details will give access to ethics committees for review:

Username: adamdemonstration Password: demo-strong-card

The website contains all the relevant participant information and consent documents along with samples of the questionnaire and the visual acuity measurement tool.

Potential participants can be directed to the website, via their healthcare professional (GP, midwives, community optometrists), posters, word of mouth, and social media. The website contains eligibility criteria, both inclusion and exclusion. The front page of the website clearly states that if somebody landed on the website because they have concerns about their eye health, they should seek professional advice.

The study website highlights that, if potential participants have concerns or questions regarding the study, they should contact the chief investigator direct, via email. Prior to progressing with the enrolment process, potential participants are encouraged to review

the sample online questionnaire and visual acuity test, to ensure they understand the study requirements.

Before enrolment, the website provides full information on the study and asks participants to check if they meet the inclusion and exclusion criteria. Potential participants with any questions are invited to contact the chief investigator or not progress further with the enrolment process.

The consent process occurs via the website, removing any potential issues around coercion. After the consent process, participants will set up their own account on the website, providing a secure repository for their personal information. Only the chief investigator will have access to this information.

After enrolment, which takes place in the first trimester, participants are asked to complete the first data collection event. Ninety days later, participants are prompted to complete the next data collection event. This prompt is via email or SMS. On receipt of a prompt there is the option for participants to opt out of the study, either by responding 'opt out' to the email or SMS or through non completion of the data collection.

Participants who do not respond to a reminder and have not opted out will be prompted on two occasions, after which no further contact will be made. This allows participants to withdraw from the study, without having to offer any explanation or continuing as an unwilling participant. If participants have any concerns during the study, they are encouraged to contact the chief investigator.

Participant data will be stored securely on a UK based server.

B. Other institutions

6. Is any other institution (e.g., University, hospital etc.) involved in this work?
(if no proceed to Section C.)
Yes

7. Institution(s) involved:London South Bank University (LSBU)

8. Contact at institution(s):

Professor Bruce Evans

School of Health and Social Care| London South Bank University | 103 Borough Road, London, SE1 0AA

email: evansb3@lsbu.ac.uk

9. Role of institution: sponsor

Awarding institution: LSBU

10. Has ethical approval been sought/granted at other institution?

Ethical approval will be sought from HRA REC and, concurrently with this application, pre-approval is being sought from LSBU.

C. Commercial sponsorship

11. Is this study being performed with commercial sponsorship?

No

12. If this project involves participation or sponsorship by the manufacturer or distributor, confirm that indemnification or no fault liability has been obtained:

No

NOTE: Where product trials are undertaken at the Institute of Optometry, this fact must NOT be used in any form of advertising, sales promotion or publicity without the express permission of the Research and Ethical Committee. It should be explicitly stated in the agreement with the funding body whether the study will be published in the public domain or not, and this decision should be followed regardless of the outcome. It is recommended that the person(s) responsible for writing the paper(s) is/are also specified in the agreement.

D. Outline of project

Research aims.

To determine whether vision changes during pregnancy. All participants will be asked to complete an online validated vision questionnaire, once in each trimester and once after the birth.

As an additional optional element, participants will be invited to complete at each stage an online

visual acuity test. A widely used validated automated online visual acuity test will be used for

those participating in this element of the research. The outcomes will be used to inform community optometrists about the effects of pregnancy on vision, improving patient management.

Research objectives.

Analysis of the data obtained from the validated questionnaire will be used to determine the presence of any statistically significant difference in vision during pregnancy and in the trimester after birth. Analysis of the data obtained from the online visual acuity test will be carried out to determine the presence of any statistically or clinically significant difference in visual acuity during pregnancy and in the trimester after birth.

Inclusion and exclusion criteria

Inclusion criteria

All pregnant women, primigravada & multigravada

Women aged between 18-40 years

Exclusion criteria

Women who are diabetic

Women who have any mucopolysaccharide diseases

Women who are taking systemic medications known to affect vision

Pregnancies facilitated by IVF

Women who have any drug or alcohol addiction

Any vulnerable women (e.g., have safeguarding issues, mental health issues)

Women with pre-existing ocular pathology known to affect vision

Sample size

A simple approach to sample size determination for research of this type is to aim for the maximum number of participants that it is feasible to test, within the time available, as more participants result in narrower confidence intervals. However, it is also important to ask what is the minimum number of participants that would be required for a clinically significant change in visual acuity to reach statistical significance. A sample size calculation was carried out with GPower 3.1.9.2, following the method and recommendations of Prajapati, Dunne and Armstrong, 2010 for repeated measures ANOVA. The calculation was based on an effect size of 0.20, alpha 0.05, power 0.80, and correlation among repeated measures of 0.5. This gives a sample size of 45. As the participant attrition rate is expected to be high, and to provide greater internal validity, recruitment will continue for a six-month period from commencement or until a maximum of 90 participants has been reached, whichever is reached sooner.

Data collection venues

This will be done by self-administered online tests.

Instrument

There are two online instruments. The validated National Eye Institute Refractive Error Quality of Life Instrument 42 (NEI RQL-42) will be completed once during each trimester and once post-partum. This is used with the permission of the Rand organisation. Visual acuity will be measured using the online Freiburg Landolt C vision test, which is used with the permission of Prof. Michael Bach.

Statistical analysis

Post data collection, individual and group data graphs of changes in visual acuity will be produced. Initially, graphs of the change in visual acuity for each participant over time will be inspected to determine whether there are trends which make it appropriate to analyse mean changes. If trends are identified, post hoc analysis will be used to investigate these. The outcomes of the vision questionnaire will be analysed. Statistical analysis will be carried out using SPSS version 26. Data will be tested for normality, followed by mixed model analysis.

13. On an additional page, using separate headings, give:

Background to the project that highlights why it is being performed.

The aim of the study is to explore women's perception of their vision throughout pregnancy using a validated questionnaire. A secondary aim is to determine whether changes to visual acuity occur using an online visual acuity test. Optometrists are encouraged to make evidence-based clinical decisions but as there is little research evidence to inform decision making, around the management of non-pathological visual changes, it is hoped that the outcomes of this research will contribute towards filling this gap.

Detailed description of the experimental protocol describing the methods to be used and outlining why specific methods were chosen.

The study design will use an observational method and take repeated measurements from within a cohort. The study does not involve any face-to-face interactions. It uses online tools which are accessed via a purpose-built website (www.visioninpregnancy.com). The website is locked during the ethics review process, but an evaluation version can be accessed using the following Login details User: adamdemonstration Password: demo-strong-card. The study comprises two components: a validated vision questionnaire and an optional visual acuity measurement test. The website provides written instructions on how to complete the questionnaire and measure visual acuity. Support will be available via the chief investigator. Participants will be asked to complete the questionnaire and measure their binocular visual acuity on four occasions, once each trimester and once more within three months after the birth. Each of these four sessions is expected to take approximately 20 mins (10 mins for the questionnaire and 10 mins for the vision test).

Contacts and introductions have been made with the community midwifery team within Nottinghamshire, the midwifery team at Sherwood Forest Hospital Trust and multiple GP practices within the Nottinghamshire area. Collaboration with health care professionals is important for this research, to facilitate participant recruitment and in the development of operational plans. These relationships continue to be nurtured and strengthened. Information on the study is available on the study website which will be signposted via posters, word of mouth, and social media. Potential participants have the option to contact the researcher with any questions prior to undertaking the consent process on the website.

E. Participants

14. Approximate number of participants:

A sample size calculation indicates a minimum sample size of 45, but in view of anticipated attrition, the goal is to recruit 90 participants.

15. Estimated age range of participants:

Women aged 18 – 40 years.

16. How will participants be recruited?

Recruitment will occur through the study website.

17. How will participant consent be obtained (it is recommended that you modify the form in the Appendix)? Confirm that signatures will be independently witnessed.

The study will be conducted online, and information about the study will be provided to participants via the study website. The website is www.visioninpregnancy.com, and the REC are invited to inspect an evaluation version of the website using the following Login details: Username: adamdemonstration Password: demo-strong-card

The consent process also takes place on the website and therefore cannot be independently witnessed. However, great care is taken on the website to ensure that participants only consent once they have read the information provided on the study and on the consent process.

18. Are your procedures potentially harmful to the participant or are participants likely to feel any pain, distress, or discomfort?

No

19. What steps, if any, will be taken to safeguard the confidentiality of the results of the investigation?

Only the chief investigator will have access to participant identifiable data. All information will be stored on a secure web server based in the UK. Participants will be assigned a reference number and only referred to by this in any correspondence between members of the research team. All computers used are password protected.

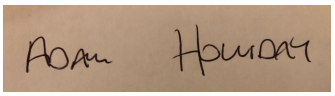
20. How will participants be kept informed of progress?

This will be done by direct communication with them, by using their preferred method: SMS or email

F. Declaration

I certify that to the best of my knowledge the information given above, together with any supporting material, is complete and correct.

Principal Investigator

Name Adam Holliday Signature 

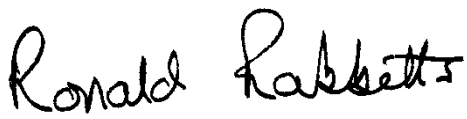
Date 9 Apr 2021

G. Approval

The above application has/has not been approved by the Departmental Research & Ethical Committee

Chairman of Research & Ethical Committee

Name Ronald Rabbetts Signature



Date 23 April 2021

Appendix: DECLARATION OF INFORMED CONSENT

For full participant information and consent form, please see:

www.visioninpregnancy.com

Evaluation version login details User: adamdemonstration Password: demo-strong-card

H. Amendment, 31 January 2022

Introduction

The Amendment is to extend the study to include a cohort of non-pregnant women to assess changes to vision in the menstrual cycle. The Amendment is sought because of difficulties recruiting pregnant women. Initially, many healthcare professionals (midwives, GPs, practice nurses, etc) offered support to the study and gave encouraging feedback about their willingness to assist with publicising the study to potential participants. However, recruitment has proved very challenging and despite considerable attempts to encourage recruitment, the number of people enrolling on the Vision in Pregnancy (VIP) website is still in single figures. Feedback indicates that healthcare practitioners are so over-worked owing to COVID-19 that they do not have time to discuss the research with potential participants. Additionally, owing to concerns about COVID-19 during pregnancy, pregnant women are not keen to volunteer for research. The additional challenge with researching vision during pregnancy is the nine-month timescale for data collection. These factors combine to make it unlikely that enough participants will be able to finish in time for the doctorate to be awarded.

Amendment

During the literature search, it became apparent that pregnancy is not the only area where there is a lack of research on the effect of female sex hormones on visual function. New research would also be valuable to investigate variations in vision during the menstrual cycle.[1]

The team, especially Adam Holliday, have put a great deal of work into researching the literature to identify a suitable validated questionnaire and online visual acuity test for data collection. An excellent website, www.visioninpregnancy.com, has been designed for data collection.

The Amendment is to expand the study to also look at vision in the menstrual cycle (VDMC). We will use the same online validated questionnaire and vision test as approved for the VIP study, hosted on a cloned website that is very similar to the already approved VIP website.

Ethical considerations

The original plan, of pregnant women completing online validated questionnaires about vision and online vision tests was considered to represent a minimal ethical risk. Indeed, our IRAS application for the VIP cohort was returned with the comment "your study does not require REC or HRA Approval". In reaching this decision, the Approvals Specialist cited the low potential of harm to participants. We contacted the HRA Approvals Specialist about the Amendment and were informed that the Amendment also will not need NHS REC or HRA approval.

Differences from original application

We will ask participants about the date of onset of their last menstrual period (LMP), to investigate the extent to which vision varies at different stages of the cycle. Research indicates most women can recall the date of their LMP reasonably well.[2]

Data collection will only take approximately one month for each participant. The differences from the original application are summarised in the table below. For details, please visit the draft website, www.28dayvision.com The website is currently locked to general access, but the following login details will give access to ethics committees for review:

Username: adamdemonstration Password: demo-strong-card

Feature	Vision in Pregnancy (VIP)	Vision during the Menstrual Cycle (VDMC)
Website domain	www.visioninpregnancy.com	www.28dayvision.com
Website heading	Vision in Pregnancy	Vision during the Menstrual Cycle
Homepage text	Thank you for taking the time to visit the site. It has been designed as part of a research project to help find out more about vision in pregnancy.	Thank you for taking the time to visit the site. It has been designed as part of a research project to find out more about vision in the menstrual cycle.
Can I take part?	Inclusion criterion: pregnant in 1st trimester Exclusion criteria: diabetes, mucopolysaccharide disease, Systemic medications affecting vision, Pregnancy facilitated by IVF, Drug or alcohol addiction, Vulnerable adult (safeguarding or mental health issues), Eye disease known to affect vision (excluding refractive error).	**Inclusion criteria:** females 18 years and older, regular (25-35 days and cycles not varying by more than 9 days)[3] menstrual cycle. **Exclusion criteria:** pregnant, breast feeding, taking progestogen contraceptive pill (Micronor, Noriday, Norgeston, Cerazette, Aizea, Cerelle, Feanolla), history of heavy menstrual bleeding, menopause, eye diseases, mucopolysaccharide disease, medications that affect vision, systemic diseases (e.g., diabetes) known to affect vision, drug or alcohol addiction, inability to give informed consent.
Test intervals	Four times: 1st trimester, 2nd trimester, 3rd trimester, after birth	Three times: Day of onset of LMP, day 12 after onset of LMP, day 21 after onset of LMP (for details, see below).[3,4]

Initial questions on enrolment	NEI VQL 42	NEI VQL 42 SANDE (2-question dry eye assessment)[5,6] Age at which menstrual periods started Date of LMP
Additional questions at end of each questionnaire	Have you developed gestational diabetes during this pregnancy? During this pregnancy, have you visited your own optometrist for a routine examination? Did this result in a changed prescription for you? Has the expected birth date changed? Are you having complications with your pregnancy? Is there anything else you would like to add about your vision?	SANDE (2-question dry eye assessment) Is there anything else you would like to add about your vision?
Other differences		None

Details of timing of data collection

The aim is for the online tests to take place when a period starts (baseline), when the oestrogen levels are highest, and when the progesterone levels are highest. For a typical 28-day cycle, oestrogen levels peak at day 12 and progesterone levels peak at day 21.[3,4] For participants whose typical cycle is shorter or longer than 28 days, these timings will be rescaled accordingly. To facilitate this:

After enrolment, the website will ask if the participant remembers the date their last period started.

If participants **cannot** remember the date the last period started, they will be asked to revisit the website on the date their next period starts. On that date, when they login the website will recognise the individual, take the first set of data, and then recontact the participant 12 days and then 21 days later (rescaled if necessary, as above) for the last two data collection events.

if participants **can** remember the date their last period started:

If this date was 12 days or fewer (rescaled if necessary, as above) before the date of enrolment, the participant will be contacted for the first data collection event on day 12, then day 21 and start of next period (these intervals will be rescaled, if necessary, as above); If the date of the start of the LMP was more than 12 days before the date of enrolment (rescaled, if necessary, as above), the participant will be asked to revisit the website on the date their next period starts. On that date, when they login the website will recognise the individual, take the first set of data, and then recontact the participant 12 days and then 21 days later for the last two data collection events. These intervals will be rescaled, as above, if the participant's typical menstrual cycle differs from 28 days.

References

1 Figueiredo, B. G. D., Rezende, M. T. C., Santos, N. A. D. & Andrade, M. J. O. Mapping changes in women's visual functions during the menstrual cycle: narrative review. *Sao Paulo Med J* **139**, 662-674, doi:10.1590/1516-3180.2020.0474.R2.03052021 (2021).

2 Wegienka, G. & Baird, D. D. A comparison of recalled date of last menstrual period with prospectively recorded dates. *J Womens Health (Larchmt)* **14**, 248-252, doi:10.1089/jwh.2005.14.248 (2005).

3 Schmalenberger, K. M. *et al.* How to study the menstrual cycle: Practical tools and recommendations. *Psychoneuroendocrinology* **123**, 104895, doi:10.1016/j.psyneuen.2020.104895 (2021).

4 Thiyagarajan, D. K., Basit, H. & Jeanmonod, R. in *StatPearls* (2022).

5 Amparo, F. & Dana, R. Web-based longitudinal remote assessment of dry eye symptoms. *Ocul Surf* **16**, 249-253, doi:10.1016/j.jtos.2018.01.002 (2018).

6 Schaumberg, D. A. *et al.* Development and validation of a short global dry eye symptom index. *Ocul Surf* **5**, 50-57 (2007).

Appendix 16 LSBU ethics VIP online

Institute of Health and Social Care

Dr. Adéle Stewart-Lord
Chair HSCSEP Ethics Panel
Institute of Health and Social Care
London South Bank University | 103
Borough Road, London, SE1 0AA
t: +44 (0)20 7815 7931|
e: stewara2@lsbu.ac.uk

20 July 2021

Dear Adam Holiday

Ethics approval **ETH2021-0114**

Study title: Vision in pregnancy

Thank you for submitting your proposal for ethical review.

I am writing to inform you that your application has now been approved.

Your project has received ethical approval from the date of this notification until 20 July 2024.

Yours sincerely,

Dr. Adéle Stewart-Lord

Chair HSC School Ethics Panel

Appendix 17 HRA ethics VIP online

From: approvals@hra.nhs.uk <noreply@harp.org.uk>
Sent: 13 July 2021 15:09
To: adam.holliday1@nhs.net; evansb3@lsbu.ac.uk; Edgar, David <D.F.Edgar@city.ac.uk>
Cc: nicola.thomas@lsbu.ac.uk
Subject: IRAS 278054. Application invalid for review

Dear Mr Holliday,
Thank you for submitting the above application.
I am writing to confirm that your application is not valid for the following reasons:
Your study does not require REC nor HRA Approval, therefore we will withdraw it.
Your study does not require REC approval due to the low potential of harm to participants and it does not require HRA Approval because no NHS sites or participants are being recruited.
Hope this helps.
Kind regards

Chris King

Approvals Specialist

Health Research Authority

London | 4000

T. 0207 104 8118

E. approvals@hra.nhs.uk

W. www.hra.nhs.uk

Appendix 18 IoO ethics VIMC

Please note: the Amendment is at the end of the

INSTITUTE OF OPTOMETRY

Application for approval of research studies

(the Institute does not have facilities for research involving animal subjects)

please submit a printed (and signed) copy of this form to Bruce Evans at the Institute and also by e-mail to bjwe@bruce-evans.co.uk*, from whom it can be obtained*

Is this project part of a degree? ☐no ☐BSc ☐MSc ☐MPhil ☐PhD ☒ Dr Optom.

A. Brief details of project

1. **Title of project:** Vision in pregnancy

2. Principal investigator: Adam Holliday

3. Other investigators involved: Bruce Evans, David Edgar

4. Source of financial support (if any): self-funding

5. Likely duration of project and where will it be carried out (if not all at IoO):

This is an observational longitudinal study and will take approximately 10 months. Data collection will be carried out by self-assessment tests via a purpose-built website (details below).

6. Abstract outlining proposed research (not more than 200 words - include the aim of the project and the principal methods to be used)

Reproduction of IRAS draft form Section A6-1: Summary of study:

Little research has been undertaken on the effects of pregnancy on vision and there remains a gap in the evidence base. Although there is some literature on the physiological changes which can occur to the eye during pregnancy, the paucity of literature on possible effects on vision presents a challenge to community optometrists when providing advice and guidance

to pregnant women, for example, on whether a change in spectacles should be recommended. The study will recruit a cohort of pregnant women and ask all participants, once in each trimester and once after the birth, to complete an online validated questionnaire about their vision. As an additional optional element, participants will be invited to complete at each stage an online visual acuity test. A widely used validated automated online visual acuity test will be used for those participating in this element of the research. The data will be analysed to investigate any changes in visual symptoms and function during and after pregnancy. The study outcomes will be used to inform community optometrists about the effects of pregnancy on vision.

Reproduction of IRAS draft form Section A6-2: Summary of main issues:

The study uses self-administered data collection tests, avoiding face-to-face encounters. Participation and data entry is via a purpose-built website, www.visioninpregnancy.com. The website is currently locked to general access, but the following login details will give access to ethics committees for review:

Username: adamdemonstration Password: demo-strong-card

The website contains all the relevant participant information and consent documents along with samples of the questionnaire and the visual acuity measurement tool.

Potential participants can be directed to the website, via their healthcare professional (GP, midwives, community optometrists), posters, word of mouth, and social media. The website contains eligibility criteria, both inclusion and exclusion. The front page of the website clearly states that if somebody landed on the website because they have concerns about their eye health, they should seek professional advice.

The study website highlights that, if potential participants have concerns or questions regarding the study, they should contact the chief investigator direct, via email. Prior to progressing with the enrolment process, potential participants are encouraged to review the sample online questionnaire and visual acuity test, to ensure they understand the study requirements.

Before enrolment, the website provides full information on the study and asks participants to check if they meet the inclusion and exclusion criteria. Potential participants with any questions are invited to contact the chief investigator or not progress further with the enrolment process.

The consent process occurs via the website, removing any potential issues around coercion. After the consent process, participants will set up their own account on the website, providing a secure repository for their personal information. Only the chief investigator will have access to this information.

After enrolment, which takes place in the first trimester, participants are asked to complete the first data collection event. Ninety days later, participants are prompted to complete the next data collection event. This prompt is via email or SMS. On receipt of a prompt there is the option for participants to opt out of the study, either by responding 'opt out' to the email or SMS or through non completion of the data collection.

Participants who do not respond to a reminder and have not opted out will be prompted on two occasions, after which no further contact will be made. This allows participants to withdraw from the study, without having to offer any explanation or continuing as an unwilling participant. If participants have any concerns during the study, they are encouraged to contact the chief investigator.

Participant data will be stored securely on a UK based server.

B. Other institutions

6. Is any other institution (e.g., University, hospital etc.) involved in this work?
   (if no proceed to Section C.)
   Yes

7. Institution(s) involved:London South Bank University (LSBU)

8. Contact at institution(s):
   Professor Bruce Evans

School of Health and Social Care| London South Bank University | 103 Borough Road, London, SE1 0AA
email: evansb3@lsbu.ac.uk

9. Role of institution: sponsor
Awarding institution: LSBU

10. Has ethical approval been sought/granted at other institution?
Ethical approval will be sought from HRA REC and, concurrently with this application, pre-approval is being sought from LSBU.

C. Commercial sponsorship

11. Is this study being performed with commercial sponsorship?
No

12. If this project involves participation or sponsorship by the manufacturer or distributor, confirm that indemnification or no fault liability has been obtained:
No

NOTE: Where product trials are undertaken at the Institute of Optometry, this fact must NOT be used in any form of advertising, sales promotion or publicity without the express permission of the Research and Ethical Committee. It should be explicitly stated in the agreement with the funding body whether the study will be published in the public domain or not, and this decision should be followed regardless of the outcome. It is recommended that the person(s) responsible for writing the paper(s) is/are also specified in the agreement.

D. Outline of project

Research aims.
To determine whether vision changes during pregnancy. All participants will be asked to complete an online validated vision questionnaire, once in each trimester and once after the birth.

As an additional optional element, participants will be invited to complete at each stage an online visual acuity test. A widely used validated automated online visual acuity test will be used for those participating in this element of the research. The outcomes will be used to inform community optometrists about the effects of pregnancy on vision, improving patient management.

Research objectives.

Analysis of the data obtained from the validated questionnaire will be used to determine the presence of any statistically significant difference in vision during pregnancy and in the trimester after birth. Analysis of the data obtained from the online visual acuity test will be carried out to determine the presence of any statistically or clinically significant difference in visual acuity during pregnancy and in the trimester after birth.

Inclusion and exclusion criteria

Inclusion criteria

All pregnant women, primigravada & multigravada

Women aged between 18-40 yrs

Exclusion criteria

Women who are diabetic

Women who have any mucopolysaccharide diseases

Women who are taking systemic medications known to affect vision

Pregnancies facilitated by IVF

Women who have any drug or alcohol addiction

Any vulnerable women (e.g., have safeguarding issues, mental health issues)

Women with pre-existing ocular pathology known to affect vision

Sample size

A simple approach to sample size determination for research of this type is to aim for the maximum number of participants that it is feasible to test, within the time available, as more participants result in narrower confidence intervals. However, it is also important to ask what is the minimum number of participants that would be required for a clinically significant change in visual acuity to reach statistical significance. A sample size calculation was carried out with GPower 3.1.9.2, following the method and recommendations of Prajapati, Dunne and Armstrong, (2010) for repeated measures ANOVA.

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Instrument

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Statistical analysis

Post data collection, individual and group data graphs of changes in visual acuity will be produced. Initially, graphs of the change in visual acuity for each participant over time will be inspected to determine whether there are trends which make it appropriate to analyse mean changes. If trends are identified, post hoc analysis will be used to investigate these. The outcomes of the vision questionnaire will be analysed. Statistical analysis will be carried out using SPSS version 26. Data will be tested for normality, followed by mixed model analysis.

13. On an additional page, using separate headings, give:

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Detailed description of the experimental protocol describing the methods to be used and outlining why specific methods were chosen.

The study design will use an observational method and take repeated measurements from within a cohort. The study does not involve any face-to-face interactions. It uses online tools which are accessed via a purpose-built website (www.visioninpregnancy.com). The website is locked during the ethics review process, but an evaluation version can be accessed using the following Login details User: adamdemonstration Password: demo-strong-card. The study comprises two components: a validated vision questionnaire and an optional visual acuity measurement test. The website provides written instructions on how to complete the questionnaire and measure visual acuity. Support will be available via the chief investigator. Participants will be asked to complete the questionnaire and measure their binocular visual acuity on four occasions, once each trimester and once more within three months after the birth. Each of these four sessions is expected to take approximately 20 mins (10 mins for the questionnaire and 10 mins for the vision test).

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18. Are your procedures potentially harmful to the participant or are participants likely to feel any pain, distress, or discomfort?

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19. What steps, if any, will be taken to safeguard the confidentiality of the results of the investigation?

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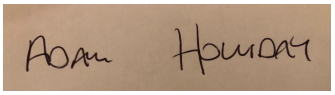
F. Declaration

I certify that to the best of my knowledge the information given above, together with any supporting material, is complete and correct.

Principal Investigator

Name Adam Holliday Signature 

Date 9 Apr 2021

G. Approval

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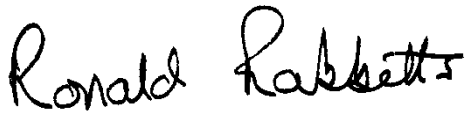
Chairman of Research & Ethical Committee

Name Ronald Rabbetts Signature



Date 23 April 2021

Appendix: DECLARATION OF INFORMED CONSENT

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Ethical considerations

The original plan, of pregnant women completing online validated questionnaires about vision and online vision tests was considered to represent a minimal ethical risk. Indeed, our IRAS application for the VIP cohort was returned with the comment "your study does not require REC or HRA Approval". In reaching this decision, the Approvals Specialist cited the low potential of harm to participants. We contacted the HRA Approvals Specialist about the Amendment and were informed that the Amendment also will not need NHS REC or HRA approval.

Differences from original application

We will ask participants about the date of onset of their last menstrual period (LMP), to investigate the extent to which vision varies at different stages of the cycle. Research indicates most women can recall the date of their LMP reasonably well.[2]

Data collection will only take approximately one month for each participant. The differences from the original application are summarised in the table below. For details, please visit the draft website, www.28dayvision.com The website is currently locked to general access, but the following login details will give access to ethics committees for review:

Username: adamdemonstration Password: demo-strong-card

Feature	Vision in Pregnancy (VIP)	Vision during the Menstrual Cycle (VDMC)
Website domain	www.visioninpregnancy.com	www.28dayvision.com
Website heading	Vision in Pregnancy	Vision during the Menstrual Cycle
Homepage text	Thank you for taking the time to visit the site. It has been designed as part of a research project to help find out more about vision in pregnancy.	Thank you for taking the time to visit the site. It has been designed as part of a research project to find out more about vision in the menstrual cycle.
Can I take part?	Inclusion criterion: pregnant in 1st trimester Exclusion criteria: diabetes, mucopolysaccharide disease, Systemic medications affecting vision, Pregnancy facilitated by IVF, Drug or alcohol addiction, Vulnerable adult (safeguarding or mental health issues), Eye disease known to affect vision (excluding refractive error).	**Inclusion criteria:** females 18 years and older, regular (25-35 days and cycles not varying by more than 9 days)[3] menstrual cycle. **Exclusion criteria:** pregnant, breast feeding, taking progestogen contraceptive pill (Micronor, Noriday, Norgeston, Cerazette, Aizea, Cerelle, Feanolla), history of heavy menstrual bleeding, menopause, eye diseases, mucopolysaccharide disease, medications that affect vision, systemic diseases (e.g., diabetes) known to affect vision, drug or alcohol addiction, inability to give informed consent.
Test intervals	Four times: 1st trimester, 2nd trimester, 3rd trimester, after birth	Three times: Day of onset of LMP, day 12 after onset of LMP, day 21 after onset of LMP (for details, see below).[3,4]
Initial questions on enrolment	NEI VQL 42	NEI VQL 42 SANDE (2-question dry eye assessment)[5,6] Age at which menstrual periods started Date of LMP
Additional questions at end of each questionnaire	Have you developed gestational diabetes during this pregnancy? During this pregnancy, have you visited your own optometrist for a routine examination? Did this result in a changed prescription for you? Has the expected birth date changed? Are you having complications with your pregnancy?	SANDE (2-question dry eye assessment) Is there anything else you would like to add about your vision?

	Is there anything else you would like to add about your vision?	
Other differences		None

Details of timing of data collection

The aim is for the online tests to take place when a period starts (baseline), when the oestrogen levels are highest, and when the progesterone levels are highest. For a typical 28-day cycle, oestrogen levels peak at day 12 and progesterone levels peak at day 21.[3,4] For participants whose typical cycle is shorter or longer than 28 days, these timings will be rescaled accordingly. To facilitate this:

After enrolment, the website will ask if the participant remembers the date their last period started.

If participants **cannot** remember the date the last period started, they will be asked to revisit the website on the date their next period starts. On that date, when they login the website will recognise the individual, take the first set of data, and then recontact the participant 12 days and then 21 days later (rescaled if necessary, as above) for the last two data collection events.

if participants **can** remember the date their last period started:

If this date was 12 days or fewer (rescaled if necessary, as above) before the date of enrolment, the participant will be contacted for the first data collection event on day 12, then day 21 and start of next period (these intervals will be rescaled, if necessary, as above);
If the date of the start of the LMP was more than 12 days before the date of enrolment (rescaled, if necessary, as above), the participant will be asked to revisit the website on the date their next period starts. On that date, when they login the website will recognise the individual, take the first set of data, and then recontact the participant 12 days and then 21 days later for the last two data collection events. These intervals will be rescaled, as above, if the participant's typical menstrual cycle differs from 28 days.

References

1 Figueiredo, B. G. D., Rezende, M. T. C., Santos, N. A. D. & Andrade, M. J. O. Mapping changes in women's visual functions during the menstrual cycle: narrative review. *Sao Paulo Med J* **139**, 662-674, doi:10.1590/1516-3180.2020.0474.R2.03052021 (2021).

2 Wegienka, G. & Baird, D. D. A comparison of recalled date of last menstrual period with prospectively recorded dates. *J Womens Health (Larchmt)* **14**, 248-252, doi:10.1089/jwh.2005.14.248 (2005).

3 Schmalenberger, K. M. *et al.* How to study the menstrual cycle: Practical tools and recommendations. *Psychoneuroendocrinology* **123**, 104895, doi:10.1016/j.psyneuen.2020.104895 (2021).

4 Thiyagarajan, D. K., Basit, H. & Jeanmonod, R. in *StatPearls* (2022).

5 Amparo, F. & Dana, R. Web-based longitudinal remote assessment of dry eye symptoms. *Ocul Surf* **16**, 249-253, doi:10.1016/j.jtos.2018.01.002 (2018).

6 Schaumberg, D. A. *et al.* Development and validation of a short global dry eye symptom index. *Ocul Surf* **5**, 50-57 (2007).

Appendix 19 LSBU ethics VIMC

From: LSBU PGR Manager <do-not-reply-pgr-manager@lsbu.ac.uk>

Sent: 24 March 2022 13:45

To: Bruce Evans <bjwe@bruce-evans.co.uk>

Subject: (CC) Decision - Ethics ETH2021-0197: Mr Adam Holliday (Medium risk)

London South Bank University

Dear Bruce

The following notification has been sent to **Adam Holliday** and is copied below for your information.

–

Dear Adam

Application ID: ETH2021-0197

Project title: Doctoral Research Project

Lead researcher: Mr Adam Holliday

Thank you for submitting your proposal for ethical review.

I am writing to inform you that your application has been approved.

Your project has received ethical approval from the date of this notification until 24th March 2026.

Yours

Dr. Adéle Stewart-Lord

Appendix 20 VIP F2F GP feedback

DR LIZ JORDAN
MB ChB, MRCGP, DFFP

DR ANDREW HOPWOOD
MB BChir, MA, MRCGP

2A HANLEY AVENUE BRAMCOTE NOTTINGHAM NG9 3HF

TEL: 0115 9224960
FAX: 0115 9229050
www.bramcotesurgery.co.uk

17th January 2017

Dear Adam,

I am sorry for the delay. You wrote to me on 17/11/16 asking for information about healthcare provision in pregnancy.

Most patients who find themselves pregnant inform their GP (but not all). They are then referred (they can self-refer) to the midwife service. Midwives take care of all routine care, investigations and liaise with the hospital. GPs main role is the management of acute problems in pregnancy. The midwives for our patients are based at the Stapleford Care Centre.

I hope this is useful.

Best wishes,

Andrew.

Dr Andrew Hopwood
GMC: 4584030

Appendix 21 VIP online midwifery poster

We're looking to recruit women early in their pregnancy, for an online study looking into the effects of pregnancy on vision

Please take a look at www.visioninpregnancy.com

Appendix 22 Points of contact

Point of contact	Date	Method	No of contacts	No of practices (ONS data 2020)	No of potential reviewers	Feedback / comments
Midwifery team leader SFHT	08.2.19 - 22.09.21	Email	1			Email threads through this time period (19 emails with lead and her team members & still ongoing)
Senior lecturer in Midwifery	13.7.21	Email	1			Awaiting response
NCT	10.08.21	Email	1			No response
Mums net	10.08.21	Email	1			Response 12.08.21
Social influencer	11.08.21		1		38,000.00	Age appropriate demographic (monthly posts)
Local optical support group (LOCSU)	28.07.21	Email mail shot	75	7,000	15,000 optometrists 6,000 dispensing opticians	4.8.21 sent out to all local optical committee

Point of contact	Date	Method	No of contacts	No of practices (ONS data 2020)	No of potential reviewers	Feedback / comments
Local medical committee (LMC)	30.07.21	Mail shot	89	7,613	27,985 registered GPs	Feedback attached
Royal college of midwives (RCM)	30.07.21	Email enquiry form				No response
Local pharmacy committee (LPC)	1.08.21	Email mail shot	52	11,826	42,900 registered pharmacists	Feedback attached
LMC highlands	03.08.21	Email	1			Provided other points of contacts
Interim Divisional General Manager - Raigmore Hospital	04.8.21	Email	1			advised to contact Darren Thomas
Head of head obstetrics - Raigmore Hospital	04.8.21	Email	1			20.08.21 response asking to call

Point of contact	Date	Method	No of contacts	No of practices (ONS data 2020)	No of potential reviewers	Feedback / comments
Neighbourhood social forums	10.08.21	Social media post	1		unknown	ongoing
Head of head obstectrics - Raigmore Hospital	26.08.21	Email	1			Conversation to be arranged
Head of head obstectrics - Raigmore Hospital	26.08.21	Phone conversation				leaflets sent 15th Sept
Optometry today	02.09.21	Online publication	1			www.aop.org.uk/ot/science-and-vision/research/2021/09/02/new-research-examines-vision-during-pregnancy
RCM - Regional officer midwifery - seen in optometry practice Nottingham	24.09.17	Face to face meeting	1			

Point of contact	Date	Method	No of contacts	No of practices (ONS data 2020)	No of potential reviewers	Feedback / comments
RCM - Director professional midwifery	24.09.17	Email	1			awaiting response
RCM	26.11.21	Email	1			Question around abstract / elevator pitch

Appendix 23 Abstract for RCM

This study is looking at the effects of pregnancy on vision and specifically the effects on refractive error and visual acuity. The pathological effects of pregnancy on the eye are well understood but there is little research literature on how pregnancy affects refractive error and visual acuity. It is known that oestrogen receptors are present in the eye which leads to the possibility that the varying levels of circulating hormones during pregnancy could have physiologically effects on the eye. Refractive errors are managed by community optometrists, who are primary eyecare professionals. There is no exact data on the prevalence or type of refractive error in women of child bearing age, but using available data it can be approximated that half of expectant mothers will have some form of refractive error and it is likely that a proportion of these women will visit their community optometrist at some point in their pregnancy. The outcome of the study is to help community optometrists and other health professionals, provide evidence-based advice to expectant mothers and to contribute to the wider knowledge base. The study aims to recruit a cohort of pregnant women, who are in their first trimester, to measure their visual experiences using a validated vision questionnaire combined with a self-administered online visual acuity test. This will be done in each trimester and post partum. To support the study, a purpose-built website was designed to manage each aspect, with participants able to enrol, consent and complete the questionnaire and visual acuity test from the website. To enable a sufficient sample size, the study will run for 18 months with results published 6 months after. The study has received full ethical approval and the research team would welcome your support to promote this study to your patients and are happy to answer any questions. (20.11.21

Appendix 24 Feedback from professional groups

Shropshire LMC	Pregnant woman are mostly seen by the community midwives who work for MPFT https://www.mpft.nhs.uk/ You may wish to contact them or even the Midwifery department at the University Hospital of North Midlands https://www.uhnm.nhs.uk/ Community midwives office: 01782 672181
Highland LMC	I have spoken to Iain about this. He said you would be better off to contact the NHS Highland Midwives. You could try contacting caron.cruickshank@nhs.scot
North wales LMC	Thank you for your email, however this is not something we are able to help with and you may be better going through your Local Optical Committee on info.cambs.loc@gmail.com
Avon LMC	Many thanks for your email and for sharing news of your research project. Unfortunately we are not able to share these types of email as we are often asked to do so. This is because we aim to try and reduce email traffic to GPs and their practices wherever possible.
Lincolnshire LPC	I am afraid we are unable to help you directly with your study. However, I can offer some advice. This kind of research would likely need to go through an NHS panel as it involves patient contact. Many large multiple groups of pharmacies would also need to approve promotion of any study of this kind through a governance panel. Can I suggest you perhaps contact your local NHS CCG who may be able to assist you. There should be easily found online. You could also consider approaching one or two large multiple (for example Boots, Lloyds or local groups to you) to see if they will be able to help you.
Gloucester LMC	Thank you for your e mail. I'm not optimistic about recruiting GPs to a study for no payment when everyone is under such pressure. I have, however, forwarded to our county's training hub in case it is of interest to any research minded GPs.

Appendix 25 VIMC poster

Vision during the menstrual cycle study

We're looking to recruit women for a short online study looking into the effects of the menstrual cycle on vison.

You'll be asked to complete an online questionnaire 3 times and optionally measure your own vision – all online and should take less than 10 mins

You can find out more by going to the website and going to the information page or emailing the researcher.

www.28dayvision.com

adam@28dayvision.com

SCAN ME

Appendix 26 Recruitment email script

Dear All

I would be very grateful if you would consider taking part in an online study which is exploring women's vision during their menstrual cycle. It's hoped that the findings will provide more information about changes in vision which some women experience.

Everything is completed from a purpose designed website and you'll be directed to the consent and sign-up page and asked for some basic details.

The study involves completing an online questionnaire and optional measurement of your own vision 3 times during your menstrual cycle. The three points in the menstrual cycle are determined by the information you provide at the initial sign-up stage and you'll be automatically notified when it's time to complete the next questionnaire.

Your help would be really appreciated, and we'll send you details of the study findings, when completed.

The website address www.28dayvision.com

Thank you
Adam Holliday (Prof doc student)

Appendix 27 Study websites

https://www.visioninpregnancy.com

Login details

User name: adamdemonstration

Password: demo-strong-card

https://www.28dayvision.com

Login details

User name: Helford

Password 20Ferry22&