Development and validation of technologically advanced patient-reported outcome measures for retinal diseases

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ABSTRACT

Background: Patient-reported outcome (PRO) instruments are increasingly being considered as an essential outcome measure in clinical practice, research, audits, and trials involving patients. The existing PRO instruments are static (paper-and-pencil based), limited in their item-content, not comprehensive enough to measure quality of life (QoL), outdated and poorly targeted to the study population. Therefore, a project (The Eye-tem Bank) is designed to develop and validate technologically advanced PRO instruments which can precisely measure comprehensive ophthalmic QoL. The Eye-tem Bank project aims to create measures of QoL for all eye diseases. Recognising that different diseases require different questions; the ideal situation is to have disease-specific item banks for all diseases. However, this is not practical. So, the major diseases have individual item banks, then less common diseases need to be split or "grouped" together. But to be valid, these groups must be of diseases with similar QoL impacts. In terms of retinal diseases item banks have been developed for age related macular degeneration, diabetic retinopathy, and retinal detachment. However, it is unclear whether the remaining retinal diseases (other vitreoretinal diseases) can be "grouped" together, or whether they need to be split into multiple separate item banks. The remaining retinal diseases include hereditary degenerations, vascular occlusion and other rare vascular diseases and vitreoretinopathies. Theoretically there would be a need to separate these further. The aim of this thesis is to create item banking for other VR diseases and determine how many item banks the remaining diseases will be split into. This will be done by looking at qualitative data on items and analyses of proposed item banks.

Methods: The other vitreoretinal diseases were grouped into hereditary retinal diseases and acquired retinal diseases. A mixed method design was used. Qualitative methods were used to explore the impact of retinal diseases on the QoL of 79 people. A systematic multi-stage process of item extraction and item revision was used to develop separate item banks for hereditary retinal diseases and acquired retinal diseases. However, only the hereditary retinal diseases item banks were pilot tested on 233 participants. Rasch analysis was used to assess the psychometric properties of the hereditary retinal diseases item banks.

Results: People with hereditary retinal diseases and acquired retinal diseases had

different QoL issues. A total of 1,217 items were extracted from 17 PRO instruments, 4 qualitative studies and 79 interviews. After 3 sessions of binning and winnowing, items were reduced to a minimally representative set (n = 411) across nine QoL domains namely; activity limitation, emotional, social, mobility, convenience, symptoms, health concerns, economic and coping. The hereditary retinal diseases and the acquired retinal diseases items banks had 345 and 254 items respectively. Psychometric assessment of the hereditary retinal diseases item banks demonstrated that five domains (mobility, economic, social, convenience and visual symptoms) required minor modifications and three domains (activity limitation, health concerns, and emotional) demonstrated multidimensionality requiring substantial modifications that resulted in the development of 5 new domains.

Conclusion: This research project resulted in the development of comprehensive and psychometrically valid items banks for hereditary retinal diseases that will enable clinicians and researchers to explore the impact of hereditary retinal diseases on QoL.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed: Mallika Prem Senthil

Date: 4 September 2017

TERMS AND DEFINITION

Abbreviation	Explanation
QoL	Quality of life
AMD	Age related macular degeneration
ARD	Acquired retinal diseases
CAT	Computer adaptive testing
CSR	Central serous retinopathy
DR	Diabetic retinopathy
ERM	Epiretinal membrane
FDA	Food and Drug administration
HRD	Hereditary retinal diseases
MH	Macular hole
PRO	Patient-reported outcome
RD	Retinal detachment
RP	Retinitis pigmentosa
WHO	World Health Organisation
DIF	Differential item functioning
IQR	Interquartile range
AL	Activity limitation
CV	Convenience
EM	Emotional well-being
HC	Health concerns
MB	Mobility
SC	Social participation
SY	Symptoms
EC	Economic
CP	Coping
GL	Glaucoma
PSI	Person separation index
PSR	Person separation reliability
PCA	Principal component analysis
MNSQ	Mean square standardised residuals
BEVA	Best eye visual acuity
LID	Local item dependency
SPSS	Statistical package for social sciences
PEM	Positive emotional
NEM	Negative emotional
CI	Confidence interval
LOA	Limits of agreement
GHC	General health concerns
CDP	Concerns about the disease progression
VSF	Visual symptoms frequency

VSS	Visual symptoms severity
VSB	Visual symptoms bothersome
OCF	Ocular comfort symptoms frequency
OCS	Ocular comfort symptoms severity
OCB	Ocular comfort symptoms bothersome
GSF	General symptoms frequency
GSS	General symptoms severity
GSB	General symptoms bothersome

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STATEMENT REGARDING INCLUSION OF CO-AUTHORED PAPERS

Chapter two, three and six of this thesis has been published in peer reviewed journals on which I was the first author. In both the papers I was responsible for the design of the work, data collection, data analysis, and interpretation, drafting the manuscript, revision of the manuscript, proof editing and final approval of manuscript prior to publication. The contribution of the co-authors in these publications are outlined below.

Chapter 2 – Impact of retinal diseases on quality of life: a literature review

Mallika Prem Senthil, Jyoti Khadka, Konrad Pesudovs. Assessment of patient-reported outcomes in retinal diseases: a systematic review. *Survey of Ophthalmology*, 2017; 62(4): 546-582.

The contribution of both the co-authors is as follows:

J Khadka – Conception and design of the work, data analysis and interpretation, revision of the manuscript and final approval of the manuscript prior to publication.

K Pesudovs - Conception and design of the work, data interpretation, critical revision of the manuscript and final approval of the manuscript prior to publication.

Chapter 3 - Listening to the voices of people with retinal diseases: a qualitative study

1. **Mallika Prem Senthil**, Jyoti Khadka, Konrad Pesudovs. Seeing through their eyes: lived experiences of people with retinitis pigmentosa. *Eye*, 2017; 31(5):741-748.

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2. **Mallika Prem Senthil,** Jyoti Khadka, Jagjit Singh Gilhotra, Sumu Simon, Konrad Pesudovs. Exploring the quality of life issues in people with retinal diseases: a qualitative study. *Journal of patient-reported outcomes*, 2017; 1: 15. https://doi.org/10.1186/s41687-017-0023-4

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3. **Mallika Prem Senthil**, Jyoti Khadka, Jagjit Singh Gilhotra, Sumu Simon, Eva K Fenwick, Ecosse Lamoureux, Konrad Pesudovs. Understanding the quality of life impacts in people with retinal vein occlusion: a qualitative inquiry. *Clinical and Experimental Optometry,* 2018. [Under review]

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Chapter 4 - Development of comprehensive item banks for other vitreoretinal diseases

Mallika Prem Senthil, Jyoti Khadka, Jagjit Singh Gilhotra, Sumu Simon, Eva K Fenwick, Ecosse Lamoureux , Konrad Pesudovs. Identification and evaluation of items for vitreoretinal disease quality of life item banks. *International Ophthalmology*. [Under review]

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Chapter 5 - Assessment of the psychometric properties of the hereditary retinal diseases quality of life item banks

Mallika Prem Senthil, Jyoti Khadka, John De Roach, Tina Lamey, Terri McLaren, Isabella Campbell, Eva K Fenwick, Ecosse L Lamoureux, Konrad Pesudovs. Development and Psychometric Assessment of Novel Item banks for hereditary retinal diseases. *Optometry and Vision Science.* [Revision]

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Chapter 6 – Does coping form a measurable construct?

Mallika Prem Senthil, Jyoti Khadka, John De Roach, Tina Lamey, Terri McLaren, Isabella Campbell, Eva K Fenwick, Ecosse L Lamoureux, Konrad Pesudovs. Developing an item bank to measure the coping strategies of people with hereditary retinal diseases. *Graefe's Clinical and Experimental Ophthalmology,* 2018. [Accepted]

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CHAPTER 1 INTRODUCTION

1.1 Purpose of the study

Quality of life (QoL) is severely compromised in people with retinal diseases.(1-4)The QoL impact in retinal diseases has been assessed using all sorts of patient-reported outcome (PRO) instruments which includes non-disease-specific, generic and disease-specific. The non-disease-specific PRO instruments (instruments developed for ocular diseases other than retinal diseases) are the most commonly used PRO instruments in retinal diseases.(5) The National Eye Institute Visual Function Questionnaire (NEI-VFQ) is one of the most commonly used non-disease-specific PRO instrument in ophthalmic research.(6, 7) It has been used to assess the QoL impacts of many retinal diseases including age related macular degeneration (AMD),(8, 9) diabetic retinopathy (DR),(10, 11) retinal detachment (RD), (12, 13) vascular occlusions, (14, 15) degenerations/dystrophies,(16, 17) macular hole (MH), (18, 19) epiretinal membrane (ERM), (20, 21) central serous retinopathy (CSR) (22, 23) and the others. Compared to other PRO instruments the NEI-VFQ looks more comprehensive purporting to measure six QoL domains, but it suffers from inadequate number of items across domains except activity limitation and socio-emotional well-being.(24) Moreover, assessment of the measurement properties of the instrument by modern psychometric methods reveals that its subscales were not psychometrically sound and do not produce valid measure of the construct they claim to measure; as an overall measure, it is flawed and multidimensional.(25)

Generic PRO instruments (instruments developed for non-ocular conditions) such as the Short Form Health Survey (SF-36) and the Hospital Anxiety and Depression Scale are often used with other non-disease-specific PRO instruments to assess the psychological well-being of patients with retinal diseases.(26-28) The problem using generic PRO instruments in retinal diseases is that the items (questions) are not relevant to retinal diseases and hence they are not sensitive to measure the QoL impact.(5) Both non-disease-specific and generic instruments fail to demonstrate benefits of treatments and interventions.(29-33) The instruments that could accurately measure QoL impact and be sensitive to treatments are disease-specific instruments, however, there are only a few retina-specific PRO instruments available and most of these were developed for AMD.(34-39) Most of the currently existing

retina-specific PRO instruments have undergone only basic validation and their content coverage is limited to measuring only a few QoL domains (mostly activity limitation). Hence, there is a need to develop comprehensive and psychometrically sound PRO instruments that can measure all aspects of QoL in retinal diseases. Currently available PRO instruments in Ophthalmology and Optometry are the traditionally described first generation and the Rasch analysed legacy instruments.(40, 41) These instruments are paper-and-pencil based and are difficult to administer, not amenable for changes, outdated, limited in their content, poorly targeted to study population and do not provide a comprehensive measurement of QoL.(42, 43) Hence, there is a need to develop instruments that can measure QoL in a holistic method which is dynamic, accurate and precise.(44) This can be achieved by developing item banks implemented via computerised adaptive testing (CAT).(43)The CAT is technologically advanced compared to the first generation and the Rasch analysed legacy instruments in the sense that large number of items can be pooled across different domains of QoL and can be administered to the patient (item administration based on the patient's previous question) in a precise and accurate method. Because the item administration is predominantly based on the patient's response to an initial question it is faster and needs very few items for testing the QoL domains. Therefore, a project (The Eye-tem Bank) has been designed to develop and validate technologically advanced PRO instruments which can precisely measure comprehensive ophthalmic QoL.

1.2 Eye-tem Bank project

The Eye-tem Bank project is a National Health and Medical Research Council funded international project (principal investigators, Konrad Pesudovs and Ecosse Lamoureux) that started in 2012. It is a collaborative study carried out at Flinders University as a lead organisation and three centres: The Queen Elizabeth Hospital, South Australia, The Royal Adelaide Hospital, South Australia, and the Royal Victorian Eye and Ear Hospital, Victoria to develop item banks for all eye diseases across all populations worldwide (Figure 1.1). As different eye diseases cause different QoL impacts, the ideal situation is to develop individual item banks for all the eye diseases. However, it is not practical to develop item banks for all the individual eye diseases as it is expensive and time consuming. The best way forward would be to develop individual item banks for major eye diseases and to group the less common eye diseases based on similar QoL impacts and develop group-specific item banks.

Item banks are being developed for nine disease groups (Figure 1.1). A systematic four-phase method was employed to develop each disease-specific modules: Phase I Content identification (items from pre-existing PRO instruments and disease-specific patient focus groups/semi-structured interviews); Phase II: Pilot testing the initial set of items for item calibration using Rasch analysis; Phase III Validation of the module-specific CAT system) and Phase IV: Evaluating Ophthalmic QoL (Figure 1.2).

Phase I data collection for cataract, RD and uveitis modules are ongoing. Phase II has been completed for DR and glaucoma. As far as retinal diseases are concerened item banks are being developed for major blinding diseases such as AMD, DR and RD.(3, 45) However, it is unclear whether the remaining retinal diseases (other vitreoretinal diseases) need separate item banks, or whether they can be “grouped” together. The remaining retinal diseases include hereditary degenerations, vascular occlusions, MH, CSR, ERM and other vitreoretinopathies. The aim of this thesis was to create item banking for other vitreoretinal diseases and determine how many banks the remaining diseases will be split into. This will be done by looking at qualitative data of the items and analyses of proposed item banks.

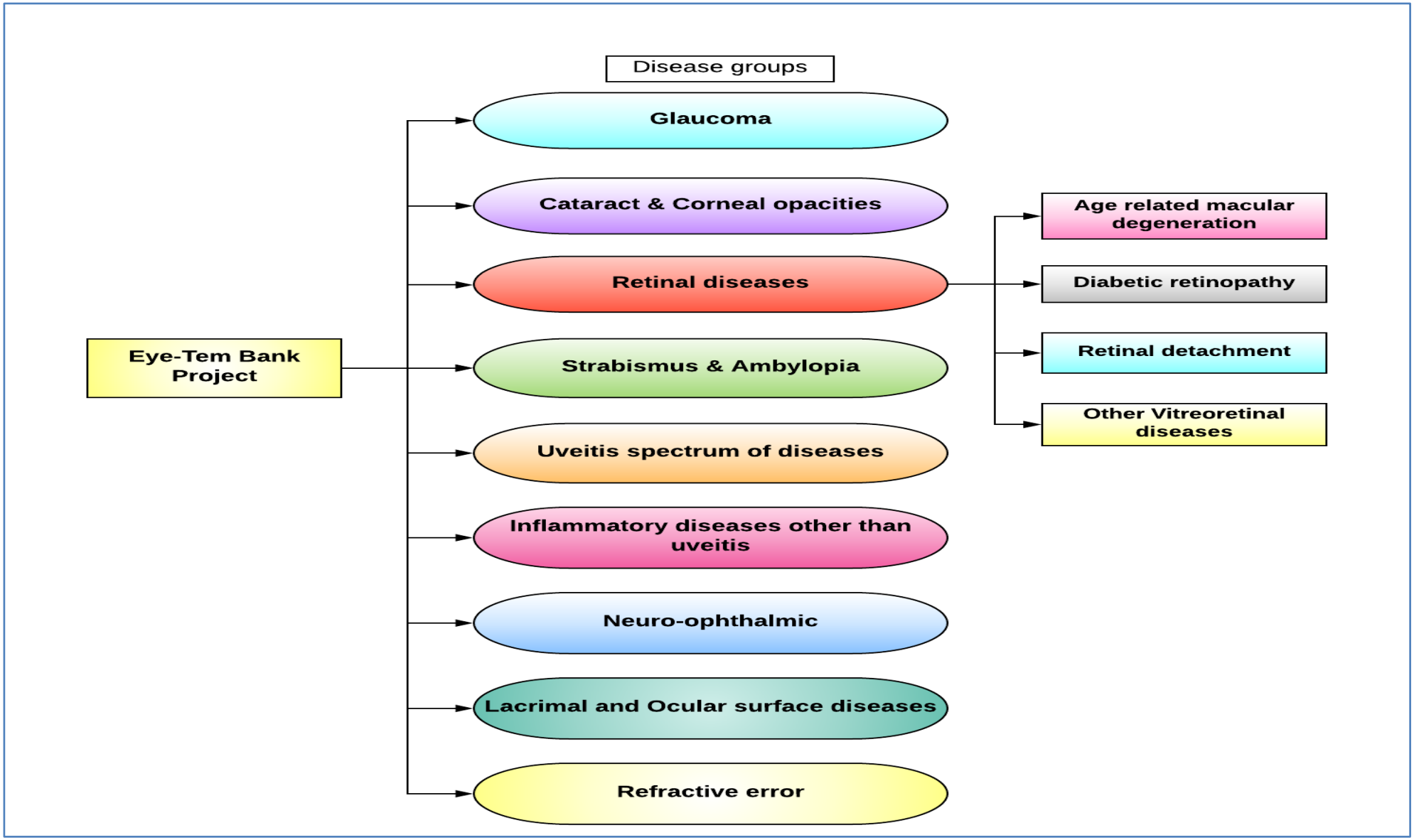

Figure 1.1 Scope of Eye-Tem Bank project in perspective of the PhD research project described in the thesis

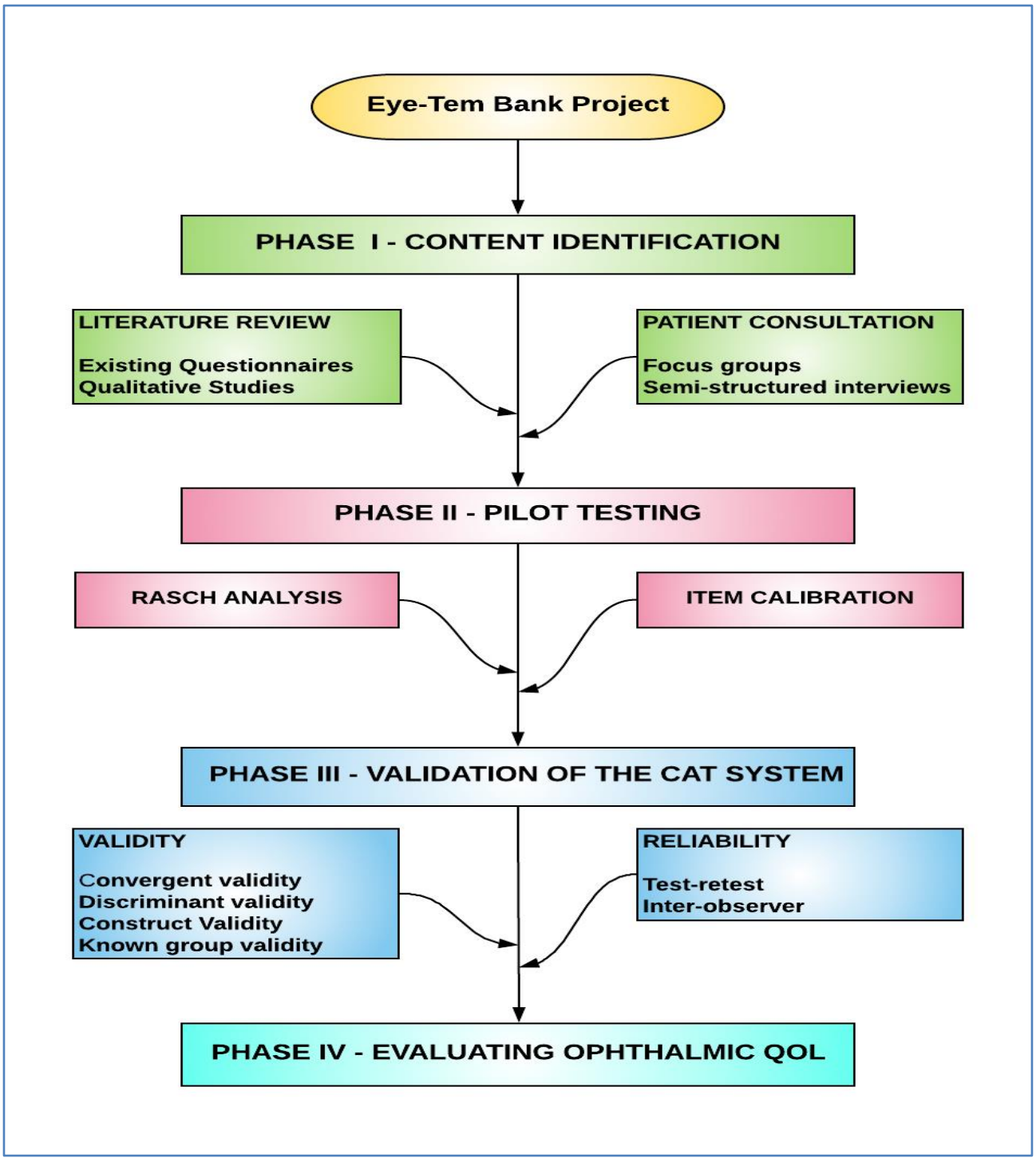

Figure 1.2 Phases of development of disease-specific modules

In this doctoral thesis, I report on the first two phases of the multi-staged effort to produce item banks for other vitreoretinal diseases. For this research project, the other vitreoretinal diseases were grouped into hereditary retinal diseases (HRD) and acquired retinal diseases (ARD). In chapter 1, I present an overview of different retinal diseases. Chapter 2 critically reviews the status of PRO instruments and QoL measurement used in retinal diseases in

terms of the content coverage of QoL and the measurement properties. Chapter 3 compares the QoL issues in HRD and ARD. Chapter 4 describes the content development for the HRD and the ARD item banks with the focus on the results of the qualitative interviews with people with different retinal diseases. Although item banks were developed for HRD and ARD, due to time constraint, only the HRD items banks were pilot tested for this thesis. Chapter 5 provides a detailed description of psychometric properties of the HRD item banks. Chapter 6 discusses whether 'coping' forms a measurable construct or not. Chapter 7 is on an overall discussion and the future direction of the testing and developing of PRO measures for other vitreoretinal diseases.

1.3 Aims and objectives of the study

The aim of the present study was to develop technologically advanced QoL survey questionnaires in the form of an item banks implemented via CAT for other vitreoretinal diseases.

The following objectives were set to obtain the aim:

1) To find a scientifically valid mechanism for splitting/grouping the other vitreoretinal diseases.
2) To identify the content of the vitreoretinal disease - specific item banks by conducting interviews with patients with different retinal diseases.
3) To develop group-specific item banks.
4) To pilot test the group-specific item banks in a sample population to assess item correlation with each other and to retain relevant items as identified by Rasch analysis.

1.4 Retina

The retina is a thin, semi-transparent tissue that lines the inner surface of the posterior aspect of the eyeball. It is approximately 500 µm thick. The thickness of the retina is not uniform throughout. The central part is thicker than the peripheral part due to the increased density of the photoreceptors. The retina is made up of 10 layers (Figure 1.3).

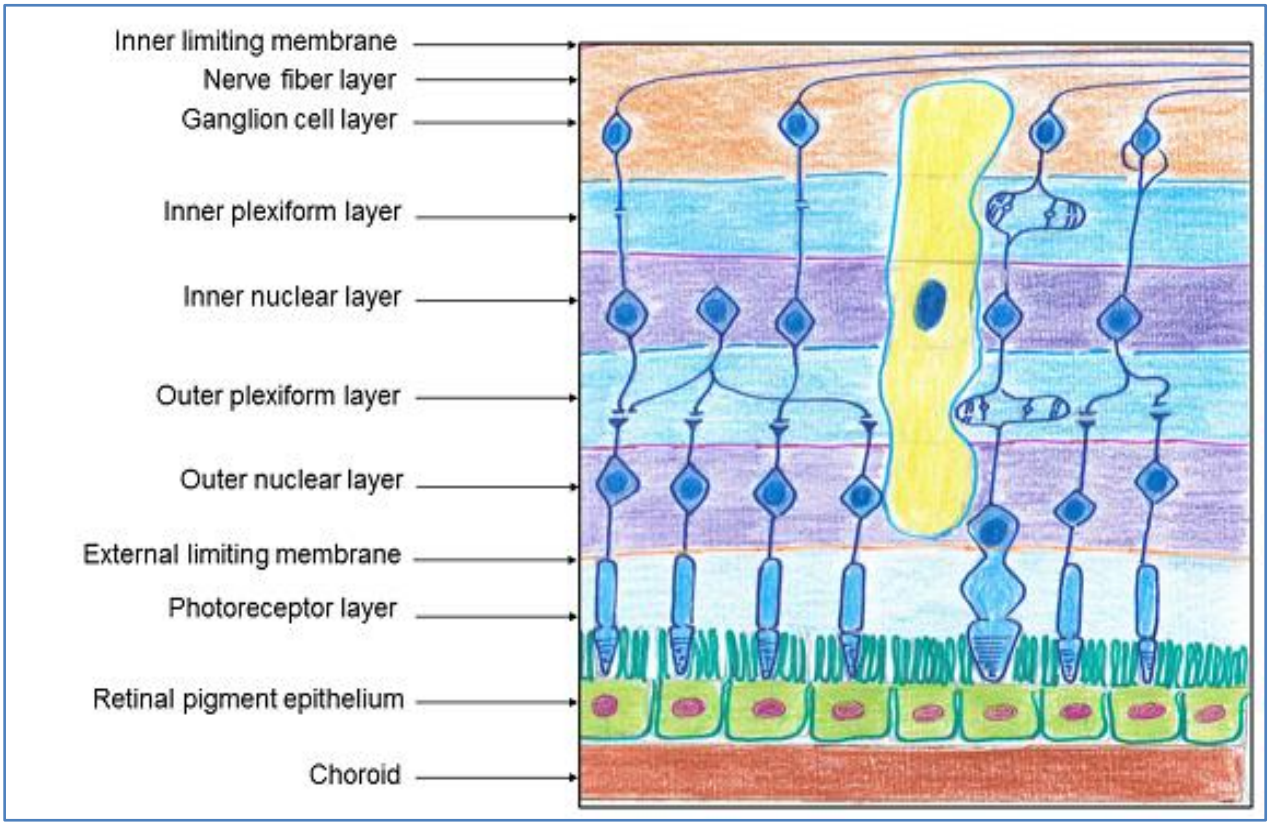

Figure 1.3 A schematic sketch of the microscopic structure of the layers of the retina

The retina is separated from the underlying choroid by the Bruch's membrane and from the overlying vitreous by the inner limiting membrane. The outermost layer of the retinal is called the retinal pigment epithelium and the remaining layers of the retina are called the sensory retina. The space between the retinal pigment epithelium and the sensory retina is called the subretinal space. The retinal pigment epithelium consists of a single layer of hexagonal cells that contain melanin pigment. This forms part of the retinal blood retinal barrier. The retinal pigment epithelium layer has several functions: (i) transportation and storage of retinoids essential for the visual cycle, (46) (ii) Phagocytosis of the shed photoreceptor membranes (47) (iii) absorption of the scattered light by melanin granules, (iv) transportation of fluid and metabolites between the choriocapillaries and the outer retina, (48) and (v)

production of growth factors.(49) The second layer is the layer of photoreceptors. The retina contains approximately 120 million rods and 6.5 million cones.(50) The rods contain the photosensitive substance rhodopsin which is responsible for night vision. The highest density of rods is at the mid-periphery. The cones contain the photosensitive substance photopsin responsible for colour vision and daytime vision. The highest density of cones is at fovea. The external limiting membrane is the third layer that helps to maintain the structure of the retina through mechanical strength.(51) The fourth layer is the outer nuclear layer formed by nuclei of rods and cones. The fifth layer is the outer plexiform layer, which contains the synapses between the rods and cones with the bipolar and the horizontal cells. The sixth layer is the inner nuclear layer consisting of the bipolar, horizontal, amacrine and Muller's cells. The seventh layer is the inner plexiform layer consisting of the synapses between the bipolar cells and the ganglion cells. The eighth layer is the ganglion cell layer consisting of the cell bodies and the nuclei of the ganglion cells. This is a single layer of cells except in the macula where it is multilayered. The ninth layer is the nerve fibre layer consisting of the axons of the ganglion cells which converge at the optic nerve head and the inner most layer is the internal limiting membrane which separates the retina from the vitreous.

1.5 Retinal examination

1.5.1 Fundus examination

The interior surface of the eye that is seen through the ophthalmoscope is called the fundus of the eye. This includes the retina, macula, fovea, and the optic disc. Fundus examination is a routine clinical examination done to determine the healthiness of the vitreous, retina and optic nerve. This is used to establish a diagnosis, assess the extent of the disease and monitor the disease condition. Fundus examination is often performed on a dilated pupil using a combination of topical phenylephrine (2.5%) and tropicamide (1%). The methods of fundus examination include; direct ophthalmoscopy, indirect ophthalmoscopy, and indirect slit lamp bio-microscopy (Figure 1.4 to 1.6). Each method has its own advantages and disadvantages. The advantages of the direct ophthalmoscope are that it forms an erect retinal image easy for interpretation and gives a magnification of 15 times that provides the examiner with retinal images which is relatively easy to interpret. The main disadvantages of the direct ophthalmoscope are that it provides a smaller field of view than all other examination methods and a lack of stereopsis. The advantages of the indirect ophthalmoscope are that it provides a large field of view (40 to 50 degrees) enabling a large

area of fundus examination, good illumination, and stereopsis.

Figure 1.4 (A) Direct ophthalmoscope (B) Retinal examination using direct ophthalmoscope

Figure 1.5 (A) Indirect ophthalmoscope (B) Retinal examination using indirect ophthalmoscope

The disadvantage of the indirect ophthalmoscope is that it forms an inverted reverse retinal image that makes interpretation difficult for beginners. In indirect slit lamp bio-microscopy an inverse retinal image is formed with hand held lenses (+60, +78 or + 90 dioptres).

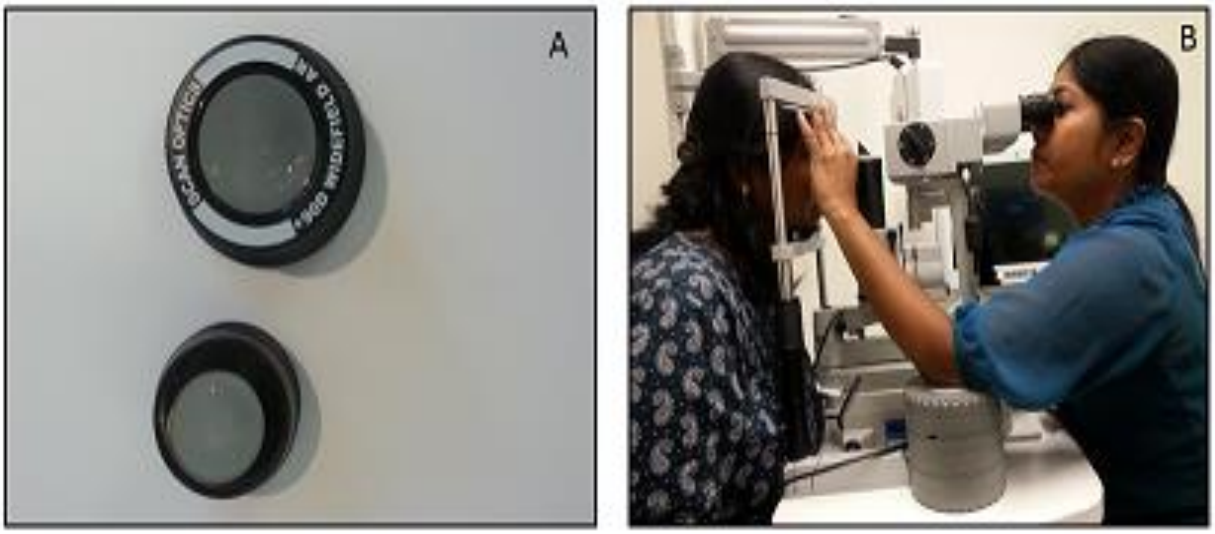

Figure 1.6 (A) Plus lenses (B) Slit-lamp examination using plus lenses

The field of view is large (30 to 40 degrees) and it can provide a 10x to 16x magnification. The normal fundus looks uniformly red. The parts of the fundus include the optic disc, vessels, macula, and periphery (Figure 1.7). The optic disc is located nasal to the macula.

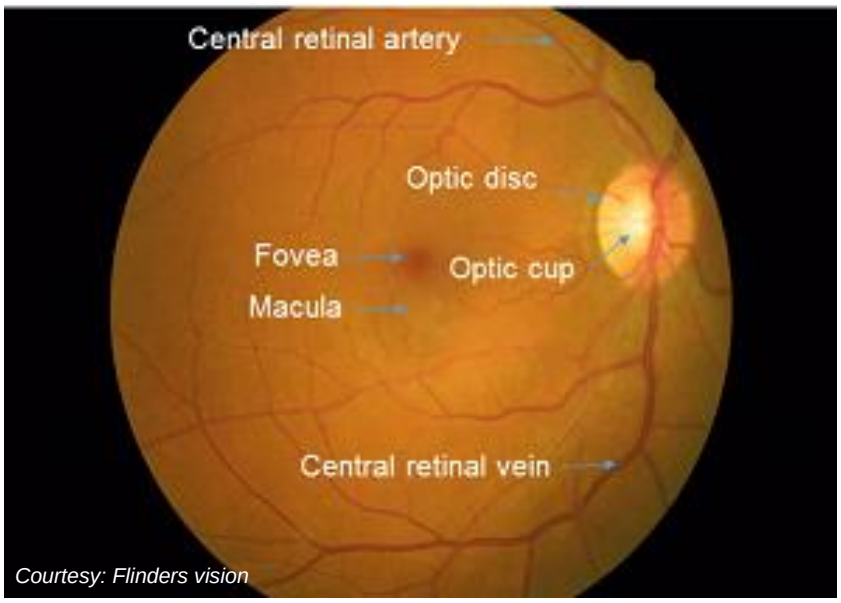

Figure 1.7 Fundus photograph of normal retina

It is oval, pale pink in colour and has regular edges. The diameter of the optic disc is 1.5 mm. The centre of the disc has a pale white cup-like area called the physiological cup. The normal cup to disc ratio is about 0.3 to 0.5. The vessels of the retinal system include; central retinal artery, central retinal vein, arterioles, venules, and capillaries. The vessels of the ciliary system include posterior ciliary arteries and choriocapillaries. The macula is a

specialised region of the retina located two-disc diameters from the temporal margin of the disc. It is yellow in colour and deeply pigmented (Figure 1.7). The fovea is the small depression in the centre of the macula composed of closely packed cones.

1.5.2 Fundus fluorescein angiography

This is an invasive procedure that uses intravenous fluorescein dye to image the retinal and the choroidal circulation in evaluating retinal diseases such as AMD, DR, vascular occlusions, choroidal neovascularisation, CSR, and cystoid macular edema (fluid accumulation in the central macula). Fluorescein is an organic dye which absorbs blue light with the wavelength of 490 nm and emits yellow-green light of 520 nm. The dye is injected into the antecubital vein and reaches the retinal circulation in less than 10 seconds. Most of the dye (80%) binds to the protein albumin and the remaining dye is in the unbound form. The retinal circulation is completely impermeable to both the bound and the unbound fluorescein and does not allow the dye to leak into the surrounding tissue. However, the choroid leaks the unbound dye into the surrounding tissue. Therefore, fundus fluorescein angiography is basically used to study the retinal circulation. Fundus fluorescein angiography is used for confirming the clinical diagnosis, determine the appropriate course of treatment, and to monitor the disease condition. The side effects of fundus fluorescein angiography range from mild to severe.(52, 53) Mild reactions include discoloration of the skin, conjunctiva and urine, nausea and vomiting. Severe reactions include anaphylactic shock, bronchospasm, myocardial infarction, cardiac arrest, seizures, and death.

The abnormalities seen with fluorescein can be grouped into two categories: hypofluorescence and hyperfluorescence. Hypofluorescence is defined as a decrease in the normal fluorescence. It may be caused by blocked fluorescence and vascular filling defects. Blocked fluorescence is caused by any opacification in front of the retinal and choroidal vessels (e.g. fluid, exudates, haemorrhages, pigment) (Figure 1.8). Vascular filling defects may be caused by obstruction of an artery, vein or capillary. Hyperfluorescence is defined as an increase in normal fluorescence. The causes of hyperfluorescence are: (1) pre-injection fluorescence, (2) transmitted fluorescence, (3) abnormal vessels and (4) leakage. Fluorescence in the eye before injecting the fluorescein is called pre-injection fluorescence. It is seen in drusen. Transmission fluorescence is increased visibility of the choroidal vasculature due to either decrease or absence of pigment in retinal pigment epithelium. It is seen in macular degeneration and angiod streaks. Abnormal vessels include

neovascularisation, telangiectasis and other collaterals (Figure 1.9).

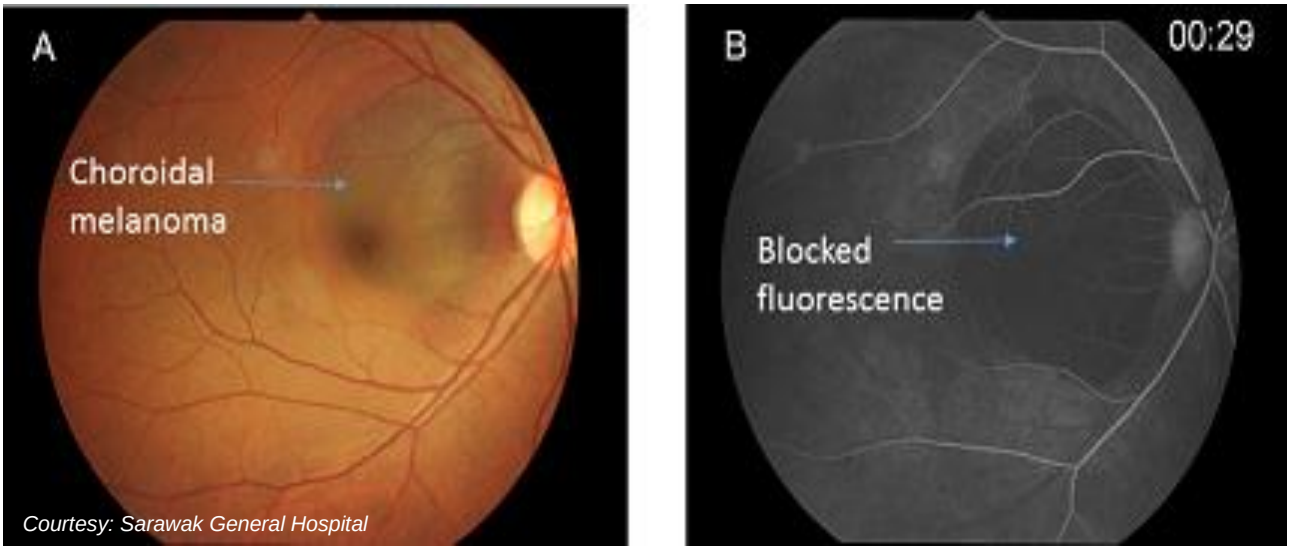

Figure 1.8 (A) Fundus photograph of an eye with choroidal melanoma (B) fundus fluorescein angiography demonstrating blocked fluorescence due to pigment in choroidal melanoma

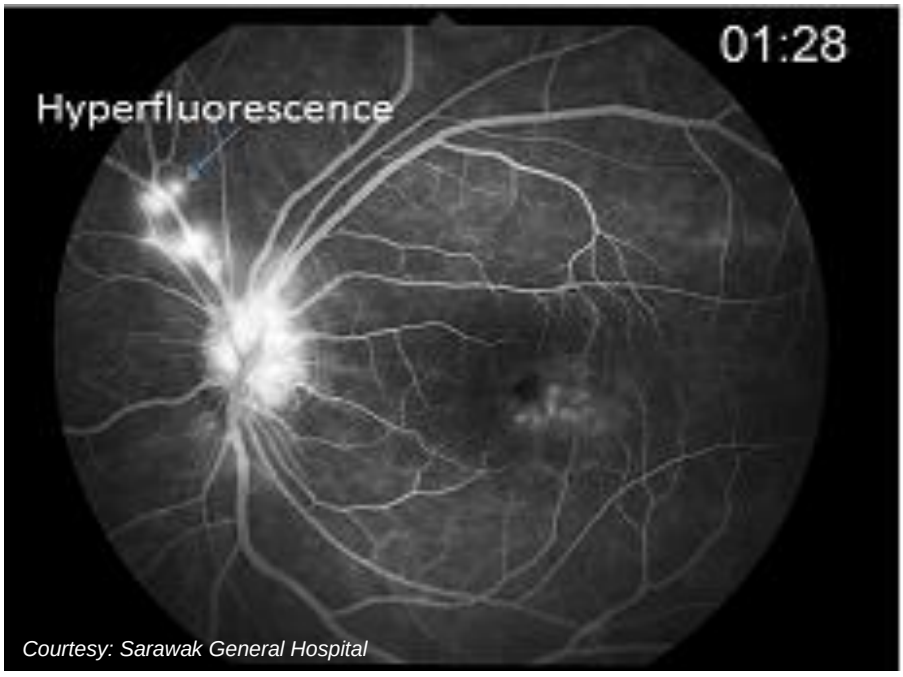

Figure 1.9 fundus fluorescein angiography photograph demonstrating hyperfluorescence in neovascularisation

Leakage occurs due to the accumulation of the fluorescein dye into a tissue space. It is seen in cystoid macular edema, CSR, and papilledema (bilateral disc swelling due to raisedintracranial pressure (Figure 1.10).

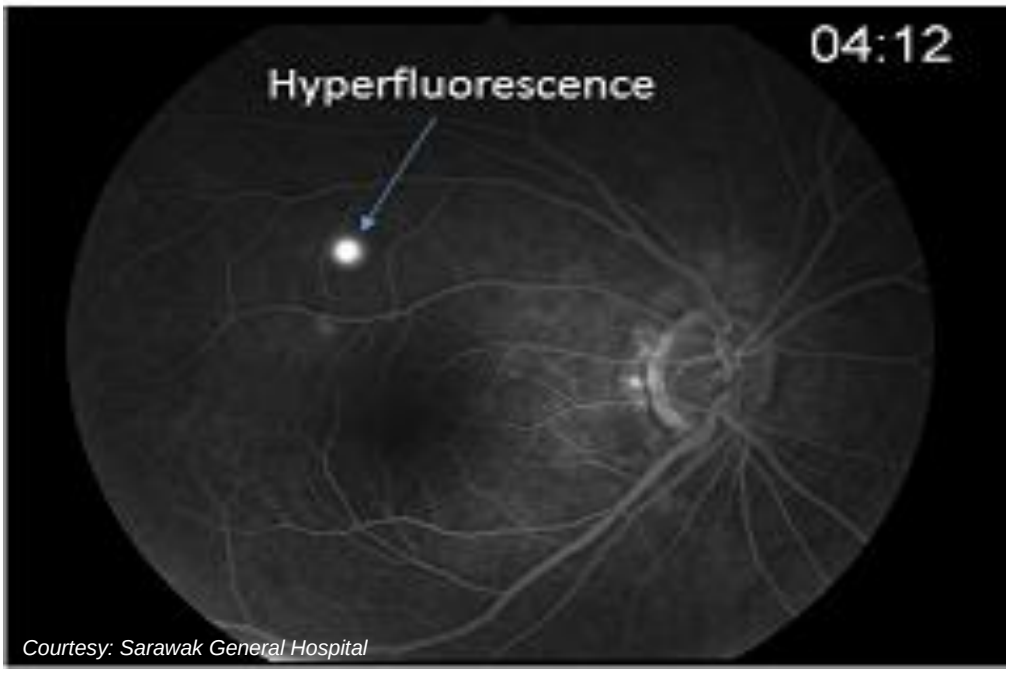

Figure 1.10 fundus fluorescein angiography photograph demonstrating hyperfluorescence due to leakage in central serous retinopathy

1.5.3 Indocyanine green angiography

This is an infrared based dye-imaging technique that provides sufficient detail of the choroidal vasculature and hence is used in the evaluation of many choroidal diseases. The difference between the indocyanine green angiography and the fluorescein molecule is that the molecule of indocyanine green angiography is larger and more protein bound. As a result, the ICG molecule remains within the choroidal circulation and makes indocyanine green angiography angiography ideal for detecting and evaluating choroidal abnormalities (Figure 1.11).

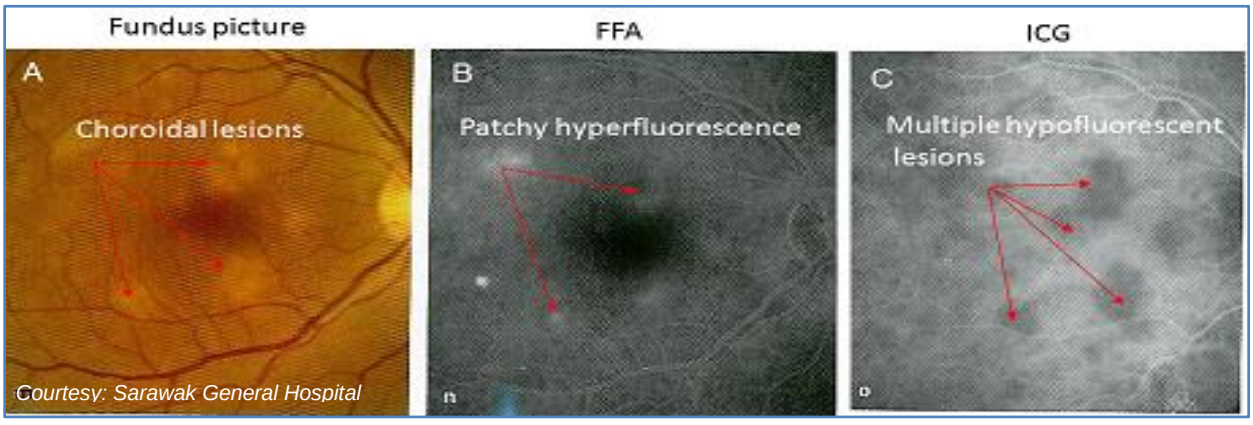

Figure 1.11 (A) Fundus photograph shows few yellow-white choroidal lesions (B) fundus fluorescein angiography shows few patchy hyperfuorescent areas corresponding to the lesions (C) indocyanine green angiography demonstrates multiple hypofluorescent areas corresponding to the lesion

The best use of indocyanine green angiography is in the detection of occult choroidal neovascularisation. There are two types of choroidal neovascularisation, classical and occult. The classic lesions (lesions that are well defined) can be easily delineated with fundus fluorescein angiography, whereas the occult choroidal neovascularisation (lesions that are not well defined), which occurs in 85% of the cases are not easily defined with fundus fluorescein angiography.(54) Hence, indocyanine green angiography is very useful in the identification and delineation of occult choroidal neovascularisation (Figure 1.12). The other advantage of indocyanine green angiography over fundus fluorescein angiography is that it is able to penetrate lipid deposits, haemorrhages and exudates.(55) Minor adverse effects of indocyanine green angiography include nausea, vomiting and discomfort. Severe adverse reaction such as anaphylactic shock is rare. It is contraindicated in patient with prior allergy to iodine.

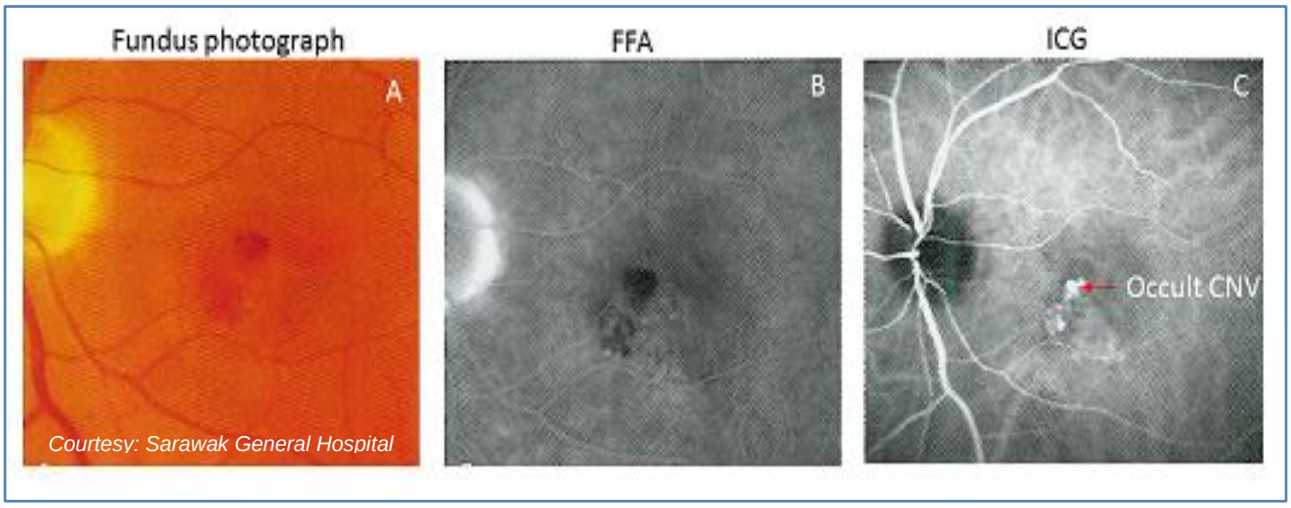

Figure 1.12 (A) Fundus photograph of age related macular degeneration (B) fundus fluorescein angiography demonstrates blocked fluorescence due to subretinal hemorrhage (C) indocyanine green angiography photograph shows a well-defined occult choroidal neovascular membrane which is not seen in fundus fluorescein angiography

1.5.4 Optical coherence tomography

This is a medical imaging procedure that provides a high resolution cross-sectional image of the retinal layers. It is the same as ultrasound, except that reflected and backscattered light is used to create images instead of sound waves. An infrared light is used to scan the retinal layers. The initial version of optical coherence tomography had a resolution of approximately 10 µm and the newer ultra-high-resolution fundus fluorescein angiography allows the resolution of the retina at cellular level. The fundus fluorescein angiography images correspond to the histologic appearance of the retina. The superior reflection

corresponds to the retinal nerve fibre layer. Different colours represent degree of light scattering from different depths of retina. Highly reflective structures are represented in bright colours (white and red). Intermediate reflectivity is shown in green and low reflectivity is shown by dark colours (blue and black) (Figure 1.13). An external red line at the bottom of the fundus fluorescein angiography scan represents retinal pigment epithelium, Bruch's membrane and choriocapillaries. Inner retinal layers have low reflectivity compared to outer retinal layers. The vitreous is black as it is not reflective. Fundus fluorescein angiography is extremely useful in demonstrating retinal and vitreoretinal disorders such as cystoid macular edema, MH, ERM and vitreomacular traction syndrome.

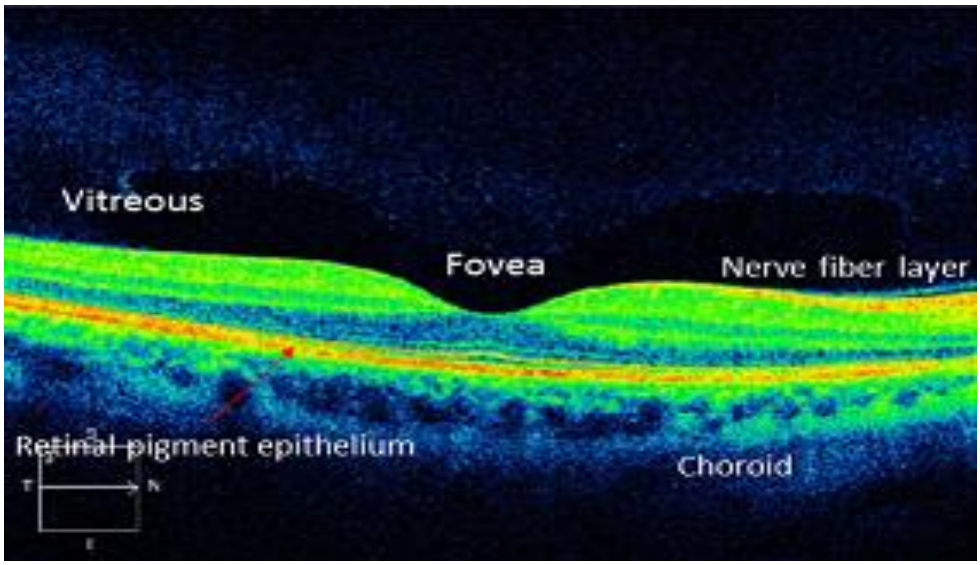

Figure 1.13 Optical coherence tomography image of a normal retina

1.5.5 Electrophysiological testing

Electrophysiological testing is a procedure that measures the function of various components of the retina. The retina converts the light energy falling on it into electrical impulses which are then conveyed via the optic nerve along the visual pathway to the visual cortex. Electrophysiological testing involves recording the electrical responses from the retina. There are two main forms of electrophysiological testing; the electroretinogram, which measures the electrical responses from the entire retina and the electro-oculogram which records the standing potential generated by the retinal pigment epithelium.

1.5.5.1 *Electroretinogram*

This is useful to diagnose retinal degeneration caused by hereditary, metabolic, toxic, retinal vascular or inflammatory causes. The different types of electroretinogram are; full-field electroretinogram, focal electroretinogram, and multifocal electroretinogram. In full-field electroretinogram a brief flash of light records a mass response generated by cells from the entire retina. Under dark-adapted conditions a single flash of light produces a response which is both rod and cone mediated. Eighty percent of this response is attributable to the rods and the remaining from the cones. Focal electroretinogram records the electrical response from a small area of the central retina (3-5 degrees). It measures exclusively the function of the foveal cones and hence is used to assess the macular function in patients with loss of central vision. In multifocal electroretinogram, multiple focal electroretinogram responses elicited from the central 40 to 50 degrees of the retina are recorded to assess the extent of retinal dysfunction. The normal waveforms in an electroretinogram include an initial negative "a" wave generated by the photoreceptors followed by a large positive 'b" wave generated by the Muller and bipolar cells of the retina (Figure 1.14).

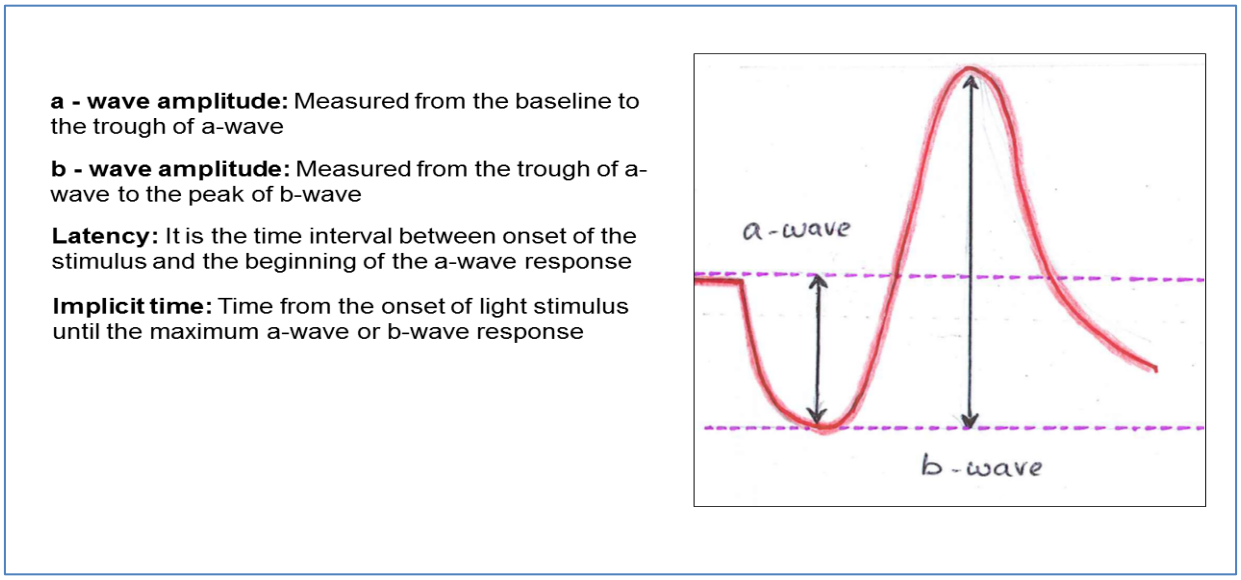

Figure 1.14 Components of a normal electroretinogram

The cone function in the electroretinogram can be easily separated by either light adapting the patient or by using a flicker stimulus. Similarly, the rod response can be easily separated by either dark adapting the patient or by using a dim white light or blue light. Electrophysiological testing is very useful in establishing loss of visual function. Also, a complete medical and ophthalmic evaluation should be done before the diagnosis.

1.5.5.2 *Electrooculogram*

Electrooculogram is used to measure the integrity of the retinal pigment epithelial layer and serves as an additional test to electrooculogram. It is useful in diagnosing certain retinal disease such as Best's vitelliform macular dystrophy and pattern dystrophy. In electrooculogram, responses are recorded under dark adapted conditions for 15 minutes and under light adapted conditions for 15 minutes. Normally the resting potential of the eye decreases progressively during the dark-adapted condition reaching a dark trough in approximately 8 to 12 minutes and progressively increases during the light adaptation condition reaching a light peak in approximately in 6 to 9 minutes (Figure 1.15). The ratio of the light peak to the dark trough (Arden ratio) ratio is normally above 1.80 and a ratio of less than 1.65 is considered abnormal.

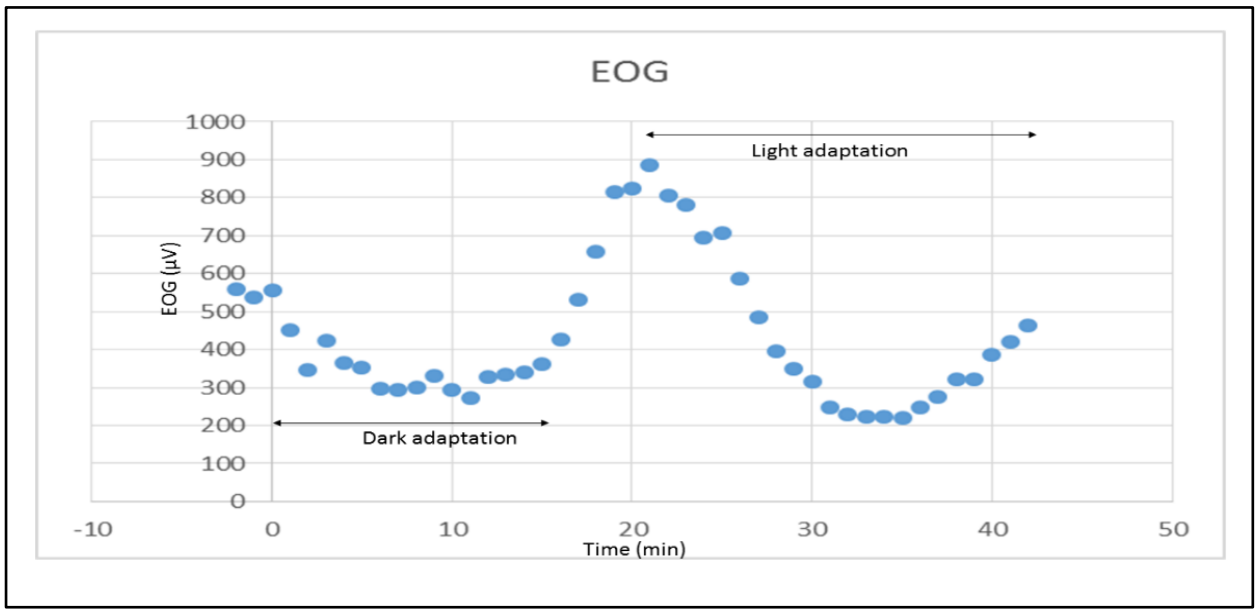

Figure 1.15 Components of a normal electrooculogram

1.6 Other vitreoretinal diseases

Other vitreoretinal diseases in this thesis refer to all the retinal diseases other than AMD, DR and RD. Uveitis is a separate item bank already so posterior uveitis (e.g. toxoplasmosis, birdshot chorioretinopathy, histoplasmosis, etc.) are not included in other vitreoretinal diseases. The other vitreoretinal diseases include hereditary degenerations/dystrophies, vascular occlusions, MH, ERM, CSR, hypertensive retinopathy, retinal telangiectasis and other rare vascular and vitreoretinopathies. These diseases are relatively uncommon but can cause severe visual impairment and blindness. Hereditary degenerations/dystrophies tend to occur at an early age, whereas ERM, MH, hypertensive retinopathy and vascular

occlusions tend to have a late onset. MH and ERM tend to occur more in women than men. Retinal arterial obstructions, CSR, hypertensive retinopathy, and hereditary degenerations/dystrophies inherited as an X-linked pattern are more common in men than in women.

1.7 Grouping the other vitreoretinal diseases

There are several ways of grouping/splitting the other vitreoretinal diseases. One way is to group them based on the disease pathology into congenital, vascular, infection/inflammatory, trauma, and tumours. This type of grouping is very elaborate and would create many disease groups. The second way is to split them into central retinal diseases and peripheral retinal diseases based on the anatomical location of the retinal disease. Diseases involving the central retina cause difficulty in performing fine motor tasks such as reading, driving, and recognising people's faces.(56, 57) Diseases involving the peripheral retina cause problems in orientation, and mobility.(58, 59) The problem with this grouping is that some retinal diseases involve both the central and the peripheral retina and hence may be difficult to group. The third and a simple way would be to group all the HRD together in one group and all the ARD together in another group. HRD differ from ARD in terms of the nature of onset, laterality, and disease progression. HRD have an early onset, involve both eyes and are progressive and ARD tend to have a late onset, mostly unilateral and could be either stationary or progressive.(60, 61) This novel way of splitting retinal diseases into HRD and ARD is based on clinical manifestations. For this thesis, the other vitreoretinal diseases were grouped into hereditary and acquired retinal diseases (Table 1.1).

Table 1.1 Classification of the other vitreoretinal diseases

Hereditary retinal diseases	Acquired retinal diseases
1. Retinitis pigmentosa and related disorders Typical retinitis pigmentosa Blue cone monochromatism Congenital red-green colour deficiency Leber's congenital amaurosis Congenital stationary night blindness 2. Macular dystrophies Stargardt disease & fundus flavimaculatus Best's disease and vitelliform dystrophy Adult vitelliform degeneration Pattern dystrophy Sorsby's macular dystrophy North Carolina macular dystrophy 3. Choroidal dystrophies Choroideremia Gyrate atrophy 4. Hereditary vitreoretinopathies Stickler's syndrome X-linked Juvenile retinoschisis Familial exudative vitreoretinopathy 5. Miscellaneous Norrie's disease Von Hipple Lindau disease Idiopathic juxtafoveolar retinal telengiectasis	1. Vascular occlusion a. Retinal arterial obstruction (i) Central retinal artery occlusion (ii) Branch retinal artery occlusion (iii) Ophthalmic artery occlusion (iv) Cilioretinal artery obstruction b. Retinal vein occlusion (i) Central retinal vein occlusion Ischemic Non-ischemic (ii) Branch retinal vein occlusion 2. Hypertensive retinopathy 3. Central serous retinopathy 4. Macular hole 5. Epiretinal membrane 6. Coat's disease and retinal telangiectasia 7. Hemoglobinopathies

The cogency of the grouping was tested using the qualitative data (described in chapter 3 and 4) by comparing QoL issues within and between the groups. These different vitreoretinal diseases are briefly discussed below.

1.8 Hereditary retinal diseases

1.8.1 Retinitis pigmentosa (RP) and related disorders

1.8.1.1 *Retinitis pigmentosa*

This is a group of inherited retinal disorders that affect the photoreceptors (rods and cones) and the retinal pigment epithelium. In rod-cone dystrophy the rods are affected first and the cones later and in the cone-rod dystrophy the cones are affected first and the rods later. The most common form of RP is rod-cone dystrophy, which is a progressive disorder presenting with night blindness initially that ultimately results in blindness after several decades. RP is the commonest hereditary retinal disease with a prevalence of about 1 in 4000.(62) Most of the disorders have a genetic basis and involve photoreceptor cell death by apoptosis. RP can be inherited as autosomal-dominant (30-40%), autosomal-recessive (50-60%) or X-

linked recessive (5-15%) trait.(62-64) RP can occur as an isolated disorder or may be associated with syndromes as in Ushers syndrome, Bardet-Biedl syndrome, and Kearns-Sayre syndrome. In Usher syndrome, RP is associated with varying degrees of hearing impairment and vestibular dysfunction. Bardet-Biedl syndrome involves pigmentary retinopathy with obesity, learning disability, hypogonadism, polydactyly, and renal dysfunction. Kearns-Sayre syndrome involves external ophthalmoplegia, cardiac block, lid ptosis, and mild RP. Retinitis pigmentosa typically starts around 10 to 12 years and progresses to severe visual impairment during the fourth and fifth decade. The classical symptoms of RP include nyctalopia (night blindness), peripheral visual loss and in advanced cases central visual loss and photopsia (seeing flashes of light).(62) Fundus findings include bone-spicule pigment deposits, waxy-pallor of the optic disc and attenuation of retinal arterioles (Figure 1.16) . The other ocular abnormalities associated with RP include posterior subscapular cataract, glaucoma, and cystoid macular oedema. RP is mainly diagnosed clinically. Electroretinogram is used to confirm the diagnosis, assess the severity of the diseases and to monitor the disease progression. Electroretinogram shows reduction in the “a” and “b” wave amplitudes and a delay in their timing. There is currently no treatment for RP. The role of vitamin A, docosahexaenoic acid in slowing down the degenerative process is not well established.(65) The newer therapeutic strategies include gene therapy, cell transplantation, retinal prosthesis, and neuroprotection.(66, 67)

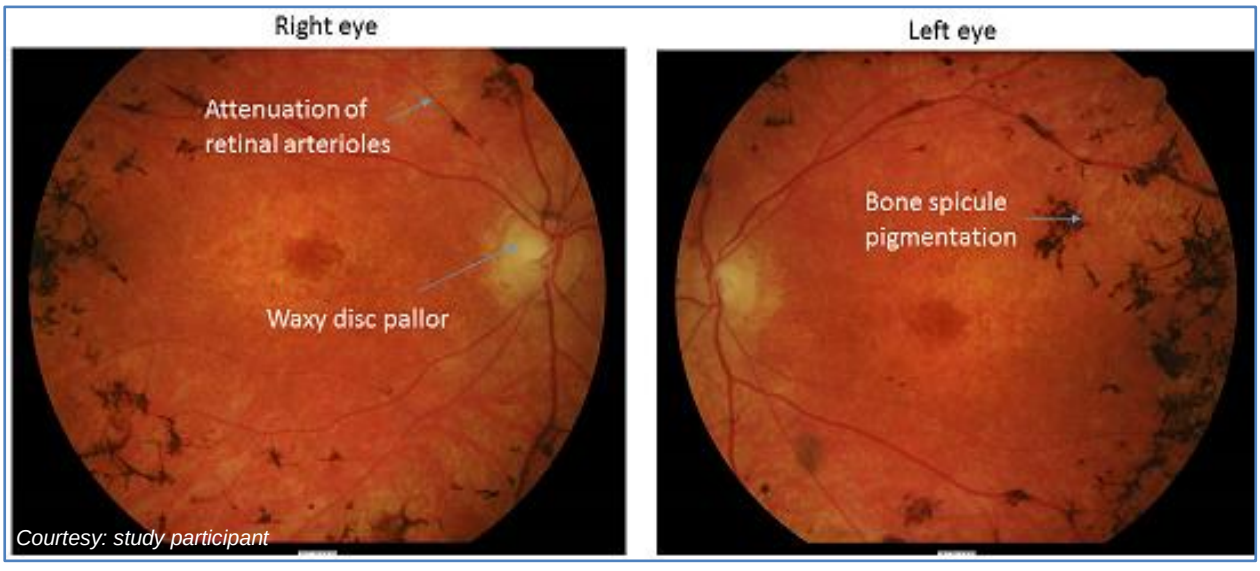

Figure 1.16 Fundus photographs of retinitis pigmentosa

1.8.1.2 *Congenital stationary night blindness*

This is an X-linked congenital disorder that is characterized by severe night blindness from birth. Unlike the night blindness in RP that is progressive, the night blindness in congenital stationary night blindness is stationary. Visual acuity is only reduced slightly and colour vision is usually unaffected. The other ocular manifestation includes short-sightedness, nystagmus (involuntary ocular movements) and strabismus (crossed eye). There are two types of congenital stationary night blindness, the complete and the incomplete form.(68) In the complete form of congenital stationary night blindness all the affected patients have night blindness and in the incomplete form all the affected individuals may not have night blindness. The clinical presentation may be confused with RP, but the fundus examination shows a normal retina. However, the optic disc may show temporal pallor or myopic shift in patients with high myopia (Figure 1.17). Visual field testing and electroretinogram are important diagnostic tests for congenital stationary night blindness. The photopic electroretinogram typically shows a wide a-wave trough. There is currently no cure for congenital stationary night lblindness.

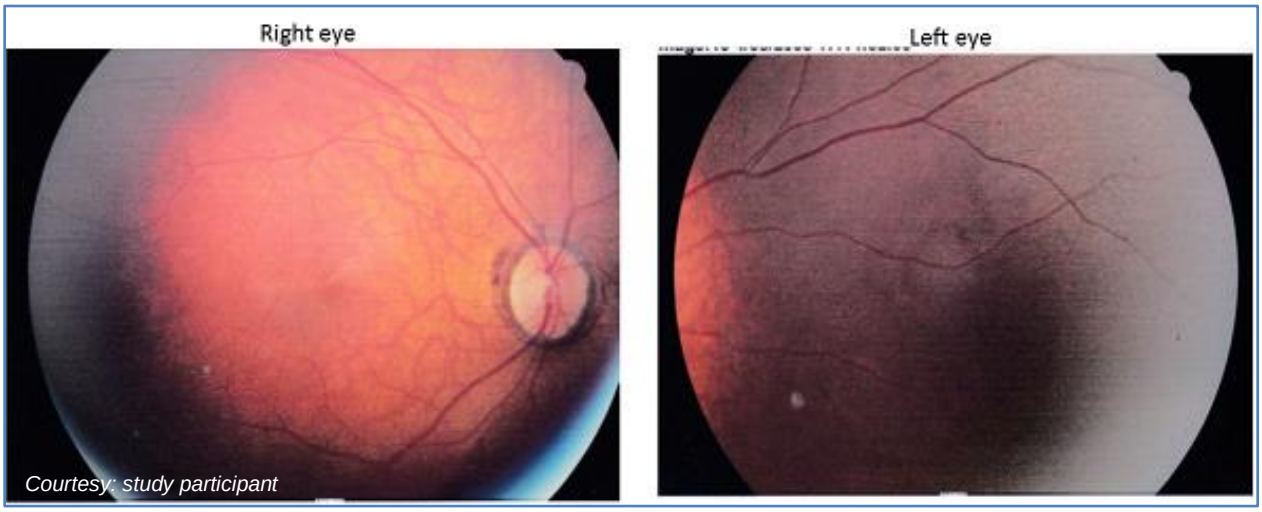

Figure 1.17 Fundus photographs of congenital stationary night blindness

1.8.1.3 *Leber's congenital amaurosis*

This is a congenital disorder that can cause severe visual impairment at birth. It is inherited as an autosomal recessive trait. Ocular problems include long-sightedness, nystagmus, and oculo-digital sign (poking or pressing the eyes with fingers). Frequent eye rubbing may result in deep set eyes and keratoconus (bulging of the cornea). Fundus findings include retinal pigmentary changes, narrowing of the retinal vessels and pale optic disc (Figure 1.18).

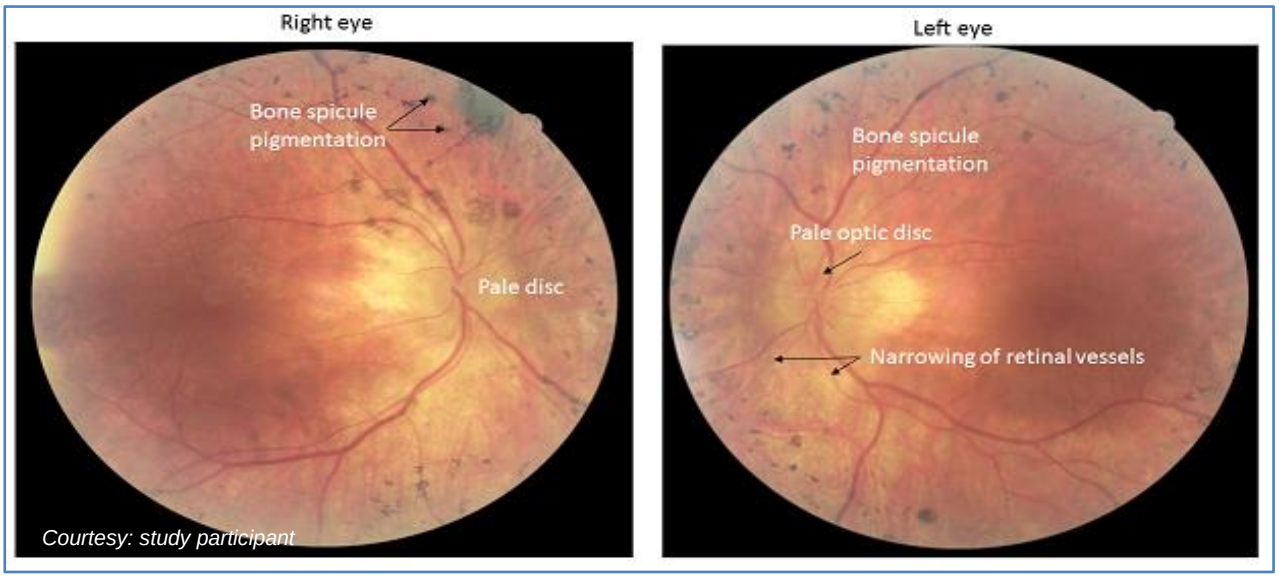

Figure 1.18 Fundus photographs of Leber's congenital amaurosis

Electroretinogram shows marked reduction in the amplitudes of all the responses and this test may be used for the differential diagnosis with other ophthalmic diseases with congenital visual loss and nystagmus. There is no treatment for Leber's congenital amaurosis**.**

1.8.1.4 *Congenital red-green colour deficiency*

Congenital red-green colour deficiency is the most common form of colour vision deficiency. It is an X-linked inherited retinal disease that is caused by lack of either red-sensitive cones (protanopia) or green-sensitive cones (deuteranopia). It is more common in males compared to females. Unlike other hereditary retinal diseases, congenital red-green colour deficiency cause no loss of visual acuity, contrast sensitivity or visual field. However, these retinal diseases are associated with difficulties in daily life, work and driving a car.(69) Hence, these retinal diseases were included in this study. Affected individuals have difficulty differentiating some shades of red, yellow and green. One of the

most widely used pseudoisochromatic screening test for congenital red-green deficiency is the Ishihara test. (70) There is no treatment for colour blindness.

1.8.2 Macular dystrophies

1.8.2.1 *Stargardt disease*

Stargardt disease is the most common macular dystrophy and occurs in 1 of 8000 to 10000 people.(71) It is an autosomal recessive disorder. It is a progressive disease which is characterised by perimacular and peripheral yellow flecks.(72) In Stargardt disease the flecks are mostly confined to the posterior pole and occur in early childhood (Figure 1.19). Fundus changes are minimal in the early stages of the disease, however, as the disease progresses more flecks may appear and atrophic changes may develop in the retina. In the late stages of the disease the atrophic patches can coalesce to give the macula a “beaten bronze” appearance”.

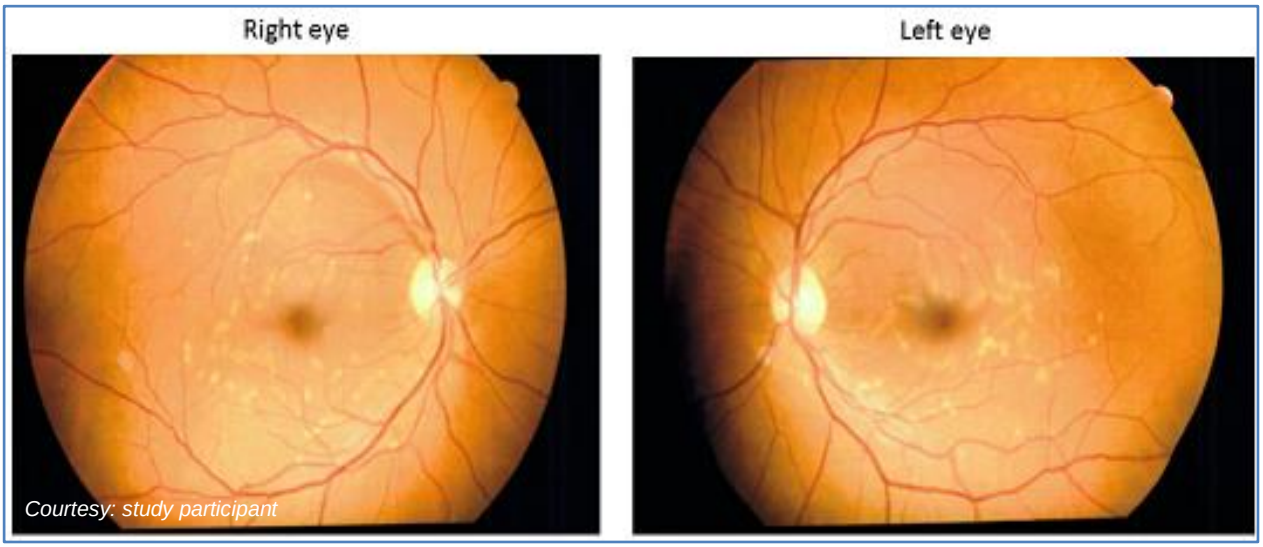

Figure 1.19 Fundus photographs of Stargardt disease

Fundus fluorescein angiography shows a characteristic phenomenon known as the “dark” or “silent” choroids, which appears as a prominent retinal circulation against hypofluorescent choroids.(61) The electroretinogram is not very useful as the changes are variable and do not correlate with the clinical findings. No known treatment exists for this disease.

1.8.2.2 *Best’s disease*

This is an extremely rare disorder that occurs in childhood. It is inherited as an autosomal dominant trait. In the early stages, the macula appears normal or has mild retinal pigment

epithelial changes. Later, a large yellow vitelliform lesion appears in the central macula which gives a typical “egg yolk” appearance (Figure 1.20). Later, the lesion ruptures resulting

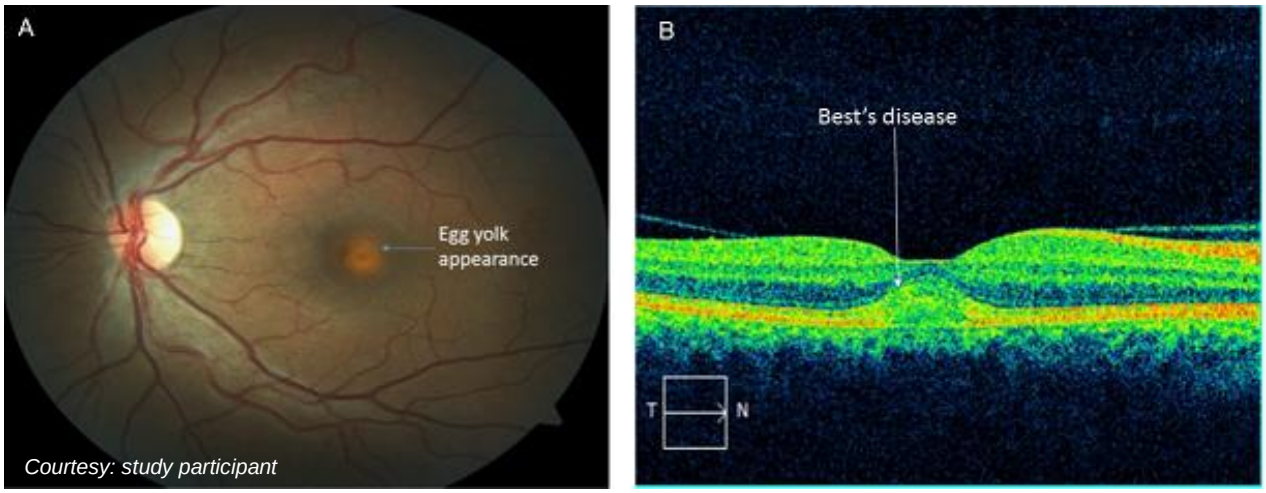

Figure 1.20 (A) Fundus photograph of Best’s disease (B) Optical coherence tomography imaging demonstrates a homogenous, round, elevated, well-demarcated yellowish lesion in Best’s disease

in a scrambled egg appearance. Visual acuity is usually good when the “yolk” remains intact and drops when scarring occurs.(73) The disease is usually diagnosed by family history, clinical presentation, fundus fluorescein angiography, optical coherence tomography and electrophysiological testing. Electroretinogram is usually normal but electrooculogram shows an abnormal retinal pigment epithelial function. This is the only disease with relatively normal electroretinogram results and abnormal electrooculogram results. There is no treatment for this disease.

1.8.2.3 *Adult vitelliform macular degeneration*

This macular dystrophy was first diagnosed by Gass in 1974. It is a rare dystrophy which is inherited in an autosomal dominant trait. The pathogenesis involves retinal pigment epithelial dysfunction and accumulation of degenerated photoreceptor outer segments in the sub-retinal space.(74)The clinical manifestation is characterized by symmetrical yellow foveal lesions that resemble the lesions of Best’s disease but are smaller (Figure 1.21). No treatment exists for this disease. It is differentiated from Best’s disease on the basis of normal electrooculogram .

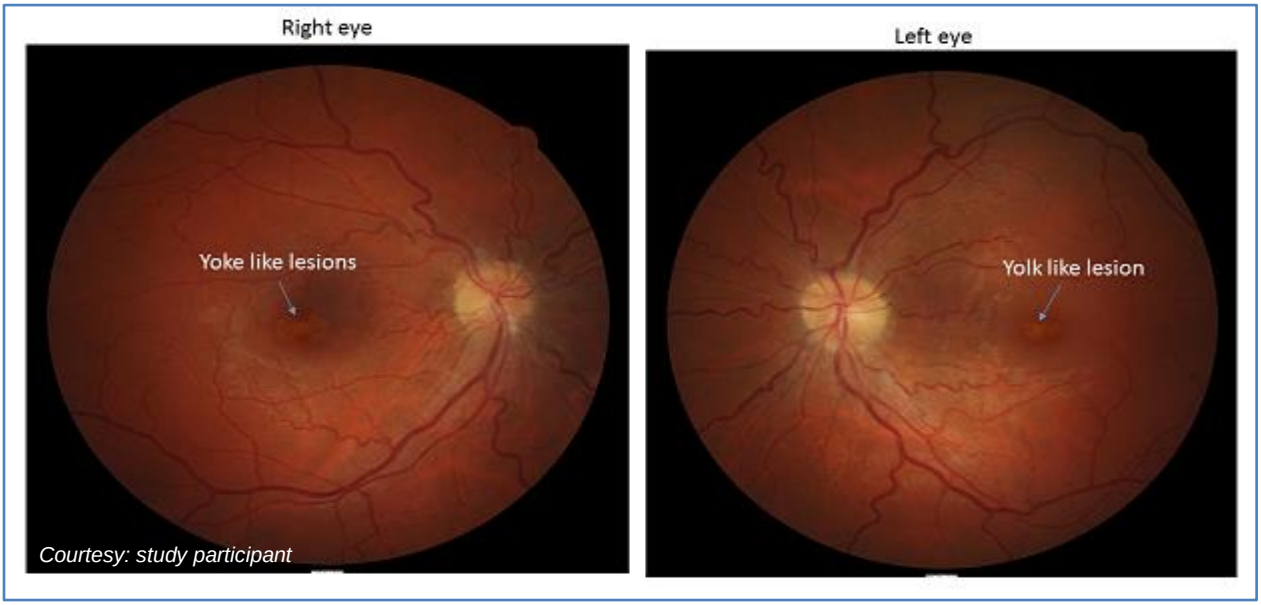

Figure 1.21 Fundus photographs of adult vitelliform macular degeneration

1.8.2.4 *Pattern dystrophy*

This is a group of rare ophthalmic dystrophies characterized by clumps of retinal pigment that are arranged in a pattern-like fashion.(75) They are commonly inherited in an autosomal dominant fashion. Several hereditary patterns are documented such as reticular dystrophy,(76) butterfly-shaped dystrophy,(77) and macroreticular dystrophy.(75) Ocular manifestations include reticular pigmentation at the level of the retinal pigment epithelium (Figure 1.22). In butterfly dystrophy, the pigment deposits radiate from the fovea in the pattern of butterfly wings. Diagnosis is usually based on the characteristic findings found on

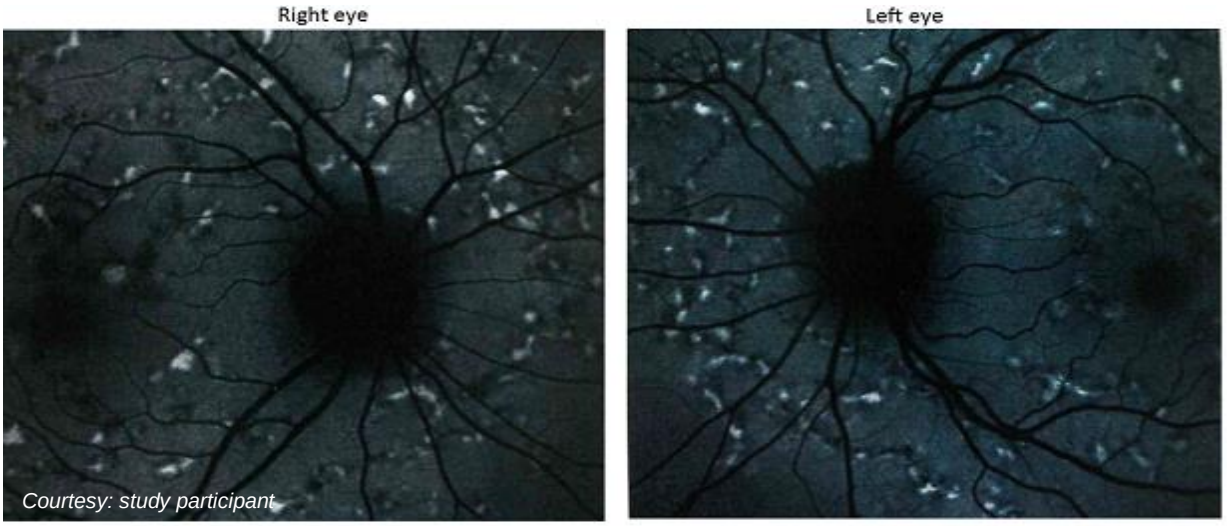

Figure 1.22 Tracking Laser tomography picture of pattern dystrophy mimicking fundus flavimaculatus

ophthalmoscopy and angiography. Electrophysiological testing results are usually normal. There is no treatment for this disease.

1.8.2.5 *Sorsby's macular dystrophy*

This is a rare disorder and is inherited in an autosomal dominant pattern. It has clinical similarities with age related macular degeneration. The visual symptoms commonly occur during the fourth or fifth decade of life. Patients present typically with a sudden and progressive loss of vision due to the development of choroidal neovascularisation or with a delayed dark adaptation.(78, 79) Fundus examination shows multiple yellowish drusen-like deposits at the posterior pole in the early stages. Late disease stages are characterised by heavily pigmented macular scars and geographical atrophy (Figure 1.23).(80, 81) There is no treatment for this disease.

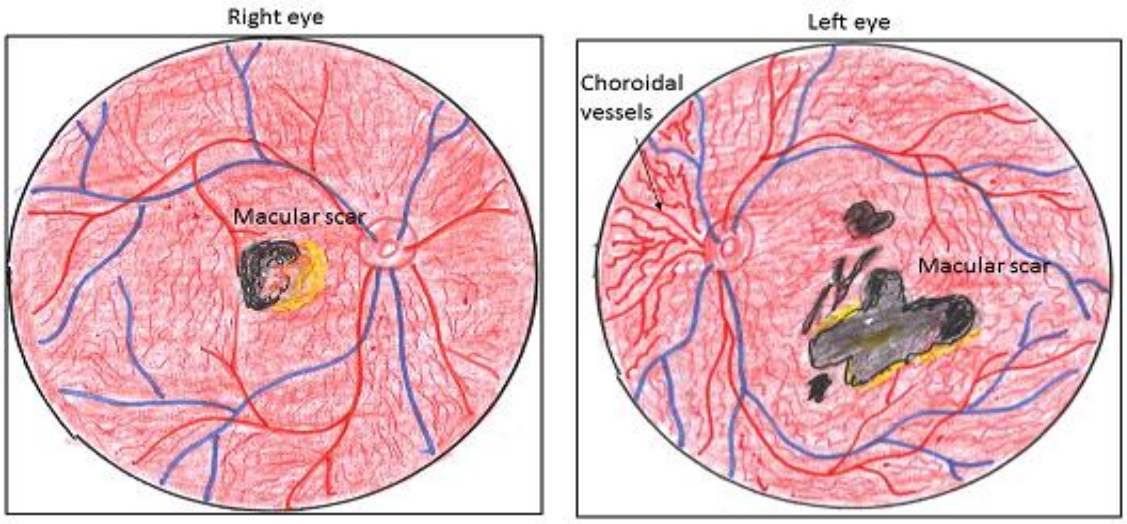

Figure 1.23 A schematic sketch of fundus photographs of Sorsby's dystrophy

1.8.2.6 *North Carolina macular dystrophy*

This is an autosomal dominant disorder and was first discovered in a large family in North Carolina. It is characterized by early macular degeneration that occurs at birth or soon after birth. This disorder is now called macular dystrophy, retinal subtype, first one mapped (MCDR1). The clinical presentation is a lifelong impaired central vision. The fundus lesion is variable ranging from drusen-like lesions involving the central macular to discifom scarring (Figure 1.24).(82)

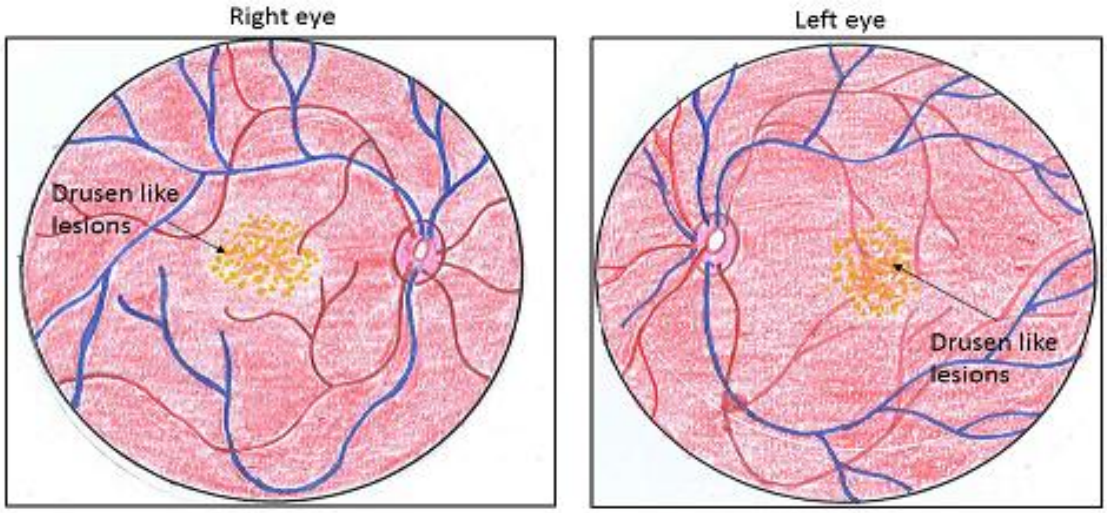

Figure 1.24 A schematic sketch of fundus photographs of North Carolina macular dystrophy

The disease is mostly stable, unless there is choroidal neovascular membrane. Electrophysiological testing is usually normal and colour vision is not affected. There is no treatment for this disease.

1.8.3 Choroidal dystrophies

1.8.3.1 *Choroideremia*

This is a rare genetic disorder which exclusively affects males. Choroideremia is a progressive dystrophy that involves both the retina and the choroid. Choroideremia results in a characteristic choriocapillaries loss with bare sclera and scalloped edges in the peripheral fundus (Figure 1.25).(83) Night blindness is the first symptom and as the disease progresses there is loss of peripheral vision and later a loss of central vision. Carriers are usually asymptomatic and the fundus picture ranges from a normal appearance to a full-blown picture of choroideremia. Choroideremia is mainly diagnosed clinically. Electrophysiological testing shows abnormal responses in the affected males and normal responses in most of the female carries.(84) At present, there is no treatment for choroideremia.

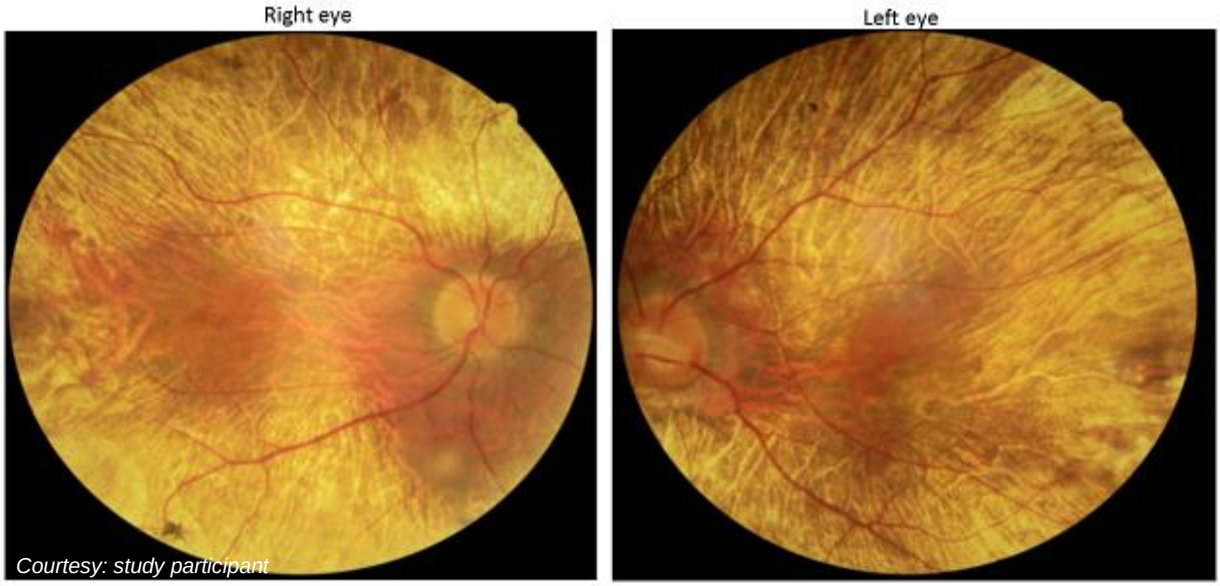

Figure 1.25 Fundus photographs of choroideremia

1.8.3.2 *Gyrate atrophy*

This is an autosomal recessive disorder which is characterized by slowly progressive chorioretinal dystrophy. This disorder is associated with deficiency of ornithine ketoacid aminotransferase enzyme which is essential for the conversion of ornithine to glutamate. Absence of this enzyme results in accumulation of ornithine in the plasma to levels of 10-15-fold above normal leading to hyperornithinemia. Patients presents with night blindness during the second to third decade of life. Fundus examination shows sharply demarcated scalloped areas of chorioretinal atrophy and pigment clumping at the margins. The lesions typically start in the mid-periphery and slowly progress towards the centre and periphery and ultimately involve the entire fundus (Figure 1.26). Visual field defects correspond to the atrophic areas in the choroid. Almost all patients with gyrate atrophy have lens changes.(85) Diagnosis is based on history of night blindness and typical fundus features of scalloped areas of choroid atrophy. High ornithine levels are found in urine, plasma, aqueous humour, and cerebrospinal fluid of these patients. Administration of a diet low in arginine to patients

with gyrate atrophy has been found to lower plasma levels of ornithine to normal.(86)

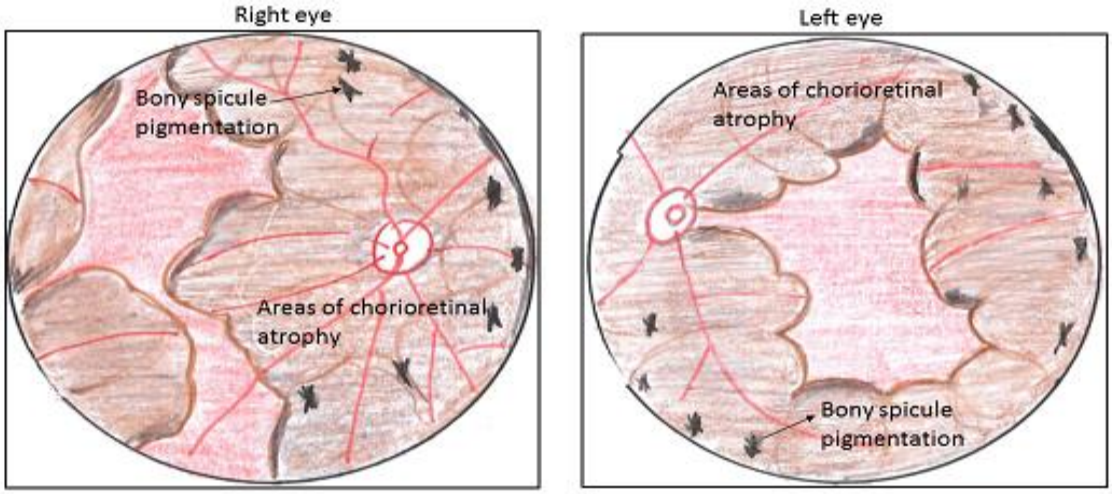

Figure 1.26 A schematic sketch of fundus photographs of gyrate atrophy

1.8.4 Hereditary vitreoretinopathies

1.8.4.1 *Juvenile retinoschisis*

This is a rare genetic disorder that affects primarily boys and young men. It is inherited as an X-linked trait. It is diagnosed by the characteristic spoke wheel pattern of the foveal and parafoveal intraretinal cysts (Figure 1.27). Electroretinogram shows a healthy rod a-wave but reduced rod b-wave with bright stimuli. There is no treatment for juvenile retinoschisis. Surgical intervention in the form of vitrectomy and intravitreal gas tamponade is necessary in secondary retinal detachments.

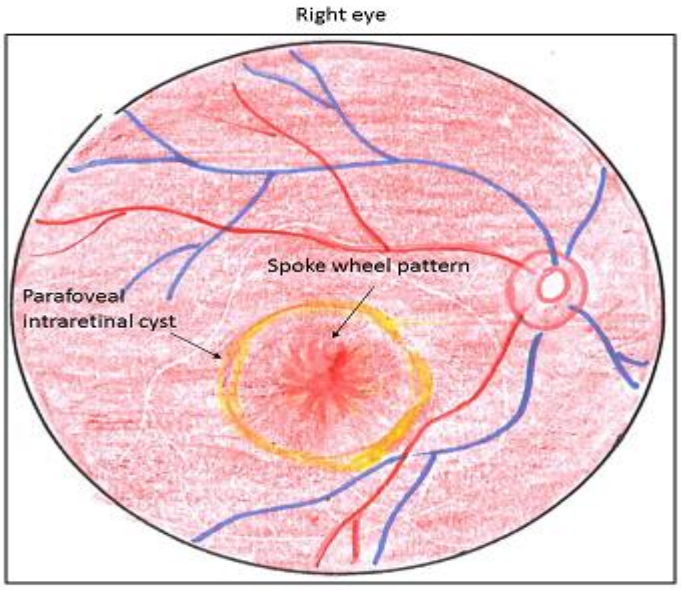

Figure 1.27 A schematic sketch of fundus photograph of Juvenile retinoschisis

1.8.4.2 *Stickler's syndrome*

Stickler's syndrome is otherwise known as hereditary arthro-ophthalmopathy. It is inherited in an autosomal dominant pattern and is caused by a mutation in the type II pro-collagen. Patients with Stickler's syndrome have high myopia, retinal detachments and degenerative changes involving the cartilage of the joints. Ocular manifestations include high myopia, optically empty vitreous with membranes and strands, perivascular pigmentary changes, retinal breaks, pre-senile cataracts, and open-angle glaucoma (Figure 1.28). Giant retinal tears are common and may lead to retinal detachment. Retinal detachments associated with Stickler's syndrome are very difficult to repair due to the abnormal adhesion between the vitreous and retina. Systemic associations include generalised epiphyseal dysplasia, cleft palate, bifid uvula, mid-facial flattening, sensorineural hearing loss and mitral valve prolapse. Diagnosis is based on oro-facial, ocular, skeletal, and auditory abnormalities with family history. There is no treatment for this disease.

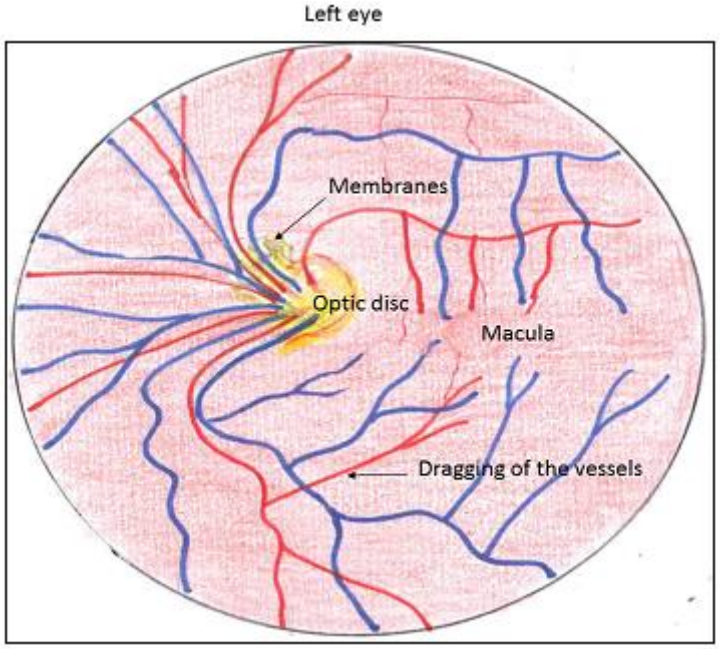

Figure 1.28 A schematic sketch of fundus photograph of Stickler's syndrome

1.8.4.3 *Familial exudative vitreoretinopathy*

This is an autosomal dominant disorder that is characterised by bilateral retinal and vitreous abnormalities. This condition is like retinopathy of prematurity, but there is no history of premature birth, respiratory distress, or oxygen therapy. The other synonyms are dominant exudative vitreoretinopathy, Criswick-Schepens syndrome and hereditary exudative

vitreoretinopathy. The clinical course of familial exudative vitreoretinopathy is divided into mild, moderate and severe forms, each of which may be seen in patients of any age.(87) In the mild form affected patients are usually asymptomatic and have good visual acuity. Fundus examination shows peripheral avascular zones, which are more extensive temporally. In most cases the peripheral avascular zone remains stable.(88) Fundus fluorescein angiography in this stage shows leakage of the dye from the vessels and arteriovenous shunts at the margins of the vascularised and non-vascularised retina. In the moderate form, in addition to the changes seen in the mild form, there is neovascularisation and both intra-retinal and sub-retinal exudation. Fibrovascular proliferation may be seen in the periphery. Contraction of the fibrovascular proliferation exert traction on the retina producing dragging of the major blood vessels, heterotopia of the macula, reduced visual acuity, and strabismus (Figure 1.29). In the severe form of the disease there is tractional and exudative retinal detachment, falciform retinal folds and massive intra-retinal and sub-retinal exudation. Late complications include cataract and neovascular glaucoma (a severe form of secondary glaucoma characterised by proliferation of fibro-vascular tissue in the anterior chamber angle). There is no treatment for this disease.

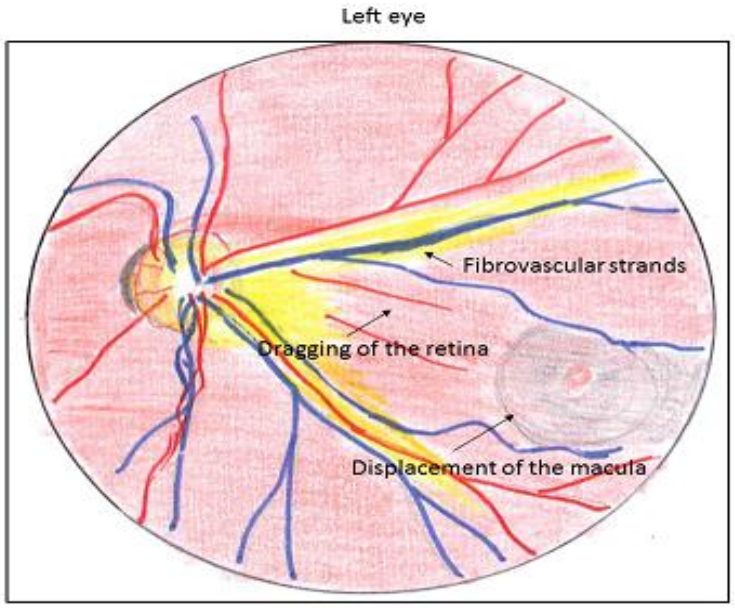

Figure 1.29 A schematic sketch of fundus photograph of familial exudative vitreoretinopathy

1.8.5 Miscellaneous diseases

1.8.5.1 *Noorie's disease*

This is otherwise known as Norrie syndrome, Norrie-Warburg syndrome, fetal iritis syndrome and Whitnall-Norman syndrome. It is rare genetic disorder that causes early blindness. It is inherited as an X-linked disease. Norrin is a protein that regulates the development of the retina. Mutation of this protein causes abnormal development of the retina. The clinical presentation of this diseases is leukocoria (i.e. white pupillary reflex). The white pupillary reflex is caused by the immature retinal cells that forms a whitish mass at the back of the eye. Peripheral retinal ischemia is seen at the early stages of the diseases. Retinal neovascularisation, scarring, fibrosis and retinal detachment are some of the complications seen in the late stages of the disease (Figure 1.30). The other ocular abnormalities that are associated with this disease are microphthalmos, iris atrophy and cataract. It is also associated with other systemic abnormalities such as progressive hearing loss, delay in growth and development and peripheral vascular diseases. There is no treatment for this disease.

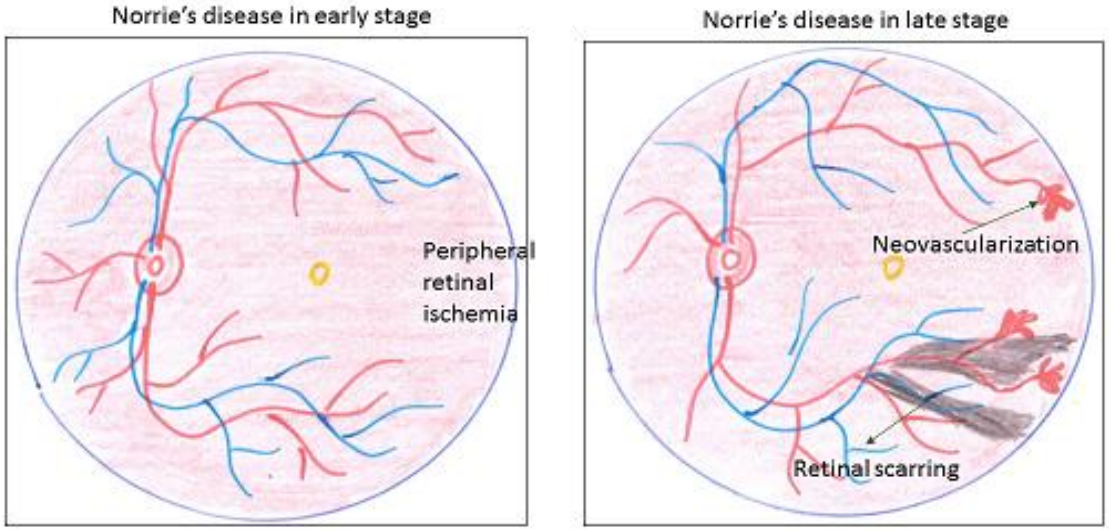

Figure 1.30 A schematic sketch of fundus photographs of Norrie's disease

1.8.5.2 *Von Hipple Lindau disease*

This is also called Von Hipple Lindau syndrome. It is a rare inherited disorder characterised by retinal and central nervous system hemangiomas, pheochromocytomas and multiple cysts in the pancreas and kidneys. It is an autosomal dominant disorder caused by mutation of the Von Hipple Lindau gene. The retinal hemangiomas arise from the retinal vessels or

the optic nerve and tend be either unilateral or bilateral and unifocal or multifocal. The average age of detection is usually between 15 and 35 years. The presenting symptom is blurred vision or loss of visual field. The retinal hemangioma appears as a reddish spherical lesion with prominent afferent and efferent vessels (Figure 1.31). Intra-retinal and sub-retinal exudation usually surrounds the lesion. Complications include proliferative vitreoretinopathy, exudative retinal detachment, vitreous haemorrhage, and neovascular glaucoma. This disease is associated with an increased risk of renal cell carcinoma. Essential lab investigations include a complete blood count and imaging of head and abdomen. Surgical treatment of retinal hemangiomas includes argon laser photocoagulation, cryotherapy, vitrectomy, scleral buckling, diathermy, and radiation.

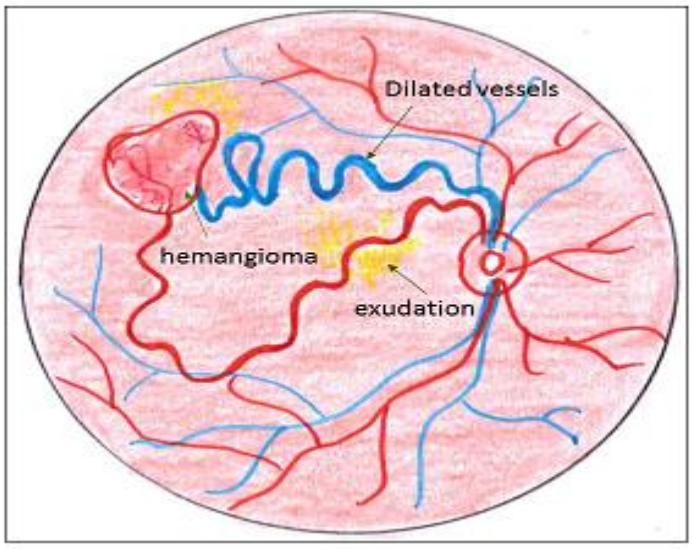

Figure 1.31 A schematic sketch of fundus photograph of Von Hipple Lindau disease

1.8.5.3 *Idiopathic juxtafoveolar retinal telangiectasis*

This is otherwise known as idiopathic macular telangiectasis. It is group of disorders that are characterised by telengiectasias (irregular dilatations) of the capillary network that only affects the foveal area of one or both eyes (Figure 1.32).

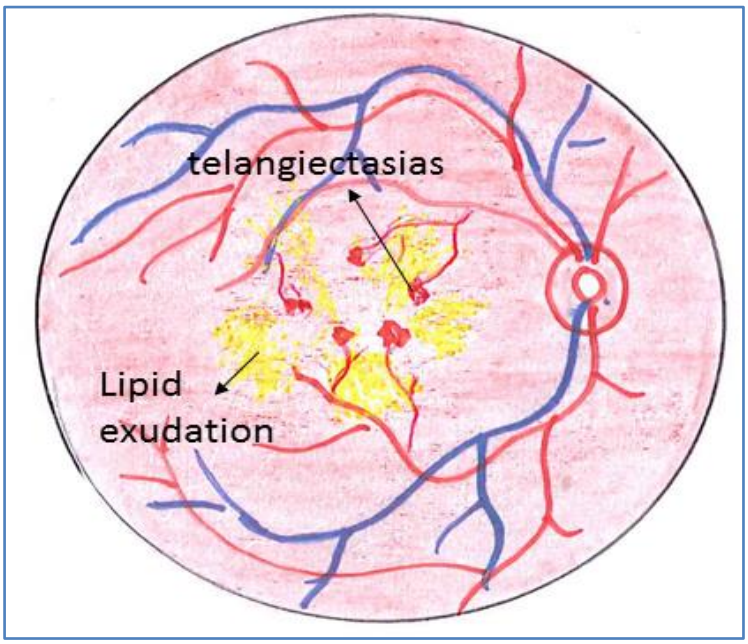

Figure 1.32 A schematic sketch of fundus photograph of idiopathic juxtafoveolar retinal telengiectasis

It is classified into three groups. Group I, is a congenital disorder that is characterised by unilateral telangiectasias and macular edema. Males are affected more than females. Group II is an acquired disorder that is characterised by bilateral telangiectasias and foveal atrophy. Group III is an extremely rare condition that causes progressive alteration of the foveal capillary network.(89) Affected individual may be either asymptomatic or present with visual loss. Visual loss is attributed to macular edema and lipid exudation.(90) Slit lamp examination shows prominent telengiectatic retinal capillaries in the macular region. Fundus Fluorescein angiography and optical coherence tomography may be used to confirm the clinical diagnosis and rule out other retinal vascular disorders. Spontaneous resolution occurs in some cases and treatment is indicated when there is progressive visual loss. Treatment modalities include laser photocoagulation, intravitreal steroids (91) and intravitreal injections of anti-vascular endothelial growth factor .(92)

1.9 Acquired retinal diseases

1.9.1 Retinal artery occlusion

The retina has a dual blood supply. The inner retina is supplied by central retinal artery which is an end artery and the outer retina is supplied by the choroidal circulation. Retinal artery

occlusion is divided into central and branch depending on the anatomical site of obstruction. In central retinal artery occlusion, the obstruction is within the optic nerve substance and in branch artery occlusion the site of blockage is distal to the lamina cribrosa of the optic nerve. Most retinal artery obstructions are due to either thrombosis or embolism.

1.9.1.1 *Central retinal artery occlusion*

Central retinal artery occlusion is an ophthalmic emergency. The incidence is estimated to be 1 in 100,000 people.(93) It is common in individuals in the sixth decade of life and more common in men compared to women. The incidence of bilateral disease is 1-2%. Risk factors for central retinal artery occlusion include systemic hypertension, diabetes, heart disease, carotid artery disease, transient ischemic attacks and renal disease.(94) The hallmark symptom of central retinal artery occlusion is abrupt painless loss of vision.(95) It causes profound monocular visual loss and the visual acuity is worse than 20/400 in 80% of the patients.(96) A visual acuity of no light perception may occur in ophthalmic artery occlusion and a normal central visual acuity may occur in the presence of a cilioretinal artery. The fundus findings in a central retinal artery occlusion include whitening of the retina due to infarction and edema, which is more pronounced in the posterior pole, attenuation of the retinal arteries and a cherry-red spot (Figure 1.33).(97) After about 4 to 6 weeks the

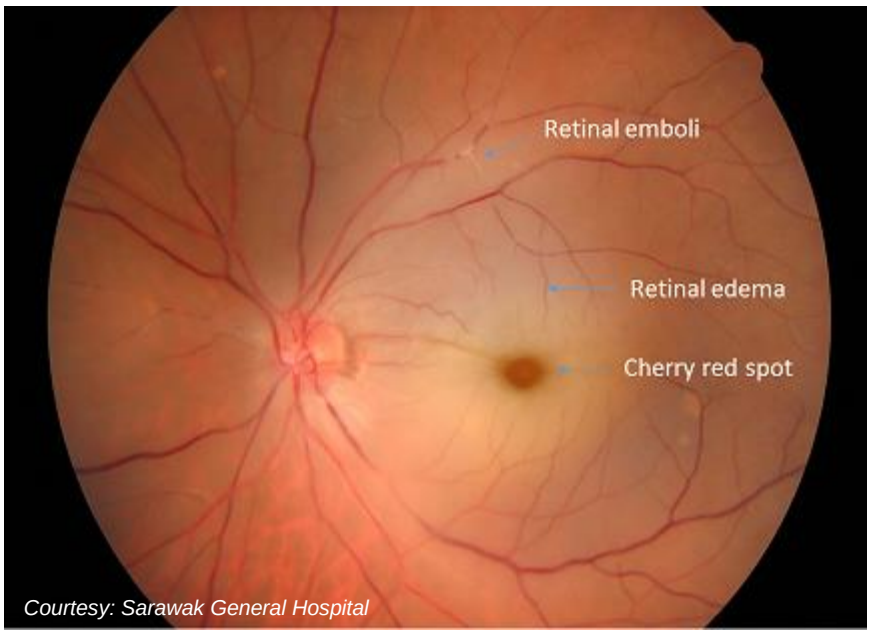

Figure 1.33 Fundus photograph of central retinal artery occlusion

whitening of the retinal resolves and the optic disc becomes pale and arterial collaterals may form on the optic nerve. There is no effective treatment for central retinal artery occlusion . Treatment strategies are focused around increasing blood flow to the retina by decreasing the intraocular pressure by ocular massage, paracentesis (a procedure in which a needle is inserted into the anterior chamber of the eye to remove fluid) and systemic administration of ocular anti-hypertensive medications.

1.9.1.2 *Branch retinal artery occlusion*

Branch retinal artery occlusion is less common than central retinal artery occlusion. In majority of the cases the occlusion is secondary to an emboli of the retinal circulation.(95, 98) Men are more affected than women and it occurs in the sixth decade. Branch retinal artery occlusion typically occurs at the bifurcation of the vessels and involves the temporal vessels in 98% of the cases.(99) Three main types of emboli have been identified which includes cholesterol, platelet-fibrin and calcific. Cholesterol emboli are yellow-orange refractive bodies that arise from the ipsilateral carotid artery atheromatous plaques. Platelet-fibrin emboli are white, smooth, long and are associated with carotid or cardiac thromboses. Calcific emboli are solid, white, and non-refractive plugs associated with calcific heart valves or aorta. Visual symptoms include acute painless loss of vision in the visual field corresponding to the territory of the arterial obstruction. Some patients present with amaurosis fugax (transient monocular or binocular visual loss). Clinical manifestations include relative afferent pupillary defect (a condition in which the pupil responds differently to light shown in one eye due to an underlying retinal or an optic nerve disease) and whitening of the retina in the territory of the obstruction (Figure 1.34).

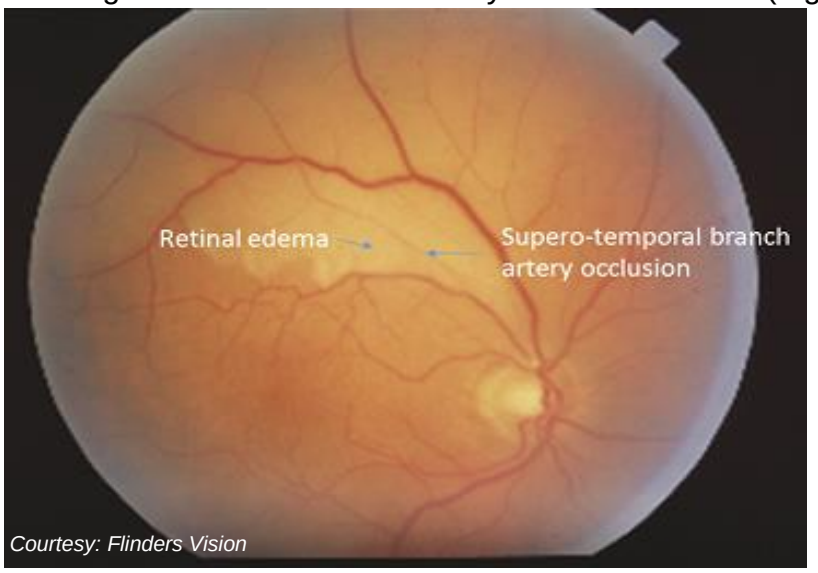

Figure 1.34 Fundus photograph of superior temporal branch retinal artery occlusion

Retinal emboli are visible and are seen in two-thirds of the eyes. Ocular massage and paracentesis can be done to dislodge the emboli. Prognosis of branch retinal artery occlusion is better than central retinal artery occlusion .

1.9.2 Retinal vein occlusion

Unlike arterial obstructive disease, venous obstructive disease of the retina is a common retinal disorder. After diabetic reinopathy, venous obstructive disease is the commonest cause of retinal vascular disorder. Retinal vein obstructions are divided into central retinal vein occlusion and branch retinal vein occlusion. Central retinal vein occlusion is further divided into ischemic and non-ischemic type. The central retinal vein differs from branch retinal vein with respect to pathophysiology, age of onset, systemic association, clinical course, and treatment.

1.9.2.1 *Central retinal vein occlusion*

Central retinal vein occlusion commonly occurs in individuals in the fourth to fifth decade of life.(100) Diabetes mellitus, hypertension and atherosclerotic cardiovascular diseases are the frequently associated underlying medical diseases. Increased intraocular pressure can cause structural alteration of the lamina cribrosa and thereby increases the risk of central retinal vein occlusion. The non-ischemic and ischemic types represent varying severity of the same underlying disease continuum. Non-ischemic central retinal vein occlusion presents with mild to moderate decreased visual acuity. Pupillary testing shows an afferent defect and fundus examination shows dot and flame shaped haemorrhages and venous tortuosity involving all four quadrants. Cotton-wool spots and neovascularisation are uncommon. Thirty-four percent of the non-ischemic central retinal vein occlusion progress to become ischemic within 3 years.(101) There is no proven treatment for the non-ischemic central retinal vein occlusion and the retinal findings usually resolve in about 6-12 months. The ischemic central retinal vein occlusion accounts for 20 -25% of all central retinal vein occlusions.(61) Clinical presentation includes a marked decrease in the visual acuity which ranges from 6/60 to hand-motion acuity. A prominent afferent pupillary defect is typical. Fundus findings include extensive retinal haemorrhages involving all four quadrants, cotton-wool spots, optic disc edema, and macular edema (Figure 1.35).

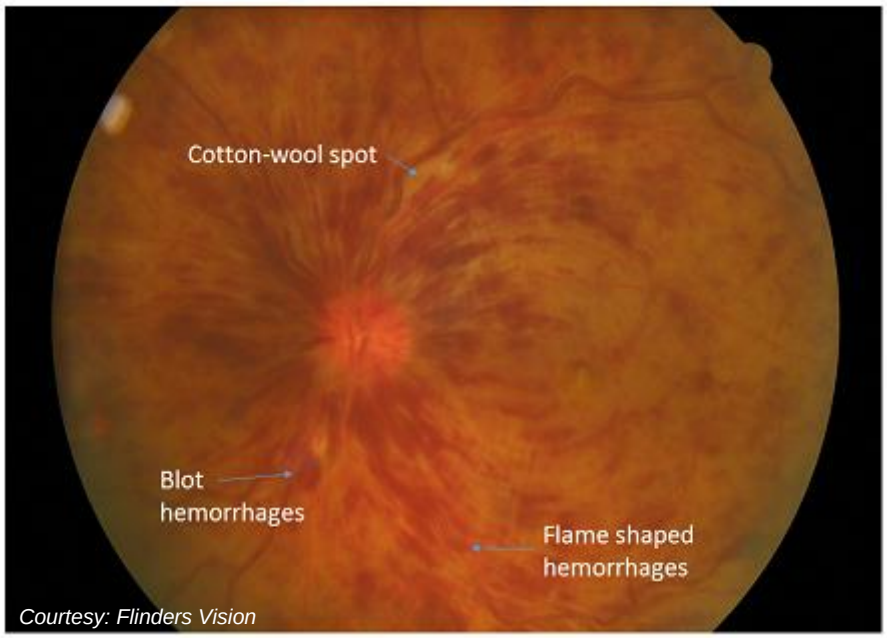

Figure 1.35 Fundus photograph of central retinal vein occlusion

The chance of anterior segment neovascularisation is higher and neovascular glaucoma may occur within 3 months of disease onset. There is no effective treatment for central retinal vein occlusion. However, it is important to identify and treat any underlying medical problems to prevent further complications. Some complications are preventable and treatable. Intravitreal injections of triamcinolone have shown to reduce macular edema and improve vision.(102) Recently intravitreal anti-vascular endothelial growth factor drugs (ranibizumab and bevacizumab) have shown to have a significant beneficial role in the treatment of macular edema and neovascular glaucoma.(103-105)

1.9.2.2 *Branch retinal vein occlusion*

The incidence of branch retinal vein occlusion is three times more than the incidence of central retinal vein occlusion. The usual age of onset is between 60 and 70 years and men and women are equally affected. Branch retinal vein occlusion almost always occurs at arteriovenous crossings and most branch retinal vein occlusions occurs superotemporally. The clinical presentation is usually a sudden onset of blurred vision or a visual field defect. Clinical findings include retinal haemorrhages and cotton-wool spots confined to the distribution of the retinal vein (Figure 1.36). Visual loss in branch retinal vein occlusion occurs due to macular edema, macular ischemia, or vitreous haemorrhage.

Fundus fluorescein angiography is used to confirm the diagnosis and assist for the treatment of branch retinal vein occlusion. In patients who have visual acuity worse than 6/12 due to macular edema, grid laser photocoagulation has found to improve the visual acuity by two or more lines.(106) Intravitreal injections of between 4 and 20 mg of triamcinolone has shown to be beneficial in the treatment of macular edema.(107) However, the treatment effect is not long lasting and associated with complications such as increase in intraocular pressure and cataract development. Moreover, frequent re-treatments are needed to sustain the beneficial effect. Early treatment with anti-vascular endothelial growth factor drugs have shown to have a beneficial role in macular edema.(108)

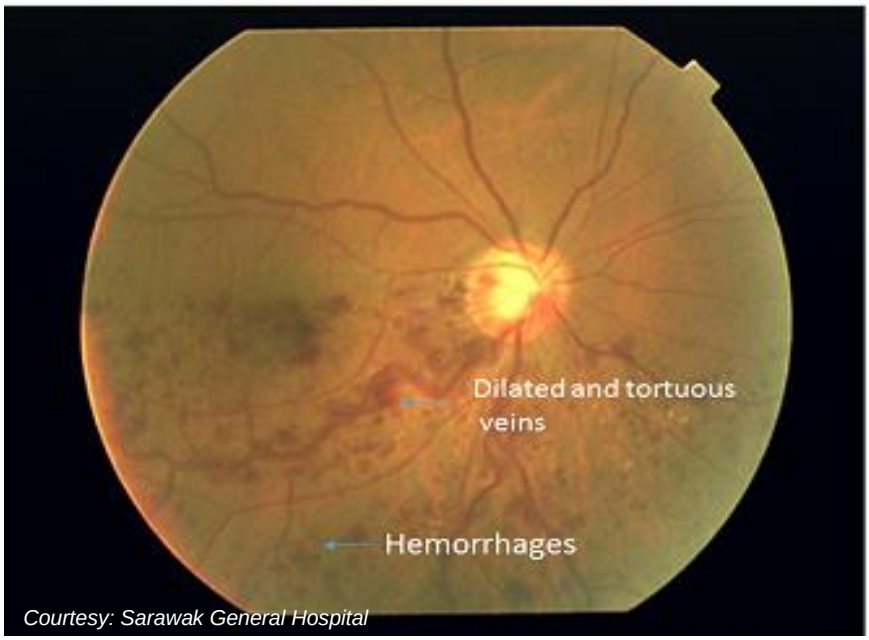

Figure 1.36 Fundus photograph of inferior branch retinal vein occlusion

1.9.3 Hypertensive retinopathy

Hypertensive retinopathy is a condition that is characterised by changes in the retinal vasculature due to systemic hypertension. The true incidence of systemic hypertension is not known due to the presence of other systemic vascular disease such as diabetes. The pure incidence of hypertensive retinopathy is 15%.(109) Both acute and chronic retinal vascular changes are seen in systemic hypertension. Common clinical findings in chronic hypertensive retinopathy include focal constriction and dilatation of the retinal arterioles, tortuosity of the retinal arterioles, an increase in the arteriolar light reflex and loss of transparency of the intra-arterial blood column. Acute retinal changes are seen in malignant hypertension, which occurs in nearly 1% of hypertensive patients. Malignant hypertension is a condition in which there is a rapid and severe elevation of the blood pressure. The

systolic pressure is above 200 mm Hg and the diastolic pressure is greater than 140 mm Hg. Ophthalmic findings in acute malignant hypertensive retinopathy include focal arteriolar narrowing, cotton-wool spots, intra-retinal transudates, macular oedema, and retinal haemorrhages (Figure 1.37). Keith-Wagner-Barker classification is one of the widely accepted classification scheme to stages.(110) In Stage I there is mild to-moderate narrowing of the retinal arterioles. In Stage II there is local and generalised narrowing of the retinal arterioles and arteriovenous crossing changes. In stage III there are all features of the stage II plus retinal edema, retinal haemorrhage, and cotton-wool spots. In Stage IV there are all the features of Stage III, but with papilledema. Treatment of chronic hypertensive retinopathy is treating the underlying systemic hypertension. Malignant hypertension is a medical emergency and lowering blood pressure in a controlled fashion will minimise end-organ damage.

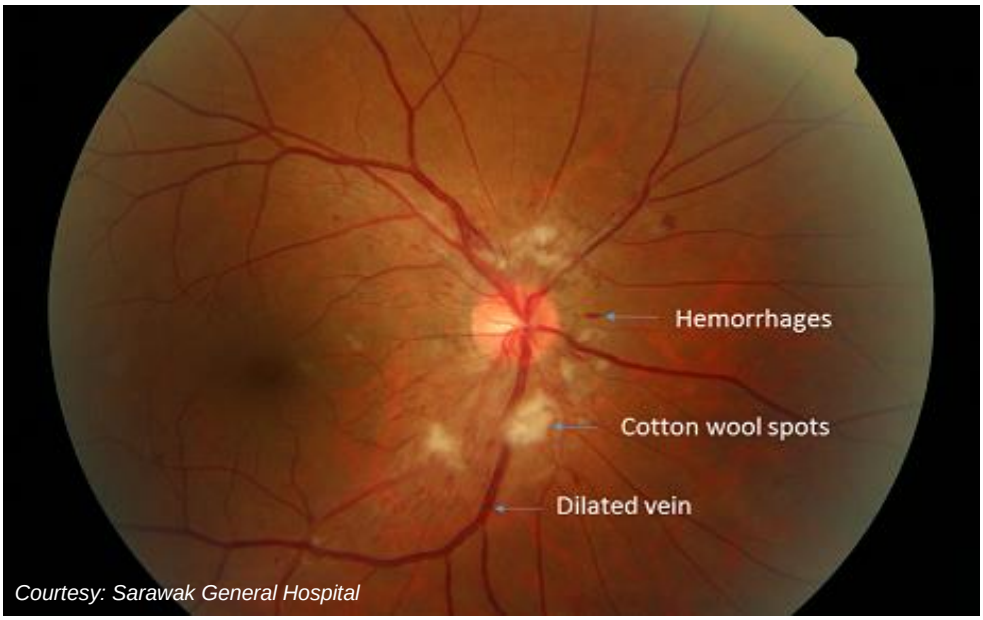

Figure 1.37 Fundus photograph of malignant hypertension (Stage IV)

1.9.4 Central serous retinopathy

CSR is defined as a circumscribed neurosensory retinal detachment secondary to one or more defects in the retinal pigment epithelium.(111) It is an uncommon disease and the incidence was found to be 5-6 per 100,000 people.(112) It is more common in males than females.(113, 114) It typically affects individuals in the age range of 20 to 50 years. The following risk factors has been associated with CSR which includes; emotional stress, type A personality (personalities that are more ambitious, competitive, and outgoing), systemic

hypertension, pregnancy, autoimmune disorders, gastroesophageal reflux, and medications such as glucocorticoids. An abnormal choroidal circulation has been implicated in the causation of CSR. The most common symptoms of CSR include blurred vision, metamorphopsia (a type of distorted vision in which straight line appear wavy) and micropsia (objects appear smaller than normal). The visual acuity of the affected individuals ranges from 6/5 to 6/60 which improves with plus lenses. Fundus shows a transparent blister in the posterior pole (Figure 1.38).

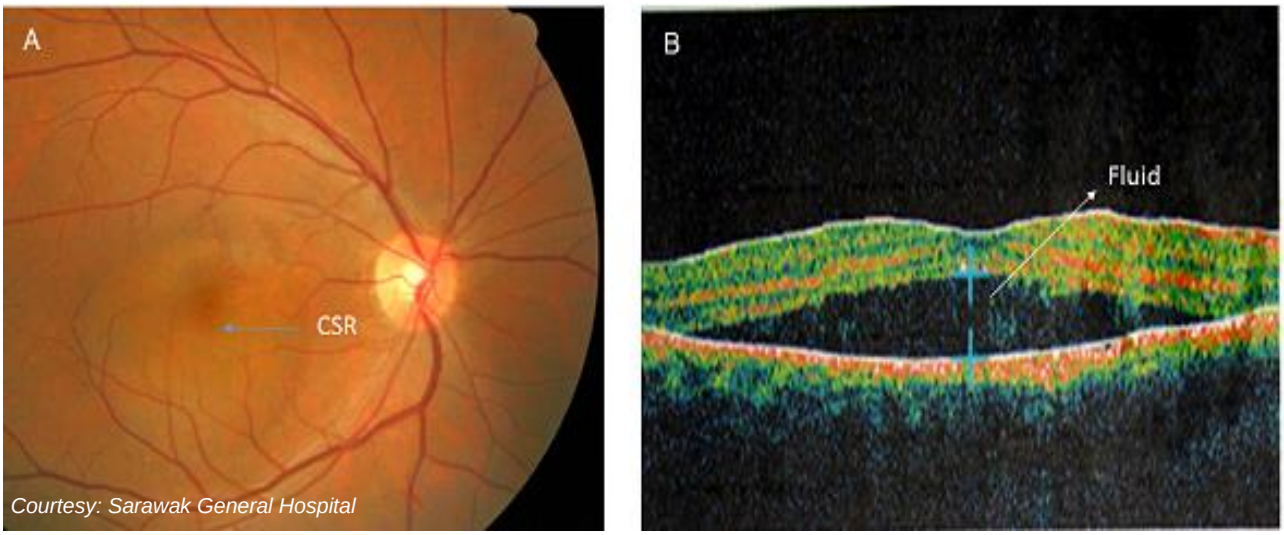

Figure 1.38 Fundus photograph of an eye with central serous retinopathy. Note the neural retinal detachment the size of two disc diameters in the macular region (B) OCT image showing sub-retinal fluid

The disease is mostly self-limiting. Permanent sequelae include metamorphopsia, decreased brightness perception and altered colour vision.(115) Diagnosis of CSR is mainly clinical and ancillary investigations such as fundus fluorescein angiography and optical coherence angiography are mainly used to confirm the diagnosis and rule out other pathologies that cause neurosensory retinal detachment. As the majority of the cases of CSR resolve spontaneously, the initial treatment options include conservative management and discontinuation of glucocorticoid medications.(116) The treatment options for CSR include laser photocoagulation and photodynamic therapy. Laser photocoagulation is applied to the site of fluorescein leak. This has been found to reduce the duration of the serous detachment but has no final visual prognosis. Generally, the prognosis for CSR is good and permanent sequelae is rare.(117)

1.9.5 Macular hole

This is a full thickness defect involving the centre of the macula. In most cases the MH is idiopathic. Idiopathic MH affects healthy individuals in the sixth to seventh decade and women are affected more than men by a ratio of 2:1.(118) The other etiological factors of MH include trauma, cystoid macular oedema, ERM, rhegmatogenous retinal detachment (a condition in which fluid from the vitreous cavity passes through a retinal defect into the sub-retinal space to cause separation of the retina from its attachment to the underlying tissue), vitreomacular traction (incomplete separation of the vitreous gel from the retina causing retinal distortion and decreased vision), laser energy, high myopia and posterior staphyloma (protrusion of the posterior shell of the eye globe that is frequently found in highly myopic eyes).(119-122) MH is a relatively rare disorder with an incidence of about 33/10,000 people over the age of 55.(123) Bilateral disease occurs in 10 to 20% of cases.(124) The pathogenesis of MH is focal shrinkage of vitreous cortex in the foveal area.(125, 126) Clinical presentation includes an acute or a subacute distortion of the central vision. Clinically four stages occur in idiopathic MH development.(127) Stage I is characterized by absence of any symptoms and the presence of a small central spot seen in ophthalmoscopy. In stage II there is a small central or eccentric full-thickness defect (100-300µm) which can be either round, oval or horse-shoe shaped. Visual acuity is reduced and varies from 6/12 to 6/120. In stage III there is a full-thickness neural retinal defect with smooth edges surrounded by a rim of subretinal fluid. The visual acuity varies from 6/60 to 6/240. Stage IV has all the features of stage III, but with complete posterior separation of the vitreous from the fovea (Figure 1.39).

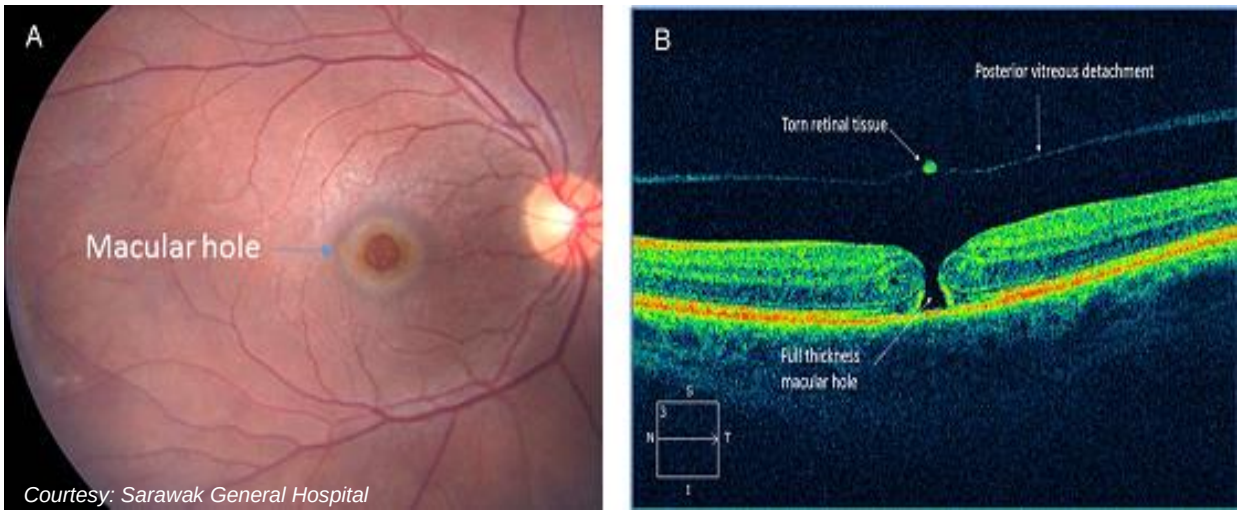

Figure 1.39 Fundus photograph of stage IV macular hole (B) Optical coherence tomography image of a stage IV macular hole

MH is mainly diagnosed clinically and optical coherence tomography is the best ancillary investigation. As spontaneous improvement occurs in 50% of cases, the treatment for stage I MH is mainly observation. The treatment for stage II and III MH is vitrectomy with either internal membrane or ERM peeling and gas tamponade. The most common complication of vitrectomy is cataract formation. The other complications are retinal tears and subsequent retinal detachment. The best surgical results are obtained if the surgery is performed within 6 months of visual loss.

1.9.6 Epiretinal membrane

ERM occurs due to proliferation of an avascular fibro-cellular membrane on the inner surface of the retina which causes varying degrees of macular dysfunction. ERM is otherwise known as macular pucker, pre-macular fibrosis or gliosis, cellophane maculopathy, and surface wrinkling retinopathy. It can occur in otherwise healthy eyes or secondary to retinal tears and rhegmatogenous retinal detachment, blunt or penetrating trauma, intraocular inflammation or vascular disease.(61) It tends to occur in older adults above the age of 50 years. The prevalence ranges from 4 to 11%.(128, 129) Women are more affected than men.(130) The ocular manifestation of ERM depends on the opacity of the membrane and the amount of macular distortion. Cellophane maculopathy is the mildest form of ERM and does not produce any retinal distortion. Loss of visual acuity and metamorphopsia occurs with more significant contraction and full-thickness distortion. Diagnosis is mainly clinical by slit lamp bio-microscopy. An abnormal glistening reflex from the inner surface of the retina is seen in the mildest form of the disease. As the disease progresses a series of fine, irregular striations or wrinkles may be seen radiating from the margins of the membrane and tortuosity of the fine macular capillaries may appear (Figure 1.40). Fundus fluorescein angiography and optical coherence tomography are mainly used to exclude other macular disorders, assess the severity of the disease and to decide the treatment plan. The Fundus fluorescein angiography findings in ERM are irregular intra-retinal leakage in the macular region. In optical coherence tomography, the ERM appears as a hyper-reflective membrane on the anterior retinal surface. No intervention is needed in patients with minimal symptoms. The treatment of choice for ERM is pars plana vitrectomy, peeling of the internal limiting membrane, peeling of the ERM and gas tamponade. Predictors of better visual outcomes include shorter duration of the diseases, preoperative visual acuity better than 20/100 and absence of tractional retinal detachment.(131)

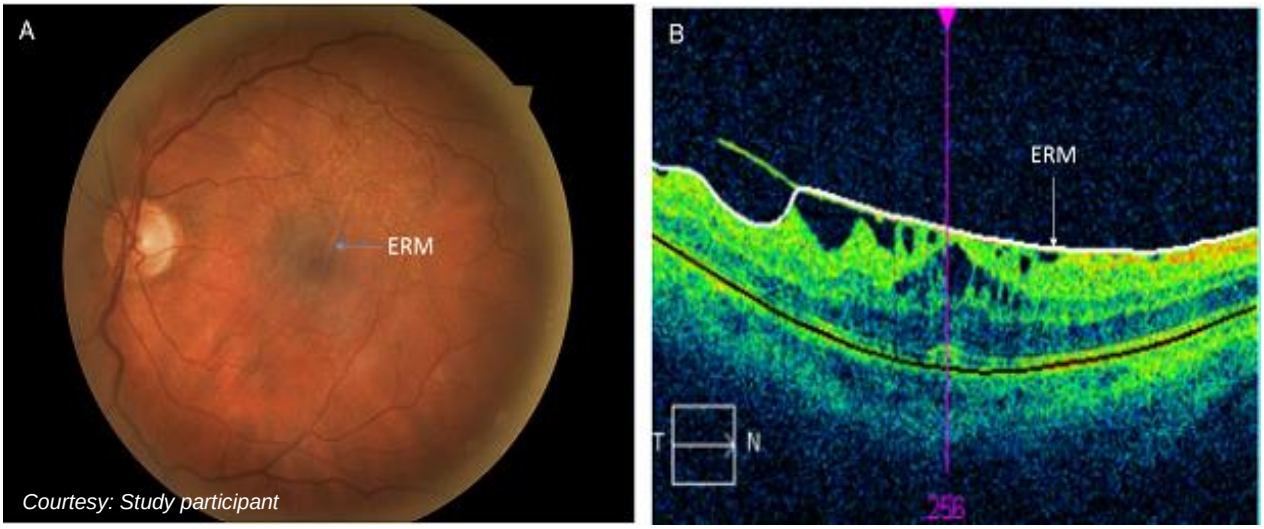

Figure 1.40 (A) Fundus photograph of an epiretinal membrane (B) Optical coherence tomography image demonstrates an epiretinal membrane and intra-retinal fluid

CHAPTER 2 IMPACT OF RETINAL DISEASES ON QUALITY OF LIFE: A LITERATURE REVIEW

2.1 Introduction

Advances in understanding of molecular, genetics and cellular biology of retinal diseases have led to development of new treatments.(132) This situation of expanding treatment options demands appropriate outcome measures for studies to detect treatment benefit. This includes patient-reported outcome (PRO) instruments as a part of comprehensive assessment of treatment effectiveness. The use of PRO instruments as one of the outcome measures is critical given the number of new treatments being developed which require thorough evaluation of their effectiveness from the patients' perspective.(133, 134) Studies have reported that quality of life (QoL) is significantly impaired in people with retinal diseases and also the lives of their close ones.(2, 3, 24, 135) Moreover, the repercussions of treatments also add on to lower the overall QoL of the individual. Over 150 PRO instruments have been developed in ophthalmology and optometry. The majority of these PRO instruments have been developed for cataract, low vision and glaucoma.(40, 42) In terms of retina-specific PRO instruments only a few diseases-specific instruments are developed when compared to the number of instruments that were developed for other diseases. A few retina-specific PRO instruments are available, but they suffer from limited content coverage of QoL. Moreover, these PRO instruments have undergone basic validation procedure and the psychometric properties are not scientifically sound to assess the patient-reported outcomes.(38, 136-138) Hence a literature review was undertaken to critically evaluate all the studies that implemented PRO instruments in retinal diseases and provide a quality assessment of the PRO instruments in terms of their measurement properties.

2.1.1 Patient-reported outcome (PRO) instrument

A patient-reported outcome instrument captures information on the health from the patients' perspective without the interpretation by a clinician or a researcher.(139) This has resulted in the development of a large number of PRO instruments across all fields of health care including in ophthalmology. Grossly PRO instruments can be defined as generic or disease-specific. The generic PRO instruments (e.g. Short Form Health Survey-36 (SF-36)) measure a broad spectrum of health concepts and are potentially suitable for a wide range of patient groups suffering from different types of diseases and general population. The disease-specific PRO instruments (e.g. Macular Disease Dependent Quality of Life (MacDQoL)) are

designed to be used in patients with a specific health problem and are intended to measure the impact of that specific disease on the person. There are many different eye diseases, so a PRO instrument developed for one eye disease but then used for a different eye disease ceases to be disease-specific, but could be called an ophthalmic PRO instrument. In this chapter, disease-specific instruments are considered as those originally developed for the specific retinal diseases (e.g. specifically for age related macular degeneration (AMD)); ophthalmic but non-disease-specific instruments are ophthalmic instruments that have been originally developed for eye disease/s other than the retinal disease under consideration and generic instruments developed for non-ophthalmic disease to measure a broad concepts of health outcomes.

PRO instruments have been developed or validated using two different approaches: the classical test theory or the item response theory approaches.(38, 136, 140, 141) The classical test theory and the item response theory approaches have differences in terms of scoring of the instrument and the assessment of the psychometric properties of the instrument. In classical test theory, the PRO instruments are scored by adding the raw scores of all the items, which are ordinal.(142) Such scores do not provide an interval measures and introduces noise that damages the sensitivity of the PRO instruments.(40, 143) Moreover, summary scores are problematic when there are ceiling (i.e. the items in a PRO instrument are too easy for the study population) or floor (i.e. the items in a PRO is too difficult for the study population) effects. On the other hand, the item response theory models such as the Rasch analysis model provides in-depth assessment of psychometric properties including the test of dimensionality and the measurement precision of a PRO instrument. The Rasch model is a probabilistic mathematical model which assumes that probability of a respondent to choose a response category for an item is the difference between the item difficulty and person ability.(144) The advantage of Rasch analysis is that it estimates interval-level scoring for both the item difficulty and respondent's ability from the PRO raw data. The interval-level scores of the respondent ability and the item difficulty on the same underlying trait makes the Rasch model a powerful method for estimating health outcome measures.(40)

2.1.2 Quality of life (QoL)

The World Health Organisation (WHO) defines QoL as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation

to their goals, expectations, standards and concerns".(145) Basically, QoL is a very broad concept that fundamentally encompasses every impact that health or disease has on a person. It is a multidimensional construct affected by the person's physical health, mental state, personal principles, and social relationships. In eye diseases, a set of 10 QoL domains have been identified as important to people with eye diseases.(45, 57, 146) The ophthalmic QoL domains are activity limitation, mobility, visual symptoms, ocular surface symptoms, general symptoms, emotional well-being, social participation, economic, health concerns and convenience. For a complete assessment of QoL impact, all these QoL domains must be included and assessed separately.

2.2 Aims and objectives

1. To identify all the PRO instruments used in retinal diseases and determine to what extent they measure QoL (content coverage of QoL).
2. To assess the quality of the PRO instruments in terms of their measurement properties (validity, reliability, and responsiveness).
3. To identify gaps between known QoL impacts of retinal diseases and QoL measured by the existing PRO instruments.

2.3 Method of literature search

A systematic review was performed to identify all the published articles that reported QoL assessment or PRO measurements or qualitative reports of patients' perspective in patients with retinal diseases. The literature search was performed using the Medline, Web of Science, EMBASE and Cochrane CENTRAL databases. The following were the key words used for the search, **vitreoretinal** OR **macula** OR **retina*** OR **retinitis** OR **maculopathy** OR **retinopathy** AND **quality of life** OR **questionnaire** OR **focus groups** OR **qualitative** OR **patients' perspective** OR **patient-reported outcomes**. The search was carried out on April 17, 2014, and it was not limited to any preceding dates. All the articles on retina-specific diseases and QoL issues were identified.

Studies on children of age <18 years and articles not written in English were excluded from this study. Types of studies excluded were epidemiological studies, studies on systemic and ocular comorbidities, studies on health valuation methods (preference-based or utility measures), studies on evaluation of health programs, studies on objective ocular assessments, articles on nutrition and diet, articles on knowledge and attitude of

practitioners, review articles, case reports and letters to editors. Figure 2.1 summarises the literature search and the number of articles included in this study.

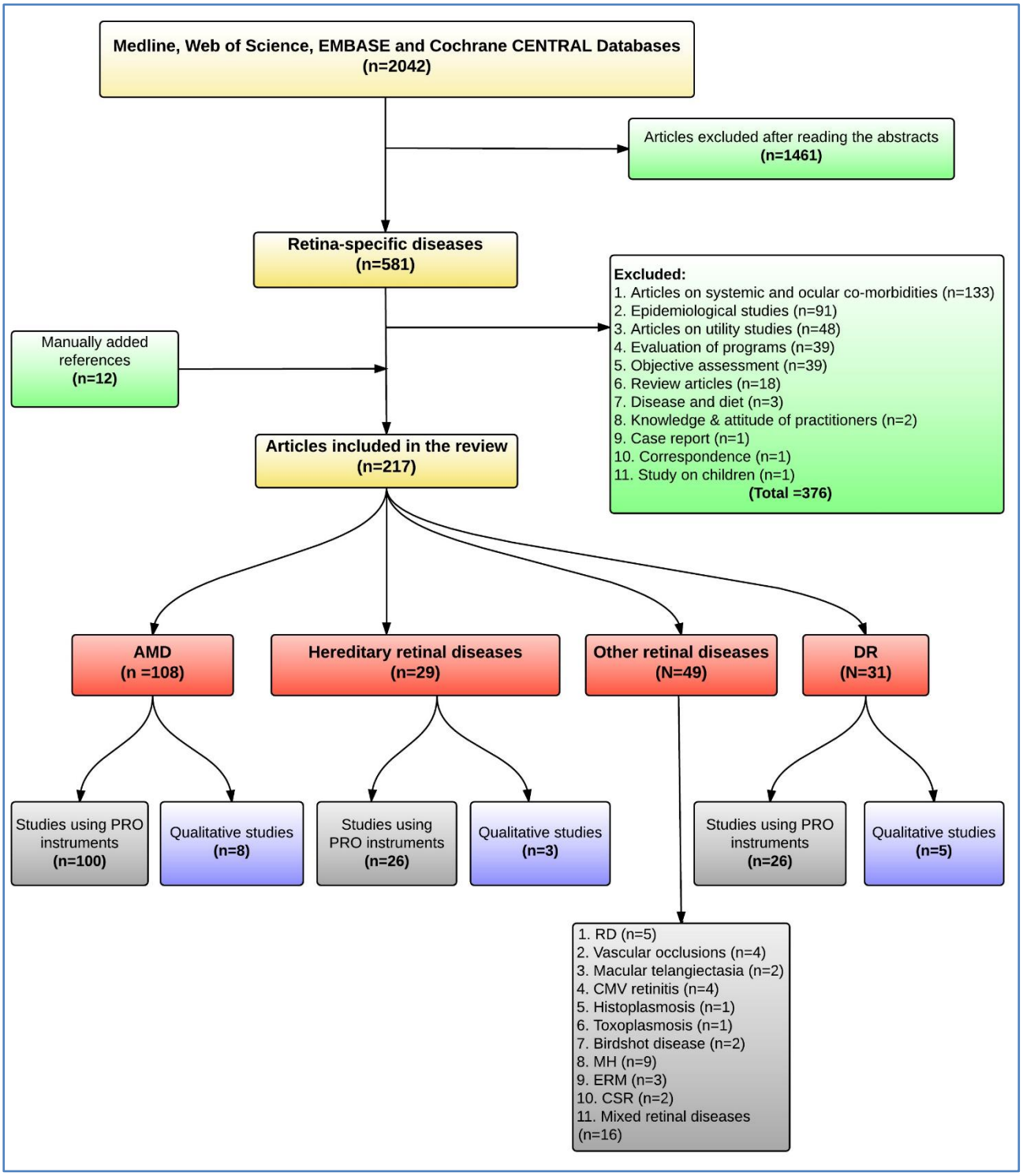

Figure 2.1 Steps involved in the literature review

AMD, age related macular degeneration; DR, diabetic retinopathy; RD, retinal detachment; CMV, cytomegalovirus; MH, macular hole; ERM, epiretinal membrane; CSR, central serous retinopathy; PRO, patient-reported outcome

2.4 Methods

To address aim 1, the retrieved articles were grouped together by disease (AMD, diabetic retinopathy (DR), retinal vascular conditions, hereditary degenerations/dystrophies, retinal infection, macular disease, and others) and further sub-grouped based on types of PRO instruments used (i.e. disease-specific, ophthalmic but non-disease-specific and generic). Similarly, the articles on qualitative studies were grouped separately. The content coverage of all the PRO instruments (disease-specific, ophthalmic but non-disease-specific and generic) was assessed across ten ophthalmic QoL domains which were identified based on extensive qualitative consultations with patients living with AMD and DR.(45, 57) The QoL domains were activity limitation, mobility, general symptoms, visual symptoms, ocular surface symptoms, social participation, emotional well-being, economic, health concerns and convenience.

Next, the PRO instruments were grouped based on a series of quality criteria (aim 2) that included the methods used in the identification and development of the PRO instrument, psychometric properties, validity, reliability, and responsiveness (see Table 2.1 for the definition and assessment of the quality criteria). PRO instruments that were summary scored were assessed using classical test theory based psychometric properties, namely acceptability, targeting and internal consistency (See Table 2.1 for definition of these quality criteria) and Rasch scaled PRO instruments were assessed using Rasch based psychometric properties namely, response categories, dimensionality, measurement precision, item fit statistics, differential item functioning (DIF) and targeting (see Table 2.1 for definition of these quality criteria).

The quality criteria used in this study is based on the US Food and Drug administration (FDA) guidelines, framework proposed by Lundström and Pesudovs and Pesudovs *et al,* and guidelines put forward by an international initiative (Consensus-based Standards for the selection of health status Measurement Instruments.(42, 147-151) The same criteria has also been used in a major systematic review which explored quality of all the ophthalmic instruments tested with Rasch analysis.(40) The criteria used in this study are similar to the criteria used in Khadka *et al* study with slight modification.The assessment criteria broadly assessed the methods undertaken in the content development, psychometric properties and validity, reliability and responsiveness of the PRO instruments. The aim was to identify the

highest quality existing instrument for retinal diseases. Each PRO instrument was assessed and was graded against the following criteria: content quality, psychometric assessment based on classic test theory and Rasch analysis, validity, reliability, and responsiveness (Table 2.1). Each of the criterion is assessed differently based on the definition given in Table 2.1 for a grade assignment of A/B/C. Each PRO instrument was given specific grades across all the criteria based on the available information and metrics. For example, the 7-item Near and Distance Vision subscale of the Daily Living Task Dependent on Vision (DLTV) as graded 'A' for 'measurement precision' because it's person reliability value was high (i.e. 0.89, according to the definition grade 'A' for any value ≥ 0.85) (Table 2.1). A PRO instrument was considered to have a superior quality if it had the highest number of grade A across the quality criteria.

For aim 3, the QoL issues expressed in qualitative studies across the ten QoL domains were compared with the content of the existing PRO instruments. This was performed to identify the gaps in the known QoL impacts of retinal diseases and QoL measured by the existing PRO instrument.

2.5 Results

A total of 2042 articles were identified from the initial search (Figure 2.1). After reading the abstracts of the articles, 1461 were excluded. The remaining 581 were matched with the selection criteria and a further 376 articles were excluded as they did not meet the selection criteria. The final phase yielded 205 articles for analysis to which 12 articles were added in the review by cross checking the references. Analysis was carried on this final 217 articles (Figure 2.1). Most articles were on AMD (n=108) followed by DR (n=31), hereditary degenerations/dystrophies (n=29), macular hole (MH) (n=9), retinal vascular conditions (n=6), retinal detachment (DR) (n=5), retinal infections (n=8), central serous retinopathy (CSR) (n=2), epiretinal membrane (ERM) (n=3) and studies on populations with mixed retinal diseases (n=16). Out of 217, 17 qualitative studies were identified and these studies were on AMD (n=8), DR (n=5), hereditary degenerations/dystrophies (n=3) and MH (n=1). Among 200 articles reporting PRO measurement, 110 different PRO instruments were identified.

Table 2.1. Quality assessment criteria for PRO instruments (42, 143, 147-149, 152)

Property	Definition/ assessment	Grade	Quality criteria
Content development			
Item identification	Identification of the initial item content	A	Comprehensive consultation with patients and literature review for that disease group
		B	Minimal consultation with the appropriate patients and expert opinion and literature review for that particular disease group
		C	No consultation with patients/developed for another disease group
Item selection	Selection of the items included in the final instrument	A	A pilot instrument developed and tested with Rasch or factor analysis, statistical justification was provided for removing items, plus items with floor and ceiling effects were removed, and the amount of missing data was considered to obtain the final set of items.
		B	Only some of the above techniques were used
		C	No pilot instrument or no statistical justification of items was included in the final instrument
Classic test theory (CTT) based psychometric properties			
Acceptability	The percentage of missing data for each item and the percentage of people for whom a PRO instrument score can be computed	A	≤ 5%
		B	5% to ≤ 40%
		C	> 40%
Targeting of the items	PRO instrument scores should span the entire range; floor (proportion of the sample at the maximum score) and ceiling (proportion of the sample at the minimum score effects should be low)	A	Either floor or ceiling effect ≤ 5%
		B	Either floor or ceiling effect 5% to ≤ 40%
		C	Either floor or ceiling effect > 40%
Rasch based psychometric properties			
Response categories	The extent to which the categories used to rate the items are chosen in a logical order (ordered categories). Evenly spaced categories (distance between category thresholds are expected to be between ≥1.4 and <5.00 logits)	A	All the categories were ordered or ordering of the categories was obtained after repairing disordered categories and evenly spaced categories.
		B	All the categories were ordered or ordering of the categories were obtained after repairing disordered categories and categories were not evenly spaced
		C	Unrepairable disordered categories
Dimensionality	The extent to which the instrument measures a single underlying construct. Principal components analysis (PCA) of the residuals based on two	A	Variance explained by the measure ≥60% and eigenvalue of the first contrast <2.0/ ≤5% of the person estimates are significantly different /% of t-tests falling outside 95% CI is ≤5%

	parameters: the amount of raw variance explained by the measure and eigenvalue of the unexplained variance in the first contrast or PCA/t-test protocol: % of t-tests of person measures obtained from the two item sets grouped based on PCA guided residual loading (1st set =≥+0.3 and 2nd set = ≤-0.3) significantly different/ % of t-tests falling outside the range ±1.96 (95% CI)	B C	Variance explained by the measure ≥50% to <60% and eigenvalue <2.0/ > 5% ≤ 10% of the person estimates are significantly different/ % of t-tests falling outside 95% CI is > 5% ≤ 10% Variance explained by the measure <50%, eigenvalue ≥ 2.0, indication of subsets of items (this indicates unidimensionality)/ >10% of the person estimates are significantly different/ the lower bound of a Binomial 95% CI of the observed proportion overlaps > 10%
Measurement precision	The extent to which an instrument distinguishes between different levels of participants' abilities. Represented by person separation index or reliability coefficient (minimum acceptable value, separation =2.00, or reliability α =0.80	A B C	≥2.50, α ≥0.85 2.0 to 2.49, α ≥0.80 to <8.50 <2.0, α <0.80
Item fit statistics	The extent to which the items in the instrument fit with the Rasch model expectation. Two fit statistics: infit and outfit mean square. Both fit statistics should have a value of 1 (acceptable range, 0.50 to 1.5)	A B C	All items with infit and outfit mean square between 0.7 and 1.3 (or) infit and outfit standardized residuals < 2 One or two items outside the 0.5 and 1.5 (or) infit and outfit standardized residuals ≥ 2 to < 2.5 More than two items outside the 0.5 and 1.5 limit (or) infit and outfit standardized residuals ≥ 2.5
Differential item functioning (DIF)	The extent to which the levels of response ability of different subgroups of the same study population differ to an item (magnitude, <0.50 logits: insignificant,0.50 to 1.0 logits: mild, >1.0 logit: notable)	A B C	All items with DIF <0.50 logits Some items 0.50 to 1.0 logits and one at the most >1.0 logits More than one item >1.0 logits DIF.
Targeting	The extent to which item difficulty matches with the level of participants' visual abilities. It is the difference between item and person means (difference of >1 logit indicates significant mistargeting)	A B C	≤ 1 logits >1 to ≤ 2 logits >2 logits
Validity			
Concurrent validity	The extent to which the instrument score correlates with the score of the clinical measure (e.g. visual acuity, contrast sensitivity, visual field etc.)	A B C	Tested against appropriate clinical measures and correlates between 0.3 and 0.9 Tested against debatable clinical measures and correlates between 0.3 and 0.9 Correlates <0.3 and >0.9

Convergent validity	The extent to which the instrument correlates with the existing instrument measuring similar instrument	A B C	Tested against appropriate instrument and correlates between 0.3 and 0.9 Tested against debatable instrument and correlates between 0.3 and 0.9 Tested and correlation <0.3 or >0.9
Discriminant validity	The extent to which the instrument correlates with the existing instrument measuring a different construct	A B C	Tested against appropriate instrument and correlates <0.3 Tested against debatable instrument and correlates <0.3 Tested and poor correlation >0.3
Known group validity	The extent to which the instrument can discriminate between clinically distinct groups	A B C	Tested in appropriate groups and significant difference between groups Tested in debate groups and significant difference between groups Tested and non- significant differences between groups
Reliability			
Test-retest reliability	The extent to which the instrument demonstrated temporal stability when administered in two different periods. Intraclass correlation (ICC) >0.8 is considered good reliability	A B C	ICC ≥0.8 ICC 0.79 to ≤0.60 ICC < 0.60
Responsiveness			
Responsiveness	The extent to which the instrument can detect clinically important changes over time (minimal importance difference (MID) is the smallest difference in score, which a patient perceives as beneficial)	A B C	Change in score shown (increase or decrease) to have statistical significance Instrument tested for responsiveness, but statistical significance not reported No change in the PRO instrument score from baseline or statistically insignificant

A, high; B, medium; C, low; NR, not reported

Adapted and modified from “Quality assessment of ophthalmic questionnaires: review and recommendations.” Khadka. J. et al 2013, Optom Vis Sci; 90(8):720-744.

More than half of these PRO instruments were generic instruments (n=62) followed by disease-specific instruments (n=29) and ophthalmic but non-retina-specific instruments (n=19) (Appendix 1). Seventy studies used more than one PRO instrument. Among the ophthalmic but non-retina-specific PRO instruments, the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ) was the most frequently used (n=104 studies) followed by the Visual Function Index (VF-14) (n=10 studies). The DLTV was the commonly used retina-specific PRO instrument (n=8 studies). Among the generic PRO instruments, the SF-36 (n=24 studies) and the Hospital Anxiety and Depression Scale (n=11 studies) were the commonly used instruments. The majority of the studies used summative scores for analysis, and only 13 studies used Rasch analysis validated PRO instruments and interval-level scoring. Only 52 studies out of 200 articles used disease-specific PRO instruments.

In the following section, I describe the types of PRO instruments used for each retinal disease. The quality of PRO instruments was assessed based on a series of quality criteria (Table 2.1) including the extent of their content coverage for each retinal disease. Qualitative studies that reported the impact of the disease from the patient's perspective were also included.

2.5.1 Age related macular degeneration

In total, there were 108 studies on AMD. Of the 108 studies, 100 studies used PRO instruments and the remaining were qualitative studies.

Nine disease-specific PRO instruments for AMD were identified (Table 2.2). These included the MacDQoL (34), DLTV (36), Age-related Macular Degeneration Self-Efficacy Questionnaire (35), Activity Limitation Questionnaire (ALQ) (37), Night Vision Questionnaire (NVQ -10) (153), Face Recognition Questionnaire (FRQ) (154), Low Luminance Questionnaire (38), Age-related Macular Degeneration Health Impact Questionnaire (155) and Discomfort Anxiety Fear Questionnaire.(156) The DLTV (n=8 studies) was the most frequently used AMD-specific questionnaire.(36, 38, 39, 155, 157-160) Most of the AMD-specific PRO instruments cover activity limitation and emotional well-being domains of QoL. The DLTV and the Age-related Macular Degeneration Health Impact Questionnaire covers a single domain.

Table 2.2 The Patient-reported outcome instruments used and their content coverage (concepts/domains being measured) in age-related macular degeneration (AMD)

Study	Ophthalmic but non-disease-specific PRO instruments /Population developed for /Types of PRO instruments	Age (years) /Target population/Country/ Sample size	Concepts /domains being measured	Generic PRO instruments	Concepts /domains being measured
Mitchell (2013)(161)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18 /AMD/Australia, Canada & Europe/345	AL, EM & SC		
Parravano (2013)(162)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/Italy/12	AL, EM & SC		
Jivraj (2013)(163)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥ 65/AMD/Canada/101	AL, EM & SC	CES-D	EM
Menon (2013) (164)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥ 60/AMD/UK/99	AL, EM & SC		
Rovner (2013) (165)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific AI /general ophthalmic population /ophthalmic but non-disease-specific	≥ 65/AMD/US/241	AL, EM & SC AL	PHQ-9 OPS	EM CP & SC
Finger (2013) (9)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/Germany/3470	AL, EM & SC		
Bressler (2013) (8)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/US/1126	AL, EM & SC		
Finger (2012)(166)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/Germany/55	AL, EM & SC		
Parodi (2012) (167)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/Italy/28	AL, EM & SC		
Šiaudvytytė (2012) (168)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/Lithuania/140	AL, EM & SC	HADS	EM
Mettu (2011) (169)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥55/AMD/US/55	AL, EM & SC		
Rovener (2011) (170)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥65/AMD/US/241	AL, EM & SC	PHQ-9 OPS	EM CP & SC
Sørensen (2011) (171)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50 /AMD/Denmark/120	AL, EM & SC		
Orr (2011) (172)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/US/92	AL, EM & SC		
Coleman (2010) (173)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥65/AMD/US/1674	AL, EM, & SC		
Berdeaux (2011) (174)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific MacDQoL /AMD /retina-specific	≥50/AMD/France, Canada, US, Italy, Germany, Netherlands, Spain, Australia, Belgium &Israel/797	AL, EM & SC AL, SC, EM & MB		
Piermarocchi (2011) (175)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/Italy/293	AL, EM & SC		

Frennesson (2010) (176)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥ 60/AMD/Sweden//30	AL, EM & SC		
Cruess (2007) (177)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/Canada/166	AL, EM & SC	HADS	EM
Soubrane (2007) (177)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/Canada, France, Germany, Spain & UK/401	AL, EM & SC	HADS	EM
Leys (2008) (178)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/US & Canada/569	AL, EM & SC		
Lotery (2007) (179)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/UK/75	AL, EM & SC	HADS	EM
Lüke (2007) (180)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥65/AMD/Germany/50	AL, EM & SC		
Rovner (2007) (181)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥64/AMD/US/206	AL, EM & SC	HDRS	GS & EM
Hudson (2006) (182)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥55/AMD/US/217	AL, EM & SC	ADL	AL
Tranos (2006) (183)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/UK/38	AL, EM & SC		
Lindbalt (2005) (184)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥55/AMD/US/4119	AL, EM & SC		
Berdeaux (2005) (185)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/US & Europe/114	AL, EM & SC		
Cahill (2005) (186)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥55/AMD/US/70	AL, EM & SC	SF-12	GH, AL, GS, EM & SC
Cahill (2005) (187)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥55/AMD/US/50	AL, EM & SC	SF-12	GH, AL, GS, EM & SC
Bass (2004) (28)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/US/996	AL, EM & SC	SF-36 HADS	GH, AL, GS, EM & SC EM
Childs (2004) (32)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/US/336	AL, EM & SC	SF-36 HADS	GH, AL, GS, EM & SC EM
Miskala (2004) (188)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/US/454	AL, EM & SC	SF-36 HADS	GH, AL, GS, EM & SC EM
Manguire (2004) (189)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/US/1052	AL, EM & SC		
Miskala (2004) (190)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/US/120	AL, EM & SC	SF-36	GH, AL, GS, EM & SC
Decarlo (2003) (191)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/US/126	AL, EM & SC	DHQ LSQ	AL MB

Brody (2001) (192)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥60/AMD/US/151	AL, EM & SC	SCID-IV GDS SIPV SIP HIQ	EM EM MB, EM, AL & SC MB, EM, AL & SC GH & SC
Dong (2004) (193)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/US/789	AL, EM & SC	SF-36 HADS	GH, AL, GS, EM & SC EM
Whitson (2013) (194)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥65/AMD/US/12	AL, EM & SC	TICS – m IADL - C WMS –R GDS	CG AL MM EM
DeCarlo (2012) (195)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/US/199	AL, EM & SC	CES-D	EM
Scilley (2004) (196)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥55//AMD/US/195	AL, EM & SC		
Odergren (2010) (197)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/Sweden/98	AL, EM & SC		
Bressler (2010) (198)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/US/1025	AL, EM & SC		
Reeves (2009) (26)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/UK/1829	AL, EM & SC	SF-36	GH, AL, GS, EM & SC
Revicki (2010) (27)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥52/AMD/US/1134	AL, EM & SC	SF-36	GH, AL, GS, EM & SC
Sun˜er (2009) (199)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥52/AMD/US/1139	AL, EM & SC		
Bressler (2009) (200)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥52/AMD/US/418	AL, EM & SC		
Chang (2007) (201)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥52/AMD/US/716	AL, EM & SC		
Marback (2007) (202)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/Brazil/108	AL, EM & SC		
Submacular Surgery Trials Research Group (2007)(203)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/US/828	AL, EM & SC		
Miskala (2004) (29)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/US/120	AL, EM & SC	SF-36	GH, AL, GS, EM & SC

Casten (2010) (204)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	AMD/US/51	AL, EM & SC	PHQ-9	
Brody (2006) (205)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific AMD – SEQ /AMD /retina-specific	≥60/AMD/US/32	AL, EM & SC AL & EM	GDS DSSI SCID – IV LOT-R HIQ	EM SC EM CP GH & SC
Rovner (2006) (206)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific MLVAI /general ophthalmic population /ophthalmic but non-disease-specific	≥65/AMD/US/160	AL, EM & SC AL	HDRS SPSI (SF)	GS & EM PS
Brody (2002) (207)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific AMD –SEQ /AMD /retina-specific	≥60/AMD/US/231	AL, EM & SC AL & EM	POMS DSSI LOT-R SCID HIQ	EM SC EM EM GH & SC
Brody (2005) (208)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific AMD-SEQ /AMD /retina-specific	≥60/AMD/US/214	AL, EM & SC AL & EM	POMS DSSI SCID HIQ	EM SC EM GH & SC
Brody (2011) (209)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific AMD-SEQ /AMD /retina-specific	AMD/US/16	AL, EM & SC AL & EM	HAM – A HAMD HIQ	GS & EM EM GH & SC
Smith (2005) (210)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific MLVQ /general ophthalmic population /ophthalmic but non-disease-specific MLVAI /general ophthalmic population /ophthalmic but non-disease-specific	AMD/UK/225	AL, EM & SC AL, EM & HC AL		
Sahel (2007) (211)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific MacDQoL /AMD /retina-specific	≥50/AMD/France, Germany & Italy/360	AL, EM & SC AL, SC, EM &MB		
Ying (2008) (153)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific NVQ-10 /AMD /retina-specific	AMD/US/1052	AL, EM & SC AL & EM		
Denny (2007) (157)	DLTV/AMD /retina-specific	AMD/UK/186	AL		
Schmier (2006) (39)	DLTV /AMD /retina-specific	AMD/US/802	AL		
Hart (2005) (158)	DLTV /AMD /retina-specific	≥50/AMD/UK/235	AL		
Stevenson (2005) (31)	DLTV /AMD /retina-specific	≥60/AMD/UK/199	AL	SF-36	GH, AL, GS, EM & SC
Stevenson (2004) (159)	DLTV /AMD /retina-specific	≥50/AMD/UK/199	AL	SF-36	GH, AL, GS, EM & SC
McClure (2000) (160)	DLTV /AMD /retina-specific	≥45/AMD/UK/100	AL		

Hart (1999) (36)	DLTV /AMD /retina-specific	≥55/AMD/UK/103	AL		
Schmier (2006) (155)	DLTV /AMD /retina-specific AMD-HIQ /AMD /retina-specific	≥18/AMD/US/803	AL SC		
Mozaffarieh (2008) (212)	VF-14 /cataract /ophthalmic but non-disease-specific	AMD/Austria/90	AL	HADS	EM
Bansback (2007) (213)	VF-14 /cataract /ophthalmic but non-disease-specific	≥40/AMD/UK/209	AL		
Hewitt (2006) (214)	VF-14 /cataract /ophthalmic but non-disease-specific	AMD/Australia/82	AL		
Armbrecht (2004) (215)	VF-14 /cataract /ophthalmic but non-disease-specific	≥50/AMD/UK/48	AL		
Riusala (2003) (216)	VF-14 /cataract /ophthalmic but non-disease-specific GAS /no information /ophthalmic but non-disease-specific	≥55/AMD/Finland/62	AL VS		
Espallargues (2005) (217)	VF-14 /cataract /ophthalmic but non-disease-specific	≥40/AMD/UK/209	AL		
Dubuc (2009) (218)	VF-14 /cataract /ophthalmic but non-disease-specific	≥50/AMD/Canada/46	AL		
Mackenzie (2002) (30)	VF-14 /cataract /ophthalmic but non-disease-specific GAS /no information /ophthalmic but non-disease-specific	AMD/Canada/159	AL VS	SF-36	GH, AL, GS, EM & SC
Finger (2012) (24)	MacDQoL /AMD /retina-specific	AMD/Germany/108	AL, SC, EM &MB		
Mitchell (2004) (34)	MacDQoL /AMD /retina-specific	AMD/UK/135	AL, SC, EM &MB		
Mitchell (2005)(140)	MacDQoL /AMD /retina-specific	AMD/UK/171	AL, SC, EM &MB		
Lamoureux (2008) (219)	IVI /general ophthalmic population /ophthalmic but non-disease-specific	≥18/AMD/Australia/219	AL, EM & MB		
Hassell (2006) (220)	IVI /general ophthalmic population /ophthalmic but non-disease-specific	≥60/AMD/Australia/106	AL, EM & MB	SF-12	GH, AL, GS, EM & SC
Mathew (2011) (221)		≥55/AMD/Australia/145		SF-36 GADS IPAQ	GH, AL, GS, EM & SC EM AL
Nguyen (2007) (37)	ALQ /AMD /retina-specific	AMD/Germany/15	AL & HC		
Owsley (2006) (222)	LLQ /AMD /retina-specific	≥50/AMD/US/104	AL & EM		
Owsley (2006) (38)	LLQ /AMD /retina-specific	AMD/US/125	AL & EM		
Tolman (2005) (223)	AVL /general ophthalmic population /ophthalmic but non-disease-specific	≥65/AMD/US/144	EM	GDS-SF	EM

Krummenauer (2005) (224)	EMQ /cataract /vision-specific	≥70/AMD/Germany/84	AL, MB & EM		
Childs (2004) (225)		AMD/US/196		SF-36	GH, AL, GS, EM & SC
Tejeria (2002) (154)	FRQ /AMD /retina-specific	≥65/AMD/UK/30	AL & EM		
Rovner (2002) (226)	FVSQ /general ophthalmic population /ophthalmic but non-disease-specific	≥64/AMD/US/51	AL	CES-D CDS	EM AL & MB
Scilley (2002) (227)	ADVS /cataract /ophthalmic but non-disease-specific	≥50/AMD/US/92	AL		
Bailie (2013) (228)	MLVQ /general ophthalmic diseases /ophthalmic but non-disease-specific	≥50/AMD/Ireland/39	AL, EM & HC		
Coco-Martin (2013) (229)		≥60/AMD/Spain/41		WHOQOL-BREF	AL, MB, GS, EM, SC & EV
Reeves (2004) (230)	VCM1 /general ophthalmic population /ophthalmic but non-disease-specific MLVQ /general ophthalmic population /ophthalmic but non-disease-specific NAS /general ophthalmic population /ophthalmic but non-disease-specific	AMD/UK/226	AL & EM AL, EM & HC EM	SF-36	GH, AL, GS, EM & SC
Haymes (2001) (231)	MLVAI /general ophthalmic population /ophthalmic but non-disease-specific	≥60/AMD/Australia/22	AL		
Harper (1999) (232)	MLVQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/AMD/UK/56	AL, EM & HC		
Chua (2009) (156)	DAF /AMD /retina-specific	AMD/UK/100	EM & OS		
Rovner (2009) (233)		≥65/AMD/US/160		GDS IQCODE	EM MM & IQ
Mangione (1999) (33)	ADVS /cataract /ophthalmic but non-disease-specific	≥45/AMD/US/201	AL	SF-36	GH, AL, GS, EM & SC
Submacular surgery trials pilot study investigators (2000) (234)		AMD/US/54		SF-36	GH, AL, GS, EM & SC

ADVS, Activity of Daily Vision Scale; **ADL**, Activities of Daily Living Scale; **AI**, activity inventory; AL, activity limitation; **ALQ**, Activity Limitation Questionnaire; **AMD-SEQ**, Age-related Macular Degeneration Self-Efficacy Questionnaire; **AMD-HIQ**, Age-related Macular Degeneration Health Impact Questionnaire; **AVL**, Adaptation to Vision Loss Scale; **CDS**, Community Disability Scale; **CES-D**, the Centre for Epidemiologic Studies Depression Scale; **CP**, coping; **CV**, convenience; **CG**, cognition; **DAF**, Discomfort Anxiety Fear Questionnaire; **DHQ**, Driving Habits Questionnaire; **DSSI**, Duke Social Support Index; **DLTV**, Daily Living Tasks Dependent on Vision; **EC**, economic; **EM**, emotional well-being; **EMQ**, Extended Mainz Questionnaire; **EV**, environment; **FRQ**, Face Recognition Questionnaire; **FVSQ**, Functional Vision Screening Questionnaire; **GAS**, Global Assessment Scores; **GADS**, Geriatric Depression Scale; **GDS**, Goldberg Depression Scale; **GH**, general health; **GHQ**, General Health Questionnaire; **GS**, general symptoms; **GV**, general vision; **HAM-A**, Hamilton Rating Scale for Anxiety; **HADS**, Hospital Anxiety and Depression Scale; **HAMD**, Hamilton Rating Scale for Depression; **HC**, health concerns; **HDRS**, Hamilton Depression Rating Scale; **HIQ**,

Health and Impact Questionnaire; **IADL**, Instrumental Activities of Daily Living Questionnaire; **IPAQ**, International Planned Activity Questionnaire scale; **IQCODE**, Informant Questionnaire for Cognitive Decline; **IVI**, Impact of Visual Impairment**; LLQ**, Low Luminance Questionnaire; **LOT-R**, Life Orientation Test Revised; **LSQ**, Life Space Questionnaire; **MacDQoL**, Macular Disease Dependent Quality of Life scale; **MB**, mobility; **MM**, memory; **MLVQ**, Manchester Low Vision Questionnaire; **MLVAI**, Melbourne Low Vision Index; **NAS**, Nottingham Adaptation Scale; **NEI-VFQ**, National Eye Institute Visual Function Questionnaire; **NVQ-10**, Night Vision Questionnaire (10 items); **OPS**, Optimization in Primary and Secondary Control Scale; **OS**, ocular comfort symptoms; **PHQ-9**, Patient Health Questionnaire; **POMS**, Profile of Mood States; **PS**, problem solving; **SC**, social participation; **SCID-IV**, Structured Clinical Interview; **SF-36**, 36-Item Short Form Health Survey; **SF-12**, 12-Item Short Form Health Survey; **SIP**, Sickness Impact Profile; **SIPV**, Sickness Impact Profile Vision; **SPSI**, Social Problem Solving Inventory; **TICS-m**, the Modified Telephone Interview for Cognitive Status; **VCM1**, Vision Core Measure 1; **VF-14**, Visual Function Index (14 questions); **VS**, visual symptoms; **WHOQOL-BREF**, WHO Quality of Life Questionnaire; **WMS-R**, Wechsler Memory Scale

The DLTV covers activity limitation and the Age-related Macular Degeneration Health Impact Questionnaire covers social participation. The ALQ, Age related Macular Degeneration Self-Efficacy Questionnaire, FRQ, Discomfort Anxiety Fear Questionnaire, and NVQ – 10 cover 2 QoL domains. The ALQ covers activity limitation and health concerns; the Discomfort Anxiety Fear Questionnaire, ocular symptoms, and emotional well-being; the Age related Macular Degeneration Self-Efficacy Questionnaire, NVQ-10 and FRQ covers, activity limitation and emotional well-being. The Low Luminance Questionnaire covers three domains, activity limitation, mobility, and emotional well-being. Among all the PRO instruments, the MacDQoL seems more comprehensive in terms of the content coverage (activity limitation, socio-emotional well-being, health concerns and economic).(24) However, it has limited number of items representing those domains.(24)

Among the nine AMD -specific PRO instruments, seven instruments were summary scored and two were Rasch scaled. The seven PRO instruments (ALQ, FRQ, Low Luminance Questionnaire , Age-related Macular Degeneration Health Impact Questionnaire, Discomfort Anxiety Fear Questionnaire , and NVQ-10) performed poorly against the quality criteria. Only the MacDQoL and the DLTV have been assessed with Rasch analysis.(24, 157) The original version of the MacDQoL is flawed due to its complex multiplicative rating scale and multidimensionality, however, after several revisions, two of its subscales (activity limitation & mobility and socio-emotional well-being) are recommended for use in AMD.(24) A PRO instrument should be specific to the concept being measured (unidimensional). Unidimensionality demonstrates that all items in an instrument are measuring the same underlying concept and is a prerequisite to allow appropriate summation of any set of items.(143)The DLTV was also assessed with Rasch analysis as a legacy instrument.(157) Both the native and the Rasch scaled versions were violated unidimensionality, and only the revised scale consisting of eleven items on activity limitation and the subscale near and distance vision consisting of seven items has been recommended for use in AMD.(157) While these are valid instruments, their QoL coverage is limited to measuring only activity limitation.

2.5.1.1 *Ophthalmic but non-disease-specific PRO instruments in AMD*

Overall thirteen non-AMD-specific but ophthalmic PRO instruments were used in AMD

(Table 2.2).These are the NEI-VFQ, Activity Inventory (AI), VF-14, Impact of Visual Impairment (IVI), Melbourne Low Vision Index (MLVAI), Adaptation to Vision Loss Scale, Global Assessment Scores, Functional Vision Screening Questionnaire, Activity of Daily Vision Scale, Manchester Low Vision Questionnaire, Vision Core Measure 1, Nottingham Adaptation Scale and Extended Mainz Questionnaire. The NEI-VFQ (n=60 studies) was the most commonly used PRO instrument followed by the VF-14 (n=8 studies), Manchester Low Vision Questionnaire (n=4), MLVAI (n=3), Activity of Daily Vision Scale (n=2), IVI (n=2), AI (n=1), Adaptation to Vision Loss Scale (n=1), Vision Core Measure1 (n=1) and the Extended Mainz Questionnaire (n=1). The AI, VF-14, MLVAI, Functional Vision Screening Questionnaire, Adaptation to Vision Loss Scale, Nottingham Adaptation Scale, Global Assessment Scores and the Activity of Daily Vision Scale cover only a single QoL domain. The AI, VF-14, MLVAI, Activity of Daily Vision Scale and Functional Vision Screening Questionnaire cover activity limitation; the Adaptation to Vision Loss Scale, Nottingham Adaptation Scale, emotional well-being and the Global Assessment Scores, visual symptoms. The Vision Core Measure 1 covers two domains, activity limitation and emotional well-being. The Extended Mainz Questionnaire, Manchester Low Vision Questionnaire and IVI cover three domains. The Extended Mainz Questionnaire covers activity limitation, mobility, and emotional well-being; the Manchester Low Vision Questionnaire covers, activity limitation, emotional well-being and health concerns and the IVI covers activity limitation, mobility and emotional well-being. Most of the ophthalmic but non-retinal -specific PRO instruments again are limited in measuring few QoL domains.

Among the thirteen PRO instruments nine were summary scored and only four (NEI-VFQ, MLVAI, IVI and VF-14) were Rasch scaled.(24, 175, 210, 214, 219) The NEI-VFQ compared to other vision-specific PRO instruments appears more comprehensive, purporting to measure six domains, but suffers from inadequate number of items across domains except for activity limitation and the socio-emotional well-being. Similarly, Rasch analysis of the instrument revealed that the NEI-VFQ has problems with the item construction, response categories and it is multidimensional.(25) The Rasch analysis revised NEI-VFQ have two valid measures of QoL: visual functioning and socio-emotional aspects of QoL only.(24) The revised scale of IVI consisting of three scales (emotional well-being, reading and accessing information and mobility and independence) was found to be a valid measure in AMD.(219) Even though, the VF-14 has been assessed with Rasch analysis, the authors provided

limited information on the metric properties to determine its suitability in patients with AMD.(214) The nine PRO instruments that were validated using the classical test theory showed poor performance in AMD.(33, 165, 210, 216, 223, 224, 226-228, 230)

2.5.1.2 *Generic PRO instruments in AMD*

A total of 28 generic PRO instruments have been used in AMD (Table 2.2). Among these, the SF-36 (n=16 studies) and the Hospital Anxiety and Depression Scale (n=9 studies) were the most commonly used PRO instruments. The SF-36 covers, general health, activity limitation, general symptoms, emotional well-being, and social participation, and the Hospital Anxiety and Depression Scale covers, emotional well-being. All these generic PRO instruments were developed for non-ocular conditions. All these PRO instruments were validated by classical test theory and performed poorly against the quality criteria.

2.5.1.3 *Qualitative studies in AMD*

Eight qualitative studies were identified. The methods of data collection in these studies were either semi-structured interviews (n=4) and/or focus groups (n=2) or both (n=2). The socio-demographics of the population of these qualitative studies are given in Table 2.3.

Patients with unilateral disease had little or no debilitating difficulties in daily living compared to patients with bilateral AMD.(1) People with AMD frequently experience difficulties carrying out important activities requiring central vision such as reading, driving, recognising faces, watching television and manual work (activity limitation).(56) The biggest difficulty raised is losing the ability to drive and its effect patient's independence (health concerns).(1) Ivanoff *et al* reported that patients with AMD usually feel incompetent at performing activities of daily living and therefore adopt strategies such as changing how the activity is performed, modification of the environment (doing things more in daytime than at night), using other senses, avoidance and asking for help.(235) Wong *et al* in their study involving 15 patients with AMD reported that patients with bilateral disease required greater concentration, planning, recall capabilities and coordination of sensory modalities like hearing and touching even to perform simple daily activities (convenience).(1)

People with AMD have a higher risk of emotional distress, depression, and social isolation. AMD patients express more negative emotional comments such as frustration, sadness, fear and inadequacy compared to the positive comments like hope and optimism (emotional

well-being).(236) Lack of understanding about AMD causes psychological problems such as depression, loss of personal control, and powerlessness (emotional well-being). Loss of independence and loss of meaningful leisure-time were found to contribute to loneliness, isolation and inactivity among AMD patients (social participation).(235) McCloud *et al* reported that inability to recognize faces often led to social isolation.(3) Suicidal tendencies were also reported by AMD patients due to social isolation (social participation).(1)

Fear of blindness, uncertainty about the future and cost of the treatment relative to the improvement were some of the health concerns.(3, 237) McCloud *et al* reported that loss of work and cost for frequent injections led to financial constraints (economic).(3) The majority of the patients in Wong *et al* study expressed dissatisfaction, anger or resentment toward their eye care providers as a result of lack of knowledge of AMD (health concerns).(1)

Table 2.3 Description of the qualitative studies

Study	Data collection	Sample size	Age (years)	Gender M =male F=female	Country	Population
Age related macular degeneration (AMD)						
McCloud (2014)(57)	Semi-structured interviews and focus groups	34	≥56	M=15 F=19	Australia	Geographic type = 6 Exudative type = 6
Wong (2004)(1)	Semi-structured interviews	15	≥60	M=7 F=8	Australia	Mild to severe AMD
Moor (2003)(237)	Interviews	8	≥65	M=8	US	Severe AMD
Moor (2000)(238)	Interviews	8	≥60	F = 8	US	Severe AMD
Owsley (2006)(236)	Focus groups	53	≥ 45	F=28 M=25	US	Mild to severe AMD
Mogk (2008)(239)	Semi-structured interviews	12	≥75	NR	US	Mild to severe AMD
Feely (2007)(240)	Interviews	7	≥60	NR	UK	Moderate to severe form of disease
Ivanoff (1996)(235)	Focus groups	25	≥65	M=10 F=15	Sweden	NR
Diabetic retinopathy (DR)						
Coyne (2004)(241)	Focus groups	15	≥18	M = 5 F = 7	US	NPDR PDR
Devenney (2011)(242)	Semi-structured interviews	10	≥18	M = 4 F = 6	Ireland	Moderate and severe DR
Fenwick (2012)(4)	Semi-structured interviews and focus groups	57	≥18	M =39 F = 18	Australia	Mild, moderate, and severe NPDR PDR
Fenwick (2013)(243)	Semi-structured interviews and focus groups	57	≥18	M =39 F = 18	Australia	PDR

Scanlon (2006)(244)	Interviews	227	≥18	NR	UK	DME PDR
Hereditary retinal degenerations/dystrophies (HRD)						
Bittner (2010)(2)	Focus groups	8	≥18	M=2 F = 6	US	RP
Combs (2013)(135)	Semi-structured interviews	25	NR	NR	UK	RP Sorsby fundus dystrophy Cone-rod dystrophy Retinoschisis Choroideremia, Cone dystrophy Leber's congenital amaurosis and Unspecified retinal or macular dystrophy
Hayeems (2005)(245)	Semi-structured interviews and focus groups	43	≥18	M = 24 F = 19	US	RP
Macular hole (MH)						
Wittich (2008)(246)	Dairy content	1	≥60	F = 1	Canada	MH

NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; DME, diabetic macular edema; RP, retinitis pigmentosa; NR, not reported.

An underlying fear that treatment would only work for a while and that eventually they would slide into blindness was expressed by AMD patients on anti-vascular endothelial growth factor treatment (emotional well-being & health concerns).(3) Relative newness of the treatment and disease progression form one eye to both the eyes also frequently caused anxiety (emotional well-being & health concerns).(3)

AMD patients also frequently expressed hope and optimism (emotional well-being).(237, 238) Patients who participate in rehabilitation programs and those who use assistive devices for their visual impairment were optimistic and hopeful (emotional well-being) compared to older adults who were socially isolated.(1) AMD patients responding to treatment and those with stable disease feel optimistic whereas people in whom the treatment has failed and those with geographic atrophy are usually subjected to more emotional impact (emotional well-being).(3) McCloud *et al* reported that painful injections, bloodshot eyes, and physical difficulties associated with monthly treatments or visits are some of the inconveniences (visual symptoms & convenience).(3)

The major QoL issues among AMD patients seem to be activity limitations because of loss of central vision. Inability to perform important activities requiring central vision frequently results in emotional impact such as depression, frustration, and anger. Other major QoL issue is health concerns among AMD patients which include their concerns about future, possibilities of losing vision, uncertainty of treatments outcomes, current level of eye care, etc.

2.5.1.4 *QoL impact vs QoL measured in AMD*

The qualitative studies highlighted a broader QoL issues in people with AMD. However, none of the existing PRO instrument provide comprehensive QoL measure and valid QoL score. Most the PRO instruments primarily assess only one or few aspects of QoL (such as activity limitation and emotional well-being) and do not provide a comprehensive assessment of QoL (Table 2.2). There are other QoL issues such as social well-being, financial implication, issues related to inconvenience and concerns not well represented in the existing PRO instruments.(1, 3, 237)

2.5.1.5 *The highest quality existing PRO instrument for AMD*

The PRO measures with the highest quality criteria (Table 2.4) for AMD are the IVI with its

Table 2.4 Quality of patient-reported outcome measures in retinal diseases

Study	Name of the PRO	Content development	Type of PRO instruments	CTT based psychometric properties	Rasch based psychometric properties	Validity	Reliability/responsiveness
Age related macular degeneration							
Finger (2012)(166)	10-item Visual functioning scale (derived from NEI-VFQ-25)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = B Measurement Precision = B Dimensionality = B Item fit = A DIF = NR Targeting = B	Concurrent = C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = A
Finger (2012) (166)	8-item Socio-emotional scale (derived from NEI-VFQ-25)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = B Measurement Precision = C Dimensionality = A Item fit = A DIF = NR Targeting = C	Concurrent = C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Piermarocchi (2011) (175)	NEI-VFQ-39	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = B Measurement Precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = A	Concurrent = C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Smith (2005) (210)	9-item Self-assessed visual functioning scale (derived from NEI-VFQ)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement Precision = NR Item fit = A Dimensionality = NR DIF = NR Targeting = NR	Concurrent = NR Known group = NR Convergent = NR Discriminant =NR	ICC = NR Responsiveness = C
Smith (2005) (210)	9-item Observed performance on tasks dependent on vision scale (derived from	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement Precision = NR Dimensionality = NR	Concurrent = NR Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = C

	MLVAI)				Item fit = A DIF = NR Targeting = NR		
Smith (2005) (210)	7-item Self-assessed ADL scale (derived form MLVAI)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency= NR	Response categories = NR Measurement Precision = NR Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = C
Lamoureux (2008) (219)	Emotional well-being scale (derived from IVI)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = A Measurement Precision = A Dimensionality = A Item fit = A DIF = NR Targeting = A	Concurrent = NR Known group = A Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Lamoureux (2008) (219)	Reading and accessing information scale (derived from IVI)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency= NR	Response categories = A Measurement Precision = A Dimensionality = A Item fit = A DIF = NR Targeting = A	Concurrent = NR Known group = A Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Lamoureux (2008) (219)[33]	Mobility and independence scale (derived from IVI)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency= NR	Response categories = A Measurement Precision = A Dimensionality =A Item fit = A DIF = NR Targeting = A	Concurrent = NR Known group = A Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Hewitt (2006) (214)	12-item modified version of the VF-14	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency= NR	Response categories = NR Measurement Precision = NR Dimensionality = NR Item fit = NR DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = A

Finger (2012)(247)	Activity limitation and Mobility scale (derived from MacDQoL)	Item identification = A Item selection = A	Retina-specific	Acceptability = NR Targeting = NR Internal consistency= NR	Response categories = A Measurement Precision = B Dimensionality = B Item fit = A DIF = B Targeting = A	Concurrent = C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Finger (2012)(247)	Socio-emotional well-being scale (derived from MacDQoL)	Item identification = A Item selection = A	Retina-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = A Dimensionality = A Measurement Precision = B Item fit = A DIF = B Targeting = A	Concurrent = C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Denny (2007) (157)	11-item Activity limitation scale (derived from DLTV)	Item identification = B Item selection = A	Retina-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = B Dimensionality = NR Measurement Precision = B Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Denny (2007) (157)	7-item Near and Distance Vision subscale (derived from DLTV)	Item identification = B Item selection = A	Retina-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = B Measurement Precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Diabetic retinopathy							
Ahmadian (2008) (248)	AI All items	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency= NR	Response categories = NR Measurement Precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Ahmadian (2008) (248)	Goals scale (derived from AI)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement Precision =	Concurrent = NR Known group = C Convergent = NR	ICC = NR Responsiveness = NR

					A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Discriminant = NR	
Ahmadian (2008) (248)	Reading scale (derived from AI)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement Precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Ahmadian (2008) (248)	Visual information scale (derived from AI)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Accepting = NR Targeting =NR Internal consistency = NR	Response categories = NR Measurement Precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Ahmadian (2008) (248)	Visual motor scale (derived from AI)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement Precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Ahmadian (2008) (248)	Mobility scale (derived from AI)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement Precision = B Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Lamoureux (2010) (249)	VF-11	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency= NR	Response categories – NR Measurement Precision –	Concurrent = A Known group = NR Convergent = NR	ICC = NR Responsiveness = NR

					B Dimensionality – NR Targeting = NR DIF = NR Item fit = NR	Discriminant = NR	
Matza (2008) (250)	NEI -VFQ	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = A to B	NR	Concurrent = A Known group = A Convergent = NR Discriminant = NR	ICC = NR Responsiveness = A
Lloyd (2013) (251)	NEI -VFQ	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = A	NR	Concurrent = C Known group = A Convergent = NR Discriminant = NR	ICC = NR Responsiveness = A
Tranos (2004) (252)	NEI -VFQ	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	NR	Concurrent = A Known group = NR Convergent = NR Discriminant = NR	ICC = A to B Responsiveness = A
Macular telangiectasia							
Lamoureux (2011) (253)	Mobility and independence scale (derived from IVI)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement Precision = A to C Dimensionality = NR Item fit = NR DIF = NR Targeting = C	Concurrent = B Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = C
Lamoureux (2011) (253)	Emotional well-being scale (derived from IVI)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement Precision = A to C Dimensionality = NR Item fit = NR DIF = NR Targeting = C	Concurrent = C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = C
Lamoureux (2011) (253)	Reading and Accessing Information scale (derived from IVI)	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Accepting = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement Precision-PSR = A to C	Concurrent = A Known group =NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = C

					Dimensionality = NR Item fit = NR DIF = NR Targeting = C		
Hereditary retinal degenerations/dystrophies							
Turano (1999)(254)	IMQ	Item identification = C Item selection = B	Retina-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement Precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = A Known group = A Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Mixed retinal diseases							
Arimura (2011) (255)	MPQ	Item identification = C Item selection = B	Retina-specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = A Measurement Precision = A Dimensionality = NR Item fit = A DIF = B Targeting = NR	Concurrent = A to C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Unver (2009) (256)	PalmPilot- VFQ	Item identification = C Item selection = B	Ophthalmic but non-disease-specific	Acceptability = NR Targeting = NR Internal consistency= A	Response categories = NR Measurement Precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = B	Concurrent = A Known group = NR Convergent = A Discriminant = NR	ICC = C Responsiveness = NR

ADL, Activity of Daily Living; AI, activity inventory; **CTT**, Classic Test Theory; **DIF**, Differential Item Functioning; **DLTV**, Daily Living Tasks Dependent on Vision; **ICC**, intraclass correlation; IMQ, Independent Mobility Questionnaire; **IVI**, impact of visual impairment; **MacDQoL**, Macular Disease Dependent Quality of Life; **MLVAI**, Melbourne Low Vision Index; **MPQ**, Metamorphopsia Questionnaire; **NEI-VFQ**, National Eye Institute Visual Function Questionnaire; **NR**, not reported; **PalmPilot-VFQ**, PalmPilot Visual Function Questionnaire; **PRO**, patient-reported outcome; **VF-14**, Visual Function Index (14 questions); **VF-11**, Visual Function Index (11 questions).

three scales (emotional well-being, reading and accessing information and mobility and independence) and the Rasch modified version of the MacDQoL with two scales (socio-emotional well-being and activity limitation & mobility). All three scales of the IVI were graded 'A' for measurement precision (i.e. person separation reliability was > 0.90, according to the definition grade 'A' for any value ≥ 0.85), item fit (i.e. fit residuals < 2.5, according to the definition grade 'A' for any value < 2), response categories, dimensionality, targeting and DIF. The two scales of MacDQoL were graded 'A' for item identification (i.e. focus group sessions with patients with macular diseases and literature review for the content development of the questionnaire, according to the definition grade 'A' if comprehensive consultation with patients and literature review for that particular disease group), item selection, response categories (i.e. no disordered thresholds, according to the definition grade 'A' if all the categories were ordered), item fit and targeting.

2.5.2 Diabetic retinopathy

In total, 31 studies were on DR. Out of the 31 studies, 26 studies employed PRO assessments (Table 2.5) and five were qualitative studies.

2.5.2.1 *Disease-specific PRO instruments in DR*

Only five studies out of the 26 studies used DR-specific PRO instruments. The Retinopathy Dependent Quality of Life (RetDQoL) and the Retinopathy Satisfaction Treatment Questionnaire were the only two PRO instruments developed for DR.(136, 137) The QoL domains covered by the RetDQoL are activity limitation, socio-emotional well-being, economic and health concerns and the Retinopathy Satisfaction Treatment Questionnaire claims to measure ocular symptoms, emotional well-being and the health concerns. Neither of the instruments was tested with Rasch analysis. The RetDQoL and the MacDQoL are almost identical. They have similar items (except for two items: (i) the way society at large reacts to me would be and (ii) my enjoyment of food would be), few items within domains (e.g. emotional well-being, has 2 items), the same multiplicative rating scale and scoring schema. The original version of the MacDQoL was found to be flawed because of its complex multiplicative scoring and multidimensionality.(24) We speculate the same holds for the RetDQoL.(24)

Table 2.5 The Patient-reported outcome instruments used and their content coverage in diabetic retinopathy, retinal detachment, and retinal infections

Study	Ophthalmic PRO instruments / Population developed for /Types of PRO instruments	Age (years)/Target population/Country/ Sample size	Concepts/domains being measured	Generic PRO instruments	Concepts / domains being measured
Diabetic Retinopathy (DR)					
Hirai (2011) (257)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	DR/US/471	AL, EM & SC		
Hariprasad (2008) (10)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥16/DR/US/33	AL, EM & SC		
Lang (2013) (258)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18/DR/Australia, Belgium, Canada, France, Germany, Greece, Hungary, UK, Spain, Switzerland, Italy & Netherlands/240	AL, EM & SC		
Loftus (2011) (259)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18/DR/Australia, Europe, India, North America & South America/260	AL, EM & SC		
Matza (2008) (250)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	DR/US/535	AL, OS, EM & SC	SF-36	GH, AL, GS, EM & SC
Mazhar (2011) (260)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥40/DR/US/1064	AL, EM & SC	SF-12	GH, AL, GS, EM & SC
Okamoto (2008) (261)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	DR/Japan//51	AL, EM & SC		
Tsilimbaris (2013) (262)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	DR/Greece/20	AL, EM & SC		
Warrian (2010) (263)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	DR/US/91	AL, EM & SC		
Tranos (2004) (252)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥17/DR/UK/55	AL, EM & SC		
Lloyd (2013) (251)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18/DR/Australia, Canada, Europe, India, South Africa & South America/235	AL, EM & SC		

Gabrielian (2010)(264)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	DR/US/104	AL, EM & SC		
Ahmadian (2008) (248)	AI /general ophthalmic disease /ophthalmic but non-disease-specific	≥18/DR/US/114	AL & SC		
Brose (2010) (265)	RetDQOL /DR /retina-specific RetTSQ /DR /retina-specific	≥19/DR/Germany/207	AL, EM, EC, SC & HC HC, OS & EM	SF-12	GH, AL, GS, EM & SC
Davidov (2009) (266)	RetDQOL /DR /retina-specific RetTSQ /DR /retina-specific	≥18/DR/Germany/207	AL, EM, EC, SC & HC HC, OS & EM	SF-12	GH, AL, GS, EM & SC
Hirai (2012) (11)		DR/US/484		CES-D	EM
Jensen (2010) (267)		≥45/DR/US/6417		CES-D STAI CBS CMHS CHD-SSI	EM EM EM EM SC
Lamoureux (2010) (249)	VF-11 /cataract /ophthalmic but non-disease-specific	≥40/DR/Singapore/357	AL		
Mirshahi (2013) (268)		DR/Iran/66		PQ	OS
Mozaffarieh (2005) (269)		≥35/DR/Austria/123		DTSQ	SF
Rees (2012) (270)		≥18/DR/Australia/400		IPQ-R SDSCA HADS	GS, OS, HC & EM & CP AL EM
Sieu (2011) (271)		DR/US/2359		PHQ-9	EM
Woodcock (2004) (136)	RetDQOL /DR /retina-specific	≥18/DR/UK & Germany/44	AL, EM, EC, SC & HC		
Woodcock (2005) (137)	RetSTQ /DR /retina-specific	≥25/DR/UK & Germany/44	HC, OS & EM		
Brose (2009) (272)	RetTSQ /DR /retina-specific RetDQOL /DR/retina-specific	≥18/DR/Germany/207	HC, OS & EM AL, EM, EC, SC & HC	SF-36	GH, AL, GS, EM & SC
Lamoureux (2004) (273)	IVI /general ophthalmic population /ophthalmic but non-disease-specific	≥18/DR/Australia/45	AL, MB & EM	SF-12	GH, AL, GS, EM & SC
Retinal Detachment (RD)					
Fabian (2013) (12)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18/RD/Israel/366	AL, EM & SC	PTSD PTDS	EM EM
Koriyama (2007) (274)	RDQ /RD /retina-specific	≥50/RD/Japan/46	OS & HC		
Okamoto (2008) (13)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	RD/Japan/51	AL, EM & SC		

Zou (2008) (275)	CLVQOL /general ophthalmic population /ophthalmic but non-disease-specific GAS /no information /ophthalmic but non-disease-specific	≥18/RD/China/163	GV, MB, AL & EM VS		.
Zou (2011) (276)	CLVQOL /general ophthalmic population /vision-specific GAS /no information /ophthalmic but non-disease-specific	≥18/RD/China/92	GV, MB, AL & EM VS		
Vascular Occlusion (VO)					
Brown (2013) (277)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18/VO/US, Canada, Columbia, India & Israel/189	AL, EM & SC		
Deramo (2003)(278)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18/VO/US/51	AL, EM & SC		
Awdeh (2010) (14)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18/VO/US/46	AL, EM & SC		
Varma (2012) (15)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18/VO/US/789	AL, EM & SC		
Macular Telengiectasia (MT)					
Clemons (2008) (279)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18/MT//France, Australia, US, Germany, Israel, India & UK/222	AL, EM & SC		
Lamoureux (2011) (253)	IVI /general ophthalmic population /ophthalmic but non-disease-specific	≥45/ MT/France, Australia, US, Germany, Israel, India & UK/22	AL, MB & EM		
CMV Retinitis (CMV)					
Kempen (2003) (280)	CMVQ /CMV /retina-specific	≥13/CMV/US/971	AL, VS, HC & EM	MOS-HIV	AL, GS, EM & SC
Martin (2001) (281)	CMVQ /CMV /retina-specific	CMV/US/279	AL, VS, HC & EM	GHRQoL	GH, AL, GS, EM, MB & SC
Matheı¨ (2011) (282)		≥80/CMV/Belgium/567		ADL LAPAQ GDS MMSE	AL AL EM MM & CG
Wu (1996) (283)	CMVQ /CMV /retina-specific	CMV/US/26	AL, VS, HC & EM		
Histoplasmosis (HS)					
Hawkins (2004) (284)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18/HS/US/225	AL, EM & SC	SF-36 HADS	GH, AL, GS, EM & SC EM

Birdshot Retinopathy (BR)					
Kuiper (2013) (285)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥25/BR/Netherlands/ 127	ALEM & SC		
Levinson (2009) (286)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	BR/France/80	AL, EM & SC		
Toxoplasmosis (TP)					
de-la-Torre (2011)(287)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥15/TP/South America/29	AL, EM & SC		

ADL, Activities of Daily Living; **AI**, activity inventory; **AL**, activity limitation; **CBS**, Chronic Burden Scale; **CES-D**, the Centre for Epidemiologic Studies Depression Scale; **CG**, cognition; **CHD-SSI**, Coronary Heart Disease patients study Social Support Instrument; **CLVQOL**, Chinese Low Vision Quality of Life questionnaire; **CMHS**, Cook-Medley Hostility Scale; **CMVQ**, Cytomegalovirus Retinitis Questionnaire; **CP**, coping; **CV**, convenience; **DTSQ**, Diabetes Treatment Satisfaction Questionnaire; **EC**, economic; **EM**, emotional well-being; **GAS**, Global Assessment Score; **GDS**, Goldberg Depression Scale; **GH**, general health; **GHRQoL**, General Health Related Quality of Life Measures; **GS**, general symptoms; **GV**, general vision; **HADS**, Hospital Anxiety and Depression Scale; **HC**, health concerns; **HDRS**, Hamilton Depression Rating Scale; **IVI**, Impact of Visual Impairment; **IPAQ**, International Planned Activity Questionnaire scale; **LAPAQ**, Longitudinal Aging Study Amsterdam Physical Activity Questionnaire; **MB**, mobility; **MM**, memory; **MOS-HIV**, Medical Outcome Study HIV Health Survey; **MMSE**, Mini-Mental State Examination; **NEI-VFQ**, National Eye Institute Visual Function Questionnaire; **OS**, ocular comfort symptoms; **PQ**, Pain Questionnaire; **PHQ-9**, Patient Health Questionnaire; **PTDS**, Posttraumatic Diagnostic Scale; **PTSD**, Post-Traumatic Stress Disorder; **RDQ**, Retinal Detachment Questionnaire; **RetDQOL**, Retinopathy Dependent Quality of Life measure; **RetSTQ**, Retinopathy Satisfaction Treatment Questionnaire; **SC**, social participation; **SDSCA**, Summary of Diabetes Self Care Activities; **SF-12**, 12-Item Short Form Health Survey; **SF-36**, 36-Item Short Form Health Survey; **STAI**, Spielberg Trait Anxiety and Trait Anger; **VF-11**, Visual Function Index (11 questions); **VS**, visual symptoms.

2.5.2.2 *Ophthalmic but non-disease-specific PRO instruments in DR*

The ophthalmic but non-diseases-specific PRO instruments used were the NEI-VFQ, AI, VF-11 and IVI. Again, the NEI-VFQ (n=12 studies) was the most frequently used PRO instrument.(10, 250-252, 257-264) The VF-11 is derived from VF-14 and measures activity limitation. The AI and the VF-11 PRO instruments were tested with Rasch analysis. The AI was shown to have good measurement precision and item fit. However, most of the information on the metric properties of the VF-11 was not available (Table 2.4). The NEI-VFQ and the IVI showed poor performance in DR.(251, 252, 273)

2.5.2.3 *Generic PRO instruments in DR*

A total of fourteen PRO instruments were used in DR (Table 2.5). Nine of them assessed the emotional well-being aspect of QoL. The 12-Item Short Form Health Survey was the frequently used generic instrument among them and QoL domains it covers are similar to SF-36. None of these PRO instruments contain items related to vision and none of them have been validated in this disease.

2.5.2.4 *Qualitative studies in DR*

There were five qualitative studies. The method of data collection in these studies were focus groups (1 study), interviews (1 study) and both focus groups and interviews (n=3 studies). The socio-demographics of the population of these qualitative studies are given in Table 2.3.

Patients with DR, like AMD, also frequently reported difficulties in executing day-to-day tasks such as reading, watching television, cooking, housekeeping, sewing, gardening, recognizing faces, hobbies and getting dressed (activity limitation).(4, 241) Visual loss in DR also affects the individual's diabetic care activities such as reading labels on the food items, insulin injections, blood testing and exercise (activity limitation).(241) They also experience a variety of visual symptoms such as blurry, wavy, hazy, or distorted vision, trouble with bright lights, flashes, floaters, and temporary blackness due to retinal haemorrhage (visual symptoms).(4) The possibility of going blind was a major concern for those with moderate and severe form of DR (health concerns).(241) Visual loss due to DR has been associated with loss of ability to perform important occupational and family roles such as working,

driving or caring for the family (social participation).(242) Driving, especially at night, was the most frequently affected activity among the DR patients (activity limitation) that frequently resulted in loss of mobility and independence (mobility).(241) DR has also been shown to cause emotional distress and depression (emotional well-being).(4) They also had substantial reduction in their social well-being (social participation).(4)

Poor diabetes control was the most commonly reported risk factor for DR. Poor eating habits, smoking, lack of exercise, lack of awareness, delay in the diagnosis, genetics and environmental factors were the other perceived risk factors for DR.(243) As DR affects younger patients compared to AMD, the visual loss has financial implications from loss of employment or restricted work hours, cost of purchasing visual aids and the cost of treatment (economic).(4) Most patients with DR also have limited understanding about laser treatment and believe that laser or related treatments made their vision worse.(243) DR patients also experience lot of inconveniences such as having to depend on others for transport during clinic visits, having multiple treatments, and having to undergo frequent dilatations at every clinic appointment (convenience).(4) Unlike AMD, patients with DR are more likely to have multiple comorbidities and the presence of renal or neurological co-morbidities can compromise QoL further.

2.5.2.5 *QoL impacts vs QoL measured in DR*

Similar to the AMD, the content coverage of the retina-specific, ophthalmic but non-disease-specific and the generic PRO instruments used in DR were limited to activity limitation and emotional well-being (Table 2.5). However, qualitative studies in DR show that these patients have issues with social participation, finance, health concern and conveniences, which have not been covered in the existing PRO instruments.(4, 241, 242)

2.5.2.6 *The highest quality existing PRO instrument for DR*

All the DR-specific PRO instruments have limited validation so score poorly on quality assessment. The highest quality PRO instruments available for DR is the AI (its subscales reading, goals, visual information, visual motor and mobility) (Table 2.4).(248) The subscales of AI (reading, goals, visual information, visual motor) were graded ‘A’ for measurement precision (i.e. person separation reliability was > 0.88, according to the definition grade ‘A’ for any value ≥ 0.85) and item fit (i.e. all items with infit mean square

between 0.99 to 1.09, according to the definition grade ‘A’ for any value between 0.7 and 1.3).

2.5.3 Retinal Vascular Diseases

There were only 6 studies on retinal vascular diseases, and these included 4 studies on vascular occlusions and 2 on macular telangiectasis (Table 2.5). There were no qualitative studies in this group. Only ophthalmic but non-disease-specific PRO instruments were used and there was no retina-specific PRO instrument developed in this group of retinal diseases.

2.5.3.1 *Ophthalmic but non-disease-specific PRO instruments in retinal vascular diseases*

Only two PRO instruments were used which were the NEI-VFQ and the IVI. Out of six studies, the NEI-VFQ was used in five studies.(14, 15, 277-279) The IVI was tested with Rasch analysis in retinal vascular diseases.(253) Three scales derived from the IVI were used and scored separately. Information on the dimensionality, item fit and DIF was not reported (Table 2.4).(253) The NEI-VFQ showed poor performance in retinal vascular diseases.

2.5.3.2 *QoL impacts vs QoL measured in retinal vascular conditions*

Only ophthalmic but non-disease-specific PRO instruments were used to assess QoL impacts in these patients. The content coverage of these PRO instruments was limited to activity limitation and emotional well-being. Moreover, there were no qualitative studies for this group of retinal diseases.

2.5.3.3 *The highest quality existing PRO instrument for retinal vascular conditions*

The IVI and subscales (reading and accessing information, mobility and independence and emotional well-being) had the highest score on quality assessment (Table 2.4).

2.5.4 Retinal Detachment

Only five studies on RD were identified (Table 2.5). All the studies used PRO instruments and there were no qualitative studies reported.

2.5.4.1 *Disease-specific PRO instruments in RD*

A single PRO instrument, the Retinal Detachment Questionnaire for the subjective assessment of the RD surgery and recovery was originally developed for RD.(274) The

instrument covers ocular symptoms and health concerns; however, it has few items in each of these domains. Moreover, the instrument was not valid for use in RD.

2.5.4.2 *Ophthalmic but non-disease-specific PRO instruments in RD*

Three PRO instruments the NEI-VFQ, Global Assessment Scores and Chinese version of the Low Vision Quality of Life Questionnaire were used. The Chinese version of the Low Vision Quality of Life Questionnaire covers general vision, mobility, activity limitation and emotional well-being. The Chinese version of the Low Vision Quality of Life Questionnaire was used in two studies (275, 276) and the NEI-VFQ in 2 studies.(12, 13) All these 3 instruments performed poorly.

2.5.4.3 *Generic PRO instruments in RD*

The Post Traumatic Distress Stress Disorder and Post Traumatic Depressive Scale PRO instruments were used to assess the stress related to RD.(12) These two instruments performed poorly against the quality criteria.

2.5.4.4 *QoL impacts vs QoL measured in RD*

Only one retina-specific PRO instrument was developed for RD, and its content coverage is limited to ocular symptoms and health concerns (Table 2.5). The content coverage of the ophthalmic but non-disease-specific PRO instruments was limited to activity limitation, emotional well-being and mobility and the content coverage of the generic PRO instruments was limited to measuring emotional well-being (Table 2.5). None of the PRO instruments has been validated in RD.

2.5.5 Retinal infections

There were eight studies identified, four on cytomegalovirus retinitis, two on histoplasmosis and one each on birdshot chorioretinopathy and toxoplasmosis (Table 2.5). There were no qualitative studies reported in this group of retinal diseases.

2.5.5.1 *Disease-specific PRO instruments in retinal infections*

The Cytomegalovirus Retinitis Questionnaire was the only cytomegalovirus-specific PRO instrument. Of the four studies, three used the Cytomegalovirus Retinitis Questionnaire .(280, 281, 283) The Cytomegalovirus Retinitis Questionnaire covers activity limitation,

visual symptoms, health concerns and emotional well-being. The Cytomegalovirus Retinitis Questionnaire was assessed by classical test theory methods and it showed a poor performance in retinal infection.

2.5.5.2 *Ophthalmic but non-disease-specific PRO instruments in retinal infections*

The NEI-VFQ was the only PRO instrument used in this group of retinal diseases (4 studies). (284-287) However, it has not been validated in this disease group.

2.5.5.3 *Generic PRO instruments in retinal infections*

Eight generic PRO instruments were used (Table 2.5). They were the Medical Outcome Study-HIV, General Health Related Quality of Life Measures, Longitudinal Aging Study Amsterdam Physical Activity Questionnaire, Mini-Mental State Examination, Goldberg Depression Scale, SF-36, ADL and Hospital Anxiety and Depression Scale. These PRO instruments were used to assess emotional impact only (Table 2.5). None of these PRO instruments were valid for use in retinal infections.

2.5.5.4 *QoL impacts vs QoL measured in retinal infections*

The content coverage of the PRO instruments used in retinal infections was limited to two QoL domains (activity limitation and emotional well-being). None of these instruments were validated for use in this group of diseases.

2.5.6 Hereditary Retinal Degenerations/dystrophies

There were 29 studies identified in total; 26 studies with PRO instruments and three qualitative studies. Most the studies were on retinitis pigmentosa (RP) (n=23) followed by two on macular dystrophies and on congenital stationary night blindness (Table 2.6). Of the three qualitative studies, two were on RP and one on mixed retinal dystrophies.

2.5.6.1 *Disease-specific PRO instruments in hereditary retinal degenerations/dystrophies*

Eleven disease-specific PRO instruments were developed to be used in hereditary retinal diseases (Table 2.6). They were the Independent Mobility Questionnaire (IMQ) (254), Mobility Difficulties Questionnaire (288), Field Expander Questionnaire (58), Perceived Visual Function Questionnaire (289), Activities of Daily Vision Questionnaire (290), Vision Related Activity of Daily Living (291), Daily Task Performance Questionnaire (292),

Table 2.6 The Patient-reported outcome instruments used and their content coverage in hereditary retinal degenerations/dystrophies, macular disorders, and other retinal conditions

Study	Ophthalmic PRO instruments / Population developed for / Types of PRO instruments	Age (years)/ Target population/Country/Sample size	Concepts /domains being measured	Generic PRO instruments	Concepts / domains being measured
Hereditary Retinal Degenerations/dystrophies					
Burstedt (2005) (16)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥5/RP/Sweden/49	AL, EM & SC		
Burstedt (2010) (293)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥5/RP/Sweden/49	AL, EM & SC		
Jonsson (2007)(294)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥20/RP/Sweden/12	AL, EM & SC		
Hahm (2008)(295)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	RP/Korea/144	AL, EM & SC	BDI	EM
Seo (2009) (296)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥15/RP/Korea/108	AL, EM & SC		
Sugawara (2010) (297)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥20/RP/Japan/40	AL, EM & SC		
Sugawara (2011) (298)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥20/RP/Japan/30	AL, EM & SC		
Menzel-Severing (2012) (17)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥35/RP/Germany/5	AL, OS, EM & SC		
Geruschat (1998) (288)	MDQ /RP / retina-specific	RP/US/22	MB		
Gordo (2001) (299)		≥10/RP/Spain/177		PSQI	Pattern & Quality of sleep
Hartong (2006) (300)	IMQ / RP/ retina-specific	≥25/RP/Netherlands/11	MB		
Hartong (2004) (301)	IMQ / RP /retina-specific	≥20/RP/Netherlands/20	MB		
Turano (1999) (254)	IMQ /RP /retina-specific	RP/US/145	MB		
Kennedy (1997) (58)	FEQ /RP /retina-specific	≥20/RP/US/10	MB (Limited information on questionnaire)		
Lodha (2003) (289)	PVFQ /RP /retina-specific	≥10/RP/Canada/68	AL & MB		
Lowe (1992) (302)	EDTQ /RP /retina-specific	≥10/RP/UK/48	AL		
Somani (2006) (291)	V-ADL /RP /retina-specific	≥30/RP/Canada/16	AL		
Szlyk (1998) (138)	ADVQ /RP /retina-specific	≥10/RP/US/72	AL & MB		

Szlyk (2001) (292)	DTPQ /RP /retina-specific	≥10/RP/US/62	AL & MB		
Szlyk (1997) (290)	ADVQ /RP /retina-specific	≥10/RP/US/167	AL & MB		
Bijveld (2013) (303)	NVQ-39 /CSNB /retina-specific	≥12/RP/Netherlands/20	MB & AL		
Bittner (2013) (304)		≥20/RP/US/37		SSS ESS PSS PANAS	GS GS EM EM
Peters (2013) (305)		≥25/RP/Germany/9		BSI	GS & EM
Bittner (2011) (306)		≥ 18/RP/US/27		SSS ESS PSS PANAS SF-36 BDI PSQI	GS GS EM EM GH, AL, GS, EM & SC EM Pattern & Quality of sleep
Sumi (2000) (307)	VDQ /RP /retina-specific	RP/Japan/93	AL & MB		
Miedziak (2000) (308)	SMDVQ /Stargardt disease /retina-specific	≥8/SD/US/203	AL & MB		
Macular Hole					
Pearce (1998) (309)	SVFQ / MH /retina-specific	≥55/MH/UK/30	HC		
Tranos 2004 (18)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥17/MH/UK/30	AL, EM & SC	SF-36	GH, AL, GS, EM & SC
Fukuda (2009) (19)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	MH/Japan/32	AL, EM & SC		
Rayat (2011) (310)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18/MH/Canada/20	AL, EM & SC		
Tranos (2007)(311)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/MH/UK/41	AL, EM & SC		
Ellis (2000) (312)	PMHQ /MH / retina-specific	MH/UK/38	HC		
Hirneiss C (2007) (313)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥50/MH/Germany/59	AL, EM & SC		
Singh (2011) (314)	MHTSQ /MH /retina-specific	MH/UK/53	HC		
Epiretinal Membrane					
Matsuoka (2012) (20)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥55/ERM/Japan/26	AL, EM & SC		
Ghazi-Nouri (2006) (21)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥25/ERM/UK/20	AL, EM & SC	SF-36	GH, AL, GS, EM & SC

Okamoto (2009) (315)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	ERM/Japan/28	AL, EM & SC		
Central Serous Retinopathy					
Conrad (2007) (22)		CSR/Germany/31		SCL–90-R TAS–20	EM EM
Spahn (2003) (23)		CSR/Germany/24		SCL 90-R F-Sozu, K-22 SLQ PFQ	GS & EM SC GS EM
Mixed Retinal Diseases					
Arimura (2011) (255)	MPQ /MD /retina-specific	MRD/Japan/131	VS		
Mitchell (2002) (316)	MDSQ /MD /retina-specific	≥18/MRD/UK/1411	HC & EM		
Hazel (2000) (317)	VCM1 /general ophthalmic population /ophthalmic but non-disease-specific	≥20/MRD/UK/28	AL & EM		
Mitchell (2001) (318)	MDSQ /MD /retina-specific	≥18/MRD/UK/1421	HC & EM	W-BQ12 ADDQoL	EM FC, SC, AL, HC, EM & MB
Unver (2009) (256)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific PalmPilot-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥18/MRD/US/135	AL, EM & SC GH & AL		
Linder (1999) (319)	VF-14 /cataract /ophthalmic but non-disease-specific GAS /no information /ophthalmic but non-disease-specific	≥15/MRD/Canada/546	AL VS	SF-36 WCS	GH, AL, GS, EM & SC AL
Scott (2001) (320)				SIP CDS GHQ VPI EPQ TICS	AL, MB, SC & EM AL & MB GS & EM VS EM & SC EM
Scott (2001) (321)		MRD/US/86		CDS GHQ	AL & MB GH & EM
Globe (2002) (322)		≥15/MRD/Canada/1081		SF-36 SF-12	GH, AL, GS, EM & SC GH, AL, GS, EM & SC

Okamoto (2010) (323)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	MRD/Japan/299	AL, EM & SC		
Schiff (2000) (324)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥55/MRD/US/5	AL, EM & SC HC		
Schulz-Key (2011) (325)	VSQ /general ophthalmic population /ophthalmic but non-disease-specific	≥30/MRD/Sweden/61	AL & HC		
Sharma (2002) (326)	VF – 14 /cataract /ophthalmic but non-disease-specific	MRD/US/323	AL		
Miskala (2003) (327)	NEI-VFQ /general ophthalmic population /vision-specific	≥18/MRD/US/483	AL, EM & SC		
Schweitzer (2011) (328)	NEI-VFQ /general ophthalmic population /ophthalmic but non-disease-specific	≥40/MRD/Canada/84	AL, EM & SC		
de Nie (2013) (329)	PSQ /general ophthalmic population /ophthalmic but non-disease-specific	MRD/Netherlands/110	GH, AL, HC & EM		

ADVQ, Activities of Daily Vision Questionnaire; **ADDQoL**, Audit of Diabetes-Dependent Quality of Life; **AL**, activity limitation; **BDI**, Beck Depression Inventory; **BSI**, Brief Symptom Inventory; **CDS**, Community Disability Scale; **CSNB**, Congenital Stationary Night Blindness; **CV**, convenience; **DTPQ**, Daily Task Performance Questionnaire; **EC**, economic; **EM**, emotional well-being; **EPQ**, Eysenck Personality Questionnaire; **ESS**, Epworth Sleepiness Scale; **FEQ**, Field Expander Questionnaire; **F-Sozu, K-22**, Symptom List Questionnaire on Social Support; **GAS**, Global Assessment Scores; **GH**, general health; **GHQ**, General Health Questionnaire; **GS**, general symptoms; **GV**, general vision; **HC**, health concerns; **IMQ**, Independent Mobility Questionnaire; **LLQ**, Low Luminance Questionnaire; **MB**, mobility; **MD**, macular diseases; **MDSQ**, Macular Disease Society Questionnaire; **MDQ**, Mobility Difficulties Questionnaire; **MEL**, Munich Life Event List; **MHTSQ**, Macular Hole Treatment Satisfaction Questionnaire; **MPQ**, Metamorphopsia Questionnaire; **NEI-VFQ**, National Eye Institute Visual Function Questionnaire; **NVQ-39**, Night Vision Questionnaire (39 Questions); **OS**, ocular comfort symptoms; **PANAS**, Positive and Negative Affect Schedules; **PFQ**, Personality Factor Questionnaire; **PMHQ**, Positioning for Macular Hole Questionnaire; **PSS**, Perceived Stress Scale; **PSQ**, Patient Satisfaction Questionnaire; **PSQI**, Pittsburgh Sleep Quality Index; **PVFQ**, Perceived Visual Function Questionnaire; **RP**, retinitis pigmentosa; **SC**, social participation; **SCL-90-R**, Symptom Checklist; **SD**, Stargardt disease; **SF-12**, 12-Item Short Form Health Survey; **SF-36**, 36-Item Short Form Health Survey; **SIP**, Sickness Impact Profile; **SLQ**, Symptom List Questionnaire; **SMDVQ**, Stargardt Macular Dystrophy Vision Questionnaire; **SSS**, Stanford Sleepiness Scale; **SVFQ**, Short Visual Function Questionnaire; **TAS-20**, 20-Item Toronto Alexithymia Scale; **TICS**, Telephone Interview for Cognitive Status; **V-ADL**, Vision-Related Activity of Daily Living; **VCM1**, Vision Core Measure 1; **VF-14**, Visual Function Index (14 questions); **VDQ**, Visual Disability Questionnaire; **VFQ**, Visual Function Questionnaire; **VPI**, Visual Phenomenon Interview; **VS**, visual symptoms; **VSQ**, Vitrectomy Satisfaction Questionnaire; **W-BQ12**, 12-Item Well-Being Questionnaire; **WCS**, Weighted Co-morbidity Scale.

Night Vision Questionnaire (NVQ-39) (303), Visual Disability Questionnaire (307), Everyday Task Questionnaire (302) and Stargardt Macular dystrophy Vision Questionnaire.(308) Of of the eleven PRO instruments, nine were developed for RP, one for congenital stationary night blindness and one for Stargardt disease (Stargardt Macular dystrophy Vision Questionnaire). The PRO instruments, Mobility Difficulties Questionnaire, Everyday Task Questionnaire, Field Expander Questionnaire and IMQ cover a single domain. The Mobility Difficulties Questionnaire and IMQ cover mobility; the Everyday Task Questionnaire covers activity limitation and the Field Expander Questionnaire covers health concerns. The Perceived Visual Function Questionnaire, Activities of Daily Vision Questionnaire, Daily Task Performance Questionnaire, Visual Disability Questionnaire, NVQ-39 and Stargardt Macular dystrophy Vision Questionnaire cover two domains, activity limitation and mobility. The IMQ was the only PRO instrument to be Rasch analysed; it has good measurement precision, item fit and validity; however, other important psychometric information such as dimensionality, DIF and targeting were not reported. The other PRO instruments performed poorly against the quality criteria.

2.5.6.2 *Ophthalmic but non-disease-specific PRO instruments in hereditary Retinal degenerations/dystrophies*

The NEI-VFQ was the only PRO instrument used in 8 studies.(16, 17, 294-297) Validity assessment of the NEI VFQ was not carried out in any of these studies.

2.5.6.3 *Generic PRO instruments in hereditary Retinal degenerations/dystrophies*

Eight PRO instruments were used: the Pittsburgh Sleep Quality Index, Beck Depression Inventory, Stanford Sleepiness Scale, Epsworth Sleepiness Scale, Perceived Stress Scale, Positive and Negative Affect Schedules, Brief Symptom Inventory and SF-36 (Table 2.6). Emotional well-being domain was the most frequently tested QoL issue among these patients. None of these instruments were validated in this disease group.

2.5.6.4 *Qualitative studies and quality of life in patients with hereditary retinal degenerations/dystrophies*

The mode of data collection was focus groups (1 study), interviews (1 study) and both (1 study). The socio-demographic of the population of these studies are given in Table 2.3.

In contrast to AMD and DR, RP causes untreatable progressive loss of peripheral vision and

involve relatively young people in their prime time of education and professional career. Therefore, people with RP have functional and psychological challenges as they need to adjust to the progressive loss of vision in their lives.(245) RP patients experience a variety of visual symptoms such as day-to-day fluctuation in vision, intermittent diplopia, photopsias, visual hallucinations, high glare, and time-of-day effects (visual symptoms). The challenge to maintain independence in the face of worsening vision is a major issue (health concerns). The chronic nature of the condition has often made people with RP more resilient and coping with the difficulties better with time.(2) The arduous and gruelling path and time taken to obtain a proper diagnosis has left many people frustrated (health concerns & emotional well-being). Inadequate communication and information supplied by their doctors about the diagnosis and prognosis was also caused frustrations among people with hereditary retinal diseases (health concerns & emotional well-being).(135)

On the positive note, patients with RP frequently adopt coping strategies to manage the stress of visual loss and humour was the frequently discussed strategy for coping.(2) Social support and communicating with other patients who have RP was also an important part of coping process among RP patients (social participation).(2) Unlike other retinal conditions, in hereditary retinal diseases the unaffected relatives also experienced difficulties like feeling guilty, especially the parents (health concerns).(135) RP patients also adopt several strategies to cope with their visual fluctuations such as scheduling important activities later in the morning or waking up early to allow adequate time to adjust to their vision.(2)

2.5.6.5 *QoL impacts vs QoL measured in hereditary retinal degenerations/dystrophies*

Most of the disease-specific PRO instruments in this disease group were developed for RP. However, the content coverage of most of these instruments is only mobility (Table 2.6). The content coverage of the ophthalmic but non-disease-specific and the generic PRO instruments were limited to activity limitation and emotional well-being. Patients with RP also have a myriad of QoL issues as suggested in the qualitative studies.(2, 135, 245) However, these issues are not well-represented in the content of the existing PRO instruments (Table 2.6). Of the eleven retina-specific PRO instruments used in this group of diseases only the IMQ was assessed with Rasch analysis. It was shown to have good validity and measurement precision, but information on the dimensionality and reliability is missing.

2.5.6.6 *The highest quality existing PRO instrument for hereditary retinal degenerations/dystrophies*

The IMQ was the highest quality instrument available for RP, although it is limited to measuring mobility. The IMQ was graded 'A' for measurement precision (person separation reliability was 0.95, according to the definition grade 'A' if any value ≥ 0.85), item fit (i.e. infit and outfit mean squares was between 0.98 to 1.01, according to the definition grade 'A' if values between 0.7 and 1.3), concurrent and known group validity.

2.5.7 Macular Hole

A total of nine studies were identified on MH (Table 2.6). Among the nine studies, eight used PRO instruments, and only one was a qualitative study.

2.5.7.1 *Disease-specific PRO instruments in MH*

Three disease-specific PRO instruments to assess the patient's satisfaction following MH surgery were developed. These were the Short Visual Function Questionnaire (309), Macular Hole Treatment Satisfaction Questionnaire (314) and Posturing for Macular Hole surgery Questionnaire.(312)The Short Visual Function Questionnaire, Macular Hole Treatment Satisfaction Questionnaire and the Posturing for Macular Hole surgery Questionnaire cover a single domain, health concerns. None of these instruments were validated for use in MH.

2.5.7.2 *Ophthalmic but non-disease-specific PRO instruments in MH*

The NEI-VFQ was the only PRO used in five studies. No validation was performed in this disease group.(18, 19, 310, 311, 313)

2.5.7.3 *Generic PRO instruments in MH*

Only one study used a generic PRO instrument, the SF-36.(18) No validation was performed in this disease group.

2.5.7.4 *Qualitative studies and quality of life in MH*

Only one qualitative study was identified. This study was based on the qualitative analysis of the content of a diary of a single patient who has undergone macular hole surgery.

Wittich *et al* reported that coping with extended face down positioning after macular hole

surgery caused both physical and psychological challenges.(246) Wittich *et al* also reported that emotional instability from prolonged rehabilitation, frustration with slow visual recovery, and lack of sleep are some of the frequent psychological challenges (emotional well-being & convenience).(246) Extended treatment and rehabilitation are health concerns. Support from family members and peers who have undergone similar treatments often help in coping with emotional instability (social participation).(246)

2.5.7.5 *QoL impacts vs QoL measured in MH*

The content coverage of the retina-specific PRO instruments developed for MH is mostly restricted to health concerns, and the content coverage of the ophthalmic but non-disease-specific and generic PRO instruments is restricted to activity limitation and socio-emotional well-being (Table 2.6). Qualitative studies, however, show that these patients have issues with convenience, which is not covered in the existing PRO instruments (Table 2.6). None of the PRO instruments used in MH have were validated in this disease group.(18, 19, 309-314)

2.5.8 Epiretinal membrane (ERM)

There were three studies in ERM and all of them were on PRO instruments (Table 2.6). There were no qualitative studies in ERM. There was no retina-specific PRO instrument developed for ERM.

2.5.8.1 *Ophthalmic but non-disease-specific PRO instruments in ERM*

The NEI-VFQ was the only PRO instrument used in all the studies.(20, 21, 315) It has not been validated in ERM.

2.5.8.2 *Generic PRO instruments in ERM*

The SF-36 was used in one study and it was not validated in ERM.(21)

2.5.8.3 *QoL impacts vs QoL measured in ERM*

Only ophthalmic but non-disease-specific PRO instruments were used to assess the QoL impacts in ERM (Table 2.6). The content coverage of these PRO instruments was limited to measuring activity limitation, emotional well-being and social participation.

2.5.9 Central Serous Retinopathy

Only two studies were identified on CSR (Table 2.6). Both the studies used generic PRO instruments. There was no qualitative study in CSR. There were no disease-specific PRO instruments developed for CSR.

2.5.9.1 *Generic PRO instruments in CSR*

Five PRO instruments were used in these two studies (Table 2.6). The PRO instruments were the Symptom Checklist 90-R, 20-item Toronto Alexithymia Scale, Symptom List Questionnaire on Social Support (F-Sozu, K-22), Symptom List Questionnaire and Personality Factor Questionnaire. The Symptom Checklist 90-R, 20-item Toronto Alexithymia Scale and Personality Factor Questionnaire cover emotional well-being, F-Sozu-K-22 covers social participation; and Symptom List Questionnaire covers general symptoms of QoL. No validation was performed in this disease group.

2.5.9.2 *QoL impacts vs QoL measured in CSR*

The QoL impacts in this disease group were assessed using generic instruments and the content coverage of these generic PRO instruments was limited to emotional well-being and general symptoms (Table 2.6).

2.5.10 Studies in population with mixed retinal diseases

There were sixteen studies on mixed retinal conditions like macular disease, vitreous floaters, and posterior vitreous detachment (Table 2.6) and there were no qualitative studies in this group of retinal diseases.

2.5.10.1 *Disease-specific PRO instruments in mixed retinal diseases*

The two disease-specific PRO instruments used in studies in population with mixed retinal diseases were the Metamorphopsia Questionnaire (MPQ) (255) and Macular Disease Society Questionnaire.(316)The MPQ covers visual symptoms and Macular Disease Society Questionnaire covers health concerns and emotional well-being. The MPQ was assessed using Rasch analysis. It has good measurement precision, response categories and item fit, however, information on the dimensionality and targeting are not available (Table 2.4).

2.5.10.2 *Ophthalmic but non-disease-specific PRO instruments in mixed retinal diseases*

Seven ophthalmic but non-disease -specific PRO instruments were used that included the NEI-VFQ (256, 323, 324, 327, 328), PalmPilot VFQ, VF-14 (319), Vision Core Measure 1 (317), Visual Function Questionnaire (VFQ) (324), Vitrectomy Satisfaction Questionnaire (325) and Patient Satisfaction Questionnaire .(329) The VFQ covers a single domain, health concerns. The PalmPilot-VFQ and Vitrectomy Satisfaction Questionnaire cover two domains. The PalmPilot–VFQ covers general vision and activity limitation and the Vitrectomy Satisfaction Questionnaire, activity limitation and health concerns. The Patient Satisfaction Questionnaire covers four domains, general health, activity limitation, emotional well-being, and health concerns. The PalmPilot –VFQ was tested using Rasch analysis and showed good measurement precision and item fit. Information about the dimensionality and DIF was not reported (Table 2.4).

2.5.10.3 *Generic PRO instruments in mixed retinal diseases*

Eleven PRO instruments were used (Table 2.6). They were the 12-Item Well-Being Questionnaire (W-BQ12), Audit of Diabetes-Dependent Quality of Life, SF-36, Weighted Co-Morbidity Scale, Sickness Impact Profile, Community Disability Scale, General Health Questionnaire, Visual Phenomenon Interview, Eysenck Personality Questionnaire, Telephone Interview for Cognitive Status and 12-Item Short Form Health Survey. Most of these instruments measured emotional well-being and activity limitation. No validation was performed in this disease group.

2.5.10.4 *QoL impacts vs QoL measured in mixed retinal diseases*

The content coverage of the PRO instruments used in this group of retinal diseases is limited to few QoL domains (e.g. emotional well-being and activity limitation) (Table 2.6).

2.5.10.5 *The highest quality existing PRO instrument for mixed retinal diseases*

The MPQ and the PalmPilot-VFQ instruments had the highest quality assessments (Table 2.4). The MPQ was graded ‘A’ for response categories (i.e. no disordered threshold were found in the response categories, according to the definition grade ‘A’ if the response categories were ordered), measurement precision (i.e. person separation reliability was 0.97, according to the definition grade ‘A’ for any value ≥ 0.85) and item fit and the PalmPilot–VFQ was graded ‘A’ for measurement precision (person separation index was

3.79, according to the definition grade ‘A’ for any value ≥ 2.50), item fit (i.e. infit and outfit mean square were between 0.98 to 0.99, according to the definition grade ‘A’ for any value between 0.7 to 1.3), concurrent and convergent validity. The MPQ is the best retina-specific PRO instrument available for general macular diseases and the PalmPilot –VFQ is the highest quality ophthalmic but non-disease-specific PRO instrument in this group of retinal diseases.

2.6 Discussion

The QoL impacts of retinal diseases were assessed using all sorts of PRO instruments which included: generic, ophthalmic but non-disease-specific and retina-specific. Out of the 110 PRO instruments used in these studies, more than half of them were generic instruments (n= 62). Most the studies (n=147) used ophthalmic but non-disease-specific instruments to assess QoL impacts. The NEI-VFQ was the most frequently used PRO instrument and was used in more than half the studies. In more than one third of the studies more than one PRO instrument was used. Only 52 studies out of the 200 studies have used disease-specific PRO instruments. Most the disease-specific instruments were developed for RP (n= 10), AMD (n=9) and DR (n=2). There are no disease-specific PRO instruments developed for vascular diseases, CSR and ERM.

There is a growing consensus among researchers that PRO measurement should be comprehensive to assess a holistic impact in QoL. However, QoL is a multi-dimensional construct. It includes, but is not limited to, activity limitation, symptoms, emotional well-being, socio-emotional impact etc. These are basically component constructs or domains of QoL which deserves separate assessment. However, all the PRO instruments used to assess the QoL impact in patients with retinal diseases in this study are limited in measuring certain domain/s of QoL, for example activity limitation, mobility, emotional-well-being or combination of these. Majority of the retina-specific PRO instruments used in AMD and DR predominantly measure activity limitation (MacDQoL, DLTV, ALQ, Low Luminance Questionnaire, FRQ and NVQ-10) and majority of the retina-specific PRO instruments used in RP predominantly measure the mobility (IMQ, NVQ-39, Mobility Difficulties Questionnaire, Perceived Visual Function Questionnaire and Everyday Task Questionnaire) aspect of QoL. Therefore, the existing retina-specific PRO instruments are less comprehensive and fail to cover all the aspects of QoL.

The majority of the PRO instruments were summary scored and only eleven PRO instruments were Rasch scaled. Classical test theory suffers two major limitations, lack of an explicit ordered continuum of items that represent a unidimensional construct and lack of an equal interval scaling both of which increase noise and reduce the statistical power thereby preventing a precise and accurate measurement of patient-reported outcomes. In contrast to the classical test theory approach, the Rasch model provides an interval level scoring that enables the examination of the hierarchical structure and unidimensionality of the PRO measure.(330) Rasch analysis is important for achieving the most extensive validation of PRO instruments.(40) Of all the retina-specific PRO instruments used in this study only three (2 in AMD and 1 in RP) were subjected to Rasch analysis. None of the retina-specific PRO instruments as a whole were found to be valid for use in any retinal diseases. However, two of the sub-scales (socio-emotional well-being and activity limitation and mobility) of the AMD-specific PRO instrument, the MacDQoL were found to be valid for use in AMD.(24) Three scales (emotional well-being, reading and accessing information and mobility and independence) of the PRO instrument, the IVI was also found to have a valid measure for AMD. Although, originally devloped for low-vision to assess the rehabilitation needs,(331) the IVI was modified as a legacy instrument and tested with Rasch analysis for validity in patients with AMD.(219, 332) (219) However, for other retinal diseases, there is no valid PRO instrument available.

Comparing the findings of the qualitative studies in AMD, DR and RP and the content coverage of the PRO instruments used in this study there is a big gap between known QoL impacts of retinal diseases and QoL measured by the existing PRO instruments. Difficulty in driving was reported as one of the major activity limitation among people with retinal diseases because a lot of data is from developed countries where driving is possible. However, there are plenty of countries where this would not have been the number one difficulty. So it is just not the diseases that dictates what people see as being important but their cultural background too. Hence a comprehensive consultation with patients are important in the content development of any PRO instrument. Qualitative studies are vital to understand a patient's experience of living with a disease and qualitative consultation with patients is very important in the content development of any PRO instrument. A PRO instrument developed without qualitative consultation will miss out important aspects of QoL issue that matters to the patients. Qualitative studies were performed only for AMD, DR and

RP.(1-3, 24, 235, 237, 238, 241) There are no qualitative studies performed for other less common retinal diseases such as RD, ERM, MH, CSR, vascular occlusive diseases, retinal infections, etc. Moreover, the QoL impact of these retinal diseases are measured using PRO instruments either developed for ocular diseases other than retinal diseases (ophthalmic non-disease-specific) or other medical diseases (generic).(12, 20, 22, 278) As these PRO instruments contain items/questions that are not relevant to retinal diseases they are not sensitive enough in measuring the QoL impact in these retinal diseases. Hence there is need to develop comprehensive retina-specific PRO instruments that can measure all relevant QoL domains.

2.7 Conclusion

This review shows that all the currently existing retina-specific PRO instruments are limited in their content coverage of QoL and their psychometric properties are not scientifically sound to assess the patient-reported outcomes. There is a need to develop new comprehensive and technologically advanced PRO instruments to assess QoL impacts in retinal diseases.

2.8 Future research and developments

Considering the number of retinal diseases/conditions and the emergence of new treatment interventions for these conditions, there exists a need for comprehensive and psychometrically robust retina-specific PRO instruments that can measure all relevant QoL domains.(133) It is impossible to achieve this with the existing PRO instruments. New instruments with a wider coverage of QoL domains and good psychometric qualities are required. A new generation PRO measurement approach in the form of item banking (third generation PROs) implemented via Computer Adaptive Testing (CAT) can provide solutions to the issues associated with the existing PRO instruments. The first step to developing such instruments is to comprehensively understand QoL impacts from patients' perspective through well designed and executed qualitative studies. Work is ongoing in this area.(3, 45)

An item bank is a large collection of items that are calibrated to measure a single underlying latent trait (e.g. functional limitations, symptoms, emotional well-being etc.).(43)The CAT system is an iterative algorithm that chooses items from the available pool of items to measure the underlying trait for an individual.(333) The items are chosen based on the

individual’s ability which is based on the respondent’s answer to previous items. Because the item administration is based on the patient’s response to the previous question; it is fast and needs very few items to complete measurement. The third generation PROs have been successfully developed and implemented in other health care fields (334-336) and is currently under construction for eye diseases.(45, 337)

CHAPTER 3 LISTENING TO THE VOICES OF PEOPLE WITH RETINAL DISEASES: A QUALITATIVE STUDY

3.1 Introduction

Qualitative research is a method of inquiry that examines people's believes, attitudes, behaviour and experiences. In contrast to quantitative research which tests theories, qualitative research is an inductive approach that can result in theory generation and exploration. Qualitative research is often described as a naturalistic and an interpretive approach, concerned with exploring phenomenon 'from the interior'.(338) One of the key strengths of qualitative research is that it studies people in their natural settings rather than in artificial or experimental one.(339) The researcher engages in a situation and attempts to make sense of it. Researchers uncover their own a priori assumptions and knowledge by using reflective strategies.(340) Qualitative research methods were introduced in the 1960s and 1970s into the health care field.(341-344) In the last decade qualitative methods have been increasing in the health service research and health technology assessment.(345) The common approaches which are used in the collection of qualitative date are phenomenology, ethnography, inductive thematic analysis, grounded theory, discourse/ conversation analysis, narrative analysis and mixed methods. The inductive thematic analysis is probably the most common qualitative data method approach employed in the social, behavioural and health sciences.(346) Qualitative research often employs different qualitative methods such as direct observation, interviews, analysis of texts or documents and the analysis of recorded speech or behaviour using audio or video tapes.

Interviews are the most familiar strategies for collecting qualitative data.(347) The main types of interviews are structured, semi-structured, and unstructured.(348, 349) The most widely used interviewing format in qualitative research is the semi-structured interview, which is generally organised around a set of pre-determined open-ended questions, with the other questions emerging during the interview process between the interviewer and the interviewee.(347) Semi-structured interviews are conducted either face-to-face or through the telephone. The quality of the textual data collected by telephone interviews are on a par with that obtained using face-to-face interview.(350)

Several researchers have used qualitative approaches to identify content area for the development of vision specific questionnaires.(3, 236, 337) This is considered as a standard

approach in eliciting quality and highly informative item content. As the present study also aimed to develop disease-specific questionnaires for other vitreoretinal diseases, a qualitative study was designed to explore the quality of life (QoL) issues of people with different retinal diseases. This chapter describes the results of the study. The information was used as an evidence-base for grouping vs splitting other vitreoretinal diseases to develop content for group-specific PRO instruments.

3.2 Aims and objectives

1. To explore the QoL issues of people with other other vitreoretinal diseases.
2. To gather qualitative evidence on QoL impact for grouping/splitting other other vitreoretinal diseases to develop group-specific PRO instruments.
3. To Compare the qualitative findings of this study with the qualitative findings of the age related macular degeneration (AMD) and the diabetic retinopathy (DR) module of the eye-tem bank project.

3.3 Methods

3.3.1 Splitting /grouping other VR diseases

We used a novel way to group the other vitreoretinal diseases into hereditary retinal diseases (HRD) and acquired retinal diseases (ARD). HRD differ from ARD in terms of the onset, presentation, and manifestation. HRD tends to have an early onset; mostly are bilateral and cause a progressive decline of vision and ARD tends to have a late onset; mostly unilateral to begin with and may be either stationary or progressive. We used a pragmatic approach to prove the novel idea.

3.3.2 Planning and preparation

A moderator guide consisting of a brief introductory script on the purpose of the study, and instructions to the participants was developed for each of the groups (Appendix 2). Similarly, a question route consisting of set of semi-structured open-ended questions for each of the disease group was developed (Appendix 2). The open-ended set of questions were developed from a comprehensive literature review and input from retinal specialists and it was validated by a panel of experts (JK and KP). The aim of the semi-structured guide was to include questions that would help to uncover all aspects of QoL (physical, social, and emotional). The moderator guide and the question route for the two groups of the vitreoretinal disease was primarily developed by the author and verified and modified by the

supervisors (JK and KP).

Prior to organising the interviews an information pack consisting of an invitation letter, research information leaflet, a consent form and, a demographic form was developed. Ethical approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee.

3.3.2.1 *Number of semi-structured interviews*

The author planned to conduct a minimum of twenty interviews for each of the diseases; however, the number of interviews for each disease group was primarily decided by the information saturation in that disease group. If thematic saturation was not achieved by twenty interviews, then more cases were recruited and analysed until information saturation was achieved.

3.3.2.2 *Recruitment of participants for the semi-structured interviews*

Participants for this study were recruited from multiple sites. Participants for the HRD group were recruited from charity and welfare organisations (The Royal Society for the Blind, Adelaide) and Retina Australia (South Australia, Queensland, Victoria, Canberra, Western Australia, and Northern territory) through flyers and emails. Participants who were interested to participate in the study were sent out an information pack with an invitation letter, participation information sheet, consent form and a demographic form. The clinical details (i.e. diagnosis of their eye condition and their visual acuity) were obtained either from the participants (self-reported) or obtained from their eye practitioners. Participants for the ARD group were recruited from the retina clinics of two major metropolitan public health care facilities (The Royal Adelaide Hospital, South Australia and The Queen Elizabeth Hospital, South Australia). Clinical records were used to identify potential participants who were then approached in person to discuss their possible involvement in the study. Participants who agreed to participate in the study were given the information pack. The clinical details were obtained from the clinical records. A time of two weeks was given to return the forms to the author and if the forms were not returned in that time the patient was given a reminder by phone. Upon receiving the consent form from both the groups, the participants were contacted through telephone to organise a date and time for the interview. All the participants were recruited to a single in-depth interview.

3.3.2.3 *Interviewers*

Two interviewers were involved. One of them was the author and the other one was the research assistant for the Eye-tem Bank project (Ms Susan Aldhous). Most of the interviews were conducted by the author.

3.3.2.4 *Technical issues*

The interviews were done either face-to-face or over the telephone. All the telephone interviews were formally conducted from the Optometry research premesis (room 150) and the face-to-face interviews were done either in the Optometry research premesis or Flinders University, Victoria Square Campus.The telephone interviews were recorded using a digital recorder.

3.3.2.5 *Conducting interviews*

For the telephone interviews the participants were called either on their landline or mobile phone for the interviews. A brief introduction was given by the author to the participants about the purpose of the study and the procedure to follow during the interview at the start of the interview. Participants were also briefed about the degree of confidentiality; i.e. participants would not be identified during the recording, the information would not be disclosed to anyone and recordings would be for research purpose only. They were also given time for questions before the sessions. The interviews were conducted following a standard protocol with minimum involvement of the interviewer and allowing maximum involvement of the interviewee. At the end of the interview, the participants were given time to add and ask questions. The interview time varied depending on the participant's eye condition. The telephone interviews were recorded using a digital recorder. The participants were given 20 AUD for travel reimbursement.

3.3.3 Audio files and transcription

The audio files from the digital recorder were labelled and transferred to a computer folder secured by a password. The audio tapes from the tape recorder were also labelled and securely locked in a cupboard at the Optometry research area, Flinders University. The audio files were transcribed verbatim by a professional transcriber and the interviewees were not identified by names in the transcripts.

3.3.4 Coding and Data analysis

The data analysis occurred after the data collection was complete. An iterative inductive analytic approach was adopted based on the constant comparative method, whereby broad themes were developed from the raw content of the transcripts. Nodes (words or phrases) to code text segments were generated after reading individual transcripts. These nodes represent the text segments coded by them as closely as possible. For this an open coding strategy was carried out which entailed a line-by-line coding approach. Each transcript was coded using these nodes in their entirety. Once coding was complete individual nodes were reorganised by assimilating them into different categories (i.e. nodes of similar concepts were brought under the umbrella of a mother node (potential major theme)) (Figure 3.1).

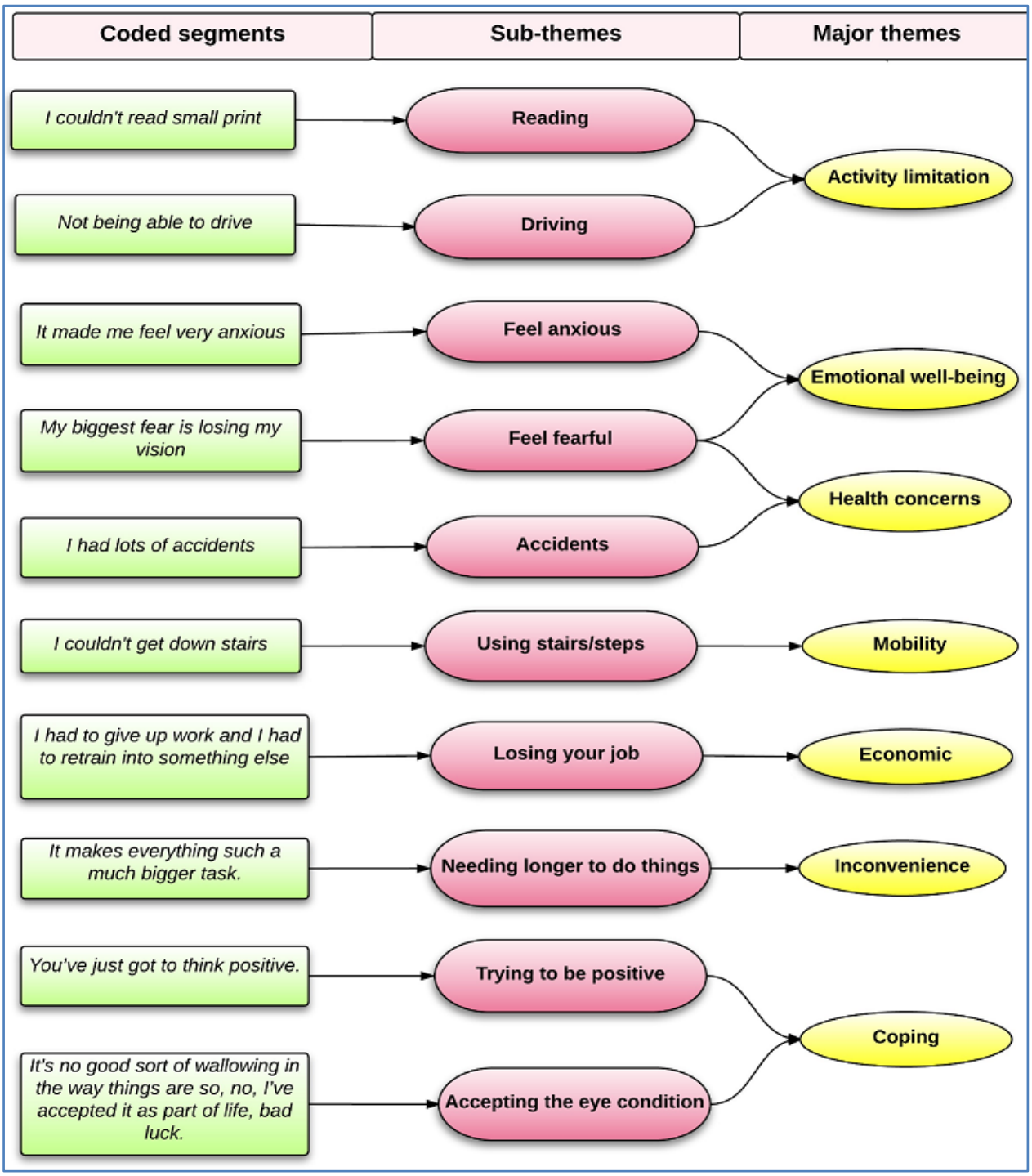

Figure 3.1 Process of data analysis

The mother nodes with component child nodes (potential sub-themes) were explored to identify linkage between similar patterns across the transcripts to identify key threads. The author and two supervisors then assessed these key threads to come to a decision whether they qualify to form a theme. Any discrepancies between the author and the supervisors were resolved by discussion. New or improved themes that emerged from later transcripts

were incorporated into the coding hierarchy and earlier transcripts were updated to reflect the modification. The QoL issues between the two groups were compared across the identified common themes. The computer program QSR NVivo 11 (QSR International Pty Ltd) was used to code the transcripts systematically.

3.4 Rigor

A range of strategies were adopted to ensure the trustworthiness of our study which included internal validity, transferability, dependability, and confirmability. Internal validity was achieved through adoption of systematic, in-depth field work and triangulation of time and space (various times of the day, week and year were used in the collection of the data and use of multi-sites for participant recruitments). Transferability was achieved through description of the clinical context of the study and description of the demographics of the participants. Dependability was achieved through in-depth description of the methodology. Confirmability was achieved through the recognition of shortcomings in the study's method and in its potential effects.

3.5 Results

3.5.1 Demographics details

Seventy-nine semi-structured interviews were conducted with participants with HRD (n = 32) and ARD (n=47). Most the interviews were conducted over the telephone (n=77). Most of the interviews were conducted by the author (n=77). The interviews with participants with HRD ranged from 30 to 90 minutes and the interviews with participants with ARD ranged from 30 to 40 minutes. The socio-demographics of the two groups were different. Participants in the HRD group were younger, mostly working, had bilateral eye disease, and were more visually impaired. Participants with ARD were older, mostly retired, had unilateral eye disease and, were less visually impaired (Table 3.1).

Table 3.1. Socio-demographics details of the study population

Variables	HRD *n = 32*	ARD *n = 47*
Age (years, n (%))		
> 55	19(59)	44(94)
Median age, IQR	57, 44 to 69	73, 65 to 78
Range	28 to 81	34 to 90
Median age of onset of disease, IQR (years)	18, 12 to 31	70, 62 to 75
Median duration of the disease (years) (years)	39, 27 to 48	3, 2 to 5
Gender, n (%)		
Female	20(63)	29(62)
Country of birth, n (%)		
Australia	25(78)	37(79)
Others	7 (22)	10(21)
Main language spoken, n (%)		
English	29(91)	42(89)
Others	3(9)	5(11)
Marital status, n (%)		
Married	19(59)	15(32)
De facto/ divorced/ separated/widowed	8(25)	27(57)
Never married	5(16)	5(11)
Education level, n (%)		
Secondary or less	10(31)	34(72)
TAFE/university degree	22(69)	13(28)
Employment status, n (%)		
Working	20 (63)	5(11)
Visual acuity (worse eye), n (%)		
Better than 6/18	3(9)	21(45)
6/18 to 6/60	17(53)	20(43)
Less than 6/60	11(34)	6(13)
Laterality, n (%)		
Bilateral	32(100)	6(13)
Ocular comorbidity, n (%)		
Yes	12(38)	16(34)
Medical comorbidity, n (%)		
Yes	16(50)	28(60)

Percentage of some variables may not be equal to 100% due to missing data

3.5.2 Retinal conditions

In the HRD group most of the participants had retinitis pigmentosa (RP) (n=23), followed by macular dystrophy (n=7) and cone dystrophy (n=2). In the ARD group, most the participants had epiretinal membrane (ERM) (n=20), followed by vascular occlusion (n=18) and macular hole (MH) (n=9). Among the macular dystrophies, Stargardt disease was the commonest (n=4), followed by Best's disease (n=3). Among the vascular occlusions branch retinal vein occlusion was the commonest (n=9), followed by central retinal vein occlusion (n=7), central retinal artery occlusion (n=1) and myopic choroidal neovascularisation (n=1). All the participants in the HRD group had bilateral disease. In the ARD group, only 6 participants had bilateral disease. In more than 60% of the participants with unilateral disease, the right

eye was commonly affected (n=28).

3.5.3 Key themes from the qualitative interviews

Nine QoL themes/ domains were identified from the qualitative interviews. However, these QoL themes were identical to the QoL themes identified in AMD and DR modules of the Eye-tem bank project.(3, 4, 337) These themes were discussed and agreed upon between the author and the two supervisors (KP and JK). The QoL themes identified in this study summarise the QoL issues relevant of people with HRD and ARD.

The nine main themes are:

1. Difficulties in performing important day-to-day activities (**Activity limitation**).
2. Facing emotional and psychological challenges (**Emotional**).
3. Concerns about their health, disease outcome and personal safety (**Health concerns**).
4. Having myriad of symptoms (visual, ocular comfort and general symptoms) (**Symptoms**).
5. Participating in social activities was problematic (**Social**).
6. Problems with mobility and orientation (**Mobility**).
7. Effect on work & finance (**Economic**).
8. Inconveniences associated with the eye condition (**Convenience**).
9. Coping with the eye condition (**Coping**).

These themes were identified as important domains of QoL. Within each major theme/domain several sub-themes were identified (Figure 3.1). For example, ‘reading’, ‘driving’, ‘shopping’ and ‘playing sports’ were some of the sub-themes within the major QoL theme/domain activity limitation. Similarly, ‘feeling frustrated’, ‘feeling shocked’ and ‘feeling anxious’ were some of the sub-themes under the major QoL theme/domain emotional well-being.

Generally, the HRD group had expressed more issues (denoted by number of coded segments) across all domains expect one (convenience) than the ARD group (Figure 3.2). Activity limitation was the most prominent QoL issue among participants with HRD and health concerns was the most prominent QoL issue among participants with ARD (Figure 3.2).

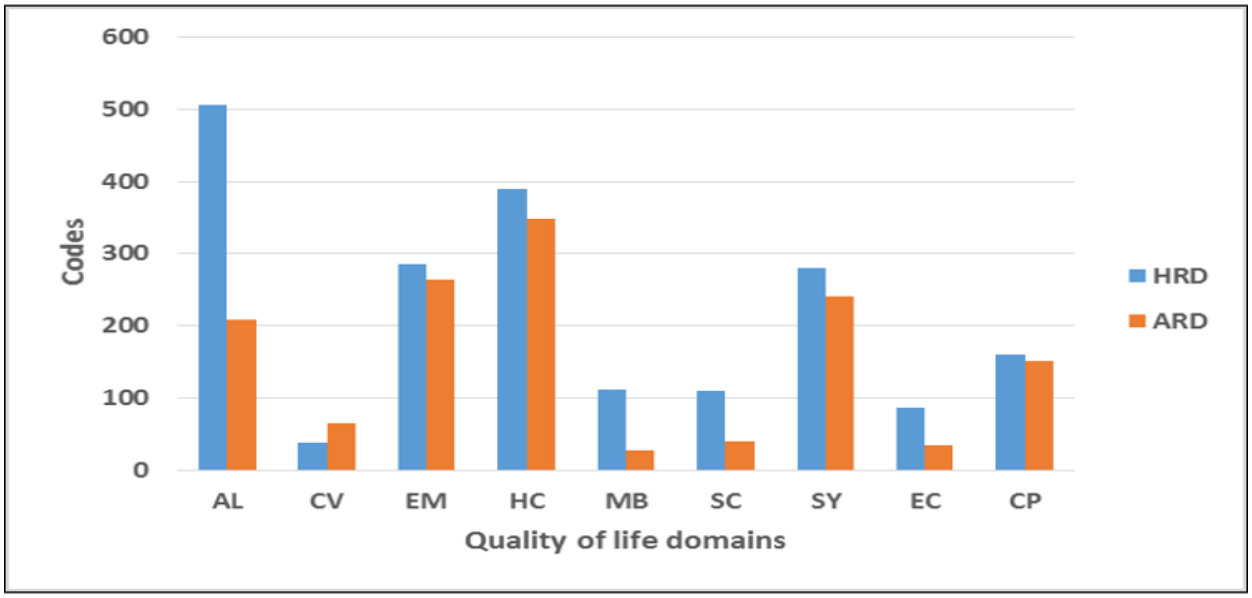

Figure 3.2 Quality of life (QoL) themes/domains in hereditary retinal diseases (HRD) and acquired retinal diseases (ARD). Codes = number of times the issue was discussed across all the transcripts analysed

X-axis represents QoL themes and Y-axis number of coded segments for each QoL theme. AL, activity limitation; CV, convenience, EM, emotional well-being; HC, health concerns; MB, mobility; SC, social participation; SY, symptoms, EC, economic; CP, coping.

Within the HRD and the ARD groups, the QoL issues were similar. More than 80% of the QoL issues were common between RP, cone dystrophy and macular dystrophy and more than 70% of the issues were common between vascular occlusion, ERM and MH. However, between the HRD and the ARD groups some of the QoL issues were common (less than 30%), but overall, many of the QoL issues were unique to the disease groups (Figure 3.3).

Participants with both HRD and ARD faced many emotional and psychological challenges (emotional). Participants with HRD had more issues with social participation (social), problems with mobility and orientation (mobility) and effect on work and finance (economic) compared to participants with ARD. Participants with HRD also reported more visual symptoms (symptoms). On the contrary, participants with ARD reported more inconveniences which were mostly attributed to their treatment. Participants with HRD were coping better compared to participants with ARD.

The QoL impact of participants with HRD and ARD is discussed below. Relevant quotations are used to exemplify the themes.

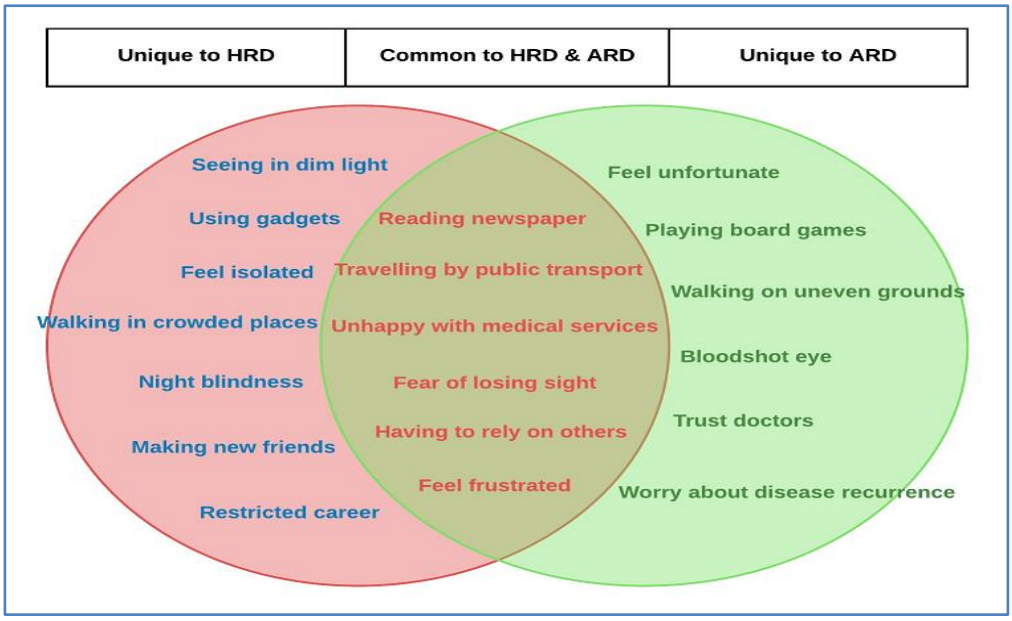

Figure 3.3 Examples of some of the quality of life (QoL) issues in people with hereditary retinal diseases (HRD) and acquired retinal diseases (ARD)

3.5.3.1 *Activity limitation*

Activity limitation was identified as the major issue among participants with HRD (Figure 3.2). The major activity limitations were difficulty in reading, seeing under different light conditions, driving, shopping, playing sports, and using computers. They reported difficulty in reading books, newspapers, menu cards, magazines, and documents.

> *"Obviously, I can't read, haven't been able to read any normal print for - oh, since I was very young but I use computers, a voice output computer, for a lot of that sort of stuff". (**cone dystrophy, female, 52 years**)*

The most significant issue was difficulty in seeing in poor lighting conditions and the limitations that this imposed for participants with HRD.

> *"Night time especially is even worse because I don't like going places that is dark and every time you go out at night places are dark, they have dim lighting. Especially when you're eating, half the time I'm trying to eat and I can't quite see what I'm eating on the plate so I have to sort of just wing it." (**RP, female, 56 years**)*

Frequent re-organising or re-arranging things in the supermarket and inability to read price tags made shopping a huge challenge.

> *"If the packaging changes in Woolworths or if Woolworths decides to move items around I'm lost until I work out where they are because I work on predictability" (**macular dystrophy, female, 56 years**)*

Many participants had to give up their driving license due to progressive visual loss. Not being able to drive was reported as a big loss as they had to depend on friends or family members for transport. They also reported difficulty in playing outdoor games especially ball games. Working long hours on the computer was also a big challenge.

In the ARD group activity limitation was only the fourth biggest issue (Figure 3.2). The individuals stated similar challenges in performing day-to-day activities as did the participants with HRD, such as difficulty in reading, driving, watching television, shopping, and taking part in leisure activities (Table 3.2).They reported difficulty especially reading fine print and street/road signs. In contrast to participants with HRD who had difficulty in playing outdoor games, participants with ARD had difficulties in playing indoor games such as board games and doing puzzles.

> *"I do a lot of Sudoku puzzles and crosswords and I've found them difficult. Sudoku, I find that hard to do because I can't scan the whole size of the puzzle." (**ERM, female, 66 years**)*

In contrast to participants with HRD who could not drive, participants with ARD were driving but expressed that driving had become challenging especially at night.

> *"I had to stop driving at night because the reason being my vision is not as good at night so I'm really limited. I can only drive during the daytime hours." (**MH, female, 65 years**)*

As ARD predominantly involves the central retina, these participants frequently had difficulty in recognizing people's faces.

> *"At the moment, I feel quite happy enough because my eyesight is generally okay but the worse thing I don't like is I can't see faces across the road, or even some metres away I don't see the faces." (**vascular occlusion, female, 85 years**)*

Some of the activities such as difficulty in reading, driving and shopping were common to both disease groups. Difficulty in seeing under different light conditions and difficulty using gadgets were some of the activity limitations unique to the HRD group. Difficulty in reading road/street signs and playing board games were unique to the ARD group. Examples of some of the common and unique QoL issues between the two disease groups are shown in Figure 3.4

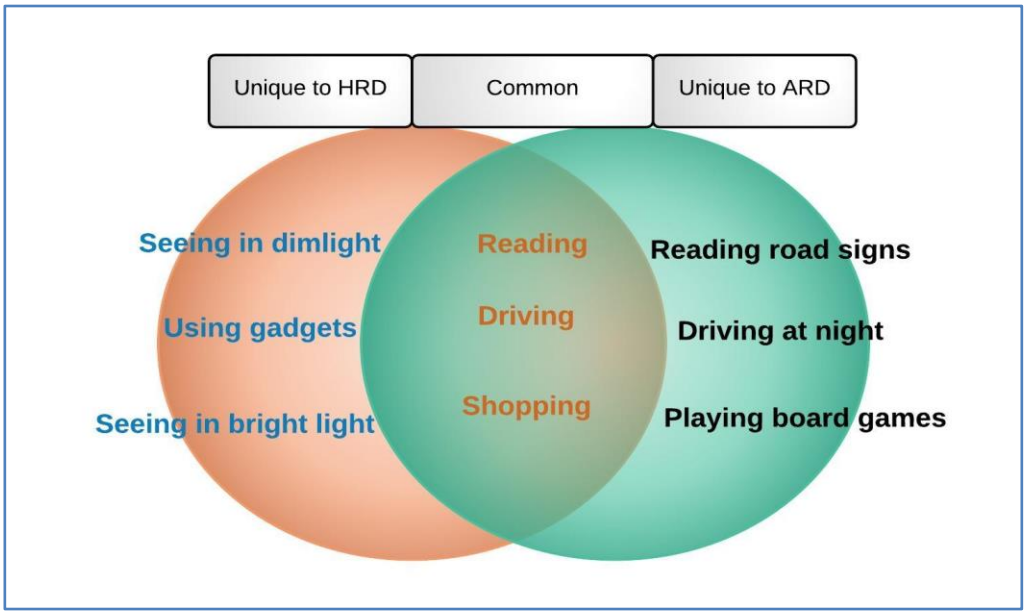

Figure 3.4 Examples of some of the unique and common QoL issues of participants with hereditary retinal diseases (HRD) and acquired retinal diseases in the QoL domain activity limitation

3.5.3.2 *Emotional*

Participants in both the HRD and the ARD groups expressed positive and negative emotional comments. However, participants with HRD expressed more negative emotions than positive emotions (Figure 3.5). The commonly expressed emotional comments in the HRD group were frustration, anxiety, feeling as a burden, shock, and depression. There was an inability to do things like others such as to read, to drive and to find a suitable job, which often resulted in frustration.

> *"I mean my problem is only driving cars - I don't mind that; I didn't like driving anyway - but reading books is frustrating, I must say, because I've always been someone who's read and read and read and read. (**macular dystrophy, male, 76 years**)*

Having to keep up with technology and not knowing how their eye condition is going to progress caused anxiety.

> *"My anxieties – I've become so reliant on technology and it's about keeping up with that technology. It's very, very hard to keep up with that technology all the time, excessively hard." (**RP, female, 68 years**)*

Table 3.2. Examples of quotes expressed by the participants with hereditary retinal diseases (HRD) and acquired retinal diseases (ARD) which feed into sub and major themes of quality of life (QoL)

Major QoL themes	Sub-themes		Hereditary retinal diseases (HRD)		Acquired retinal diseases (ARD)
Activity limitation	Reading	Responses = 66 Participants = 22	*"During the teenage years I could read large print. After that I lost the vision to read and I've only got light perception now"*	Responses = 21 Participants =12	*"That's right, I just went and got an eye test and they said 'you need glasses for reading' because I can't read properly so they did bifocals but it wasn't until later that I was told that my eyesight was – something wrong with it"*
	Seeing in different light conditions	Responses = 55 Participants = 21	*"I really can't do much by myself, I need someone to help me around at night"*	Responses = 9 Participants = 5	*"I can still see at night with the headlights on but I don't go out much at night."*
	Driving	Responses = 42 Participants = 16	*"The first manifestation was when I was driving I couldn't see the white lines on the road and I was trying to share lanes with other car drivers"*	Responses = 37 Participants =17	*"I see nothing hardly but my left eye is good so - but with driving and that I find, you know, I've got to turn my head right around or else I don't see what's coming from my right"*
	Shopping	Responses = 49 Participants = 22	*"I really do feel that my sight now is impacting on my independence so being able to go out and shop on my own is becoming extremely difficult to do"*	Responses = 8 Participants = 7	*"Another thing is when you go to the supermarket and you stand at the top of the aisle and look down you can't read what the products are so you've got to walk up and down each one looking at the - but minor things, minor things for me."*
Emotional well-being	Feel frustrated	Responses = 45 Participants =15	*"It's frustrating because you want to do what everybody else can do and sometimes it's the little things that becomes most frustrating"*	Responses = 24 Participants = 9	*"Probably the clinics are very busy and you're there for quite a while sometimes. There's days where I'm in there for three to four hours and it can get very frustrating.*
	Feel anxious	Responses = 29 Participants = 13	*"Being able to go places that I'm not familiar with on my own, I find that difficult until I get quite anxious about it now because I know how hard it is"*	Responses =16 Participants =14	*"I suppose any anxiety I have might just be that the injections don't work as well as they were hoping them to because I have already had eight and originally they said normally with these injections you get about six to eight and then hopefully it's working by then but with mine no shunts were really formed to drain my eye.*
	Feel hopeful	Responses = 18 Participants = 5	*"That wouldn't worry me because I haven't got much vision as it is. The only thing I can lose now is light perception and that's it. I just hope I don't lose that but that's about all I can lose."*	Responses = 47 Participants =16	*"Well I am hoping that when I do have the laser treatment, that I'll notice a real difference and the strength of my glasses will be reduced. I just feel I will notice a difference. I won't have those floaties and things."*

	Feel shocked	Responses = 20 Participants =16	*"It was frustrating because when they give you the diagnosis that you've got this eye condition and you're going to go blind you're in so much shock and you don't really know what to do. What probably would have helped would have been one of the staff to say 'look, here is a bunch of information."*	Responses = 22 Participants = 11	*"I got a terrible shock when I tried to read an eye chart because, as I say, looking with two eyes you can't notice any difference."*
Social well-being	Interacting socially with people	Responses = 37 Participants = 20	*If I'm out with people and in a bunch of people, even people I know, and they're all chattering and I can't see which one is which and I can't see which one is talking to me.*	Responses = 7 Participants = 6	*"No, not because of that, because my friends come out home, we have a few drinks and then we go and cook tea, watch TV and go to bed."*
	Strain in personal relationships	Responses = 5 Participants = 5	*"I was 31 when I was actually diagnosed with RP and that occurred – my marriage had just broken up and I had two children who were 7 and nine"*	Responses = 0 Participants = 0	NA
	Getting help and support from family and friends	Responses = 109 Participants = 24	*When I tried to explain it to my mother and my father – and of course my mother had RP – my father ordered me out of the house and told me he had enough of putting up with his wife for 50 years with RP and he didn't want another person with RP in the family and told me to get out.*	Responses = 39 Participants = 20	*"No, I've told them the full story and my family's lovely, they're confident for me and, yeah, they always reassure that everything will be okay and all that sort of stuff"*
	Being part of social activities	Responses = 26 Participants = 15	*Well, yeah, it does because I just can't do things with – like you're left out with the parent groups at school and stuff because I can't get to the coffees;*	Responses = 20 Participants = 9	*"I play in a thing called a fun band where we go around and play music at Helping Hand centres and aged care facilities and all of that."*

Health concerns	Not getting enough information from medical staff	Responses = 55 Participants = 26	*"I had been told by a misinformed medical practitioner when I was in my teens that I would go blind and not be able to see within a few years so my life absolutely turned upside down. That person was wrong and I only found that out in my 30s"*	Responses = 85 Participants= 32	*"He said 'if you had surgery on your eyes as they are now' he said 'you could go blind' but he wouldn't tell me why so - excuse the language but I was absolutely pissed off with him."*
	Bumping into people or objects	Responses = 36 Participants = 20	*"I've had a few trips. I fell down some stairs, just two or three stairs, and sprained both ankles"*	Responses = 8 Participants = 6	*"Well I mean I've fallen over several times walking down the street and I've broken my tooth, broken the front tooth."*
	People not understanding your visual impairment	Responses = 32 Participants = 8	*"Also people's perception; people would accuse me of being drunk or on drugs and they didn't understand."*	Responses = 2 Participants = 1	*"I have some cousins and they're concerned, they ask me how it happened and what treatment and stuff so some people understand but then other people – yeah, when you listen to other people's problems you feel kind of a bit helpless so you don't really want to ask.*
	Going blind	Responses = 39 Participants =16	*"My biggest fear is that perhaps I will lose it all. I've been fighting all these years to retain my vision and my biggest fear is losing it all"*	Responses = 24 Participants =14	*"I was worried that I didn't – that what they suggested that I have done, I definitely wanted to have the operation because I didn't want to go blind in my eye and I thought that was most important, to get that fixed if I could".*
Symptoms	Night blindness	Responses = 68 Participants = 23	*"I haven't had any night vision for a long, long time."*	Responses = 0 Participants = 0	NA
	Distorted vision	Responses = 0 Participants = 0	NA	Responses = 26 Participants =11	*"No, it's just a – just say if I'm looking at a straight line the line's crooked. It's not straight, it's crooked out of my right eye, and I can't see faces if I'm too far away from people"*
	Restricted field of vision	Responses = 46 Participants = 21	*"Well put it this way, ever since I was young I've never had much field of vision; I've always had tunnel vision."*	Responses = 8 Participants = 2	*"You know, sure I could lose my sight altogether with the retina peeling off but they never mentioned that this would affect my peripheral vision, which was as clear as a bell prior to that, and as far as I'm concerned that's not on"*
	Distinguishing colours	Responses = 28 Participants = 20	*"well, to some extent - but with colour vision I see dark colours as either black or dark blue or dark brown; I can't differentiate between those colours"*	Responses = 0 Participants = 0	NA

Mobility	Walking around unfamiliar areas	Responses = 34 Participants = 17	*"Being able to go places that I'm not familiar with on my own, I find that difficult until I get quite anxious about it now because I know how hard it is"*	Responses = 0 Participants = 0	NA
	Crossing a street/road	Responses = 4 Participants = 4	*"You know, crossing roads is very difficult."*	Responses = 5 Participants = 2	*"I have to be careful crossing roads because I can't see that far up the road to what's coming"*
	Walking in crowded situations	Responses = 17 Participants = 10	*"I found that I was finding it really difficult in shopping centres and I was starting to avoid going to those places"*	Responses = 0 Participants = 0	NA
	Using steps/stairs	Responses =13 Participants = 9	*"I mean going down steps is the most difficult thing. Ramps are good but steps are not good"*	Responses = 1 Participant = 1	*"When I get off, you know, steps and kerbs and things it's kind of not where it should be so I have to stop and kind of do it carefully and look where I'm going."*
Economic	Ability to find employment	Responses = 73 Participants = 22	*"I guess it affected my work because I can't get fulltime work because people don't want to employ visually impaired people,"*	Responses = 0 Participants = 0	NA
	Costs associated with treatment of the eye condition	Responses = 0 Participants = 0	NA	Responses = 4 Participants = 2	*"No, well, I always basically have to pay – I just have to pay, like anything you get from the chemist really, the Warfarin, it's like – I think it's about 13 bucks a bottle or something. They're just 50 little pills and I usually have to take at least two a day so I suppose that adds up,*
	Not being able to work	Responses = 54 Participants = 20	*"I was a nurse and then I was a disability support worker in a mental institution, like in a – what would you call it now – community houses I think they are. I was 2IC in a community house when my vision started to deteriorate so I just - actually I was lucky enough to be able to get a package and leave."*	Responses = 9 Participants = 5	*"Well actually as my eyes are now I wouldn't be able to do what I used to do years ago. I wouldn't be able to do that job now, it'd be too dangerous."*
	Financial impact from loss of income	Responses = 12 Participants = 8	*"I was earning a very good income and that was cut completely. Well now, as a remedial massage therapist I do have an income but it's still very small"*	Responses = 5 Participants = 3	*I suppose it has because the work I do, I'm on a casual rate which means when I have to go to hospital in Adelaide I actually don't get paid at all when I'm not there.*

Convenience	Having to do positioning after surgery	Responses = 0 Participants = 0	NA	Responses = 42 Participants = 15	*"Well after you had the surgery you've got to lay on your belly for two weeks and that is absolute murder."*
	Having to rely on others for help	Responses =37 Participants = 18	*"Not at all. Well, yes, because I've got to call on my - I have two children and I've got to call on them to read my mail to me and to do some computer work for me sometimes, little things like that"*	Responses = 8 Participants = 8	*"I think the inconvenience was mostly the need for regular visits for anti-VEGF injections because I don't like driving right after an injection because I've got one eye patched and it's pretty sore and bloodshot and so somebody else goes with me and that – you know, you're doing that every six weeks for a while and so it's an inconvenience, not only to me but to somebody else."*
	Having to plan and organize for the things beforehand	Responses = 8 Participants = 5	*I can't go down the Gold Coast and have a swim, that would be too big a project now, whereas if I could drive that's no problem. For me to go to the beach I've got to plan ahead, so it's that lack of ability to participate in something spontaneously."*	Responses = 0 Participants = 0	*NA*
	The amount of time needed for eye appointment	Responses = 2 Participants = 1	*"It was a morning appointment and I felt like I was there all morning, like it was hours."*	Responses = 8 Participants = 7	*"Just sitting around for three or four hours, it's very frustrating and you get very tired and you just want to get in and get out"*
Coping	Trying to be positive	Responses = 28 Participants = 15	*"you know, being blind and alive is better than being young and dead so, no, I'm quite strong about that and I always think on the positive"*	Responses = 12 Participants = 12	*Yes, I probably will then but the way I am now I'm not frightened of anything. You've just got to think positive. You start thinking negative you'll just go backwards.*
	Thinking that there are people much worse than you	Responses = 8 Participants = 8	*"When I go to like to the Royal Society for the Blind and stuff there's always people so much worse you feel bad complaining"*	Responses = 7 Participants = 6	*"Not until you go down there and see them and there's a lot of people worse than me"*
	Attributing the eye condition to ageing	Responses = 0 Participants = 0	NA	Responses = 15 Participants = 12	*"My eyes have deteriorated more through age because I've just turned 60 so your eyesight is not as sharp."*
	Accepting the eye condition	Responses = 26 Participants = 11	*"Cry and then pull myself up by my socks and get on with it"*	Responses = 36 Participants = 21	*Well, I've just got to accept it'. You can't say 'oh no, I don't want it'. It's not going to go away"*

NA, not available

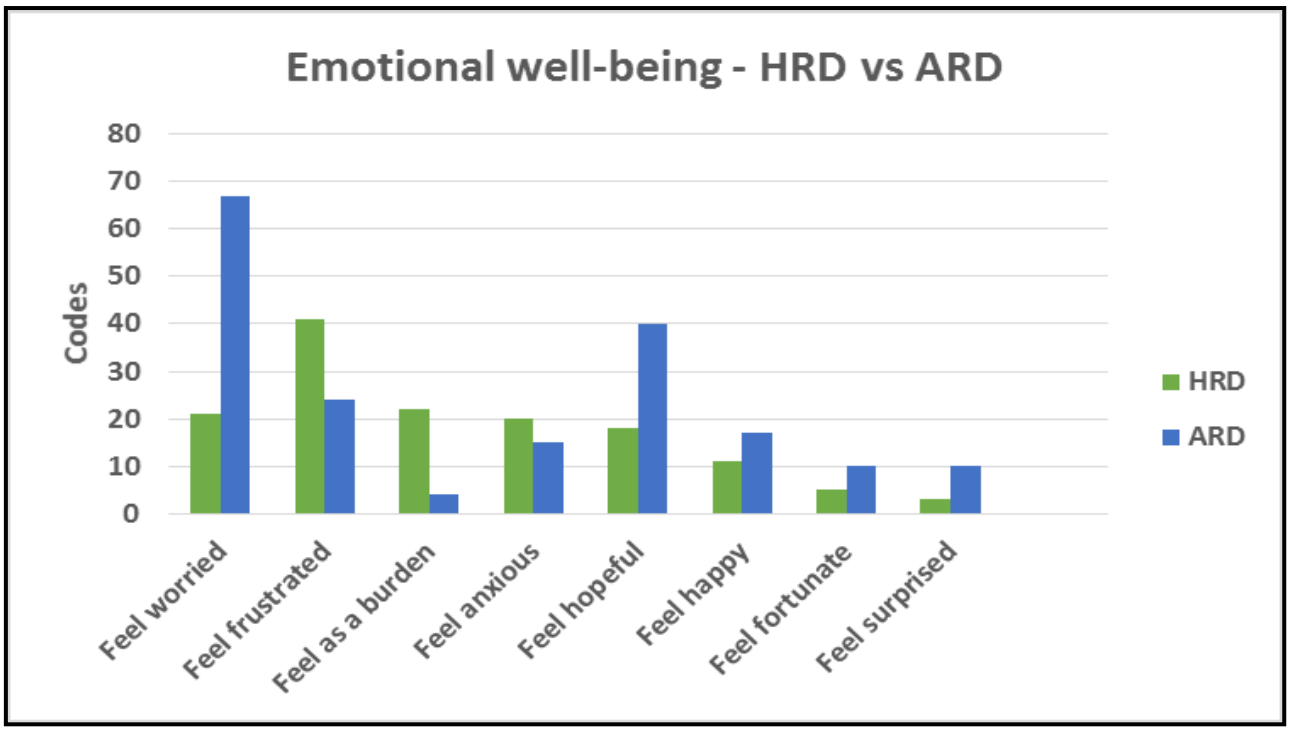

Figure 3.5 Positive and negative emotional comments expressed by participants with hereditary retinal diseases (HRD) and acquired retinal diseases (ARD)

X-axis = emotional comments, Y-axis = codes (number of times the attribute was discussed across all the transcripts

Generally, not being able to drive and having to depend on others for everything made them feel a burden.

> *"Obviously I rely on people to drive me around which is difficult for them, so being a burden on people."(**cone dystrophy, female, 36 years**)*

They expressed that being diagnosed as legally blind was more shocking than being diagnosed with the eye condition. Uncertainty about the future and the feeling that their life is different to everybody else's caused depression.

In contrast to participants with HRD, participants with ARD expressed more hope and optimism towards their eye condition (Figure 3.5). They believed that treatment would make their eye condition better.

> *"I'm expecting to get back, that I can see properly, as like before, then I can go to the optician and get the new glasses." (**MH, female, 70 years**)*

Participants whose vision had not improved with treatment worried about losing their

sight and involvement of the other eye.

> *"I'd say the stage between 2010 and 2011, when I had trouble - when the right eye's starting to go wrong and the left one wasn't quite fixed yet, yeah, I had concerns then, a few worries there." (**ERM, male, 54 years**)*

Inability to read and drive, having to wait for hours in the clinic, frequent eye appointments and having to adopt positioning after eye surgery were the reasons for frustration among this group of participants. They feared the repeated eye injections and laser treatments.

> *"When they first said to have a needle, I was scared stiff because I don't like things coming towards my eye as it is, let alone a needle".(**vascular occlusion, female, 71 years**)*

Some of the emotional reactions such as frustration, anxiety, shock, and depression were common to the two groups. However, 'feeling isolated' and 'feeling traumatised' were unique to the HRD group and 'grief for loss of vision' and 'feeling agitated' were unique to the ARD group. Examples of some of the common and unique QoL issues between the two groups are shown in (Figure 3.6)

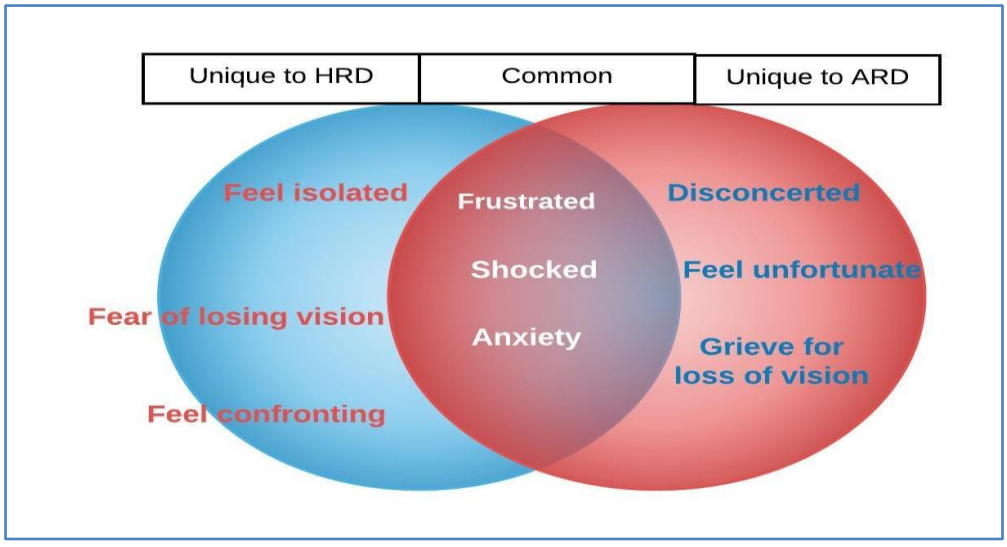

Figure 3.6 Examples of some of the unique and common QoL issues of participants with hereditary retinal diseases (HRD) and acquired retinal diseases (ARD) in the QoL emotional well-being

3.5.3.3 *Social*

Social interaction was difficult among participants with HRD (Figure 3.2). They experienced more difficulty in getting help and support from friends and family members compared to participants with ARD. Some of the participants experienced

strain in their personal relationships especially with their partners, because of their visual impairment.

> *"I was 31 when I was actually diagnosed with RP and that occurred – my marriage had just broken up and I had two children who were seven and nine". (**RP, female, 69 years**)*

Despite the lack of support, most of them learned to be independent. Difficulty in recognising faces, social cues and body language made them feel isolated in social gatherings and meetings.

> *"If people don't know me, well, I can't go into a room and find someone and start chatting to them, for example, because I can't see them to do that, so I think my ability to make new friends as my sight's got worse does get harder because I just can't make the level of interaction that I would have done when I was younger, just go into a room and - or seek them out."(**cone dystrophy, female, 52 years**)*

They frequently associated themselves with societies/government organisations to keep themselves updated about their eye condition.

> *"I keep up with the Retina Australia group and they send out a newsletter and they talk about research and the treatments and all that and I'll read through that… (**RP, male, 52 years**)*

Interacting with people with similar eye conditions was important for this group of participants.

Participants with ARD did not rely on their friends and family members for support.

> *"Well I help in my daughter's shop two days a week and I look after my great grandchildren and go off and do things with the family and friends so there's nothing; it doesn't stop me doing anything, no." (**vascular occlusion, female, 79 years**)*

Meeting up regularly with family members and friends and being part of social activity groups such as fun bands, Facebook groups, church groups, and book clubs were some of the social activities among them.

> *"I go fishing a lot and crabbing. I've just been over to Ardrossan where a mate of mine lives. I've been over there three days out in the boat crabbing and do a bit of fishing every now and then." (**ERM male, 75 years**)*

> *"I play in a thing called a fun band where we go around and play music at Helping Hand centres and aged care facilities and all of that". (**MH, male, 86 years**)*

The participants shared that they often had to discuss their eye condition with their family members to increase their awareness.

Maintaining role and responsibilities in community organisations and being part of social groups were common to the two disease groups. However, strain in personal relationships; getting help and support from government organisations and interacting with people with similar eye condition were unique to the HRD group. Talking to family and friends about their eye condition was unique to the ARD group. Examples of unique and common QoL issues between the two groups are shown in Figure 3.7.

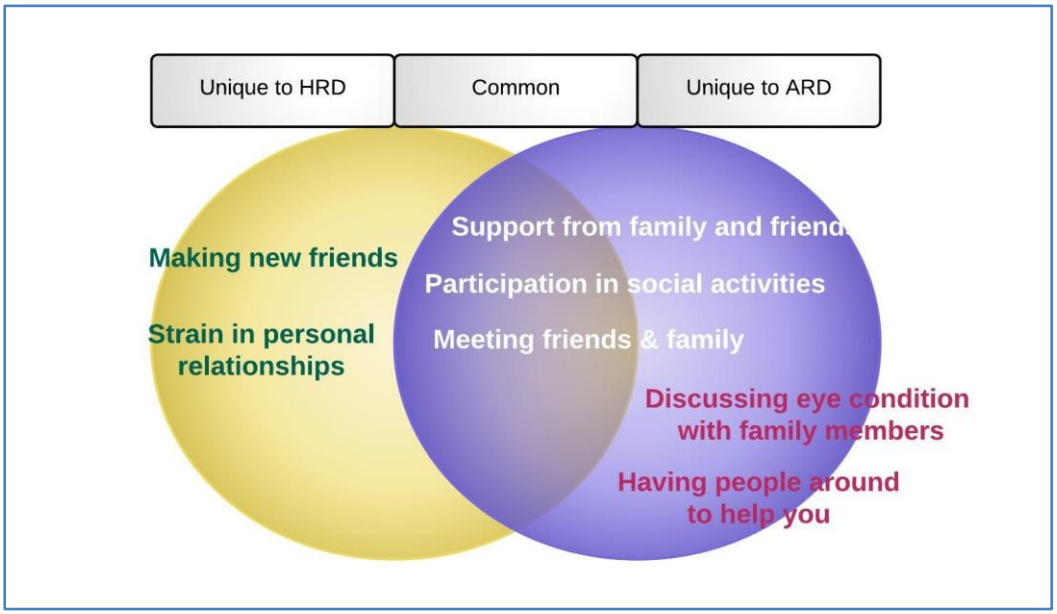

Figure 3.7 Examples of some of the unique and common QoL issues in participants with hereditary retinal disease (HRD) and acquired retinal disease (ARD) in the QoL domain social participation

3.5.3.4 *Health Concerns*

Health concern was a major issue in both the disease groups, but was more prominent in participants with ARD (Figure 3.2). Participants in the HRD group were often concerned about accidents such as falling, tripping, and bashing into things due to their limited peripheral vision.

> *"I've always had lots of accidents and bumping into stuff; my judgment's not very good." (**cone dystrophy, female, 36 years**)*

Many participants felt that the information they received from the medical staff was inadequate and they had to do their own research to get more information.

> *"I had been told by a misinformed medical practitioner when I was in my teens that I would go blind and not be able to see within a few years so my life absolutely turned upside down." (**macular dystrophy, female, 56 years**)*

This group often worried about going blind and having to live on their own. Generally, this group of participants felt that their friends and family members did not understand their visual impairment. They also expressed unhappiness about people's attitude towards them and some participants felt they were being discriminated against due to their visual loss. Not knowing what is going to happen in the future, fear of passing the disease on to the kids and not being able to handle emergencies such as bush fires and thunderstorms were some of the other health concerns in this group.

> *"I suppose the big thing I didn't want to happen was any of my kids to get it, or grandchildren; that would be the big thing." (**RP, male, 69 years**)*

Most participants in the ARD group were not aware of their eye condition. They expressed unhappiness towards their medical service providers who they often felt did not communicate well about their disease.

> *"No. I think the only thing is that when I go to the hospital they don't tell me – they do all the testing and the examination but – so I never really know what's wrong". (**ERM, female, 75 years**)*

Treatment outcomes were the main concern among participants who were undergoing treatments. Participants with treatment failure expressed concerns about the possibilities of disease recurrence and involvement of the other eye.

> *"I manage quite well with only vision in one eye, but if they were to tell me that the condition I have is going to affect both my eyes, yes, that would really concern me, really bad." (**vascular occlusion, male, 83 years**)*

Postoperative positioning after vitrectomy was a major concern in participants with ERM and MH.

> *"I don't know how I could do that 50 minutes of every hour with my head down." (**MH, male, 86 years**)*

Individuals with HRD and ARD had different health concerns regarding their eye condition. Inadequate information from the medical staff and unhappiness with the medical service providers were common to the two groups. Individuals with HRD were more concerned about their disease progression and individuals with ARD were more concerned about the treatment outcome. Examples of some of the unique and

common QoL issues between the two groups are shown in Figure 3.8.

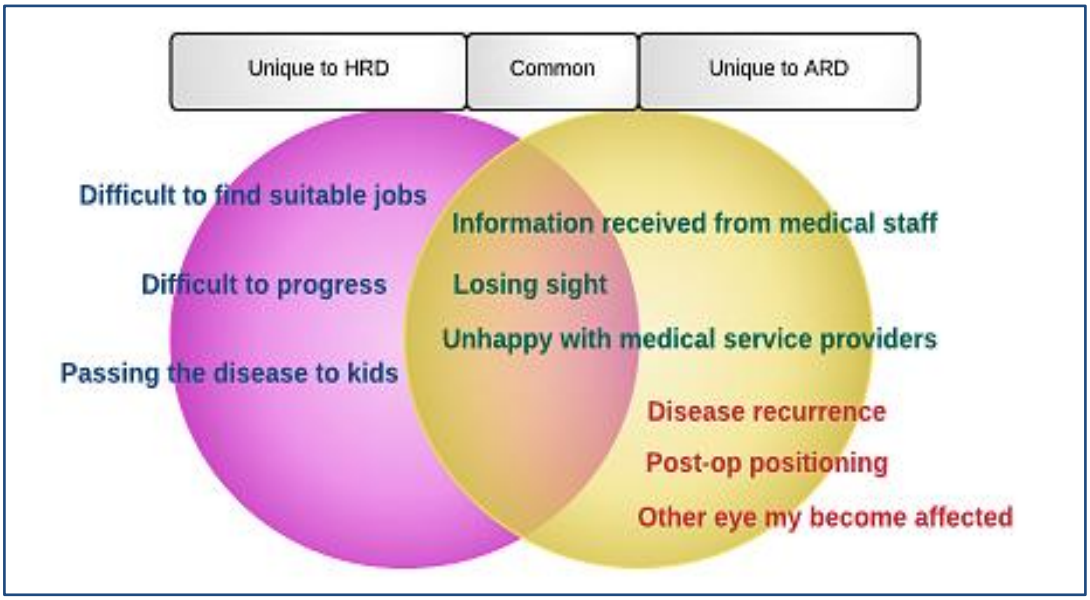

Figure 3.8 Examples of some of the unique and common QoL issues in participants with hereditary retinal diseases (HRD) and acquired retinal diseases (ARD) in the QoL domain health concerns

3.5.3.5 *Symptoms*

Participants in both the disease groups reported a myriad of visual symptoms (Figure 3.2). Night blindness, restricted field of vision, difficulty in discerning colours, and difficulty in light adaptation were the prominent symptoms among participants with RP.(351)

> *"Gradually not being able to see things when I was out at night." (**RP, female, 78 years**)*

> *"Yeah, well, when I was 21 I was tested for that so I do have some colour blindness but the primary colours are okay, but that's a separate issue." (**macular dystrophy, male, 70 years**)*

Difficulty with central vision was the prominent symptom among participants with macular dystrophy. Participants with HRD experienced progressive loss of vision.

> *"Then I went to school one day after the Christmas holidays, so quite a long break, and suddenly I couldn't see the blackboard from the back of the classroom and I went to the front of the classroom so there was a very big difference over the Christmas period and it really just started to deteriorate then." (**cone dystrophy, female, 52 years**)*

Difficulty with central vision was common to participants with vascular occlusion ERM

and MH. Participants with vascular occlusion experienced sudden loss of vision, seeing floaters, and seeing dark patches in the field of vision.

> *"I had woken up the next morning not realising what had happened and I had what we – well they looked like little spider webs in my right eye and that concerned me." (**vascular occlusion, female, 82 years**)*

Eye pain and bloodshot eyes were reported after eye injections. Participants with ERM reported blurry vision, distortion of vision or crooked vision and difficulty in focussing.

> *"No, it's just a – just say if I'm looking at a straight line the line's crooked. It's not straight, it's crooked out of my right eye." (**ERM, female, 56 years**)*

Blurry vision, seeing black spots in the central vision and issue with depth perception were some of the prominent symptoms in MH. Participants who have undergone vitrectomy and gas tamponade reported double vision and wobbly vision

> *"I still see with that eye, blurry, sometimes double, and I don't know that will go lately or not." (**MH, female, 73 years**)*

Blurry vision and difficulties with depth perception were common to the two groups. Night blindness and fluctuating vision were unique to the HRD group and double vision and floaters were unique to the ARD group. Examples of some of the unique and common QoL issues between the two disease groups are shown in Figure 3.9.

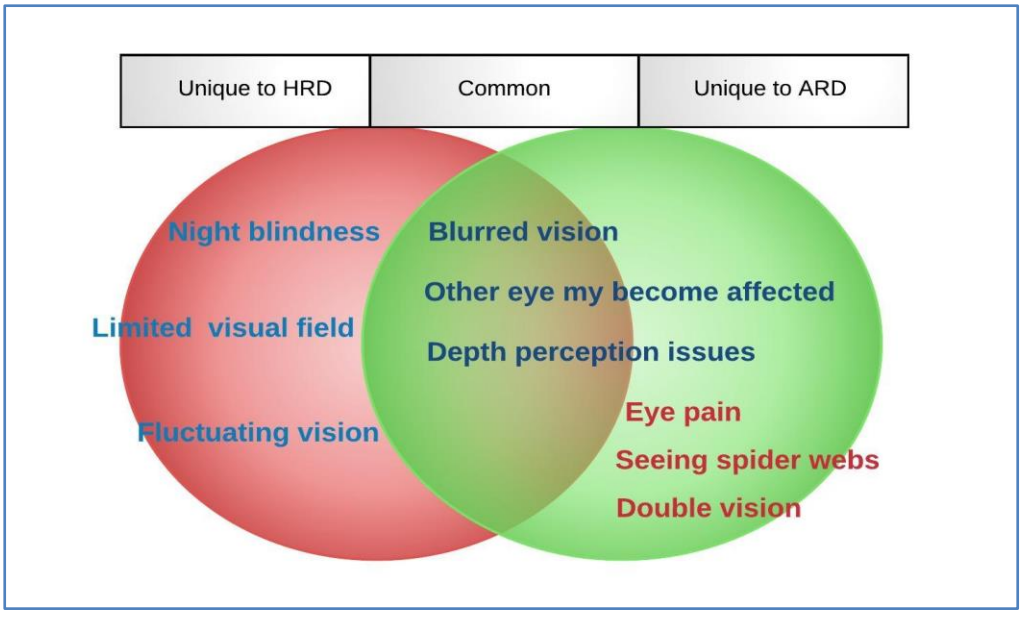

Figure 3.9 Examples of some of the unique and common QoL issues in participants with hereditary retinal disease (HRD) and acquired retinal diseases (ARD) in the QoL domain symptoms

3.5.3.6 *Mobility*

Mobility was a major issue in participants with HRD (Figure 3.2) especially in RP.(351) participants with HRD often reported difficulty walking outdoors, walking in a cluttered environment, and navigating in unfamiliar places.

> *"Going out, I'm not too keen going out by myself into unfamiliar areas."(**cone dystrophy, female, 52 years**)*

They also reported difficulty using steps and walking in crowded places such as shopping malls and airports.

> *"I found that I was finding it really difficult in shopping centres and I was starting to avoid going to those places". (**RP, female, 46 years**)*

> *"I mean going down steps is the most difficult thing. Ramps are good but steps are not good". (**macular dystrophy, male, 76 years**)*

The major mobility difficulties reported among participants with ARD were crossing a street/road, walking in the dark/night, and walking on uneven grounds.

> *"I have to be careful crossing roads because I can't see that far up the road to what's coming." (**MH, male, 86 years**)*

> *"Yes, I do find that I'm not as fleet of foot as I used to be. I have to watch more carefully in the dark and all those things." (**vascular occlusion, male, 83 years**)*

> *"When I get off, you know, steps and kerbs and things it's kind of not where it should be so I have to stop and kind of do it carefully and look where I'm going." (**vascular occlusion, female, 78 years**)*

Difficulty in navigating in unfamiliar places and crowded places were unique to participants with HRD. Difficulty in walking on uneven ground was unique to participants with ARD. Examples of some of the unique and common QoL issues between the two disease groups are shown in Figure 3.10.

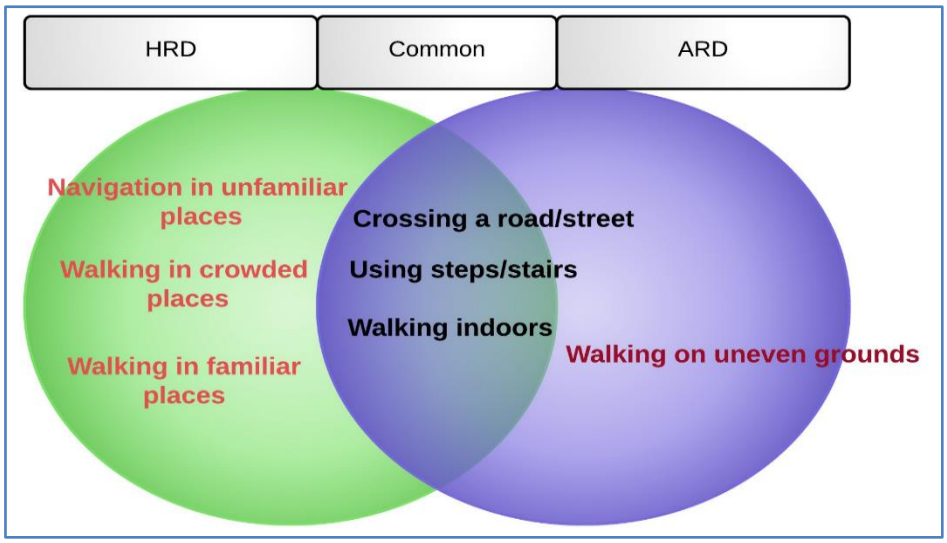

Figure 3.10 Examples of some of the unique and common QoL issues of participants with hereditary retinal disease (HRD) and acquired retinal diseases (ARD) in the QoL domain mobility

3.5.3.7 *Economic*

Work and finance was a major issue among participants with HRD (Figure 3.2) because most of them were young and working (Table 1.2). Participants with HRD were more concerned about the economic and financial impact due to their eye condition. Participants in this group felt that their eye condition restricted their career choice. Not being able to get employment often caused fear and anxiety.

> *"Yeah it's a lot harder for me to find work because I have to be somewhere I can physically get to which rules out the majority of jobs". (**cone dystrophy, female, 36 years**)*

They also reported difficulty in getting help and support from government and other social welfare organisations.

> *"I did put in to go through employment, specialised employment agencies. I dealt with two and I would say neither really had any trained staff there to really deal with people with blindness or vision impairment and quite often I was told 'blind people are so hard to place in work." (**RP, female, 61 years**)*

Lack of mobility and inability to drive restricted their job opportunities. Many participants in this group had to give up their jobs and go for an early retirement due to deterioration of vision. Loss of income associated with loss of job caused financial constraints.

> *"Well, yes, it has because I had to retire early and obviously, my earning capacity was limited as a result and when you're living on a blind pension, you know, it's not as good as if you were working as well so I've got to cut back." (**macular dystophy, male, 76 years**)*

Costs associated with looking after guide dogs and attending training courses were some of the other financial implications specific to participants with HRD.

Participants with ARD had less job-related constraints due to their eye disease as most of them were retired. Some of the financial implications were due to the costs associated with seeing a specialist, costs associated with buying medications, and undergoing eye procedures.

> *"Well, when I had the surgery it's always dearer than the Medicare rebate so that was a bit of a cash outlay." (**MH, male, 76 years**)*

> *"I just have to pay, like anything you get from the chemist really, the Warfarin, it's like – I think it's about 13 bucks a bottle or something." (**vascular occlusion, male, 34 years**)*

> *"Also, too, we grow vegetables and so we've lost crops and we've been behind in planting. I mean my husband is – so that's been a big financial – so we haven't picked any crops now for two months so it's starting to impact now on our income." (**ERM, female, 66 years**)*

Participants with HRD and ARD had different economic and financial impacts. Reduced job opportunities and restricted career choice were unique to the HRD group and costs incurred for eye procedures and buying medications were unique to the ARD group. Examples of the some of the common and unique QoL issues between the two groups are shown in Figure 3.11.

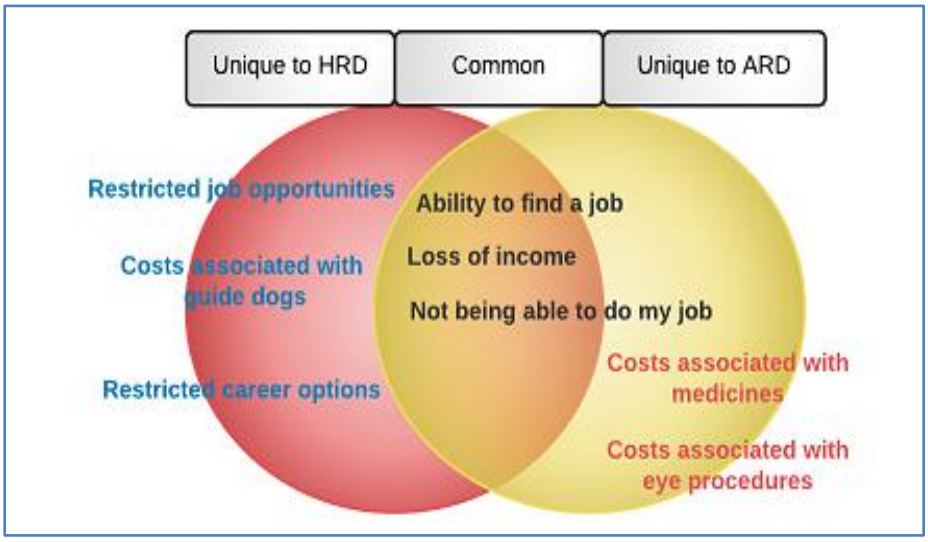

Figure 3.11 Examples of some of the unique and common QoL issues of participants with hereditary retinal diseases (HRD) and acquired retinal diseases (ARD) in the QoL domain economic

3.5.3.8 *Convenience*

Participants with both HRD and ARD reported a myriad of inconveniences because of having to live with their diseases. Between the two groups, participants with ARD expressed more inconveniences in their day-to-day life (Figure 3.2). Most of these inconveniences were associated with their treatment. Having to keep a face/head position (e.g. face down positioning after vitrectomy) for a prolong time was reported as a major inconvenience by participants with ERM and MH.

> *"Well after you had the surgery you've got to lay on your belly for two weeks and that is absolute murder." (**MH, male, 62 years**)*

Having to maintain positioning during travelling and during clinic visits was also reported as an added inconvenience. Those individuals with vascular occlusion, the major inconveniences were having to undergo repeated lasers, injections, and repeated eye tests. Long waiting hours in the clinic and frequent eye appointments were some of the inconveniences unique to this group.

> *"Just sitting around for three or four hours, it's very frustrating and you get very tired and you just want to get in and get out". (**vascular occlusion, male, 34 years**)*

> *"I think the inconvenience was mostly the need for regular visits for anti-VEGF injections because I don't like driving right after an injection because I've got one eye patched and it's pretty sore and bloodshot and so somebody else goes with me and that – you know, you're doing that every six weeks for a while and so it's an inconvenience." (**ERM, male, 72 years**)*

The major inconveniences in the HRD group often resulted from having to depend on others for doing things for them and travelling by public transport.

> *"Obviously, I rely on people to drive me around which is difficult for them, so being a burden on people." (**cone dystrophy, female, 36 years**)*

Not being able to read and walk without assistance was also a major inconvenience.

> *"you know I used to love to curl up in bed and read a book, well now I have to sit at a reading machine and it's so slow and you're trying to follow the line across and the whole enjoyment of that is gone because of the way that you have to do it." (**RP, female, 46 years**)*

Inability to participate in things spontaneously, everything requiring planning and organisation and a longer time taken to get things done were some of the other inconveniences in this group.

> *"Not having access to information easily and everything is difficult, everything." (**macular dystrophy, female, 56 years**)*

HRD and ARD caused different sets of inconveniences. Inconvenience of having to rely on others was common to both the disease groups. Misplacing/losing things and requiring assistance for reading and moving around were unique to the HRD group. Having to adopt face/head positioning after surgery was an issue unique to the ARD group. Examples of some of the common and unique QoL issues between the two groups are shown in Figure 3.12.

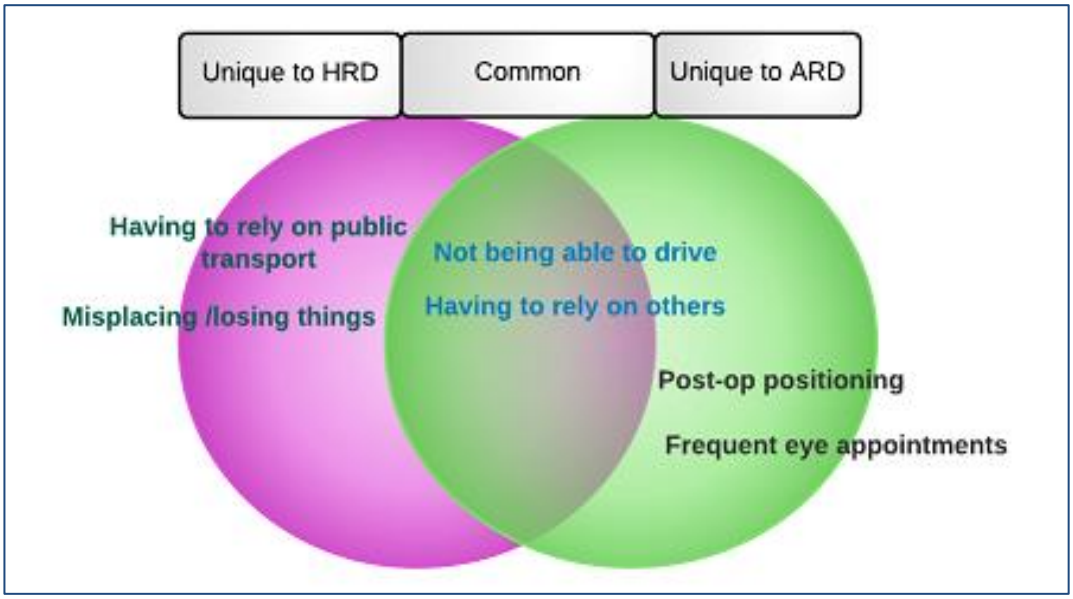

Figure 3.12 Examples of some of the unique and common QoL issues of participants with hereditary retinal diseases (HRD) and acquired retinal diseases (ARD) in the QoL domain convenience

3.5.3.9 *Coping*

The use of coping strategies to manage the stress of visual loss was common in both the disease groups. Participants with HRD were coping better compared to participants with ARD (Figure 3.2). Most participants in the HRD group learned to accept their eye condition and maintained a positive attitude despite the visual loss.

> *"I've got a pretty positive attitude so it doesn't really worry me too much now." (**macular dystrophy, male, 70 years**)*

These people also kept themselves distracted by engaging in useful activities such as listening to audio books, playing sport, and engaging in adventurous activities such as sky-diving, skiing, SCUBA diving and hiking.

> *"No, I've just found different ways of doing it I think and in some ways, it's probably made me a little bit more adventurous. I've been hiking to Everest and scuba diving and skydiving." (**RP, female, 39 years**)*

Learning to do things in a different way was an important coping mechanism. Seeing other family members adapting to their eye condition also helped them to cope.

> *"I've had years and years of watching other people in my family adapt and get around and guide dogs and canes and what not; I've grown up around that." (**RP, female, 46 years**)*

Attributing their eye condition to ageing was a common coping response used by participants with ARD.

> *"My eyes have deteriorated more through age because I've just turned 60 so your eyesight is not as sharp." (**vascular occlusion, female, 60 years**)*

The other coping responses were trying to ignore their eye condition and indulging in engaging activities such as knitting, reading and gardening.

> *"I played guitar for a long time and I bought a ukulele a couple of months ago, and I thought 'I should have done this a long time ago; it's great fun'. So that helps me sort of forget about other things." (**ERM, male, 68 years**)*

Trusting their doctors, praying, and meditating were some of the unique coping strategies among participants with ARD.

> *"I think as a child I've been trained to trust the doctors and I've done that all my life". (**MH, male, 75 years**)*

The coping strategies adopted by participants with HRD and ARD were different. Trying to stay positive and accepting the visual loss were some of the coping strategies common to the two groups. Trying to use other senses and learning from others were some of the coping strategies unique in the HRD group. Being realistic and trusting God were some coping strategies unique in the ARD group. Examples of some of the common and unique QoL issues between the two groups are shown in Figure 3.13.

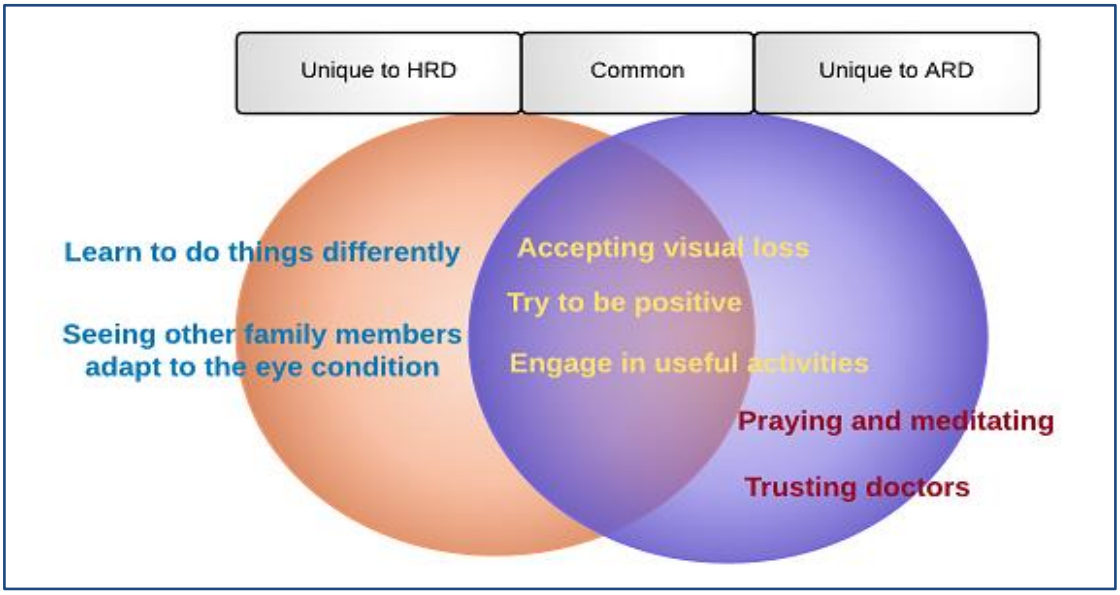

Figure 3.13 Examples of some of the unique and common QoL issues of participants with hereditary retinal diseases (HRD) and acquired retinal diseases (ARD) in the QoL domain Coping

3.5.4 Comparing the QoL issues in HRD and ARD with age related macular (AMD) degeneration and diabetic retinopathy (DR)

Of the nine QoL themes that were identified in this study eight themes were similar to the themes identified in AMD and DR.(3, 4) Coping was identified as one of the major theme in this study but not in AMD and DR. Comparing the QoL issues in people with HRD and ARD with those in people with AMD and DR showed that people with HRD have more QoL issues compared to people with AMD and DR and people with ARD have fewer QoL issues compared to people with AMD and DR.

3.6 Discussion

The study results showed that participants with HRD experience more QoL issues compared to participants with ARD. In fact, participants with HRD were more visually impaired compared to participants with ARD and that could be one of the reasons for the greater QoL issues iterated in the HRD group. The QoL themes/domains across the disease groups were identical, but when compared with the domains specific issues, they were mostly different between the two groups. The apparent differences could be due to the differences in the disease in terms of age of onset, duration of the disease, severity of visual loss and employment status. In the HRD group the predominant loss of vision was peripheral and binocular, however, in the ARD group it was mostly central and monocular. The duration of the disease was longer in the HRD group and shorter in participants with ARD. Most participants in the HRD group were working and most participants in the ARD group were retired (Table 3.1). Participants in the HRD group had severe visual impairment and participants in the ARD group had mild to moderate visual impairment.

The nine QoL domains were determined from the emerging themes during the analysis. These domains are also important ophthalmic domains of QoL identified in other eye diseases.(3, 45, 146) The QoL issues were different in the HRD and the ARD group. The most prominent QoL parameter among participants with HRD was activity limitation, which might be attributed to the fact that participants with HRD had a bilateral eye condition and were living with severe visual impairment. On the contrary, concerns (e.g. concerns of going blind, treatment outcomes etc.) were the prominent QoL issues in ARD. This could be because most ARD are acute and treatable. Participants with HRD and ARD faced lots of emotional and psychological

challenges. Participants with HRD expressed more negative comments compared to participants with ARD and this could be because these participants continuously face progressive loss of vision for which there is currently no cure. In contrast, participants with ARD expressed more positive comments because most of these conditions are treatable. Frustration, anxiety, fear and depression were the common emotional reactions expressed by participants with HRD in this study and similar findings were reported in previous qualitative studies.(2, 59)

Participants with HRD had more issues with social interaction, mobility and work and finance compared to participants with ARD. Inability to identify social clues, facial expressions, body language and difficulty in participating in social activities at night affected the social life of participants with HRD. The mobility issues may be attributable to the loss of peripheral visual field.(352) Participants with HRD had greater economic and financial impacts due to their disease than participants with ARD because most of these participants were working (Table 3.1). Participants with HRD were also more symptomatic than participants with ARD because HRD are progressive diseases. Night blindness, progressive visual field loss and difficulty in light adaptation were the common symptoms reported by participants with RP in this study. In contrast, a previous study has reported a different set of symptoms (day-to-day visual fluctuations, intermittent diplopia, photopsia, high glare and visual hallucinations).(2)

The type of coping strategies used by an individual depends on the situation they face. Coping that implies a positive attitude has shown to improve health related quality of life and a passive attitude has shown to worsen health related quality of life.(353, 354) The coping responses used by participants with HRD mostly implied positive attitude (e.g. trying to be positive, acceptance of their eye condition and engaging in useful activities). The coping responses used by participants with ARD implied passive attitude (e.g. trying not to think or worry about their eye condition and attributing their eye disease to ageing). Participants with HRD were reported to cope better than participants with ARD as they used positive attitude.

The QoL issues in participants with different HRD were compared. Similarly, QoL issues in participants with vascular occlusion, ERM, and MH were compared. This was done to justify the grouping of the other vitreoretinal diseases into HRD and ARD. The QoL issues in RP, cone dystrophy and macular dystrophy were similar. RP and

cone dystrophy have similar pathogenesis (degeneration of the photoreceptors) and so had similar QoL issues. The only difference is that in RP the rods are affected first followed by the cones, whereas in cone dystrophy the cones are affected first followed by the rods. However, macular dystrophy differ from both RP and cone dystrophy in the pathogenesis. In macular dystrophy, the central retina is involved and in RP the peripheral retina is predominantly involved. Both RP and macular dystrophy are progressive diseases and in late stages of the diseases, both the central and the peripheral retina is involved. During the early stages of the diseases, the QoL issues between macular dystrophy and RP are slightly different. In macular dystrophy the QoL issues are mostly attributed to loss of central vision and in RP it is attributed to loss of peripheral vision. But in late stages the QoL issues in these two diseases are mostly similar. Moreover, RP and macular dystrophy have other common characteristics such as early onset, bilateral eye involvement and progressive nature of the diseases that contribute to similar QoL issues. Similarly, QoL issues in people with vascular occlusion, ERM and MH were identical because in all these eye conditions the central retina is predominantly involved. Like HRD, ARD also share common characteristics such as late onset and unilateral eye involvement.

Comparing the QoL impact of people with HRD and people with major blinding retinal diseases such as AMD and DR show that people with AMD and DR frequently experience difficulty carrying out activities requiring central vision such as reading, driving and recognising faces.(4, 57) Whereas people with HRD experience difficulties carrying out important activities that require both central and peripheral vision (e.g. reading, driving, shopping and walking in unfamiliar and crowded places). The major health concerns in people with and DR are mostly related to their treatment outcome. However, the major health concerns among people with HRD was uncertainty about eye condition and future as no proven treatment is available in this group. Early onset of the disease caused a greater economic and financial implications among people with HRD. Similarly people with HRD are more symptomatic. As the disease is progressive and incurable people with HRD express more negative comments compared to people with AMD.

The QoL themes identified in this study were already reported in the AMD and DR module of the Eye-tem bank project.(3, 4) Coping was identified as a unique theme in

this study and not in AMD and DR because HRD are chronic progressive diseases and incurable and hence, patients with HRD learn to live with their eye condition by adopting several coping startegies. Coping is not part of QoL but plays an important role in preserving the health related QoL. (353)The main reason for including coping as one of the QoL domains is to see whether it forms a measurable construt or not. If the coping domain forms a measurable construct it can be used to understand how people with retinal diseases cope with the stress associated with visual loss.

Despite the low prevalence, HRD and ARD can lead to severe visual impairment and blindness. Similarly, new treatment modalities are fast emerging for these diseases. It is considered very useful for clinicians to understand the impact of these diseases from the patients' perspective. There is no comprehensive and widely validated PRO instrument for these diseases. The way forward is to develop one for each retinal disease. However, it is not feasible to do so because there are too many retinal diseases with a relatively low prevalence rate in the general population. The best way forward is to group/split these diseases. There are several ways of grouping/splitting the other vitreoretinal diseases diseases. A simple way would be to group all the HRD together in one group and all the ARD together in another group. HRD differs from ARD in the onset, presentation, and manifestation. HRD tend to have an early onset; they are mostly bilateral and cause a progressive decline of vision. On the contrary, ARD have a late onset and are mostly unilateral to begin with. The division into HRD and ARD is also supported by our findings, which compared QoL issues within and between these two groups.

The results of this study provide an evidence-base to answer an important question about splitting vs grouping less common but potentially blinding retinal diseases to develop retina-specific PRO instruments. The stark differences in the socio-demography, nature/ age of onset and the QoL issues suggest that these two disease groups are completely different. Putting together these findings, it could be argued that a single PRO instrument would not serve both the disease groups. Therefore, I propose to split the other vitreoretinal diseases diseases into two groups for developing PRO instruments, where all the hereditary retinal conditions were grouped into the HRD group and all acquired retinal conditions into the ARD group.

3.7 Conclusions

Quality of life issues are different between the two disease groups, which may be due to the difference in the onset, presentation, and manifestation of the retinal diseases. Hence, these two disease groups would need separate PRO instruments to capture group-specific QoL impact.

3.8 Limitations

This study had some limitations. The decision to split the other VR diseases into HRD and ARD could have caused some bias in the data interpretation. There are several ways of classifying the retinal diseases and the Ideal would be to split them based on their diseases. However, it would create several groups and as these retinal diseases have low prevalence it is not feasible to have an adequate sample size in each group. Hence, a decision was made to split the retinal diseases into HRD and ARD. This decision is supported by the findings of the qualiattive study that compared the QoL issues within and across the groups. The moderator guide was developed from a comprehensive literature review and input from retinal specialists and all issues important to HRD and ARD may not have been explored. However, open-ended questions were used to explore the QoL issues of the participants and at the end of the interview the participants were given time to add and ask questions. The method of data collection was interviews and not focus groups. However, focus groups are the gold standard method for exploring people's feelings, motivations, insight, and experience on any topic. As this study involved uncommon retinal conditions, organising focus groups was difficult. The other limitation was that the HRD group had fewer participants with macular dystrophy and cone dystrophy than RP. This could have contributed to some bias in the data interpretation. Having equal number of participants with cone dystrophy and macular dystrophy could have avoided the bias. This was difficult to achieve because of the difference in the prevalence rates of these hereditary degenerations. RP is the most common degeneration with a prevalence of 1 in 4000.(62) The prevalence of macular dystrophies range from 1 in 8000 to 10000.(355) Cone dystrophies s are very rare disorders with a prevalence of 1 in 40000.(356) Hence it was difficult to have an equal number of participants with these retinal conditions in this group. Colour vision deficiency are relatively common inherited retinal diseases, however, the study sample did not have any participants

with these disorders because the participants for this study were recruited from charity and welfare organisations through flyers, newsletter and emails and only participants who gave their consent were contacted to organise the interviews. Moreover, the ARD group had only participants with vascular occlusion, MH and ERM and did not have participants with other retinal condition such as central serous retinopathy and hemoglobinopathies. This might limit the relevance and generalisability of our findings to all ARD.

CHAPTER 4 DEVELOPMENT OF COMPREHENSIVE ITEM BANKS FOR OTHER VITREORETINAL DISEASES

4.1 Introduction

The lack of an appropriate retina-specific patient-reported outcome (PRO) instruments restricts our understanding of the full impact of other vitreoretinal diseases (i.e. vascular occlusions, macular hole (MH), degenerations/dystrophies, epiretinal membrane (ERM), central serous retinopathy (CSR), and other vitreoretinopathies) and their treatment on quality of life (QoL). Understanding patients' perspective is critical as new treatment modalities such as anti-vascular growth factor intravitreal injections and gene therapy are gaining momentum especially for vascular occlusions and hereditary degenerations. However, it is not feasible and practical to develop PRO instruments for all the vitreoretinal diseases. It would be ideal to split or group these vitreoretinal diseases based on similarities and differences in QoL impact to develop group-specific PRO instruments. Qualitative investigation (Chapter 4) of QoL issues of people with other vitreoretinal diseases illustrated that the people with hereditary retinal diseases (HRD) and acquired retinal diseases (ARD) have different QoL issues. Hence, based on the QoL issues iterated the overall other vitreoretinal diseases could be split into HRD and ARD to develop group-specific item bank modules. This chapter therefore, describes the content development of the HRD and the ARD-specific item banks. The content development involved a systematic multi-stage process of item extraction from literature and qualitative interviews and item refinement and revision.

4.2 Aims and objectives

The aim of this study was to develop comprehensive item banks for other vitreoretinal diseases.

1. To identify and develop QoL domains and a comprehensive set of items with a superior level of information for HRD.
2. To identify and develop QoL domains and a comprehensive set of items with a superior level of information for ARD.
3. Compare the final set of items between the two-disease group to look for unique and common items.
4. To compare the final set of items of the HRD and the ARD item banks with the age

related macular degeneration (AMD), diabetic retinopathy (DR) and glaucoma item banks.

4.3 Methods

Development of item banks for other vitreoretinal diseases involved two main stages: Stage 1, item identification (item extraction) and, Stage 2, item evaluation (item refinement and item revision). For the stage I item extraction, items were extracted from three sources: (1) pre-existing PRO instruments developed for other vitreoretinal diseases, (2) pre-existing qualitative studies on other vitreoretinal diseases and (3) semi-structured interviews with patients with retinal diseases. The stage 2 item refinement and revision included three stages namely, binning (grouping) and winnowing (reduction), expert panel opinion and cognitive interviews with patients. (Figure 4.1). The development process used in this study is similar to that used in AMD, DR and glaucoma modules of the Eye-tem bank project.(3, 45, 146)

4.3.1 Stage 1- Item identification

Items for the vitreoretinal item banks were extracted mainly from literature review and qualitative interviews with patients.

4.3.1.1 *Identification of extant items from PRO instruments and qualitative studies*

An extensive literature review was conducted using the Medline, ISI Web of Science, EMBASE and Cochrane CENTRAL databases. The search was carried out on April 17, 2014, and it was not limited to any preceding dates. The following key words were used for the search, vitreoretinal OR macula OR retina* OR retinitis OR maculopathy OR retinopathy AND quality of life OR questionnaire OR focus groups OR qualitative OR patient perspectives OR patient reported outcomes. My search yielded 2042 articles. Twelve references were added manually. All the articles were reviewed against the following search criteria: PRO instruments specifically developed for other vitreoretinal diseases, content available in English and developed using valid content development methods such as structured/semi-structured interviews, focus groups and/or literature reviews. This search identified seventeen PRO instruments and four qualitative studies on these vitreoretinal diseases.

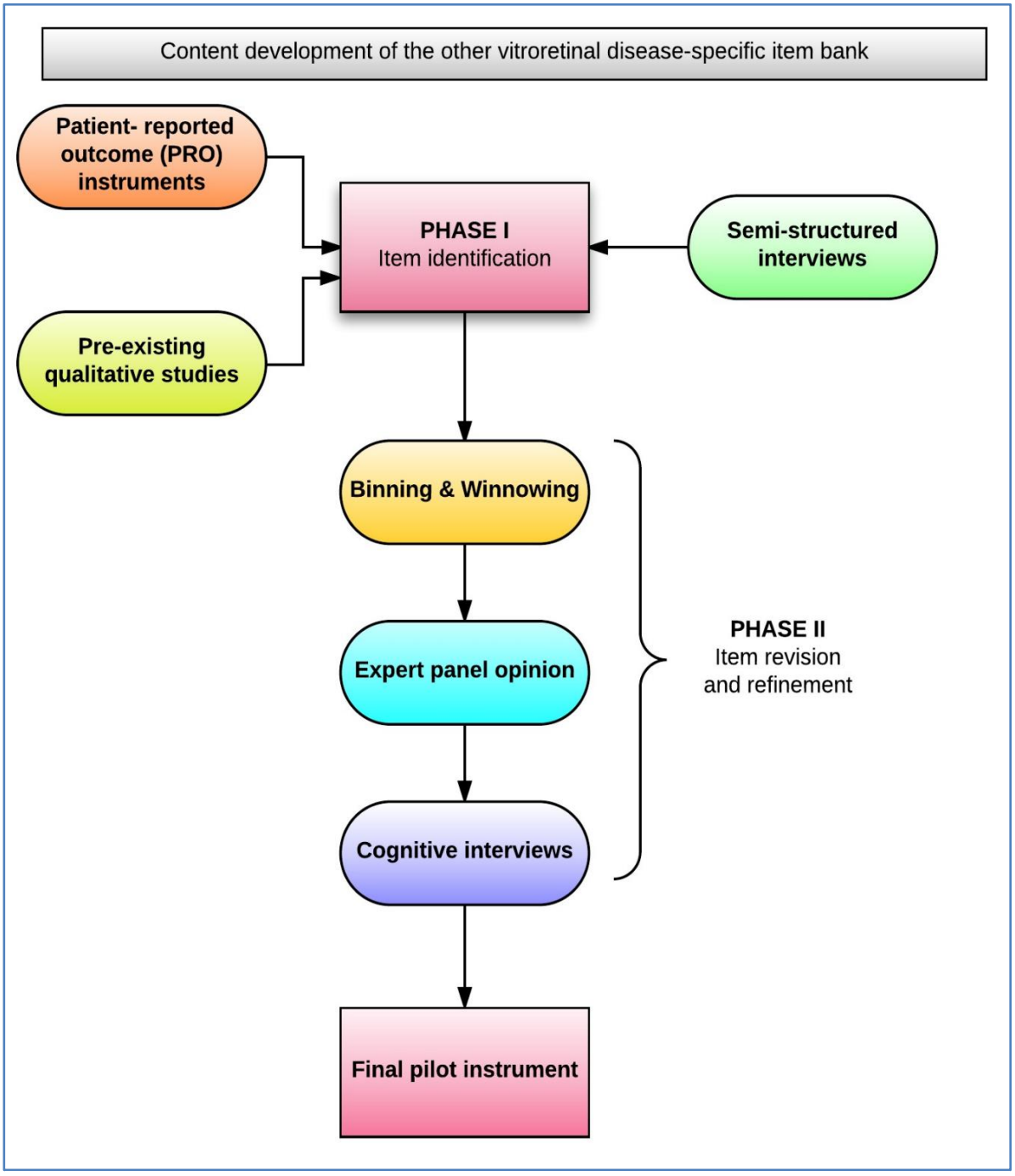

Figure 4.1 Flow chart showing the process of content development of other Vitreoretinal-specific item banks

4.3.1.2 *Semi-structured interviews*

Seventy-nine participants with other vitreoretinal diseases were recruited through a non-probability convenient sampling method. The sample was categorised into HRD and ARD for data collection and data analysis. Participants for the HRD group were recruited form welfare organisations and participants for the ARD group were recruited form the retinal clinics of two major metropolitan public health care facilities.

The HRD group included dystrophies such as retinitis pigmentosa (RP), macular dystrophies and cone dystrophy. The ARD group included relatively less common retinal diseases such as vascular occlusion, MH and ERM. As the aim of this study was to develop item banks for other vitreoretinal diseases, people with major blinding retinal diseases (AMD and DR) were excluded. The inclusion criteria included participants above the age of 18 years, those who spoke English and those without any hearing or cognitive impairment. Participants who consented for the study were invited for a single in-depth interview. The interviews were conducted either face-to-face or over the telephone. All the interviews were done at the Optometry building or at the Flinders University City Campus, Victoria Square, Adelaide. All the interviews were conducted using a topic guide (Appendix 2) , which was prepared based on the literature review and input from ophthalmic specialist. All the interviews occurred between July 2014 and September 2015. Interviews were carried out until thematic saturation occurred.

All the interviews were audio-recorded and transcribed verbatim. An inductive analytic approach was adopted based on the constant comparative method, whereby broad themes were developed from the raw content of the transcripts. Nodes (words or phrases) to code text segments were generated after reading the individual transcripts. As the main aim of the study was to identify items that represent QoL, I specifically looked for key words, phrases and quotes regarding activity limitation, symptoms (ocular, visual & general), treatment effects, social, emotional, and work and economic impact of vitreoretinal diseases expressed by the participants. The themes were reviewed by the author and the supervisors (JK & KP) and identified as possible QoL domains. The items extracted from these interviews were added with the items from the literature.

4.3.1.3 *Identification of QoL domains, item stem and response categories*

A total of nine QoL domains were identified in both the disease groups. The QoL domains were activity limitation, emotional, social, health concerns, symptoms (ocular comfort and general), mobility, economic, convenience, and coping. The definition of the domains is given in Table 4.1.

Table 4.1. The quality of life domains and their definition (357)

Table 4.1 has been removed due to copyright restrictions

The item stem and the response format for each of the QoL domains were formulated based on literature review and consensus between the author and the supervisors (JK and KP) (Table 4.2).

Table 4.2. Item stems and response categories for all the quality of life (QoL) domains

QoL domains	Item stem	Response categories
Visual symptoms	**How often do you experience…?** (frequency scale) **How severe is/are the …?** (severity scale) **How much of a problem is/are the …?** (bothersome scale)	Never Occasionally Quite often Very often Not at all Mild Moderate Severe None A little Quite a bit A lot
Activity limitation	**How much difficulty do you have…?**	None A little Quite a bit A lot Unable to do because of my vision This task is not relevant to me/don't do the task Refuse to answer
Mobility	**How much difficulty do you have…?**	None A little Quite a bit A lot Unable to do because of my vision This task is not relevant to me/don't do the task Refuse to answer
Emotional	**During the past four weeks how often have you felt…?**	None of the time A little of the time Some of the time Most of the time All the time Refuse to answer
Health concerns	**How concerned are you about…?**	Not at all A little bit A moderate amount A lot Extremely This issue is not relevant to me Refuse to answer
Social	**How much of a problem do you have…?**	None A little Quite a bit A lot Unable to do because of my vision This task is not relevant to me/don't do the task Refuse to answer
Convenience	**How much trouble is it…?**	None A little bit A moderate amount Quite a lot Extremely This task is not relevant to me/don't do the task Refuse to answer

Economic	**Currently, how concerned are you about...?**	Not at all A little bit A moderate amount Quite a bit Extremely This issue is not relevant to me Refuse to answer
Coping	**Given that you know your eye condition, do you cope by…?**	Not at all A little bit A moderate amount A lot Extremely Refuse to answer

The item stem is the beginning part of the item that states the item (e.g. 'how much difficulty do you have?'). A response format is gradation or a continuum that measures a variable (e.g. strongly agree, agree, disagree, and strongly disagree). An optimally functioning item stem and response category labels and numbers were chosen from existing Rasch developed and validated PRO instruments.(358)The final items developed in this study will be compared with the items from the other disease modules of the Eye-tem Bank project to find out the percentage of items that are common between different disease modules. The AMD, diabetic retinopathy and glaucoma data were obtained from the supervisors (KP & JK).

4.3.2 Stage 2 – Item refinement and item revision

The initial set of items extracted from the literature and semi-structured interviews were subjected to revision and refinement. The process of item refinement and revision included binning, winnowing, expert panel opinion and cognitive interviews. Three sessions of binning and winnowing were done before the expert panel opinion.

4.3.2.1 *Binning*

This is a systematic process where items are grouped together based on the same colloquial meaning under specific QoL domains.(359) For example, 'reading', 'driving', 'seeing in different light conditions' and 'shopping' became a bin within the activity limitation domain. Similarly, 'frustration', 'fear', 'anxiety' and 'depression' became a bin within the emotional domain. This process enabled the identification of redundant items. It is a way to organise the items by grouping them together so that the final set of items emerging from this process represents the domains.

4.3.2.2 *Winnowing*

This is a systematic process of reducing large numbers of items to a representative set of items as per a set of inclusion and exclusion criteria.(359) The following criteria were used to remove items from the initial item banks: (1) items inconsistent with the domain definition, (2) item similar to another item/s, (3) item content too narrow to have wider applicability, and (4) item confusing or unclear.(359) Examples of items eliminated at the winnowing stage are given in Table 4.3.

Table 4.3. Examples of items eliminated at the winnowing stage

Item stem	Domain	Reason for removal
Locate small article such as coin or key at table level	Activity limitation	Inconsistent with the domain definition
Who will be my future doctor?	Health concern	Item too narrow
Feel guilty that you have to depend on others	Emotional	Item redundancy (“feel as a burden”)
Do you primarily walk alone or with others?	Mobility	Inconsistent with the domain definition
I closed one eye and looked at the other, I could see what I call a star in it.	Visual symptoms	Item vague
Hard to get a meaningful job	Economic	Item redundancy (“your ability to find employment or get a new job”)
Will reading worsen my eye condition?	Health concerns	Too narrow
Being philosophical	Coping	Item vague
Prepare food in the kitchen	Activity limitation	Item redundancy (“cooking”)
Do you feel difficulty in dining because of your visual problems?	Activity limitation	Item confusing

4.3.2.3 *Expert panel opinion*

The process of binning and winnowing was followed by the expert panel opinion where the author and the supervisors (JK and KP) reassessed the items for clarity and appropriateness using the above four criteria. The authors JK and KP are internationally recognised experts in PRO development and validation. JK and KP are also optometrists with an extensive clinical experience. Items which were ambiguous and confusing were re-worded or re-phrased and any discrepancies were resolved with discussion. (e.g. ‘I cannot read the clock’ was re-worded to ‘telling time from the clock’).

4.3.2.4 *Cognitive interviews*

A cognitive interview entail administration of survey questions to a participant to assess participants's understanding of the questionnaire item and are very important in the content development of an instrument.(360) A cognitive interviewing process was designed to elicit respondent feedback on all the individual items for the HRD and the ARD item banks. The interviews for HRD and ARD item banks were done separately.

For the ARD group, participants were recruited from the retina clinics of two major public hospitals in Adelaide (The Royal Adelaide Hospital and The Queen Elizabeth Hospital). Participants who gave consent to take part in the cognitive interviews were given the hard copy of the pilot questionnaire. The ARD item banks had 257 items. Participants were asked to go through all the items and give feedback on the language, comprehensibility, relevance, and coverage across each domain. A time and date was fixed for the cognitive interviews which were conducted both face-to-face (n = 2) and over the telephone (n = 9). As part of the cognitive interview process, participants were also queried about the clarity of the instructions, items, and response options.

For the HRD group, the pilot questionnaire, comprising 345 items, was developed using the SurveyMonkey tool. Participants for the HRD group were recruited using email lists provided by Retina Australia (New South Wales, Queensland and Victoria) and The Royal Society for the Blind (Adelaide). Those who responded to participate in the study (n = 11), the electronic version of the pilot questionnaire was sent to them to review the questions and provide feedback with a reply email. Upon receiving the feedback through emails, participants were called over the telephone to ask if there're any other comments.These interviews helped to assess whether the item banks had adequate content coverage and whether the items were relevant to the participants. Eleven cognitive interview were conducted in both the groups. However, after the first nine interviews no new concerns raised and so the cognitive interviews were stopped after 11 interviews. Necessary changes were made to the item banks after the feedback from the cognitive interviews.

4.4 Results

4.4.1 Stage 1 – Item identification

4.4.1.1 *Identification of extant items from PRO instruments*

Of the seventeen PRO instruments identified in various vitreoretinal diseases eleven were developed for HRD (RP = 9, congenital stationary night blindness = 1 and Stargardt disease =1) and six for ARD (MH = 3; macular diseases = 2 and retinal infections = 1) (Table 4.4).

Table 4.4. Extraction of items from patient-reported outcome (PRO) instruments developed for other vitreoretinal diseases

PRO Instruments	Developed for	No of items	Content developed from
Bijveld *et al* (2013)	CSNB	40	Other instruments
Lodha *et al* (2003)	RP	39	Other instruments
Szlyk *et al* (2001)	RP	53	Literature review/other instruments
Geruschat *et al* (1998)	RP	4	Not reported
Miedziak *et al* (2000)	SD	29	Other instruments/interviews
Pearce *et al* (1998)	MH	5	Not reported
Singh *et al* (2011)	MH	5	Not reported
Wu *et a*l (1996)	CMV	18	Other instruments/interviews
Mitchell *et a*l (2002)	MD	Not reported	Literature/expert input
Arimura *et al* (2011)	MD	10	Expert input
Szlyk *et al* (1997)	RP	33	Other instruments
Ellis *et al* (2000)	MH	3	Not reported
Sumi *et al* (2000)	RP	35	Not reported
Kennedy *et al* (1997)	RP	25	Not reported
Drasdo *et al* (1978)	RP	7	Not reported
Turano *et al* (1999)	RP	35	Expert input and opinion
Somani *et al* (2006)	RP	23	Other instruments

No, number; CSNB, congenital stationary night blindness; RP, retinitis pigmentosa; SD, Stargardt disease; MH, macular hole; CMV, cytomegalovirus; MD, macular diseases.

All the items were extracted from the seventeen PRO instruments. Global items and items that really did not have meaningful or relevant content were excluded. For example, the item ‘when I walk I go from lamp post to lamp post’ in the Night Vision Questionnaire-39 items (NVQ-39) was excluded. Similarly, items that did not qualify as QoL issues were excluded. For example, the item ‘which type/colour glasses do you use’ in Independent Mobility Questionnaire (IMQ) was excluded. Most instruments focussed primarily on vision related activity limitation and mobility. A total of 212 items were extracted from the 17 PRO instruments. Most the items were on activity limitation

(n= 112).

4.4.1.2 *Identification of extant items from qualitative studies*

Four qualitative papers that explored the impact of hereditary degenerations and MH on patient's QoL using focus groups and semi-structured interviews were analysed for relevant QoL domains and themes. A total of 67 items were extracted from these qualitative studies. Most the items were on coping (n=18). The total number of items extracted from the literature was 279 (PRO instruments = 212; qualitative studies = 67). Most these items were again on activity limitation (n = 121).

4.4.1.3 *Semi-structured interviews*

A total of 79 semi-structured interviews were conducted with people with HRD (n=32; median age = 57 years; range 28 to 81 years; 21 females) and ARD (n=47; median age =73 years; range = 34 to 90 years, 32 females). HRD included people with RP (n=23), cone dystrophy (n=2) and macular dystrophy (n=7) and ARD included people with vascular occlusion (n=18), ERM (n=20) and MH (n=9). A total of 938 items were extracted from these qualitative interviews. Of these, 279 had already been identified in the extant PRO instruments and qualitative literature review and therefore 659 (70%) were new items. Table 4.5 provides examples of items that were drawn from the semi-structured interviews.

Table 4.5 Examples of some of the items extracted from the interviews

Quality of life domains	Participant's statement	No of times the issues were discussed	Item content
Activity limitation	It doesn't matter what you do, hanging out the washing, doing the housework, everything you do has to be done differently. Often it is longer, it is often slower.	17	doing household chores
	As I said, well, surfing was one of them that I couldn't continue.	26	doing leisure activities
Mobility	No, I'm conscious and so I'm very careful. I mean going down steps is the most difficult thing. Ramps are good but steps are not good.	14	using steps/stairs
	I have to be careful crossing roads because I can't see that far up the road to what's coming.	7	crossing a street / road
Emotional	Well I guess it's just the unknown of how is this going to progress and my anxiety is I hope to God it doesn't deteriorate much past this.	35	feeling anxious
	I mean there's nothing I can do to make it any better. I mean all I can do is wait until I have the operation and hope it works.	58	feeling hopeful
Health concerns	I've been fighting all these years to retain my vision and my biggest fear is losing it all.	30	going blind
	"I suppose the big thing I didn't want to happen was any of my kids to get it, or grandchildren that would be the big thing"	10	passing eye condition onto your children
Symptoms	As soon as I walk from outside to go inside a shopping centre or from outside to inside my eyes take a very long time to adjust to the light.	30	light / dark adaptation
	I just get a slight blurring right in the centre of the eye and so if I'm trying to read something, you know, the letters seem to go into each other; they blur.	52	blurring of vision
Economic	Well, being an area manager I actually had to travel in a car to go and see the six other managers around the place so because I couldn't drive a car we used to then	31	losing your job

	get one of the girls from work who would then drive me and of course that wasn't – that's not built into budgets and so forth, that you have a driver to drive you everywhere, so I decided that I'd get out.		
	I'm on a casual rate which means when I have to go to hospital in Adelaide I actually don't get paid at all when I'm not there.	8	financial impact from loss of income
Social	The rest of my brothers and sisters don't understand it and they call me a liar and a cheat and I've been sort of disconnected from that side of the family, which also broke my heart	3	with strain in family relationships
	I used to go the pub a lot; that's where I used to get my company from, but I don't go there anymore.	9	making new friends
Convenience	Well not being able to drive is probably the biggest inconvenience.	12	not being able to drive
	I have no complaints whatsoever, other than the waiting time where sometimes you could wait there for hours.	13	the amount of time needed when attending your eye appointment
Coping	I try and keep myself very busy and not think about things too much because I'm thinking well, if I do lose all my eyesight worrying about it now isn't going to help things so I keep myself really busy so I don't think about it too much.	2	keeping yourself busy
	Cry and then pull myself up by my socks and get on with it.	3	doing things to let your unpleasant feeling escape

There were more items in the initial sets for the HRD group (n =685) compared to the ARD group (n=488). In the HRD group most of the items were on activity limitation (n=191) and health concerns (n=143). In the ARD group, most of the items were on activity limitation (n=126) and emotional (n=102).

Most the QoL issues were unique to the disease groups. The QoL domain; social had the maximum number of common QoL issues and the domain, health concern had the least number of common issues between the disease groups. Across all the QoL domains the percentage of common QoL issues between the HRD and the ARD groups was less than 30%.

Overall the number of items extracted from the qualitative interviews were more compared to the items extracted from the literature across all the QoL domains except for mobility (Figure 4.2).

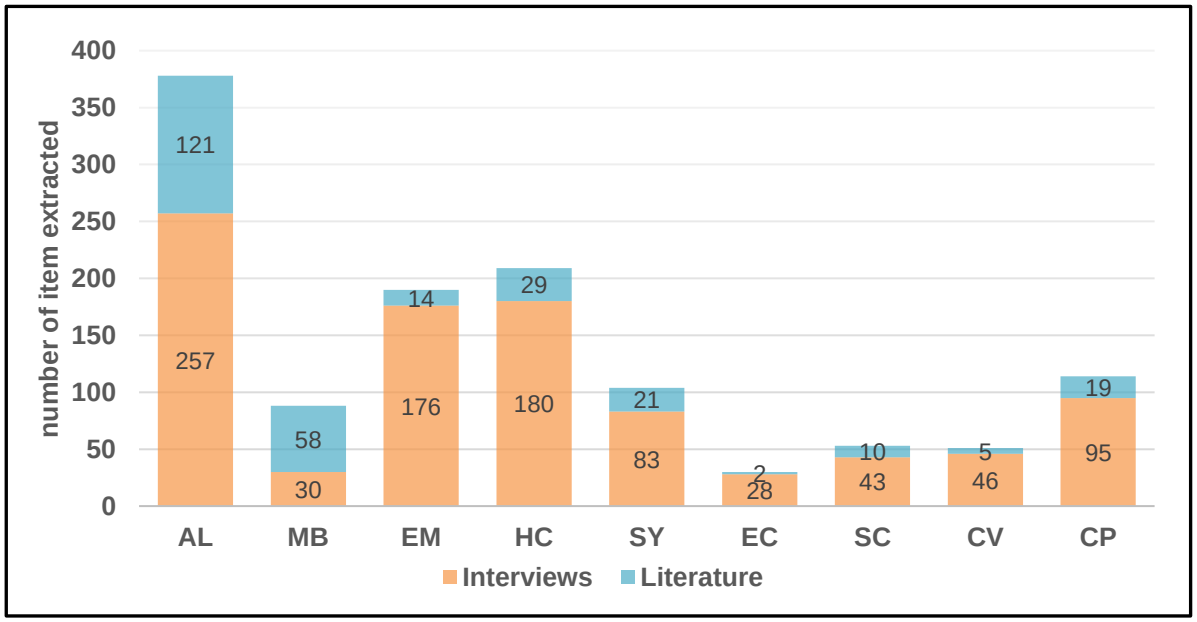

Figure 4.2 Total number of items extracted from literature and interviews

X-axis represents the quality of life (QoL) domains and Y-axis represents number of items extracted. AL, activity limitation; MB, mobility; EM, emotional ; HC, health concerns; SY, symptoms; EC, economic; SC, social ; CV, convenience; CP, coping.

4.4.2 Stage 2 – Item refinement and item revision

4.4.2.1 *Binning*

The content development phase yielded 1,217 items (literature = 279, interviews =938)

in the initial phase (Table 4.6).

Table 4.6 Total number of items generated across three sources of content development

Sources of content development	Number of items generated
Validated patient-reported outcome instruments (n=17)	212
Qualitative articles (n=4)	67
Qualitative interviews (n=79)	938
Total	**1,217**

Most the items from the existing PRO instruments and interviews were on activity limitation and most the items from the qualitative studies were on coping (Table 4.7).

Table 4.7. Initial number of items from literature and interviews

Quality of life domains	Interviews	Questionnaires	Qualitative studies	Total
Activity limitation	257	112	9	378
Mobility	30	57	1	88
Emotional	176	13	1	190
Health concern	180	14	15	209
Symptoms	83	12	9	104
Economic	28	0	2	30
Social	43	2	8	53
Convenience	46	1	4	51
Coping	95	1	18	114
Total	**938**	**212**	**67**	**1,217**

The item refinement and revision included three sessions of binning and winnowing. Binning is a process of grouping items with similar meaning together thereby eliminating redundant and unnecessary items. An example of a working ‘bin’ in the item banks is ‘doing household chores’ under the activity limitation QoL domain. Thus, all the items referring to difficulty in doing household chores such as ‘doing the dishes’, ‘mopping the floor’ and ‘cleaning toilets/showers’ were grouped together. This process was carried out by the author and later verified by an expert panel (KP and JK). The process of binning also revealed items that were incorrectly classified into a domain. For example, ‘travelling by public transport’ was moved from activity limitation to the mobility domain. Similarly, the item ‘feeling stigmatised due to disability’ was moved from emotional to the health concerns domain. The binning process also exposed a poorly conceived QoL domain, ‘treatment’, which was subsequently dissolved and the

items dispersed across the existing QoL domains such as health concerns and convenience.

4.4.2.2 *Winnowing*

Once items were binned, the winnowing process began whereby potential items for deletion were identified and each bin was reduced to a minimally representative set of items. For example, the items 'reading letters in dictionary' and 'reading numbers in a telephone directory' were eliminated because of the existence of a similar item, 'reading small print'. Some items which were too specific were also deleted. For example, 'seeing golden floaters' was removed because 'seeing floaters' already exists.

The initial 1,217 items were reduced to 532 items after the first session of binning and winnowing. Redundant items were removed and items with similar concepts were merged together. A further 106 items were removed in the second session leaving 426 items. In the third session, another 14 items were removed and the final number of items after the three sessions of binning and winnowing was 412 (Table 4.8).

Table 4.8. The process of development of the item banks – from item extraction (Phase 1) to item revision and refinement (Phase 2)

	AL	MB	EM	HC	SY	EC	SC	CV	CP	Total
Initial pool of items	341	78	178	19	93	45	50	60	118	1,158
Binning and winnowing _1	141	35	86	87	48	21	35	34	45	532
Binning and winnowing _2	98	26	84	58	44	19	29	31	37	426
Binning and winnowing _3	97	26	76	54	43	19	29	31	37	412
Expert panel opinion	97	26	75	54	43	19	29	31	37	411

AL, activity limitation; MB, mobility; EM, emotional; HC, health concerns; SY, symptoms; EC, economic; SC, social; CV, convenience; CP, coping

4.4.2.3 *Expert panel opinion*

After the binning and winnowing, the remaining 412 items were thoroughly reviewed by the author and the supervisors (JK and KP) for wording, fit to question format and meaning. Some of the items were re-worded or re-phrased (e.g. the item, 'losing people I am with' was changed to 'becoming separated from the people you are with').

Some of the items with opposite meanings were also removed (e.g. the items 'feeling hopeful' was retained and the item 'feeling hopeless' was removed). The final number of items after the item refinement and revision was 411. Of these 411 items 345 items were unique to the HRD group and 257 items were unique to the ARD group (Table 4.9).

Table 4.9. Total number of items in the hereditary retinal diseases (HRD) and acquired retinal diseases (ARD) groups across the nine quality of life domains

Quality of life domains	HRD	ARD
Activity limitation	87	62
Mobility	23	10
Emotional	66	51
Health concerns	47	27
Symptoms	32	34
Economic	17	10
Social	28	18
Convenience	16	21
Coping	29	24
Total	**345**	**257**

Overall across all the QoL domains 189 items were common to the disease groups (Table 4.10).

Table 4.10. Number of common and unique items between hereditary retinal disease (HRD) and acquired retinal disease (ARD) groups across the nine quality of life domains

Quality of life domains	Common item between HRD and ARD	Unique items in HRD	Unique items in ARD
Activity limitation	54	34	8
Mobility	6	17	4
Emotional	41	24	9
Health concern	20	28	7
Symptoms	22	9	10
Economic	8	9	2
Social	17	11	1
Convenience	7	9	14
Coping	14	15	10
Total	**189**	**156**	**65**

The QoL domain activity limitation had the maximum number of common items and the domains mobility and convenience had the least number of common items. In the HRD item banks 156 items were unique items and in the ARD item banks 65 items were unique.

4.4.2.4 *Cognitive interviews*

After 11 cognitive interviews with participants with HRD, 3 items were deleted, 3 items were added and 23 items were re-phrased (Table 4.11).

Table 4.11. Examples of item modification in hereditary retinal disease (HRD) item banks following cognitive interviews

Quality of life domains	Item	Type of change	Reason for change
Activity limitation	'How much difficulty do you have seeing what's going on at a sporting event, e.g. cricket, tennis?'	Added	Participant suggestion
Health concerns	'How concerned are you about not being able to handle emergency situations, e.g. bushfire, thunderstorm?'	Added	Participant suggestion
Coping	'Given that you know your eye condition, do you cope by attributing to ageing?'	Re-phrased	Item confusing and re-phrased as 'do you cope by attributing your eye condition to ageing'
Emotional	'During the past four weeks, how often do you feel overwhelming?'	Re-phrased	Item confusing and re-phrased` as 'things are overwhelming'
Social	'How much of a problem do you have maintaining your friendship?'	Re-phrased	Item confusing and re-phrased as 'maintaining your friendships'
Convenience	'How much trouble is having to plan and organise for the things you do beforehand?'	Re-phrased	Item confusing and re-phrased as 'plan and organise the things'
Economic	'Currently, how concerned are you about having to reduce the work hours?'	Re-phrased	Item confusing and re-phrased as 'reduce your work hours'
Symptoms	'How often do you feel you have gradual loss of vision?'	Item deleted	Item similar in content to another item, namely 'how often do you experience deteriorating vision'
Mobility	'How much difficulty do you have stepping on and off a train?'	Re-phrased	Item modified based on participant's suggestion as 'how much difficulty do you have stepping on and off a train or a tram'

In addition, 5 changes were made in the preamble (e.g. the statement, 'please only consider your retinal disease when you answer these questions' was changed to 'please consider only your retinal disease when you answer these questions' (Appendix 3). The item stems of two QoL domains, convenience and emotional were also changed. For example, the item stem of the QoL domain convenience, 'how much trouble is…?' was changed to 'how much trouble is it…?' The final number of items after the cognitive interviews in the HRD group was 345. After 11 cognitive interviews with patients with ARD, three items were deleted. For example, the item 'how often do you experience poor vision in one or both eyes' was deleted due to existence of an

item with similar content ‘blurred vision’. Participants with ARD however, did not have any issues with the clarity of the instructions, item stem or response categories. The final set of items in the HRD item pool was 345 (Appendix 4) and in the ARD item pool was 254 (Appendix 5). There were no major changes in the HRD and the ARD item banks after the cognitive interviews.

4.4.3 Comparing the final vitreoretinal -specific item banks with AMD, DR and glaucoma item banks.

The vitreoretinal -specific item banks had nine QoL domains, whereas AMD, DR and the glaucoma item banks had only eight QoL domains. The vitreoretinal -specific item banks had an additional domain ‘coping’. In terms of the number of total items, the HRD and the glaucoma item banks had more numbers of items compared to ARD, AMD, and DR item banks (Table 4.12)

Table 4.12. Number of items in each disease-specific item banks across the quality of life domains

Quality of life domains	HRD	ARD	AMD	DR	GL
Activity limitation	86	62	101	120	88
Mobility	23	10	22	19	20
Emotional	66	50	50	48	49
Health concerns	48	27	38	36	45
Social	28	18	20	21	23
Convenience	16	21	29	30	39
Economic	17	10	15	12	22
Symptoms	31	32	29	28	58
Coping	30	24	-	-	-
Total	**345**	**254**	**304**	**314**	**344**

HRD, hereditary retinal diseases; ARD, acquired retinal diseases; AMD, age related macular degeneration; DR, diabetic retinopathy; GL, glaucoma.

The number of items within each QoL domain was different for each of the disease groups. The DR item banks had more number of items in the domain activity limitation compared to the HRD, ARD, AMD, and glaucoma item banks and the HRD item banks had more number of items in the domain emotional compared to the other disease-specific item banks (Figure 4.3). The main difference seems to be with activity limitation which reflects the fact that the AMD, DR and glaucoma items have come from existing PRO instruments where there is an emphasis on activity limitation.

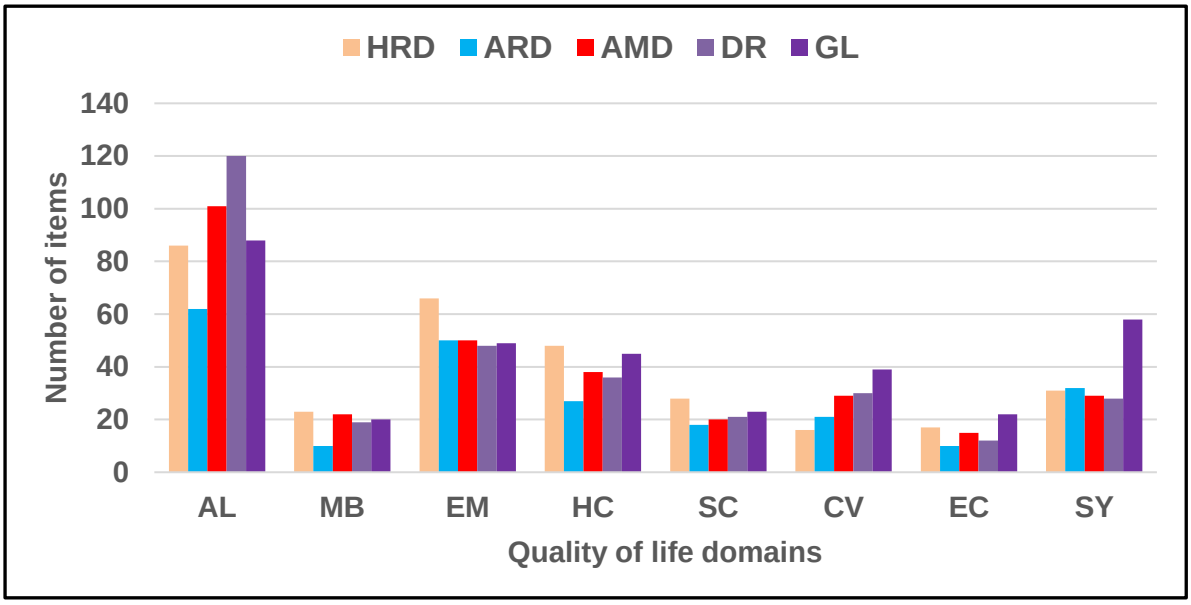

Figure 4.3 Comparing the items of different disease-specific item banks across the quality of life domains. HRD, herediatry retinal diseases; ARD, acquired retinal diseases; AMD, age related macular degeneration; DR, diabetic retinopathy; GL, glaucoma; AL, activity limitation; MB, mobility; EM, emotional; HC, health concerns; SC, social; CV, convenience; EC, economic; SY, symptom

Approximately 50% of the items were common between the HRD item banks and the AMD, DR and glaucoma item banks (Table 4.13).

Table 4.13. Common items between HRD item banks and ARD, AMD, DR, and glaucoma-specific item banks

QoL domains	ARD	AMD	DR	GL
Activity limitation	54	59	57	38
Mobility	6	17	14	14
Emotional	41	29	21	23
Health concerns	20	23	20	23
Social	17	16	14	18
Convenience	7	9	12	10
Economic	8	7	5	10
Symptoms	22	16	16	14
Total	**175**	**176**	**159**	**150**

QoL, quality of life; HRD, hereditary retinal diseases; ARD, acquired retinal diseases; AMD, age related macular degeneration; DR, diabetic retinopathy; GL, glaucoma

Approximately 45% of the items were common between the ARD item banks and AMD DR, and glaucoma item banks (Table 4.14).

Table 4.14. Common items between ARD item banks and HRD, AMD, DR, and glaucoma item banks

QoL domains	HRD	AMD	DR	GL
Activity limitation	54	47	44	39
Mobility	6	7	7	7
Emotional	41	26	19	17
Health concerns	20	16	11	18
Social	17	10	8	11
Convenience	7	9	8	8
Economic	8	9	6	9
Symptoms	22	19	13	19
Total	**175**	**143**	**116**	**128**

QoL, quality of life; HRD, hereditary retinal diseases; ARD, acquired retinal diseases; AMD, age related macular degeneration; DR, diabetic retinopathy; GL, glaucoma

4.5 Discussion

Utilising a multi-stage systematic and rigorous process of content identification and item refinement, the content of the two comprehensive QoL pilot item banks specific to HRD and ARD were developed. Both the pilot item banks include all the important ophthalmic QoL domains and the corresponding items feeding into the traits referred to by these domains. The methods used have ensured that high quality and highly informative unique items were generated. Furthermore, the process used has also ensured that the content coverage in these item banks are as extensive as possible because I exhausted the two sources of item extraction (source 1: the extant content from the existing instruments and qualitative papers in the literature, source 2: supplemented by patients' consultations). This suggests that the items in these item banks will cater for the full spectrum of people at different stages and severity of the other vitreoretinal diseases.

Studies have shown that the QoL of people with other vitreoretinal diseases is significantly compromised.(246, 278, 315, 361) These studies have used PRO instruments which were not specifically developed for retinal diseases (non-disease-specific), nor have undergone comprehensive validation in retinal diseases.(288) To date, only a few PRO instruments are available for other vitreoretinal diseases. Most of these PRO instruments were developed for RP.(58, 254, 288, 292) There are no PRO instruments developed for vascular occlusion, ERM and CSR. Most of the items extracted from the pre-existing vitreoretinal -specific PRO instruments were on mobility

and activity limitation, which shows that the existing vitreoretinal-specific PRO instruments are limited in measuring few QoL domains and do not provide a comprehensive QoL measure and valid QoL score. Moreover, the items extracted from the previous qualitative studies were on health concerns and coping strategies showing that there is also a disparity in the known QoL impacts and the actual QoL impacts measured by the existing PRO instruments. Hence, there is a need to develop PRO instruments that provide a comprehensive assessment of the disease or the treatment impact from the patients' perspective. Hence, a systematic and multi-phased content development method was used to identify items for the item banks for other vitreoretinal diseases.

A topic guide was prepared for the semi-structured interviews to include issues that were underrepresented in the currently existing PRO instruments (health concerns, work & finance, convenience, and coping) thereby ensuring that the item banks would cover a wide range of vitreoretinal-specific QoL issues. Nine QoL domains were identified, which show that people with HRD and ARD have a myriad of QoL issues. These domains are also important ophthalmic domains of QoL identified in other eye diseases.(3, 45, 146) The reason for having similar QoL domains in the other vitreoretinal module is because these domains has been already identified as important ophthalmic domains in other major retinal diseases. Moreover, having similar QoL domains in all the Eye-tem bank disease modules will help to compare the QoL impact across disease groups.It is also important to have an adequate number of items across all the QoL domains to enable measurement precision. Most of the existing PRO instruments developed for ARD have very few items and do not form a valid scale of measurement. For example, the Short Visual Function Questionnaire and the Positioning for Macular Hole questionnaire have less than six items across the QoL domains.(309, 362) Moreover, these PRO instruments have not been validated in retinal diseases. The number of items extracted from the literature was 279. The initial item pool was supplemented with items from the qualitative interviews. Most the items (70%) for the vitreoretinal -specific item bank were extracted from the qualitative interviews.

The item refinement and revision phase enabled systematic classification of items into different domains and removal of redundant and unnecessary items. This method has

been successfully used in the development of the Patient-Reported Outcomes Measurement Information System item bank.(359)There were however, subtle differences in the technique used by the Patient-Reported Outcomes Measurement Information System item bank study and this study. Most of the items for the Patient-Reported Outcomes Measurement Information System item bank were extracted from the existing PRO instruments, and focus groups were done to confirm the domain definitions and identify items not covered by the Patient-Reported Outcomes Measurement Information System item bank. In this study, however, qualitative studies were used mainly to identify the items for the vitreoretinal item banks. The Patient-Reported Outcomes Measurement Information System item bank therefore had majority of the items from the existing literature and not from the patients' perspective, whereas the item banks developed by this study used qualitative interviews as the major source of item extraction thereby having more items from the patients' perspective. This suggests that the technique used in this study could be superior to that used in Patient-Reported Outcomes Measurement Information System item bank, because a PRO instrument is intended to capture information from the patients' perspective.

The final HRD item banks had more number of items than the ARD item banks because people with HRD have more QoL issues than people with ARD. The HRD group had more unique items than the ARD group. This may be because HRD differs from ARD in terms of the onset, presentation, and manifestation. The QoL domain 'activity limitation' had more number of common items because functional limitation due to loss of central vision was common to both the disease groups. In addition, HRD causes loss of peripheral vision which may be the reason for more number of items in the domains of 'activity limitation' and 'mobility'. The QoL domain 'health concerns' had less number of common items between the two disease groups. This is because people with HRD have different health concerns compared to people with ARD. Hence, these two disease groups would need separate item banks to assess the impact on QoL and treatment outcomes.

The QoL domains identified in this study were similar to the QoL domains identified in previous studies.(3, 45, 146) However, the vitreoretinal - specific item banks has an additional domain 'coping'. Coping came out as one of the major themes during the

qualitative analysis and that was the reason for the addition of this domain in the item banks. However, it is unclear whether the coping forms a construct or not. Psychometric analysis of the items within the 'coping' domain will give more information of whether it forms a construct or not. The HRD, AMD, DR and glaucoma item banks had more number of items than the ARD item banks, which shows that HRD, AMD, DR and glaucoma have greater impact on QoL than ARD. There were more numbers of common items between the HRD item banks and the other disease-specific item banks, which may be because, all these groups cause a greater impact on QoL. The ARD item banks had the least number of items compared to the other disease-specific item banks, which may be because this group of people have less QoL issues than other disease groups. This explains the lower number of common items between ARD item banks and the other disease-specific item banks.The greater number of items in the domain activity limitation in the AMD, DR and glaucoma item banks reflects the fact that the items have come from existing PRO instruments where there is emphasis on activity limitation.

4.6 Limitations

The study had few limitations. One of the main limitations of this study is that, the HRD and the ARD groups had people with some but not all rare retinal conditions. RP is the most prevalent hereditary degenerations followed by macular dystrophy and hence the HRD group had more participants with RP and macular dystrophies. Cone dystrophies, choroidal dystrophies and other hereditary vitreoretinopathies are rare diseases and so it was difficulty to include these degenerations in the study sample. Similarly, vascular occlusions, ERM and MH were common acquired retinal diseases which dominated the ARD group. Despite our best effort to approach societies, foundations, tertiary ophthalmic hospitals, and optometry practices, we could not include and consult people with all rare retinal conditions. This might limit the relevance and generalisability of our findings to all HRD and ARD. Another limitation is the small number of cognitive interviews conducted. To fully explore all the issues with the items and the response options, more cognitive interviews are necessary. However, after nine interviews no new concerns were raised for both the disease groups and so further the cognitive interviews were stopped after 11 interviews.

4.7 Conclusions

Two item banks were developed for other vitreoretinal diseases. Due to time constraints only the HRD item banks will be pilot tested using Rasch analysis and the ARD item banks will not be considered further in this thesis. The ARD pilot testing will continue after completion of the HRD pilot testing. The HRD item banks will be pilot tested in a large sample of patients. The psychometric properties of items within each QoL domain will be tested using Rasch analysis (chapter 5). Item calibration and development of the disease-specific item module will follow this. A CAT system will be developed to administer the items.

CHAPTER 5 ASSESSMENT OF THE PSYCHOMETRIC PROPERTIES OF THE HEREDITARY RETINAL DISEASES QUALITY OF LIFE ITEM BANKS

5.1 Introduction

Patient-reported outcome (PRO) instruments are developed and validated using two types of psychometric assessment methods: classical test theory or the Item response theory.(38, 136, 140, 141)The classical test theory uses traditional summary scoring that assumes that each item on the questionnaire has the same difficulty level and therefore scores them equally. For example, the items 'reading small print' and 'reading a large print book' are given the same weight. However, 'reading small print 'is considered more difficult than 'reading a large print book' by the participants. Hence, these two items should be scored and weighted differently. Also, the ordinal integer response used for each item assumes equal separation and uniform changes between the response categories.(363) Both these assumptions damage the ability of classical test theory scored instruments to measure precisely and accurately. Moreover, with classical test theory an overall score obtained by summing the ordinal numbers obtained from Likert type scales does not generate an actual interval level measurement scale.(43) The summary scores are likely to be noisier and less sensitive which is further exacerbated when there is ceiling and floor effect. On the other hand, the item response theory is item driven and it synergistically analyses the item difficulty and the respondent ability and places them mathematically on the same metric scale providing interval-level scoring. This process also minimises noise in the measurement which in turn improves sensitivity to change and correlation with other variables.(40) The item response theory scores the respondent's ability and the item difficulty on the same underlying trait making it a powerful method for estimating health outcome measures. Rasch analysis is one of the most commonly used item response theory models that also provides detailed insights into the psychometric properties of the instrument compared to the traditional methods.

Two item banks, one for hereditary retinal diseases (HRD) and one for acquired retinal diseases (ARD) were developed for other vitreoretinal diseases (chapter 4). Due to time constraints, only the HRD item banks were pilot tested. Rasch analysis was used to test the psychometric properties of the HRD item banks to ensure that each item

bank was capable of measuring what it was intended to measure and to calibrate items to set up a computererised adaptive testing (CAT). This chapter explores the psychometric properties of the HRD item banks.

5.2 Aims and objectives

1. To assess the psychometric properties of the HRD item banks using Rasch analysis.
2. To calibrate (assign appropriate weights) the HRD items using Rasch analysis to set up computer algorithms for the CAT.
3. To demonstrate the effectiveness of CAT in obtaining precise measurement of QoL using only a few items.

5.3 Methods

5.3.1 Study design and participants

Participants for this study were recruited from multiple sites: The Royal Society for the blind, Adelaide, Retina Australia (Queensland, Canberra, Western Australia, South Australia, Victoria, New South Wales, Northern Territory and Tasmania), Retina New Zealand, Australian Inherited Retinal Diseases Registry and DNA Bank , the Guide Dogs, and the Vision 2020 Australia through flyers, emails, and newsletters. The inclusion criteria included participants above the age of 18 years with a primary diagnosis of any HRD, those who spoke English and those without any hearing or cognitive impairment. An online survey of the pilot item banks was developed using the SurveyMonkey software, in addition to the hard copy version. The online survey had 10 sections totally. Section 1 contained information about the study, instructions to complete the survey and questions on the socio-demography (https://www.surveymonkey.com/r/MLXJ5ZF). Section 2 to 10 contained questions related to the nine QoL domains. Participants had the option of completing the survey in multiple sessions. The pilot item banks were sent either by post (hard copy) or by attaching the link of the online version through emails. Written consent was obtained either through posts or emails. Ethical approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee and the study adheres to the Tenets of Declaration of Helsinki.

5.3.2 Assessment of HRD and visual acuity (VA)

The clinical details (i.e. diagnosis of their eye condition and their visual acuity) were obtained either from the participants (self-reported) or obtained from their eye practitioners. To compute the average visual acuity, the values of Snellen acuity was converted to logMAR equivalent and then the average of the logMAR was taken. Counting fingers was given a value of 2.6, hand motion 2.7, light perception 2.8 and no light perception 2.9.

5.3.3 Development of the HRD item banks

Items for the HRD item banks were generated from a literature review and 32 semi-structured interviews with people with different retinal diseases. Item refinement and revision were done during three stages, namely binning, and winnowing, expert panel opinion, and cognitive interviews with patients (described in detail in chapter 4). The final set of the HRD item banks had 345 items across nine QoL domains.

5.3.4 Rasch analysis

The Rasch model was proposed by the Danish mathematician Georg Rasch in 1960.(364) It is a probabilistic mathematical model that conceptualises the obtained raw scores as the difference between the item difficulty (Di) and person ability (Bn).(144) This difference (raw score) is considered to be the equivalent of the odds ratio of probability of doing an item (Q) divided by the probability of not being able to do the item (P). The formula can be expressed as: Q/P. If we transform the odds ratio using the natural log we get logit which is expressed as: Logit = Log (Odds). As mentioned earlier, in item response theory we can put the items and the examinee attributes on the same scale. The item difficulty and person ability are two difference measure and how can we compare two different measures on the same scale? The trick is to convert the values from two measures into a common scale: logit. Logits are a measurement unit of latent variables for the measurement of psychometric properties. The value of the logits goes from negative infinity to positive infinity. This establishes a linear relationship between the questionnaire raw scores (converted to log odds) and the underlying construct, so that changes in the measure of the latent trait represents the same amount of change in the underlying construct across the entire range of the construct.

There are two types of Rasch models that are used to analyse a questionnaire with polytomous rating (i.e. a questionnaire with more than two response categories) namely, the Andrich rating scale model (365) and the Master's partial credit model.(366) In an Andrich rating scale model all the items in a questionnaire share the same rating scale structure. In this model all items must have the same number of thresholds. The thresholds are points at which a subject has more probability to choose one category option over another. In contrast, the Rasch-Masters partial credit model permits each item to have its own unique rating scale. This model assumes that the distance between the categories thresholds are different across all the items, unlike the Andrich rating scale model.

Rasch analysis has several advantages over traditional psychometric techniques. Traditional psychometric techniques provides assessment of very basic psychometric properties such as internal consistency and pay less attention to equal interval scaling, unidimensional, and hierarchical order.(144) Rasch analysis on the other hand transforms the ordinal score into a linear, interval-level score that enables the examination of the hierarchical structure and the unidimensionality of the patient-reported outcome measure making it a very powerful method to evaluate any PRO instrument.

Rasch analysis allows for a unified approach to several measurement issues, all of which are required for the validity of the transformation of the ordinal data to interval-level scoring; appropriate category ordering, testing the ability of the instrument to distinguish between different levels of participant's abilities, testing the internal construct validity of the scale for unidimensionality, testing how well the item difficulty matches person ability, and differential item functioning (DIF) (whether different subgroups respond differently to certain items).

5.3.4.1 *Category threshold order*

It is used to determine to what extent the categories used to rate the items are chosen in a logical order (ordered categories).(358, 367) Disordering of the categories occur, if the response categories are not chosen in a logical order. Disordering of the categories may occur due to overutilisation, underutilisation or unclear definitions, or when the numbers of categories exceeds what the respondents can distinguish.(358) When disordering of the categories occur, it may indicate multidimensionality and may

be detrimental to a PRO instrument. Disordered thresholds are addressed by either collapsing some of the response categories, renumbering the categories or dropping items.

5.3.4.2 *Measurement precision*

The extent to which of an instrument distinguishes different level of participants abilities.(40) The measurement precision is assessed using person separation index (PSI) and person seperation reliability (PSR) scores. A PSI value of > 2 .0 and a PSR value of > 0.8 are considered adequate and represent the capacity of the scale to distinguish three levels of person ability.(367)

5.3.4.3 *Unidimensionality*

Unidimensionality refers to whether an instruments measures a single underlying construct.(25) The dimensionality of an instrument is assessed using two statistics: (1) item fit statistics (mean square statistics) and (2) principal component analysis (PCA) of the residuals. Fit statistics indicates the extent to which the items in the instrument fits the Rasch model expectation. There are two fit statistics: 'infit' and 'outfit' statistics. The infit statistics measures the difference between the observed and expected response for those items that have a difficulty level near the person's ability level.(368) The outfit includes the differences for all the items, irrespective of how far the item difficulty is from the person's ability. In other words, the infit statistics are more sensitive to inliers and the outfit statistics are more sensitive to outliers. Thus, the infit statistics is a weighted fit statistic that gives greater weight to responses to items close to person's ability level.(369) For the development of short PRO instruments where reducing the number of items is important, a value of 0.7 to 1.3 for the mean square fit statistics (MNSQ) may be used.(370) For large item sets such as an item bank where the item reduction is less important, a value of 0.5 to 1.5 can be used.(371)

5.3.4.3.1 Dealing with misfitting items

When evaluating the item fit, infit was considered first followed by outfit. Each misfitting items were assessed individually to explore the source of misfit. An item misfit could occur if the item wording is confusing or complicated, unexpected responses by the respondents or when the item does not belong to the construct. Confusing or complicated wording provided evidence for deletion. The unexpected responses to an item by the respondents were diagnosed by exploring the z-residuals in Winsteps 11.1.

Respondents with higher z-residuals were given a weighting of 0. This process mutes the influence of these respondents' responses on measures or fit statistics of other items or person but their measures and fit statistics would be reported. This is followed by re-assessment of the fit statistics of the item. If the weighting these responders at 0 improved the fit statistics to acceptable levels then the items were retained. However, if the item showed misfit despite fixing the responses, it was considered for deletion. All the misfitting items were iteratively given a weighting of 0 and re-assessed. This process was continued till all the items showed satisfactory fit statistics. This way unnecessary deletion of items was avoided. If items showed only slight misfit and if it was considered an important item, then the item was retained.

5.3.4.3.2 Dealing with multidimensionality

Principal component analysis suggest the presence or absence of a second dimension. In this study, the PCA residuals was assessed on two parameters; the amount of raw variance explained by the measure and the eigenvalue of the unexplained variance in the first contrast. If the variance explained by the measure is > 50%, this may indicate that the scale was unidimensional. The first contrast in the residuals indicated whether there are other patterns within the variance that are not explained by the PCA. An eigenvalue of the first contrast suggest the presence or absence of a second dimension. If the eigenvalue of the first contrast is > 3 (strength of the dimension is more than 3 items) then it means there is a possibility of a second dimension (suspect cluster) within the main dimension (Rasch item cluster). Given that as few as 2 items could form a valid functional scale, if a second dimension was suspected (i.e. eigenvalue was > 3.0), a series of post-hoc tests were carried out. The first one was the assessment of dis-attenuated correlation (Pearson's correlation calculated after controlling for the standard errors of person measures) between the person measures of each cluster of items. Dis-attenuated correlation values are obtained from Winsteps Table 23.1.

If the dis-attenuated correlation between the person measures of the main item cluster (Rasch item cluster) and the suspect cluster (second dimension) was high, then the suspect cluster is measuring the same trait as the main cluster. If the dis-attenuated correlation between the person measures of the main item cluster and the suspect cluster was low, then the suspect cluster is measuring a different trait. Generally, a

correlation above 0.82 indicate a unidimensional scale and a correlation below 0.57 indicate two independent measure (i.e. multidimensional scale).(357) In addition, Pearson correlation coefficient and Bland & Altman test was performed to test the independency of the measures. For the Pearson correlation coefficient a value of < 0.3 was considered weak correlation, a value of ≥ 0.3 to < 0.5 as moderate correlation and ≥ 0.5 as strong correlation. If the correlation between the suspect item cluster and the Rasch main cluster is weak, then the suspect item cluster is an independent measure. Bland and Altman test defines the interval of agreement, it does not say whether those limits are accepatble or not.(372) The narrower the limits of agreement, the higher the agreement between the scale. This means the two scales are measuring the same latent trait and if the limits are wide, then the two scales are measuring different latent traits.

5.3.4.4 *Targeting*

Targeting refers to how well the difficulty of the items matches the abilities of the participants in the sample.(25) Targeting can be assessed by either visually inspecting the person-item map or by the comparing the item mean with the person mean. Person-item map shows item hierarchy, item redundancy and item gaps. Mistargeting occurs when the item difficulty doesn't match the participant's ability level. Perfect targeting occurs when the difference between the item mean and the person mean is 0. If it is more than 1 logit it indicates mistargeting.(373, 374)

5.3.4.5 *Differential item functioning (DIF)*

DIF is a measure that detects whether different subgroups (e.g. gender, age groups) respond differently to certain items despite having the same underlying ability.(375) Small DIF is defined as a difference of less than 0.5 logit, minimal as a difference between 0.5 to 1.0 logit and notable more than 1 logit. In this study, item with a DIF value of 1 logit was reported. DIF is sample size dependent (376) and a value of < 0.5 logits is usually used in the development of short PRO instruments and for large number of items like item banks a value of > 1 logits may be used. If the value of DIF for an item is > 1 logit, then it indicates that interpretation of the item may be biased for some participant subgroups.(377) The participants in this study were stratified by gender, age (< 50 years vs ≥ 50 years), best eye visual acuity (BEVA) (6/60 and better vs worse than 6/60), diseases groups (retinitis pigmentosa (RP) vs other diseases)

and ocular comorbidity.

5.3.4.6 *Measurement range*

It is determined by calculating the difference in logits between the hardest and the easiest to endorse items. If the measurement range is smaller, it indicates that the items provide less information about the construct being measured and if it is larger, it indicates that the items provide more information about the measured construct.

5.3.4.7 *Item discrimination*

Item discrimination indicates the extent of information of the construct available in an item.(378) An ideal estimated item discrimination approximates 1. Items with values > 1 can discriminate between high and low performers, but do not contain enough information about the measure. Whereas, items with value < 1 neither discriminate between high and low performers nor provide enough information about the measure. Therefore, items with values < 1 were considered for deletion.

5.3.4.8 *Local item dependency*

Items in a test should not be related to each other after the effect of the underlying trait is conditioned out. Local item dependency results in artificially small standard error of estimates and overestimation of reliability. This may cause serious problems in CAT, where the standard error of estimate is often used as the termination criteria.(379) A correlation of > 0.3 among the residuals suggest local item dependency.(380) To prevent the local item dependency from impacting item difficulties, person measures of only the local item dependency free items were generated. All the person measures were then anchored to those generated using the local item deficiency free items.

5.3.4.9 *Computer adaptive testing simulation*

A CAT simulation was done to calculate the average number of items required to gain precise measurement of each QoL domain. A real data simulation is important as it allow researchers to estimate important features of CAT application such as the test length, score precision that CAT would produce and the size of the item bank necessary to produce the desired precision of the examinee scores.(381) The stopping technique that was used was the standard error stopping criteria, which terminates an adaptive test when a predetermined standard error has been reached for the most recent examinee trait estimate. The first simulation was used to calcuate the average

number of items required to obtain a standard error of measurement of 0.521 which is calculated using the formula: $\alpha = 1 - \text{standard error of measurement}^2$ and the second simualtion was used to calculate the average number of items required to obtain a standard error of measurement of 0.387. The justification for using two standard error of measurements is that the value 0.521 approximates to a reliability of 0.85 and represents high precision which might be required for an individual assessment and th value of 0.387 approximates to a reliability of 0.72 and represents moderate precision which might be required for group assessment. For both the levels of precisions correlations were calculated between the full item banks and the CAT simulation person measure estimates using the EAP (*expected a posteriori estimator*). An estimate of the examinee's true scaore is theta. CAT simulations started with items located at theta 0.0 (i.e. of average difficulty value) and subsequent items were selected at random form the best item available at the current theta estimate.

Each QoL domain (item bank) behaves as a separate scale, hence each QoL domain was subjected to Rasch analysis as a separate scale (separate item bank). The following psychometric properties were assessed: functioning of the response categories, measurement precision, unidimensionality, fit statistics, targeting of the scale to the study population and DIF. Domains that show multidimensionality will be split into separate scales. Agreement between the domain scores will be tested using the Bland and Altman test of agreement. The domains that demonstrate high agreement will be considered for collapsing into a single domain. DIF was tested for socio-demographic, clinical variable, and comorbidity.

5.4 Statistical analyses

The socio-demography and clinical statistics were analysed using the IBM SPSS statistics software for windows, version 22 (SPSS Inc., Chicago, ill, USA)). Rasch analysis was done using the Winsteps software, version 3.91.2 (Linacre, 2009) using the Andrich single rating scale model. Bland and Altman test was done using the MedCalc software, version 17.2 (Ostend, Belgium, 2016) and CAT simulation was done using the Firestar-D software (version 1.3.2, Chicago IL, USA).

5.5 Results

A total of 233 participants answered (via the telephone = 22 and online = 196) the 345 items (median 58 years; range 18 to 94 years; RP, 71%; bilateral eye disease, 98%; females, 59%) (Table 5.1). One hundred and ninety-six participants completed all the 9 domains and 37 participants did not. The median age of the participants who completed all the QoL domains was 51 years (IQR, 30.5 to 64.5) and the median age of participants who completed one or more domains was 56.5 years (IQR, 46.7 to 68). There was no significant difference in the median age between the two groups (Mann-Witney test, p = 0.115). Nearly half of the participants had visual acuity 6/60 or better in the best eye. Most of the participants were using low visual aids (n = 167). The majority of the participants had RP followed by macular dystrophy and juvenile retinoschisis. Even though red-green colour deficiency has a higher prevalence rate compared to macualr dystrophies only 3 participants consented to take part in the study.

Overall the psychometric properties of the domains were promising. The psychometric assessment and properties of each of the domain (item bank) except the coping domain are discussed in detail below. The psychometric properties of the coping domain will be discussed in chapter 6.

Table 5.1 Socio-demographic and clinical characteristics of the participants

Variables	
Age (n = 233) (years)	
Median, IQR	58, 45 to 67
Range	18 - 94
Gender, n (%)	
Female	137 (59)
Male	96 (41)
Hereditary retinal diseases, n (%)	
1.Retinitis pigmentosa and related disorders	
Retinitis pigmentosa	165 (70.8)
Congenital stationary night blindness	1 (0.4)
Congenital red-green colour deficiency	3 (1.2)
Leber's congenital amaurosis	6 (2.5)
2.Macular dystrophy	
Best's disease	9 (3.8)
Fundus flavimaculatus	2 (0.8)
North Carolina macular dystrophy	1 (0.4)
Pattern dystrophy	4 (1.7)
Stargardt disease	21 (9)
Sorsby's macular dystrophy	3 (1.2)
Adults vitelliform macular degeneration	4 (1.7)
3.Choroidal dystrophy	
Choroideremia	4 (1.7)
Gyrate atrophy	1 (0.4)
4.Hereditary vitreoretinopathies	
Juvenile retinoschisis	6 (2.5)
5.Miscellaneous	
Idiopathic juxtafoveolar retinal telangiectasis	1 (0.4)
Noorie's disease	1 (0.4)
Von Hipple Lindau disease	1 (0.4)
Eyes involved, n (%)	
Bilateral	228 (98)
Unilateral	5 (2)
Visual acuity (better eye); LogMAR (Snellen equivalent)	
Mean	1.0 (6/60)
Range	- 0.20 to 2.90 (6/4 to NPL)
Ocular comorbidities, n (%)	
Yes	125 (54)
No	108 (46)
Medical morbidity, n (%)	
Yes	126 (54)
No	107 (46)
Marital status, n (%)	
Married/de facto	162 (70)
Divorced/separated/widowed	28 (12)
Never married	39 (17)
Employment, n (%)	
Retired	63 (27)
Working	86 (36.9)
Disability pension	60 (25.7)
Unemployed	10 (4.2)
Volunteer work	14 (6)

Percentage of some variables may not be equal to 100% due to missing data.

5.5.1 Convenience domain

The 16-item convenience scale demonstrated good precision (PSI = 2.78) and targeting (0.58) (Table 5.2).

Table 5.2 Psychometric properties of the Convenience domain

Parameters	Rasch model expectations	First iteration	Final iteration
Disordered thresholds	No	No	No
Number of items	-	16	16
Person separation index	>2.0	2.78	2.80
Person reliability	> 0.8	0.89	0.89
PCA, variance by 1st factor	>50%	59.3%	59.3%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	2.3, **6%**	2.3, **5.9%**
PCA, % raw variance explained by items		30.4%	30.1%
Item fit (infit MnSq)	< 1.5	None	None
Item fit (outfit MnSq)	< 1.5	**CV 9 (2.00)** **CV 10 (1.75)**	None#
LID ‖	> 0.3	3 pairs, 2.5%	3 pairs, 2.5%
DIF**	<1.0 logits and p<0.05	None	None
Measurement range		2.07	2.24
Targeting, difference between person & item means	<1.0 logits	0.58	0.52

CV 9 = The amount of time needed when attending your eye appointment; CV 10 = Having to travel a long way to attend your eye appointment
#The misfit of the two items were resolved by diagnosing misfit through unpredictable individual responses (total n = 5) and giving errant responders a weighting of 0.
‖ LID dealt with using the process outlined in the methods. LID item pairs: Final iteration: 1/9, 4/16, 5/16. Percentage refers to proportion of LIDpairs of total number of correlated items.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease group, and ocular comorbidity.
Number of participants responded to the items: CV 9 (n = 2); CV 10 (n = 1)
Bolded values represent poor fit to the Rasch model.
CV, Convenience; PCA, principal component analysis; MnSq, mean square; LID, local item dependency; DIF, differential item functioning

The explained variance of the measure was 59.3% and the eigenvalue of the first contrast was 2.3, suggesting unidimensionality (Table 5.2). Of the 16 items, 2 items (9 & 10) showed misfit and the remaining 14 items showed good fit statistics. The item misfit for the 2 items was resolved by diagnosing misfit through unpredictable individual responses and giving the errant responders a weighting of 0. Following this, all the items showed good fit statistics. There was no DIF for age, gender, BEVA,

disease groups and ocular comorbidity. The response categories of the 16-item convenience scale were ordered (Figure 5.1). If the response categories are ordered then each response curve will have a distinct peak and the category thresholds (intersection of the curves) follow order (i.e. in a four category response categories curves 1 and 2 intersect first followed by 2 and 3 and then 3 and 4). If the response categories are disordered the peaks of the response curves are not discrete and the category thresholds do not follow order.

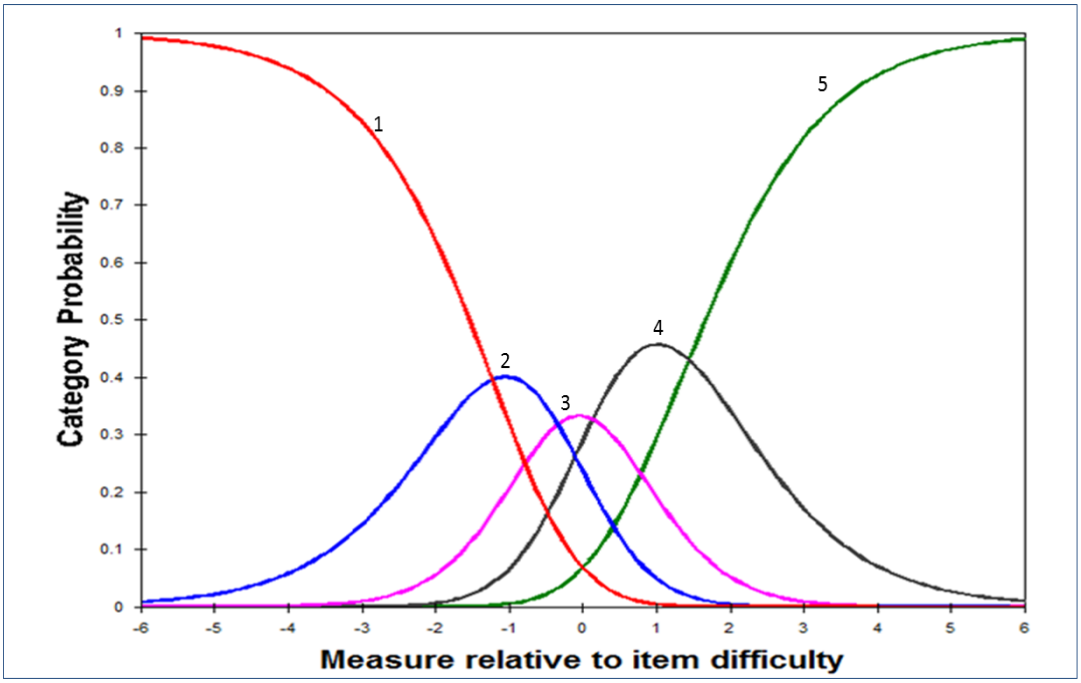

Figure 5.1 Category probability curves showing ordered thresholds for the five - response categories for the Convenience scale

5.5.2 Economic domain

The 17-item economic scale demonstrated a borderline precision (PSI = 1.89), but good targeting (0.55) (Table 5.3). The explained variance of the measure was 60.7% and the eigenvalue of the first contrast was 3.3. An eigenvalue of 3.3 shows that the strength of the first contrast was at least 3 items. PCA analysis showed that 6 items were grouping together with a loading > 0.4 forming a suspect item cluster. However, the dis-attenuated correlation between the suspect item cluster and the main Rasch item cluster was very high 1.00 (i.e. a perfect correlation), indicating that even though the suspect item cluster was grouping together, it was measuring the same latent trait as the main Rasch item cluster. Moreover, the 6 items that were grouping together did

not form a meaningful construct. Hence, these 6 items were retained within the main economic scale. Of the 17 items, 2 items (11 & 2) showed misfit and the remaining 15 items showed good fit statistics. The misfit of item 11 was resolved by diagnosing misfit through unpredictable individual responses and giving errant responders a weighting of 0.

Table 5.3. Psychometric properties of the Economic domain

Parameters	**Rasch model expectations**	**First iteration**	**Final iteration**
Disordered thresholds	No	No	No
Number of items	-	17	17
Person separation index	>2.0	**1.89**	**1.91**
Person reliability	> 0.8	0.78	0.78
PCA, variance by 1st factor	>50%	60.7%	60.8%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	3.3, **7.7%**	3.3, **7.7%**
PCA, % raw variance explained by items	-	9.7%	10%
Item fit (infit MnSq)	< 1.5	**EC 11 (1.69)** **EC 2 (1.61)**	**EC 2 (1.66) †**
Item fit (outfit MnSq)	< 1.5	None	None
LID ‖	> 0.3	4 pairs, 2.9%	4 pairs, 2.9%
DIF**	<1.0 logits and p<0.05	None	None
Measurement range		1.23	1.31
Targeting, difference between person & item means	<1.0 logits	0.55	0.53

EC 2 = Limitation on the types of jobs you can do e.g. jobs that require a driving licence, lots of reading or computer work; EC 11 = The cost associated with seeing your eye specialist.
†Item 2 was retained as it was an important item within the domain.
‖ LID dealt with using the process outlined in the methods. Item pairs: Final iteration: 5/6; 4/8; 1/2; 6/7. Percentage refers to proportion of LIDpairs of total number of correlated items.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups and ocular comorbidity.
Number of participants responded to the items: EC 2 (n = 12); EC 11 (n = 4)
Bolded values represent poor fit to the Rasch model.
EC, economic; PCA, principal component analysis; MnSq, mean square; LID, local item dependency; DIF, differential item functioning

However, item 2 did not show any errant responders. Item 2 was retained as it was an important item. The response categories of the 17-item economic scale were ordered (Figure 5.2). There was no DIF.

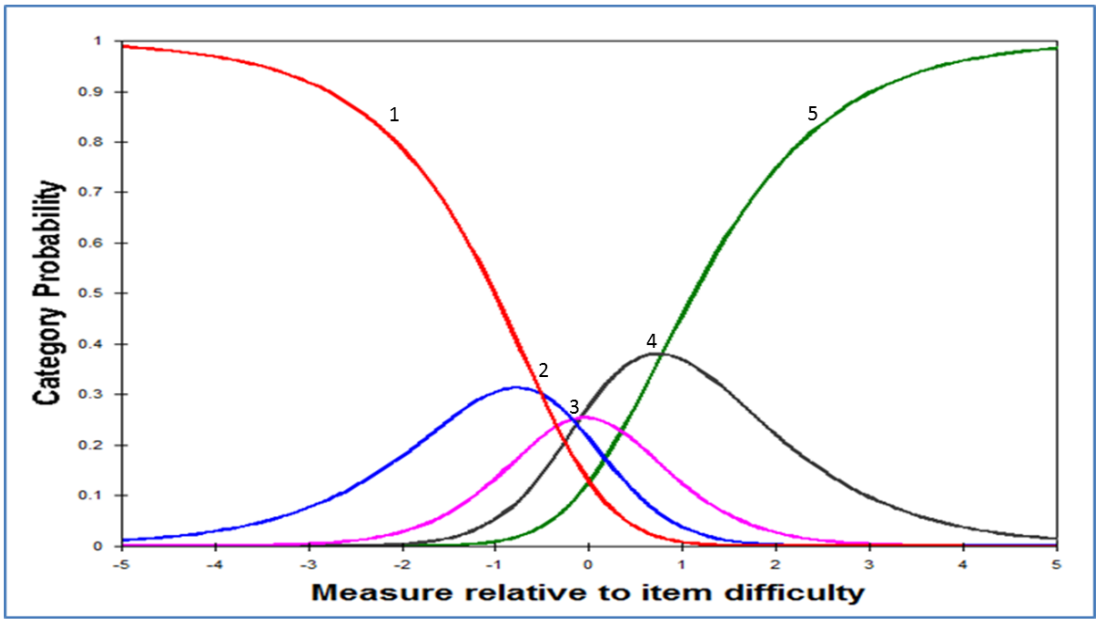

Figure 5.2 Category probability curves showing ordered thresholds for the five - response categories for the Economic scale.

5.5.3 Social domain

The 28-item social scale demonstrated good precision (PSI = 2.78), but poor targeting (2.06) (Table 5.4). The explained variance of the measure was 56.9% and the eigenvalue of the first contrast was 3.1, suggesting unidimensionality. Two items (17 and 27) showed misfit and the remaining 26 items showed good fit statistics. The fit statistics of the 2 items improved after giving errant responders a weighting of 0. The response categories of the 28-item social scale were ordered (Figure 5.3). There was no DIF.

Table 5.4. Psychometric properties of the Social domain

Parameters	Rasch model expectations	First iteration	Final iteration
Disordered thresholds	No	No	No
Number of items	-	28	28
Person separation index	>2.0	2.78	2.79
Person reliability	> 0.8	0.89	0.89
PCA, variance by 1st factor	> 50%	56.9%	56.9%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	3.1, 4.8%	3.1, 4.8%
PCA, % raw variance explained by items	-	17.1%	17.1%
Item fit (infit MnSq)	< 1.5	**SC 17 (1.55) ‡**	None#
Item fit (outfit MnSq)	< 1.5	**SC 27 (1.66) ‡**	None#
LID ‖	> 0.3	5 pairs, 1.3%	5 pairs, 1.3%
DIF**	<1.0 logits and p<0.05	None	None
Measurement range		3.71	3.74
Targeting, difference between person & item means	<1.0 logits	**2.06**	**2.06**

SC 17 = Maintaining your roles and responsibilities in community organisations (e.g. church groups, volunteering groups); SC 27 = With your family members being over protective.
‡SC 17 had poor discrimination (0.50); SC 27 had poor discrimination (0.54).
#The misfit of the two items were resolved by diagnosing misfit through unpredictable individual responses (total n = 3, for each misfitting item) and giving errant responders a weighting of 0.
‖LID dealt with using the process outlined in the methods. LIDitem pairs: Final iteration: 14/21; 9/10; 13/14; 4/16; 3/6. Percentage refers to proportion of LIDpairs of total number of correlated items.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups and ocular comorbidity.
Number of participants responded to the items: SC 17 (n = 51); SC 27 (n = 1)
Bolded values represent poor fit to the Rasch model.
SC, social; PCA, principal component analysis; MnSq, mean square; LID, local item dependency; DIF, differential item functioning

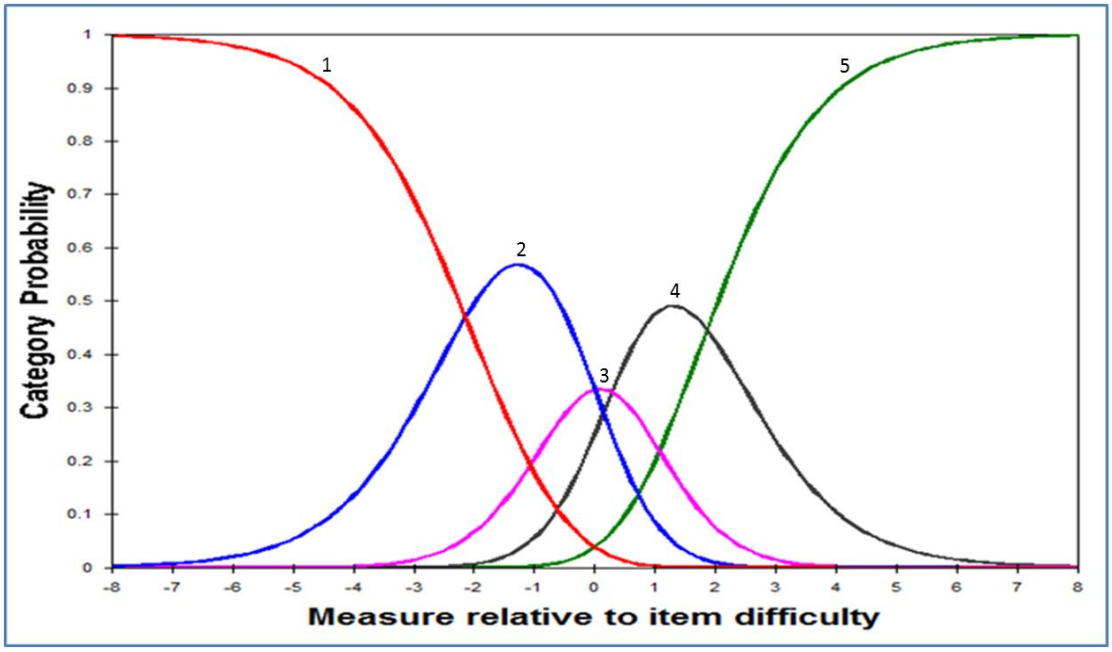

Figure 5.3 Category probability curves showing ordered thresholds for the five - response categories for the Social scale

5.5.4 Mobility domain

The mobility scale had 23 items. This scale demonstrated excellent precision (PSI = 4.31), but borderline targeting (1.11) (Table 5.5). The explained variance of the measure was 69.5% and the eigenvalue of the first contrast was 3.8. An eigenvalue of 3.8 suggests that the strength of the first contrast was at least 4 items. PCA showed that 6 items related to walking in challenging situations (1, 2, 3, 4, 5 & 12) were grouping together to form a suspect item construct with a loading > 0.4 to the first contrast. The removal of the 6 items reduced the precision of the remaining 17-item mobility scale from 4.31 to 3.59. The explained variance of the measure also worsened to 67.6% from 69.5%. However, the eigenvalue of the first contrast showed only a slight improvement from 3.8 to 3. The 6-item scale formed a stand-alone unidimensional scale with excellent precision (PSI = 3.45) and other promising Rasch-based metric properties (Appendix 6).

A series of post-hoc tests (dis-attenuated correlation and Bland & Altman test) were done to make a final decision whether to retain or separate the 6-item scale from the main mobility scale. The dis-attenuated correlation between the suspect item cluster and the main Rasch cluster was high 0.9.

Table 5.5 Psychometric properties of the Mobility domain

Parameters	Rasch model expectations	First iteration	Final iteration
Disordered thresholds	No	No	No
Number of items	-	23	23
Person separation index	>2.0	4.31	4.40*
Person reliability	> 0.8	0.95	0.95
PCA, variance by 1st factor	>50%	69.5%	69.5%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	**3.8**, **5.1%**	**3.8**, **5.1%**
PCA, % raw variance explained by items	-	30.2%	29.9%
Item fit (infit MnSq)	< 1.5	**MB 21 (1.65)** **MB 22 (1.55)**	**MB 21 (1.52) ŧ**
Item fit (outfit MnSq)	< 1.5	**MB 6 (6.38)** **MB 22 (1.62)**	None#
LID ‖	> 0.3	17 pairs, 6.7%	17 pairs, 6.7%
DIF**	<1.0 logits and p<0.05	No DIF by age and gender	**BEVA:** **MB 12 (1.45, p < 0.0001)** **Disease groups:** **MB 13 (-1.04, p < 0.001)**
Measurement range		3.86	4.05
Targeting, difference between person & item means	<1.0 logits	**1.11**	**1. 06**

MB 6 = Walking around your home; MB 12 = Navigating in dim light; MB 13 = Crossing a street or road; MB 21 = Going on long journeys; MB 22 = Travelling somewhere independently.
*Precision improved after fixing the misfitting items
ŧItem 21 was retained as it was an important item.
#Misfit of two items was resolved by diagnosing misfit through unpredictable individual responses (n = 30) and giving errant responders a weighting of 0.
‖LID item pairs; Final iteration:1/2; 1/5: 2/3; 2/4;3/4; 4/12; 7/9; 7/8; 8/9; 14/15; 14/17; 14/18; 15/17; 18/19; 21/22; 22/23, 15/18.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups and ocular comorbidity
Number of participants responded to the items: MB 6 (n = 2); MB 12 (n = 1); MB 13 (n = 4); MB 21 (n = 1); MB 22 (n = 19)
Bolded values represent poor fit to the Rasch model.
MB, mobility; PCA, principal component analysis; MnSq, mean square; LID, local item dependency; DIF, differential item functioning

Bland and Altman test showed that the 6-item scale had a high correlation (r = 0.82, 95% CI= 0.77 to 0.86), but moderate agreement (mean bias, 1.4 logit; 95% limits of agreement , -2.8 to 5.6) with the main mobility scale (Figure 5.4).

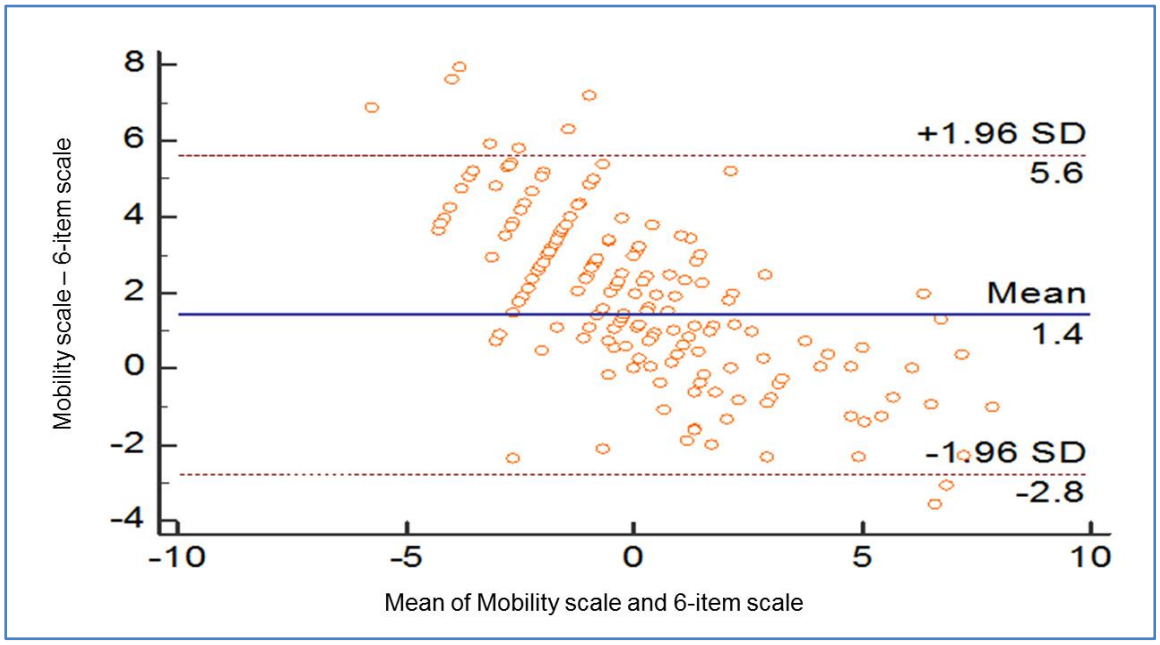

Figure 5.4 Bland and Altman plot showing the limits of agreement (mean difference and 95% confidence interval) between the Mobility scale and the 6-item scale

Results of the post-hoc tests suggest that the 6-item scale was measuring the same underlying trait. Even though the 6-item scale formed a stand-alone measure, it was decided to retain the 6 items within the mobility scale, because removing these 6 items significantly lowered the precision, the variance explained by the measure and together they did not form a meaningful construct. The final mobility scale had 23 items.

Three items (6, 21 & 22) showed misfit. The misfit of the 3 items were resolved by identifying the unpredictable individual response and giving the errant responders a weighing of 0. The response categories of the final mobility scale were ordered (Figure 5.5). Out of 23 items, only 2 items (8.6%) demonstrated DIF. Item 12 demonstrated DIF (DIF contrast = 1.45) by visual acuity, indicating that people with visual acuity either 6/60 or better in the better eye found item 12 difficult than people with visual acuity of less than 6/60. Item 13 showed DIF (DIF contrast =1.04) by disease type indicating that people with other hereditary retinal diseases found this item more difficult.

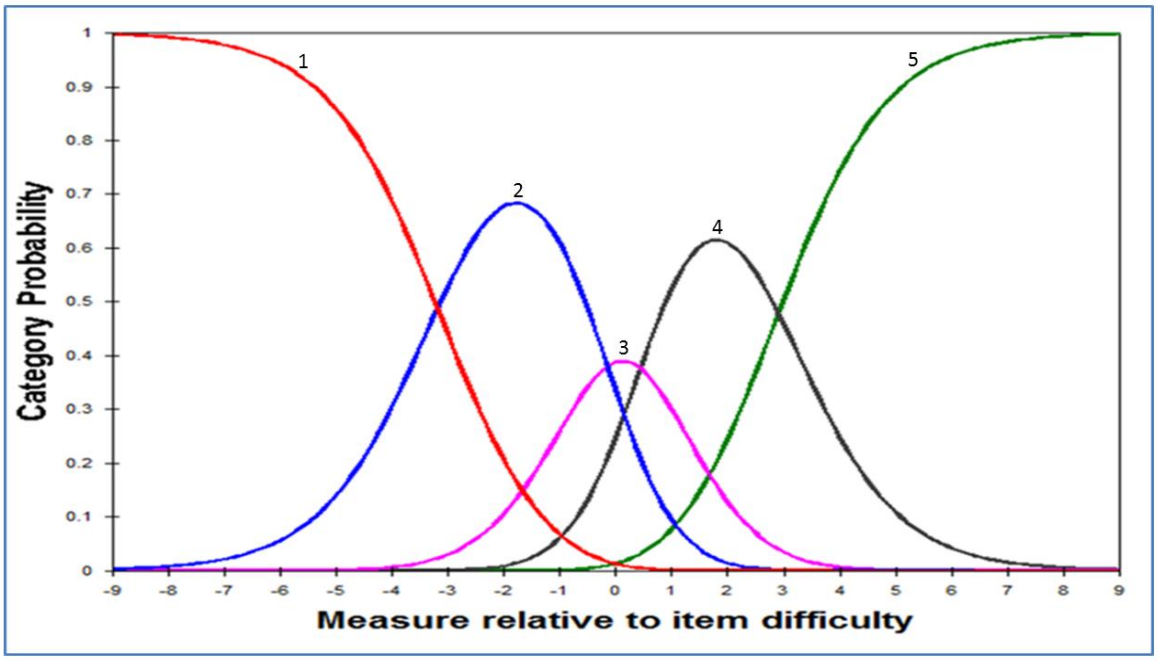

Figure 5.5 Category probability curves showing ordered thresholds for the five-response categories for the Mobility scale

5.5.5 Emotional domain

The emotional scale had 66 items. Overall, this scale demonstrated excellent precision (PSI = 4.28), but poor targeting (1.62) (Table 5.6). The explained variance of the measure was 54.1% and the eigenvalue of the first contrast (i.e. second dimension) was 5.5, which indicated that it had a strength of at least 5 items. PCA analysis showed that 6 items related to positive emotions (1, 2, 3, 5, 6 & 7) were grouping together to form a suspect item cluster. Moreover, the 6-item scale formed a stand-alone unidimensional scale with good precision (PSI = 2.46) and other promising Rasch-based metric properties (Table 5.6). Post-hoc tests were done to make a final decision whether to retain or separate the 6-item scale from the main emotional scale. The dis-attenuated correlation between the suspect item cluster and the main Rasch item cluster was low 0.6. Bland and Altman test showed that the 6-item scale had a moderate correlation (r = 0.49, 95% CI = 0.38 to 0.58) and a moderate agreement (mean bias, 1.4 logit, 95% limits of agreement, -2.2 to 5 logit) with the main emotional scale (Figure 5.6). Results of the post-hoc tests suggest that the 6-item scale forms a separate dimension.

Table 5.6. Psychometric properties of the Emotional domain

Parameters	**Rasch model expectations**	**All items**	**First iteration**	**6-item scale (Positive emotional) (PEM)**	**Final iteration (Negative emotional) (NEM)**
Disordered thresholds	No	No	No	No	No
Number of items	-	66	60	6	53
Person separation index	>2.0	4.28	4.07	2.46	4.27
Person reliability	> 0.8	0.95	0.94	0.86	0.95
PCA, variance by 1st factor	>50%	54.1%	56.6%	61.7%	61.5%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	**5.5,** 3.8% (6 items on positive emotions loaded > 0.5)	**4.1**, 3.1%	2.4, **15.7%**	**4.1**, 3.1%
PCA, % raw variance explained by items	-	25.7%	23.8%	23.2%	23.7%
Item fit (infit MnSq)	< 1.5	**EM 4 (3.02)** **EM 6 (2.02)** **EM 7 (1.90)** **EM 66 (2.01)** **EM 5 (1.65)** **EM 18 (2.00)** **EM 3 (1.63)** **EM 16 (1.76)** **EM 23 (1.56)**	**EM 4 (3.46) ‡** **EM 66 (2.19) ‡** **EM 18 (2.15) ‡** **EM 16 (1.90) ‡** **EM 37 (1.66) ‡** **EM 23 (1.64) ‡**	None	None#
Item fit (outfit MnSq)	< 1.5	**EM 4 (3.93)** **EM 6 (2.18)** **EM 7(2.15)** **EM 66 (2.09)** **EM 5 (2.05)** **EM 18 (1.96)** **EM 3 (1.81)** **EM 16 (1.67)** **EM 1 (1.54)**	**EM 4 ((5.32)** **EM 66 (2.21)** **EM 18 (2.16)** **EM 16 (1.92)** **EM 37 (1.88)** **EM 31 (1.53)**	**EM 5 (1.56) ŧ**	None#

		EM 31 (1.54)			
LID ‖	> 0.3	37 pairs, 1.7	37 pairs, 1.7	3 pairs, 20%	16 pairs, 1.1%
DIF**	<1.0 logits and p<0.05	None	No DIF for age and gender	None	None
Measurement range		4.43	4.43	2.02	4.35
Targeting, difference between person & item means	<1.0 logits	**1.62**	**1.93**	0.29	**2.31**

EM 1 = Feel hopeful; EM 3 = Feel appreciative; EM 4 = Feel surprised; EM 5 = Feel relieved; EM 6 = Feel fortunate; EM 7 = Feel grateful; EM 16= Feel shocked by what your eye specialist have told you about your eyes; EM 18 = Feel reluctant to talk about your eye problem; EM 23 = Have trouble accepting that your eye problems are permanent; EM 31 = Feel disoriented; EM 37 =: Feel unlucky; EM 66 = Feel stuck with your eye condition and treatment.

‡ EM 4 had a very poor discrimination (-2.28), it was a confusing item that showed misfit with both positive and negative items; EM 16 had poor discrimination (0.50) and missing value (17%); EM 18 had a poor discrimination (0.08); EM 23 had a poor discrimination; (0.68); EM 37 had a poor discrimination (0.42); EM 66 had a poor discrimination (-.25)

ŧItem 5 was retained as it was an important item

#After deleting items EM 4, EM 16, EM 18, EM 23, EM 31, EM 37and EM 66, remaining item fit of one item was resolved by diagnosing misfit through unpredictable individual responses and giving errant responders a weighting of 0.

‖LID dealt with using the process outlined in the methods. LID item pairs: Final iteration: 25/26; 38/43; 32/40; 26/27; 25/27; 6/43; 52/53; 6/7; 39/42; 49/58; 22/58; 4/5; 16/33; 14/15; 34/58; 39/51; Percentage refers to proportion of LID pairs of total number of correlated items.

**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups, and ocular comorbidity.

Number of participants responded to the items: EM 1(n = 18); EM 3(n = 3); EM 4(n = 4); EM 5(n = 3); EM 6(n = 6); EM 7(n = 3); EM 16(n = 20); EM 18(n = 3); EM 23(n = 2); EM 31(n = 4); EM 37(n = 4); EM 66(n = 1).

Bolded values represent poor fit to the Rasch model.

EM, emotional; PCA, principal component analysis; MnSq, mean square; DIF, differential item functioning; LID, local item dependency

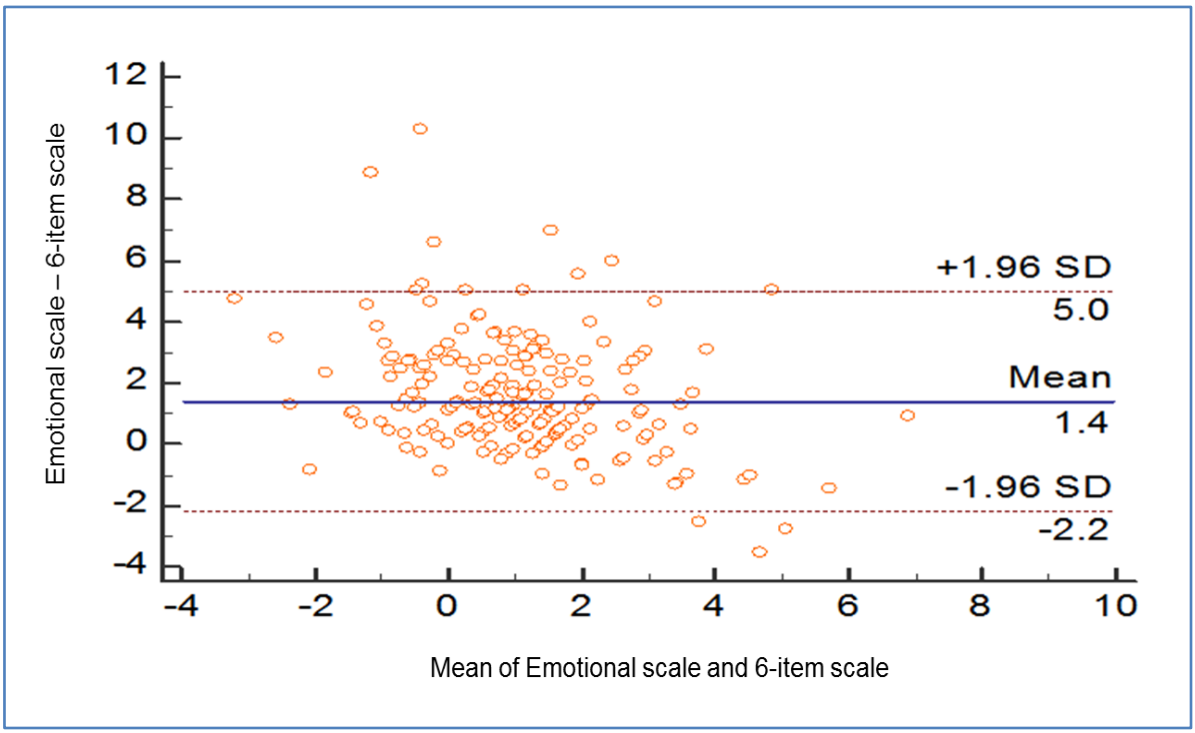

Figure 5.6 Bland and Altman plot showing the limits of agreement (mean difference and 95% confidence interval) between the Emotional scale and the 6-item scale

The 6-item scale was separated from the EM scale because of the following reasons: the dis-attenuated correlation was low (0.6), the scale showed moderate correlation and moderate agreement with the main emotional scale, the eigenvalue of the new first contrast significantly improved with the separation of the scale and the scale formed a meaningful construct. The 6-item scale was named as positive emotional.

Separating the 6 positive items reduced the precision of the remaining 60-item emotional scale (PSI = 4.07) (Table 5.6). The unexplained variance of the new first contrast reduced to 4.1 eigenvalues, thus moving closer to Rasch model criterion of unidimensionality. The first contrast still had a strength of at least 4 items and PCA analysis showed that 3 items loaded together by > 0.4 to the first contrast. However, the dis-attenuated correlation between the two item clusters (i.e. the second suspect item cluster and the main Rasch item cluster) was 1.00 (i.e. a perfect correlation), suggesting that that the 3 items even though were grouping together to form a suspect item cluster were measuring the same latent trait as the rest of the emotional items. Moreover, the 3 items that grouped together did not form a meaningful construct. Therefore, the suspect item cluster was retained within the emotional scale. The main

emotional scale had 60 items.

The 60-item emotional scale demonstrated 7 misfitting items (4, 66, 18, 16, 37, 23 & 31). Removing the errant responders of the misfitting items did not resolve the misfit of the 7 items and hence, these 7 items were deleted (see notes in Table 5.6 for the reason for deleting each of these items). After deleting the 7 items, the precision of the emotional scale improved from 4.07 to 4.27 (Table 5.6, final iteration). The explained variance of the measure also improved from 56.6 to 61.5%. The final emotional scale now had 53 items which demonstrated similar precision as the initial 66-item scale. The 53-item emotional scale was renamed as negative emotional. The response categories of the final 53-item negative emotional scale and the 6-item positive emotional scale were ordered (Figure 5.7) and there was no DIF.

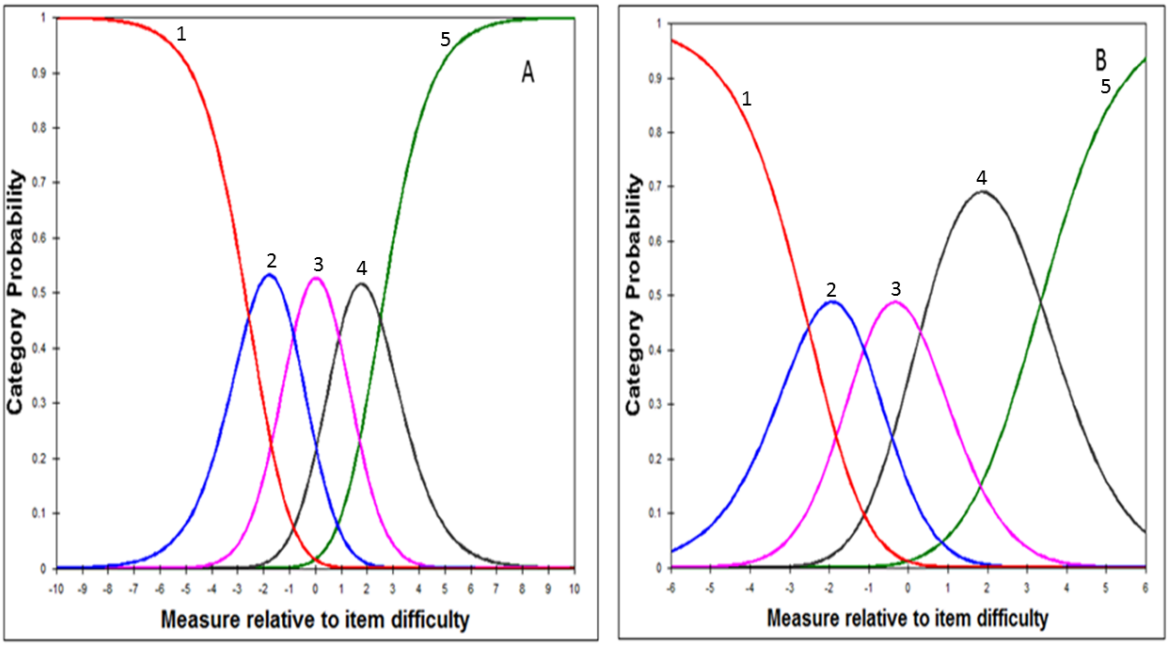

Figure 5.7 Category probability curves showing ordered thresholds for the five-response categories for the (A) the Negative Emotional and the Positive Emotional scales

5.5.6 Health Concerns domain

The 48-item health concerns scale demonstrated excellent precision (PSI = 4.01) and good targeting (0.38) (Table 5.7). The explained raw variance of the measure was 59.1%. The first contrast had an eigenvalue of 5.8, which indicated that it had a strength of at least 6 items. PCA showed that 7 items related to concerns about the disease progression were grouping together to form a suspect item cluster. These 7

items loaded to the first contrast by more than > 0.4. The 7-item scale formed a stand-alone unidimensional scale with good precision (PSI = 2.75) and other Rasch based metric properties (Table 5.7). Post-hoc tests were done to make a final decision whether to retain or separate the 7-item scale from the main health concerns scale. The dis-attenuated correlation between the suspect item cluster and the dominant Rasch item cluster was 0.9. Bland and Altman test demonstrated that the 7-item scale had a high correlation (r = 0.78, 95% CI = 0.73 to 0.83, p < 0.0001), but a moderate agreement (mean bias, 0.9 logit; 95% limits of agreement , -2.3 to 4.1 logit) with the main health concerns scale (Figure 5.8).

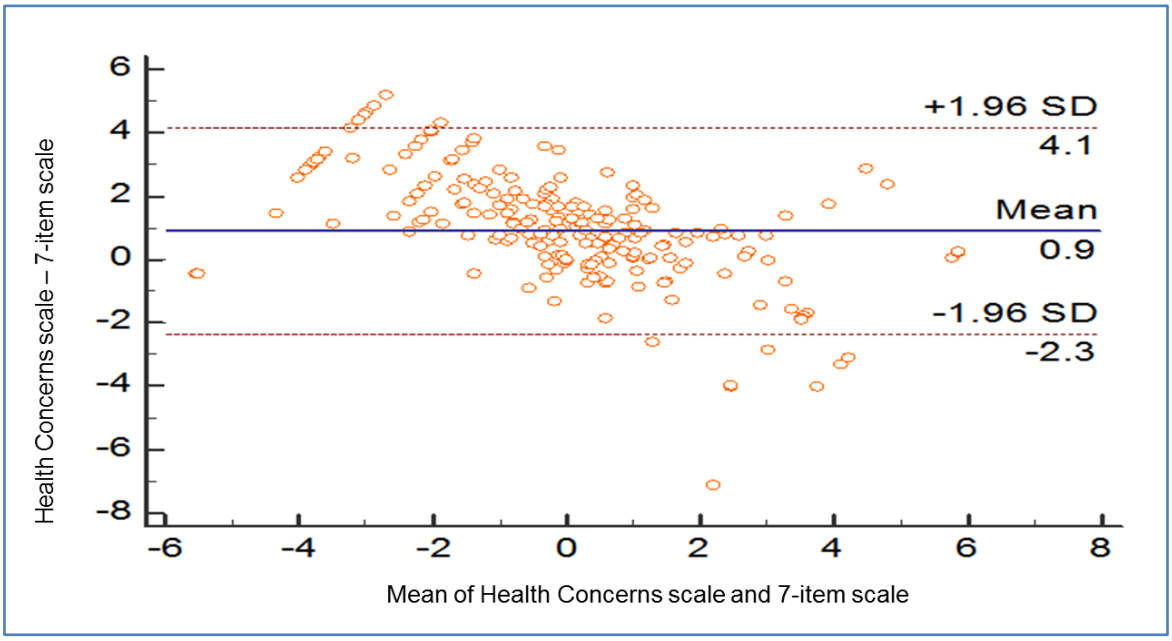

Figure 5.8 Bland and Altman plot showing the limits of agreement (mean difference and 95% confidence interval) between the Health Concerns scale and the 7-item scale

Results of the post-hoc tests suggest that the 7-item scale probably was measuring a similar underlying trait as the main health concerns scale. However, the 7-item scale was separated into a separate scale because removal of the 7 items significantly improved the eigenvalue of the new first contrast from 5.8 to 4.1 and formed a meaningful construct. Removal of the 7 items reduced the precision (PSI = 3.64) of the remaining 41-item health concerns scale. The explained variance of the measure was 58.7% and the unexplained variance eigenvalue dropped to 4.1, moving closer to Rasch based criterion of unidimensionality. The 41-item health concerns scale showed 11 misfitting items (11, 16, 29, 30, 31, 34, 36, 38, 41, 44 and 45).

Table 5.7. Psychometric properties of the Health Concerns domain

Parameters	**Rasch model expectations**	**All items**	**First iteration**	**7-item scale**	**Final iteration*** **
Disordered thresholds	No	No	No	No	No
Number of items	-	48	41	7	32
Person separation index	>2.0	4.01	3.64	2.75	3.54
Person reliability	> 0.8	0.94	0.93	0.88	0.93
PCA, variance by 1st factor	>50%	59.1%	58.7%	69.8%	59.9%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	**5.8,** 5% (7 items on concerns about the disease progression loaded > 0.4)	**4.1**, 4.2% (5 items on concerns about disease progression loaded > 0.4)	1.7, **7.5%**	**4.2**, **5.3%**
PCA, % raw variance explained by items	-	16.4%	15.4%	22.7%	13.3%
Item fit (infit MnSq)	< 1.5	**HC 29 (2.05)** **HC 30 (2.06)** **HC 38 (2.00)** **HC 45 (1.90)** **HC 31 (1.72)** **HC 36 (1.64)** **HC 16 (1.70)** **HC 34 (1.56)** **HC 41 (1.52)**	**HC 29 (2.19) ‡** **HC 30 (1.98) ‡** **HC 38 (1.84) ‡** **HC 45 (1. 82) ‡** **HC 31 (1.71) ‡** **HC 44 (1.58) ‡** **HC 16 (1.64) ‡** **HC 36 (1.62) ‡** **HC 11 (1.62) ‡** **HC 41 (1.61)**	None	**HC 39 (1.60) #**
Item fit (outfit MnSq)	< 1.5	**HC 29 (2.61)** **HC 30 (2.13)** **HC 38 (2.05)** **HC 45 (1.83)** **HC 31 (1.81)** **HC 36 (1.72)** **HC 34 (1.55)**	**HC 29 (3.48)** **HC 30 (2.05)** **HC 38 (1.84)** **HC 45 (1.77)** **HC 31 (1.79)** **HC 44 (1.65)** **HC 36 (1.64)** **HC 41 (1.64)** **HC 34 (1.57)** **HC 11 (1.53)**	None	None

			HC 41 (1.64)		
LID ‖	> 0.3	38 pairs, 3.3%	23 pairs, 2.8%	None	17 pairs, 3.4%
DIF**	<1.0 logits and p<0.05	**BEVA: HC 29 (1.44, p > 0.05) HC 38 (1.30, p < 0.05) HC 41 (1.04, p < 0.001)**	No DIF for age and gender	None	**BE VA: HC 41(1.81, p < 0.0001)**
Measurement range		2.51	2.49	1.04	2.17
Targeting, difference between person & item means	<1.0 logits	0.38	0.49	-0.43	0.55

HC 11 = Having accidents (motor vehicle related); HC 16 = Delay in getting a diagnosis; HC 29 = Losing your driver's license; HC 30 = The way you are treated by your eye care practitioner; HC 31 = How well your eye treatment is working; HC 34 = Not getting enough information or explanation from medical staff; HC 36 = Passing eye condition onto your children; HC 38 = Starting a family or having more children; HC 41 = Putting other people in danger by driving; HC 44 = The way people react to you; HC 45 = Becoming separated from the person you are with.

‡HC 11 had poor discrimination (0.57); HC 16 had poor discrimination (0.88); HC 29 had a very poor discrimination (0.64); HC 30 had poor discrimination (0.69); HC 31 had poor discrimination (0.88); HC 36 had poor discrimination (0.52); HC 38 had poor discrimination (0.39); HC 44 had poor discrimination (0.71); HC 45 had poor discrimination (0.33) and the item wording was confusing.

***As the 5-item scale showed high agreement with the HC scale, the items were retained within the HC scale.

#After deleting HC 11, HC 16, HC 29, HC 30, HC 31, HC 36, HC 38, HC 44 and HC 45, item 39 showed slight misfit. Item 39 was retained as it was an important item.

‖LID dealt with using the process outlined in the methods. LID item pairs: final iteration: 3/4; 4/5; 3/6; 3/7; 10/15; 4/7; 3/5; 4/6; 21/23; 16/17; 6/7; 2/8; 22/23; 17/29; 13/18; 14/15; 21/22. Percentage refers to proportion of LID pairs of total number of correlated items.

**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups, and ocular comorbidity.

Number of participants responded to the items: HC 11(n = 15); HC 16(n = 5); HC 29(n = 4); HC 30(n = 33); HC 31(n = 3); HC 34(n = 55); HC 36(n = 8); HC 38(n = 1); HC 41(n = 5); HC 44(n = 8); HC 45(n = 4)

Bolded values represent poor fit to the Rasch model.

HC, health concerns; PCA, principal component analysis; MnSq, mean square; DIF, differential item functioning; LID, local item dependency

The fit statistics of items 34 and 41 improved after giving errant responders a weighting of 0, however, 9 items still showed considerable misfit. These 9 items were deleted (11, 16, 29, 30, 31, 36, 38, 44, 45) iteratively one at a time (note Table 5.7). After removing the 9 items, item 39 (vision not improving with glasses) showed slight misfit. This item was retained because the content was relevant to the disease group and it reported by several participants (n = 6). Moreove, the outfit value was within the recommended value of < 1.5 and the infit showed a slight misfit. was an important item. The main HC scale now had 32 items. After fixing the misfit items, the explained variance of the measure improved to 59.9% and the eigenvalue of the first contrast slightly worsened from 4.1 to 4.2, suggesting that the first contrast still had a strength of at least 4 items. PCA metric showed that 5 items related to concerns about accidents were loading together by > 0.4 to the first contrast. The 5-item scale formed a stand-alone measure with excellent precision (PSI = 3.09) and other Rasch-based metric properties (Appendix 7). Post-hoc tests were done to decide whether to retain or separate the 5 items from the remaining items. The dis-attenuated correlation between the two item clusters was high 0.9. The 5-item scale had a high correlation (r = 0.75, 95% CI = 0.69 to 0.80, p < 0.0001) and an excellent agreement (mean bias, -0.1 logit; 95% limits of agreement, -5.1 to 4.8 logit) with the main health concerns scale (Figure 5.9).

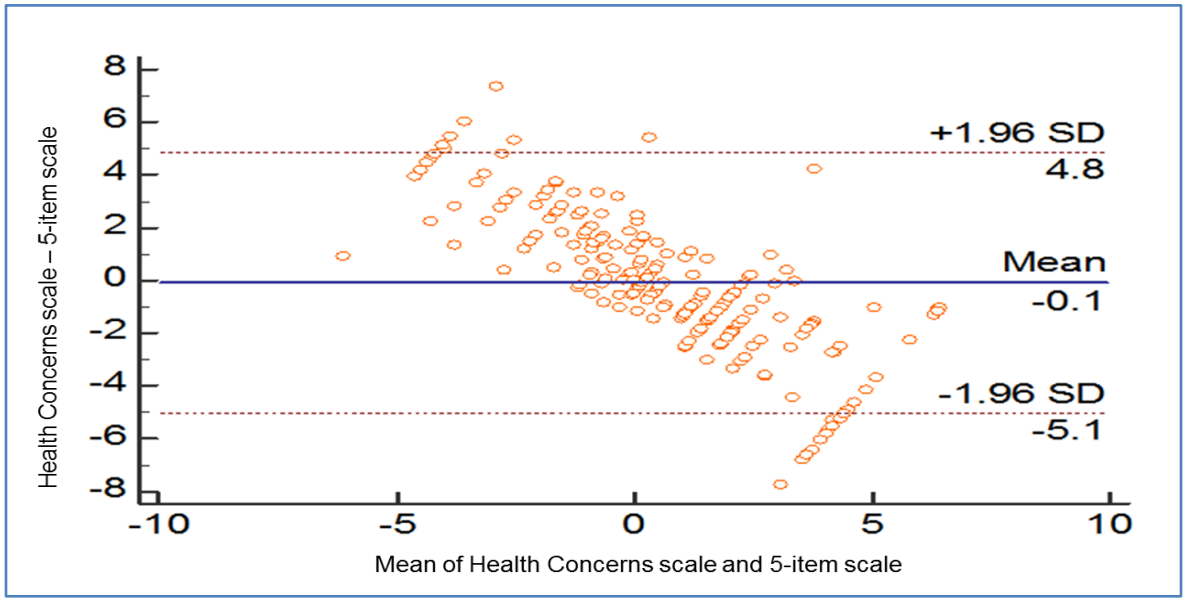

Figure 5.9 Bland and Altman plot showing the limits of agreement (mean difference and 95% confidence interval) between the Health Concerns scale and the 5-item scale

Results of the post-hoc tests suggest that the 5-item scale was a secondary trait within the main scale and not a separate measure. Moreover, the 5-item scale did not form a meaningful construct and for all the reasons the 5-item scale was retained within the main health concerns scale.

The 32-item health concerns scale showed 3 misfitting items (41, 34 & 39). The misfit of the items 34 and 41 was resolved by diagnosing misfit through unpredictable individual responses and giving errant responders a weighting of 0. Item 39, however, still showed some misfit, but was retained as it was considered an important item. When assessing DIF for best BEVA, item 41 showed a contrast difference of 1.81 logit, indicating that people with vision of 6/60 or better reported more concerns than people with visual acuity worse than 6/60.

The main 32-item health concerns scale was renamed as general health concerns and the 7-item scale was named concerns about the disease progression. The response categories of the general health concerns and the concerns about the disease progresion scales were ordered (Figure 5.10).

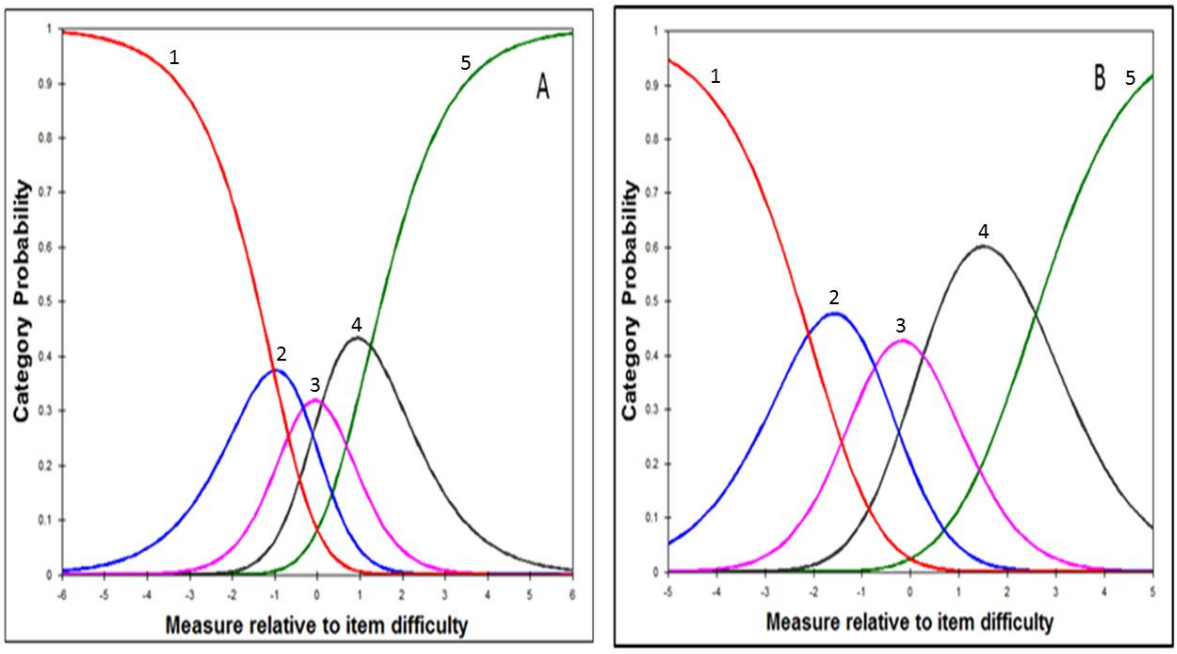

Figure 5.10 Category probability curves showing ordered thresholds for the five-response categories for the (A) General Health Concerns scale and the (B) Concerns about the Disease Progression scale.

5.5.7 Activity limitation domain

The 86-item activity limitation scale demonstrated excellent precision (PSI = 7.56) (Table 5.8). Although, the explained variance of the measure was 72.1%, the first contrast (i.e. second dimension) had an eigenvalue of 10.2, which indicated that it had a strength of more than 10 items. Fifteen items on reading loaded to the first contrast by more than > 0.4. The 15 reading items formed a stand-alone unidimensional scale with an excellent precision (PSI = 3.91) and demonstrated other promising Rasch-based metric properties (Table 5.9).

Table 5.8. Psychometric properties of the Activity Limitation domain

Parameters	**Rasch model expectations**	**All items**	**First iteration †**	**Second iteration ‡**	**Final iteration ٩**
Disordered thresholds	No	No	No	No	No
No. of items	-	86	71	62	47
Person separation index	>2.0	7.56	7.02	6.65	5. 61
Person reliability	> 0.8	0.98	0.98	0.98	0.97
PCA, variance by 1st factor	>50%	72.1%	72.3%	70.8%	70.5%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	**10.2, 3.3%** (15 reading items loaded > 0.4)	**8.07**, 3.1% (9 items related to driving loaded > 0.4)	**6.2,** 2.9% (11 items related to lighting loaded > 0.4)	**4.6**, 2.9%
PCA, % raw variance explained by items		29.2%	31.3%	28.8%	22.9%
Item fit (infit MnSq)	< 1.5	**AL 78 (2.58)** **AL 50 (1.74)** **AL 76 (2.23)** **AL 56 (1.58)** **AL 75 (2.13)** **AL 67 (1.97)** **AL 77 (1.88)** **AL 82 (1.86)** **AL 84 (1.82)** **AL 83 (1.54)** **AL 79 (1.53)**	**AL 78 (2.37)** **AL 50 (1.67)** **AL 76 (2.08)** **AL75 (1.89)** **AL 82 (1.79)** **AL 67 (1.78)** **AL 77 (1.73)** **AL 84 (1.64)**	**AL 76 (2.20)** **AL 75 (2.12)** **AL 50 (1.63)** **AL 67 (1.86)** **AL 77 (1.83)**	**AL 65 (1.53) #**
Item fit (outfit MnSq)	< 1.5	**AL 31 (9.19)** **AL 78 (1.94)** **AL 50 (2.51)** **AL 76 (2.28)** **AL 56 (2.14)** **AL 75 (1.64)** **AL 67 (1.82)** **AL 77 (1.84)**	**AL 31 (7.77)** **AL 78 (1.61)** **AL 50 (2.16)** **AL 56 (1.84)** **AL 67 (1.54)** **AL 6 (1.77)** **AL 77 (1.58)**	**AL 31 (5.13)** **AL76 (2.03)** **AL 75 (1.70)** **AL 50 (2.07)** **AL 67 (1.54)** **AL 77 (1.64)** **AL 56 (1.71)** **AL 6 91.53)**	

		AL 6 (1.76) **AL 49 (1.68)** **AL 52 (1.59)** **AL 55 (1.55)**			
LIDǁ	> 0.3	188 pairs, 5.1%	112 pairs, 4.5%	65 pairs, 3.4%	34 pairs, 3.1%
DIF**	<1.0 logits and p<0.05	**BEVA:** **AL 3 (- 1.00, p < 0.0001)** **AL 6 (1.07, p < 0.001)** **AL 7 (- 1.75, p < 0.05)** **AL 50 (1.36, p < 0.0001)** **AL 78 (- 2.16, p > 0.05)** **AL 79 (- 2.03, p < 0.05)** **AL 80 (- 1.77, p < 0.05)** **AL 82 (- 1.10, p < 0.05)** **AL 83 (- 1.07, p > 0.05)** **AL 84 (- 2.18, p < 0.05)** **AL 85 (- 1.31, p > 0.05)** **AL 86 (- 2.18, p < 0.05)**	**BEVA:** **AL 50 (1.28, p < 0.0001)** **AL 78 (-2.23, p > 0.05)** **AL 79 (-2.06, p < 0.05)** **AL 80 (-1.83, p < 0.05)** **AL 82 (-1.16, p < 0.05)** **AL 83 (-1.06, p > 0.05)** **AL 84 (-2.18, p < 0.05)** **AL 85 (-1.33, p > 0.05)** **AL 86 (-2.19, p < 0.05)** **Disease group:** **AL 68 (-1.21, p < 0.0001)**	**BEVA:** **AL 46 (-1.06, p < 0.05)** **AL 50 (1.24, p < 0.0001)** **Disease group:** **AL 50 (1.04, p < 0.0001)** **AL 68 (-1.12, p < 0.0001)** **AL 76 (1.76, p < 0.0001)** **AL 77 (1.20, p < 0.0001)**	**Disease group:** **AL 46 (-1.04, p > 0.05)** **AL 68 (-1.32, p < 0.0001)**
Measurement range			5.21	4.64	4.41
Targeting, difference between person & item means	<1.0 logits	-.06	.0	0.26	0.66

AL 3 = Reading a large print book; AL 6 = Reading in dim light conditions; AL 7 = Reading musical notes; AL 31 = Pouring a drink; AL 49 = Seeing in poorly lit surroundings; AL 50 = Seeing at night; AL 52 = Seeing in bright sunlight; AL 55 = Adjusting to bright light after the lighting has been rather dim; AL 56 = Adjusting to dark indoor lighting after being in bright light; AL 67 = Playing blind sports, e.g. blind cricket, blind tennis; AL 75 = Riding a bike in the daytime; AL 76 = Riding a bike in the dark (but with a flash light/bicycle light/headlight); AL 77 = Riding a bike in twilight or more than sufficient street light; AL 78 = Riding motorcycle/moped; AL 79 = Driving during the day; AL 80 = Driving in unfamiliar areas; AL 82 = Noticing when the car in front of you is speeding up or slowing down; AL 83 = Driving towards oncoming headlights; AL 84 = Changing lanes in traffic; AL 85 = Driving at dusk or dawn; AL 86 = Seeing road markings clearly when driving.

†After removing reading items

‡After removing the driving items

ǂ After removing the lighting items

#After deleting items 67, 75, 76 and 77, the misfit of 3 items were resolved by diagnosing misfit through unpredictable individual responses and giving errant

responders a weighting of 0.
‖LID dealt with using the process outlined in the methods. LID item pairs: Final iteration: 3/5; 4/5; 39/40; ¾; 37/38; 7/8; 45/46; 10/12; 35/37; 7/14; 35/38; 8/14; 15/20; 6/8; 6/7; 26/27; 10/11; 6/14; 27/34; 31/33; 15/16; 16/43; 1/5; 25/26; 11/13; 19/13; 11/12; 21/26; 26/34; 17/22; 20/40; 9/25; 3/36; 14/45. Percentage refers to proportion of LID pairs of total number of correlated items.
**DIF was assessed for age, gender, best eye visual acuity (BCVA), disease groups, and ocular comorbidity.
Number of participants responded to the items: AL 3(n = 8); AL 6(n = 1); AL 7(n = 1); AL 31 (n = 0), this item was extracted from the existing questionnaire; AL 49(n = 15); AL 50(n = 55); AL 52(n = 9); AL 55(n = 1); AL 56(n = 3); AL 67(n = 5); AL 75(n = 10); AL 76(n = 0); AL 77(n = 0); AL 78(n = 3); AL 79(n = 42); AL 80(n = 5); AL 82(n = 2); Al 83(n = 0); AL 84(n = 0); AL 86(n = 0). Items 76, 77, 83, 84 and 86 were extracted from existing instuments and not from interviews.
Bolded values represent poor fit to the Rasch model.
AL, activity limitation; PCA, principal component analysis; MnSq, mean square; DIF, differential item functioning; LID, local item dependency

Table 5.9. Rasch based psychometric properties of Reading, Driving and Lighting scales

Parameters	Reading	Driving	Lighting
Number of items	15	8	11
Response categories ordering	Ordered	Ordered	Ordered
Precision (PSI)	3.91	2.72	3.43
Item infit MNSQ > 1.5	0	0	1
Item outfit MNSQ > 1.5	0	0	1
PCA analysis % variance explained by measure	78.1%	83.5%	71%
PCA analysis eigenvalue 1st contrast	2.3	2.1	2.2
Items loaded > 0.4 to 1st contrast	-	-	-
Targeting	-.75	-3.96	- 1.45
DIF by age, gender	None	Gender: AL 84 (-1.35, $p < 0.05$) Ocular co-morbidity AL 84 (1.45, $p < 0.05$)	None

PSI, person separation index; MNSQ, mean square; PCA, principal component analysis; DIF, differential item functioning; AL, activity limitation

Post-hoc tests were done to decide whether to separate or retain the reading scale from the main activity limitation scale. Dis-attenuated correlation between the suspect item cluster and the main Rasch cluster was high 0.9. Bland and Altman test showed that the 15-item reading scale had a low correlation ($r = 0.38$, 95% CI = 0.26 to 0.48, $p < 0.0001$), but a moderate agreement (mean bias, 0.7 logits; 95% limits of agreement , -5.7 to 7 logit) with the activity limitation scale (Figure 5.11).

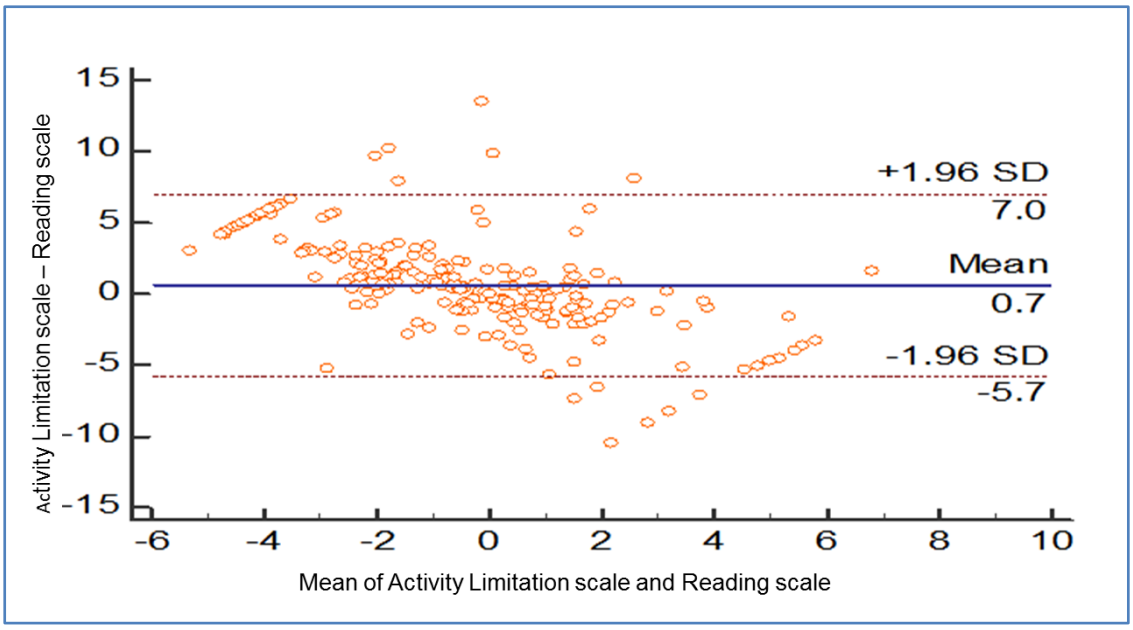

Figure 5.11 Bland and Altman plot showing the limits of agreement (mean difference and 95% confidence interval) between the Activity Limitation scale and the Reading scale

Results of the post-hoc tests suggest that the reading scale is part of the main activity limitation scale. However, it was decided to separate the reading items from the remaining items for the following reasons: removal of the reading items from the main scale improved the eigenvalue of the new first contrast from 10.2 to 8.07 and the 15 items formed a meaningful construct (i.e. reading). The removal of the 15 reading items slightly reduced the precision of the remaining 71-item activity limitation scale (PSI = 7.02) (Table 5.8). The unexplained variance of the new first contrast was dropped to 8.07. The first contrast still had a strength of at least 8 items. PCA analysis showed that 9 items related to driving loaded together by > 0.4 to the first contrast. The 9 driving items formed a stand-alone unidimensional scale with borderline precision (PSI = 1.95) (Table 5.9). However, the response categories were disordered (Figure 5.12) and 3 items (83, 78, & 82) showed misfit. More than two-thirds of the participants reported that they were unable to drive due to their visual loss (Table 5.10).

Table 5.10 Summary of category structure

Category label score	Observed count	Observed count %	Andrich threshold
1 (Unable to do because of my vision)	917	69	None
2 (A lot)	54	4	-1.15
3 (Quite a bit)	43	3	-.39
4 (A little)	115	9	-.41
5 (None)	194	15	1.94

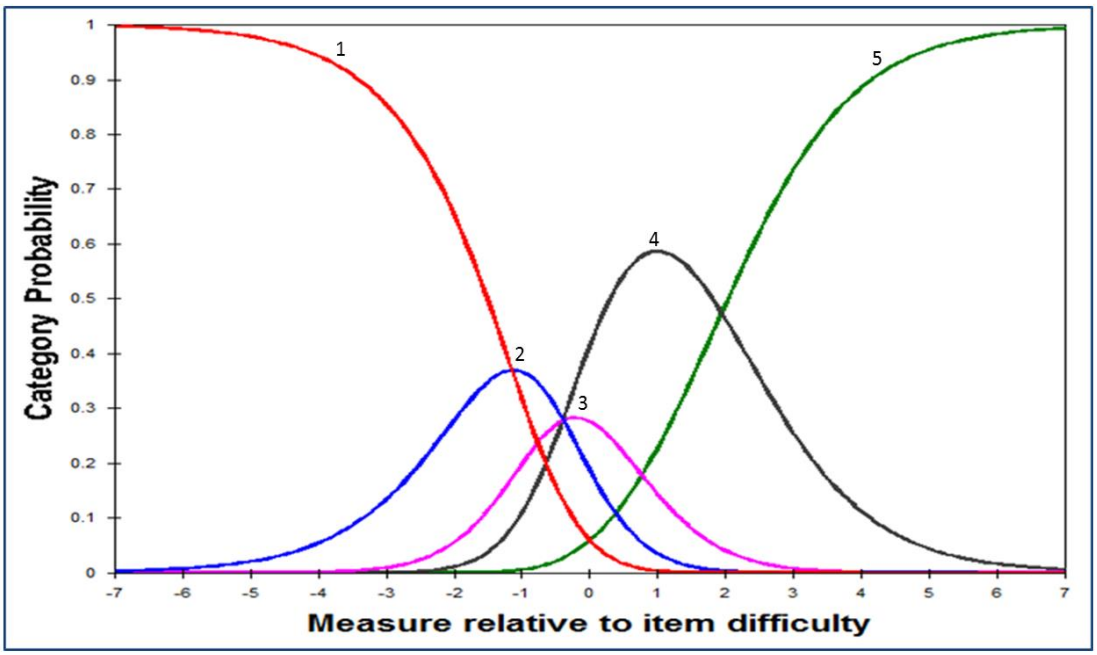

Figure 5.12 Category probability curves showing disordered thresholds for the five - response categories for the 9-item Drivng scale. The peak of the middle category 3 is submerged and disordered. Moreover, the curve 2 is intersecting curve 4 before intersecting curve 3

The fit statistics of item 82 and 83 improved after giving the errant responders a weighting of 0, but item 78 still showed misfit. Therefore, item 78 ('riding motorcycle/moped') was deleted as its content was different to the other driving items, which were basically on driving four wheel vehicles (i.e. cars). After fixing the misfitting items, the fit statistics of the remaining items improved and the response categories showed ordering of the thresholds. The final driving scale had 8 items. Post-hoc tests were done to decide whether to separate or to retain the driving items from the main activity limitation scale. The dis-attenuated correlation between the two measures (i.e. driving as suspect cluster and remaining 71 activity limitation items) was 0.9. Bland and Altman test showed that the 8-item driving scale had a moderate correlation (r =

0.58, 95% CI = 0.49 to 0.66, p <0.000) and a very low agreement (mean bias, 3 logit; 95% limits of agreement , -4.2 to 10.3 logit) with the main activity limitation scale (Figure 5.13). Results of the post-hoc tests suggest that the 8-item driving scale forms a separate dimension. It was decided to separate the 8 items into a scale for the following reasons: removal of the 8 items improved the unexplained variance of the first contrast

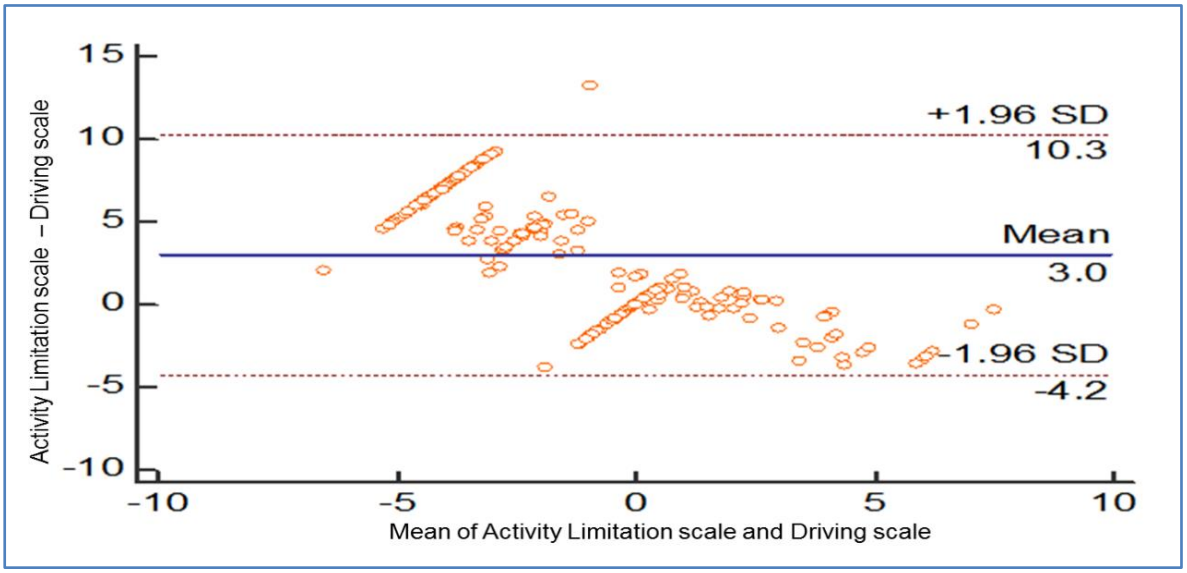

Figure 5.13 Bland and Altman plot showing the limits of agreement (mean difference and 95% confidence interval) between the Activity Limitation scale and the Driving scale

of the remaining activity limitation scale from 8.07 to 6.2, the 8-item scale demonstrated low agreement with the main activity limitation scale and the overall the items formed a meaningful construct.

The removal of the 9 driving items reduced the precision of the remaining 62-item activity limitation (PSI = 6.65) (Table 5.8). However, the unexplained variance of the first contrast dropped to 6.2 eigenvalues. The first contrast still had a strength of at least 6 items. PCA analysis showed that 8 items related to lighting grouped together with a loading more than > 0.4 to the first contrast. Apart from the 8 lighting items that were grouping together, there were 3 other items related to lighting in the activity limitation scale ('reading in dim light conditions', 'reading street signs at night' and 'reading a menu in a dimly lit restaurant'). These 3 items, however, did not load together with the 8 lighting items, but as the content of these 3 items were fitting into

the lighting items, they were clubbed together and analysed. The lighting scale now had 11 items. The 11 lighting items formed a stand-alone unidimensional scale with excellent precision (PSI = 3.43) and other promising Rasch-based metric properties (Table 5.9). Post-hoc tests were done to decide whether to separate or retain the lighting items from the main activity limitation scale. The dis-attenuated correlation between the two measures (i.e. the 8-item suspect item cluster and the main Rasch measure) was 0.8. The 11-item lighting scale had a high correlation (r = 0.8, 95% CI = 0.75 to 0.8, p<0.0001) and a very low agreement (mean bias, 2 logits; 95% limits of agreement, -1 to 5.1 logit) (Figure 5.14) with main activity limitation scale. The results of the disattenuated correlation and the pearson correlation suggest that the two scales are measuring the same thing. However, the limits of agreement suggest that the two scales are measuring different things.

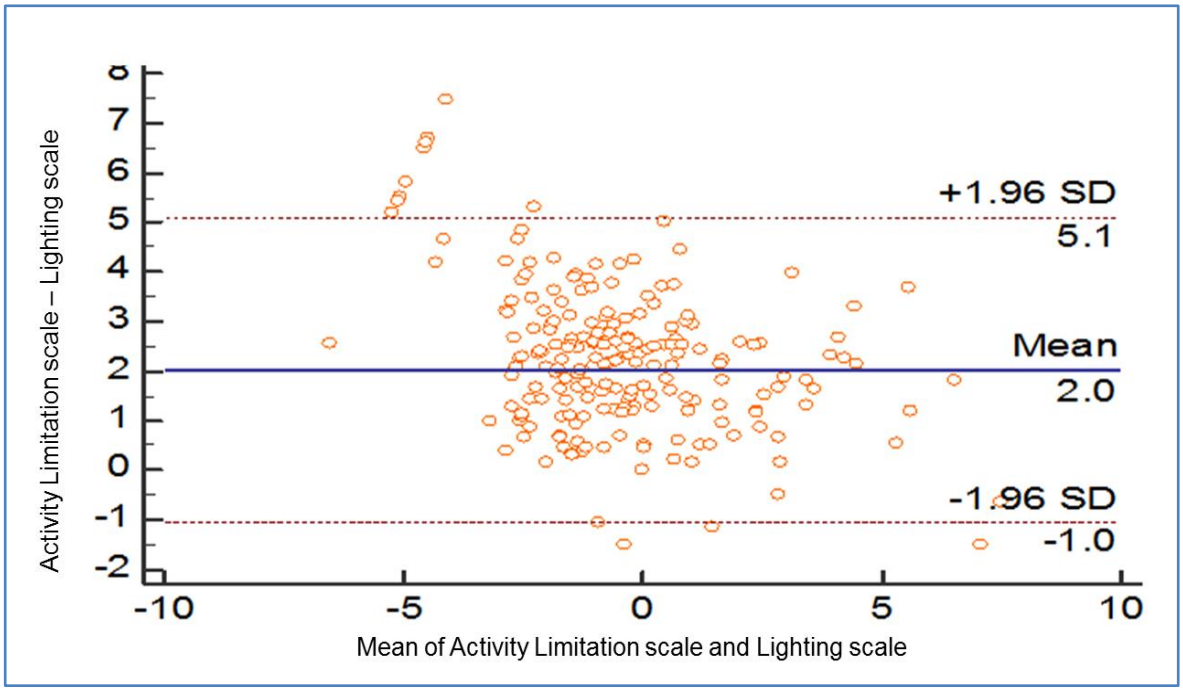

Figure 5.14 Bland and Altman plot showing the limits of agreement between (mean difference and 95% confidence interval) the Activity Limitation scale and the Lighting scale

Although the results of the post-hoc tests were inconclusive, it was decided to separate the 11-item lighting scale from the main activity limitation scale for the following reasons: removal of the 11 items improved the eigenvalue of the new first contrast from 6.2 to 4.8, it showed very poor agreement with the main activity limitation scale

and the 11 items formed a meaningful construct.

The removal of the 11 items further reduced the precision of the remaining 51-item activity limitation scale (PSI = 5.48) (Table 5.8). However, the unexplained variance of the new first contrast dropped to 4.8, thus moving closer to Rasch model criterion of unidimensionality. The first contrast still had a strength of at least 5 items. PCA analysis showed that 7 items loaded together by > 0.4 to the first contrast. The dis-attenuated correlation between the suspect item cluster and the main Rasch item cluster was high 0.9. Although some of the items within this construct had similar meaning, the item cluster did not form a meaningful construct to form a separate scale and hence, it was decided to retain the 7 items within the remaining activity limitation scale. The activity limitation scale now had 51 items.

In the 51-item activity limitation scale, 7 items (31, 76, 75, 77, 67, 65 & 40) showed misfit. Fixing the person responses of these misfitting items improved the fit statistics of 3 items (31, 40, and 65), but 4 items (67, 75, 76, and, 77) still showed misfit. After deleting the 4 misfitting items, the precision and the fit statistics of the remaining 47-item scale improved. The eigenvalue of the first contrast also dropped to 4.6 (Table 5.8). The response categories of the final 47-item activity limitation scale and the new scales (reading, driving, and lighting) were ordered (Figure 5.15). Only 2 items (2.3%) had DIF. Item 46 (DIF contrast = -1.04 logit) and 68 (DIF contrast = -1.32 logit) showed DIF by disease group, indicating that people with other hereditary retinal diseases reported these items as more difficult than the people with RP.

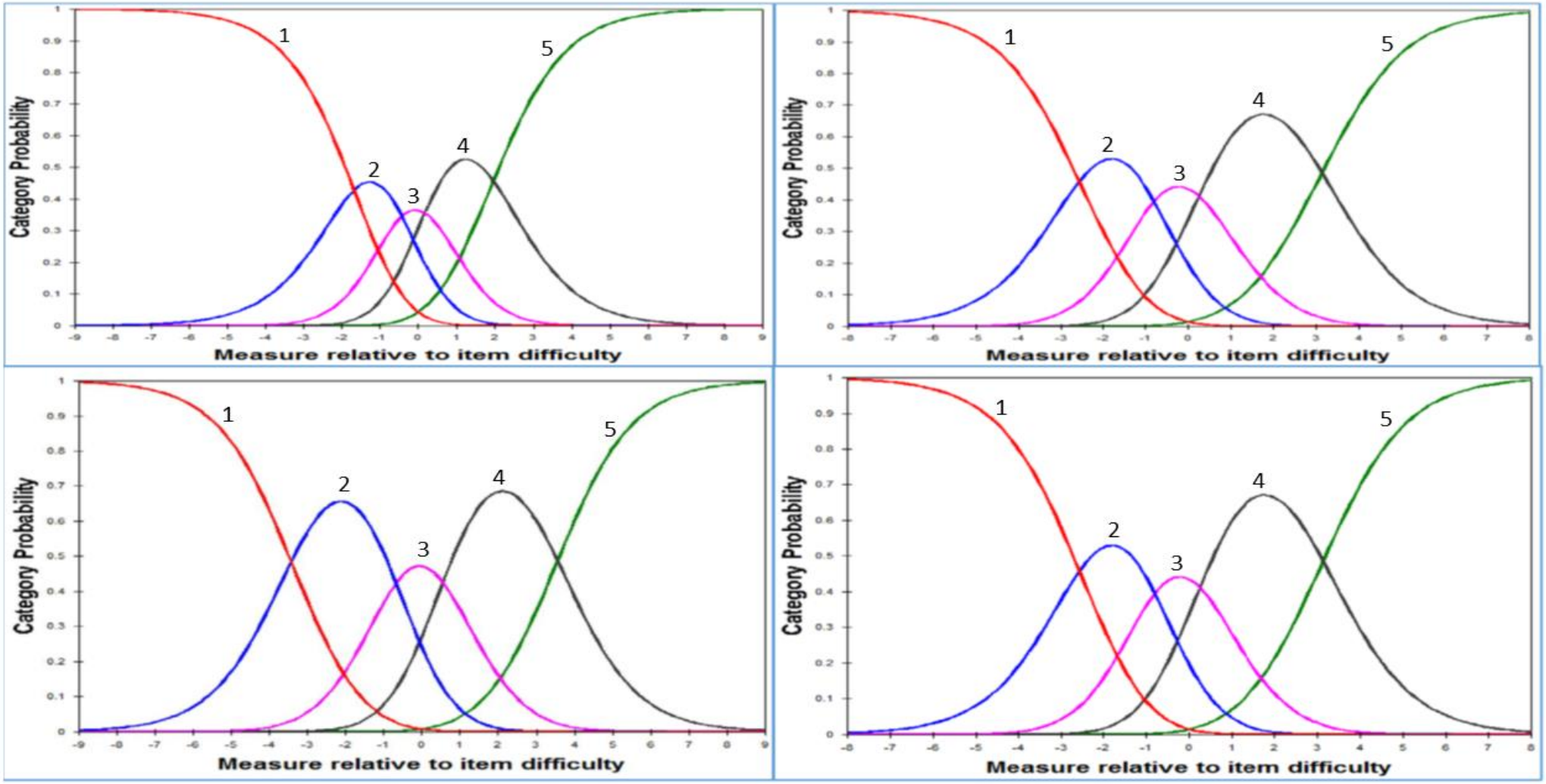

Figure 5.15 Category probability curves showing ordered thresholds for the five response categories for the (A) main Activity limitation (AL) scale, (B) Reading, (C) Lighting, and (D) Driving scales

5.5.8 Symptoms domains

The HRD module had three symptom domains, namely visual symptoms, ocular comfort symptoms and general symptoms. Each symptom domain had three scales: frequency, severity and bothersome. This categorisation of the symptom domain into visual, ocular comfort and general was based on the other disease modules of the Eye-tem bank project.(45) The visual symptoms domain had 20 items, the ocular comfort symptoms domain had 5 items and the general symptoms domain had 6 items.

5.5.8.1 *Visual Symptoms Frequency domain*

The visual symptoms frequency scale demonstrated good precision (PSI = 2.48) and targeting (Table 5.11).

Table 5.11. Psychometric properties of the Visual Symptoms Frequency domain

Parameters	**Rasch model expectations**	**First iteration**	**Final iteration**
Disordered thresholds	No	Yes	Yes
Number of items	-	20	20
Person separation index	>2.0	2.48	2.43
Person reliability	> 0.8	0.86	0.85
PCA, variance by 1st factor	>50%	**48.5%**	51.3%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	2.8, **7.2%**	2.4, **6.3%**
PCA, % raw variance explained by items		30.2%	30.6%
Item fit (infit MnSq)	< 1.5	**VSF 19 (1.95) ‡**	**VSF 19 (1.80) ŧ**
Item fit (outfit MnSq)	< 1.5	**VSF 13 (2.05) ‡** **VSF 19 (1.99) ‡** **VSF 4 (1.54) ‡**	**VSF 19 (1.71)**
LID ‖	> 0.3	6 pairs, 3.1%	6 pairs, 3.1%
DIF**	<1.0 logits and p<0.05		**BEVA:** **VSF 16 (1.09, p < 0.05)** **Disease groups:** **VSF 5 (-1.19, p < 0.001)** **VSF 6 (1.53, p < 0.001)** **VSF 19 (1.99, p < 0.0001)**
Measurement range		3.08	3.29
Targeting, difference between person & item means	<1.0 logits	0.03	-.01

VSF 4 = Floaters in your vision; VSF 5 = Distorted vision (lines you know are straight appear curved or distorted); VSF 6 = Loss of your peripheral vision; VSF 13 = Difficulty distinguishing colours; VSF 16 = Double vision; VSF 19 = Tunnel vision.

‡VSF 4 had poor discrimination (0.44); VSF 13 had poor discrimination (0.42); VSF 19 had poor discrimination (0.41)

‖LID dealt with using the process outlined in the methods. LID item pairs: Final iteration: 6/19; 6/7; 4/9; 5/9; 4/10; 7/19. Percentage refers to proportion of LID pairs of total number of correlated items.

ŧItem 19 was retained as it was an important item.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups, and ocular comorbidity.
Number of participants responded to the items: VSF 4(n = 1); VSF 5(n = 2); VSF 6(n = 46); VSF 13(n = 28); VSF 16(n = 1); VSF 19(n = 1)
Bolded values represent poor fit to the Rasch model.
VSF, visual symptoms frequency; PCA, principal component analysis; MnSq, mean square; DIF, differential item functioning; LID, local item dependency

The explained variance of the measure was 48.5% and the eigenvalue of the first contrast was 2.8. Of the 20 items, 17 items showed good fit and 3 items (13, 19 & 4) showed misfit. The fit statistics of item 13 and 4 showed improvement after giving the errant responders a weighting of 0, but item 19 still showed misfit (in-fit = 1.86; outfit = 1.76). Item 19 was retained as it was considered an important item. The response categories of the 20-item visual symptoms frequency scale were disordered (Figure 5.16). As the visual symptoms frequency scale had only four categories it was decided not to collapse the response categories as it will reduce the response categories to 3 and compromise the functioning of the CAT system.

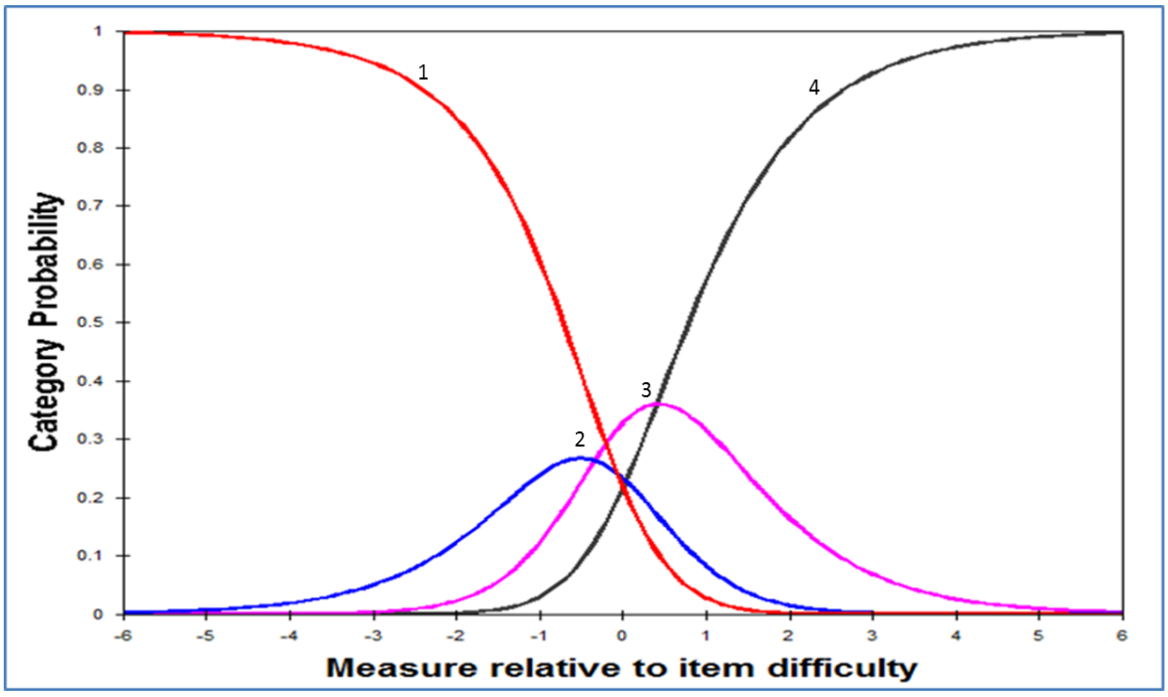

Figure 5.16 Category probability curves showing disordered thresholds for the four - response categories for the Visual Symptoms Frequency scale.

When assessing the DIF for BEVA, item 16 (seeing double vision) had a contrast difference of 1.09 logit, indicating that people with visual acuity 6/60 or better vision found this item more difficult than people with visual acuity worse than 6/60.When assessing the DIF for RP

and other hereditary eye diseases, items 5,6 and 19 had contrast difference of -1.19, 1.53 & 1.99 logit respectively, indicating that people with other hereditary retinal diseases found item 5 more difficult and people with RP found items 6 and 19 more difficult.

5.5.8.2 *Visual Symptoms Severity domain*

This scale demonstrated good precision (PSI = 2.66) and targeting (Table 5.12).

Table 5.12. Psychometric properties of the Visual Symptoms Severity domain

Parameters	**Rasch model expectations**	**First iteration**	**Final iteration**
Disordered thresholds	No	No	No
Number of items	-	20	20
Person separation index	>2.0	2.66	2.66
Person reliability	> 0.8	0.88	0.88
PCA, variance by 1st factor	>50%	51.1%	51.1%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	2.9, **7.2%**	2.9, **7.2%**
PCA, % raw variance explained by items	-	30.8%	30.6%
Item fit (infit MnSq)	< 1.5	**VSS 19 (1.95) ‡**	**VSS 19 (1.89) †**
Item fit (outfit MnSq)	< 1.5	**VSS 13 (2.10) ‡** **VSS 19 (1.98) ‡**	**VSS 19 (1.81) †**
LID ‖	> 0.3	4 pairs, 2.1%	4 pairs, 2. 1%
DIF**	<1.0 logits and p<0.05		**BE VA:** **VSS 2 (-1.41, p < 0.001)** **Disease group:** **VSS 5 (- 1.20, p < 0.0001)** **VSS 6 (1.52, P <0.0001)** **VSS 19 (1.75, p < 0.0001)**
Measurement range		3.33	3.42
Targeting, difference between person & item means	<1.0 logits	0.14	0.11

VSS 2 = Poor vision in one or both eyes; VSS 5 = Distorted vision; VSS 6 = Loss of your peripheral vision; VSS 13 = Difficulty distinguishing colours; VSS 19 = Tunnel vision.
‡VSS 13 had poor discrimination (0.38); VSS 19 had poor discrimination (0.20)
†Item 19 was retained as it was an important item
‖LIDdealt with using the process outlined in the methods. LID item pairs: Final iteration: 6/19; 6/7; 4/10; 7/19; Percentage refers to proportion of LID pairs of total number of correlated items.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups, and ocular comorbidity. Number of participants responded to the items: VSS 2(n = 45); VSS 5(n = 2); VSS 6(n = 46); VSS 13(n = 28); VSS 19(n = 1)
Bolded values represent poor fit to the Rasch model.
VSS, visual symptoms severity; PCA, principal component analysis; MnSq, mean square; DIF, differential item functioning; LID, local item dependency

The explained variance of the measure was 51% and the eigenvalue of the first contrast

was 2.9. Of the 20 items, 2 items (13 & 19) showed misfit and 18 items showed good fit. Item 13 showed improvement in the fit statistics after giving the errant responders a weighting of 0, but item 19 still showed misfit. Item 19 was considered an important item and was retained within the domain. The response categories of the 20-item visual symptoms severity scale were ordered (Figure 5.17). When assessing the DIF for BEVA, item 2 had a contrast difference of -1.41, indicating that people with visual acuity worse than 6/60 found item 2 more difficult than people with visual acuity 6/60 or better. When assessing the DIF for RP and other hereditary retinal diseases, items 5, 6 & 19 showed contrast differences of -1.20, 1.52 & 1,75 logit respectively, indicating that people with other hereditary retinal diseases found item 5 more difficult and people with RP reported more of an impact of items 6 and 19.

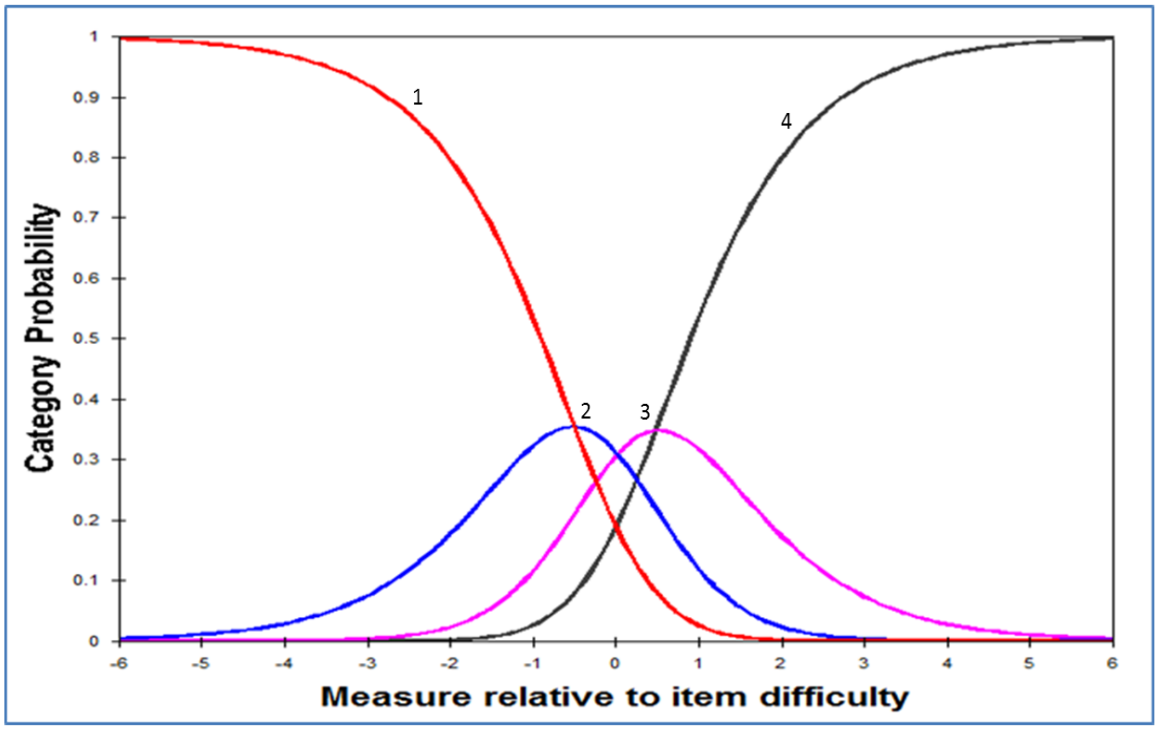

Figure 5.17 Category probability curves showing ordered thresholds for the four-response categories for the Visual Symptoms Severity scale

5.5.8.3 *Visual Symptoms Bothersome domain*

This scale demonstrated good precision (PSI = 2.71) and targeting (Table 5.13). The explained variance of the measure was 53.6% and the eigenvalue of the first contrast was 2.7, indicating that this scale is unidimensional. Of the 20 items, items 19 & 13 showed misfit and the remaining items showed good fit. The fit statistics of item 13 showed improvement

after giving the errant responders a weighting of 0, however, item 19 still showed misfit.

Table 5.13. Psychometric properties of the Visual Symptoms Bothersome domain

Parameters	Rasch model expectations	First iteration	Final iteration
Disordered thresholds	No	No	No
Number of items	-	20	20
Person separation index	>2.0	2.71	2.73
Person reliability	> 0.8	0.88	0.88
PCA, variance by 1st factor	>50%	53.6	53.6
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	2.7, **6.5%**	2.7, **6.4%**
PCA, % raw variance explained by items		30.9%	30.6%
Item fit (infit MnSq)	< 1.5	**VSB 19 (2.02) ‡**	**VSB 19 (1.84) †**
Item fit (outfit MnSq)	< 1.5	**VSB 19 (2.61) ‡** **VSB 13 (2.25) ‡**	**VSB 19 (1.77)**
LID ‖	> 0.3	5 pairs, 2.6%	5 pairs, 2.6%
DIF**	<1.0 logits and p<0.05		**BE VA:** **VSB 16 (1.00, P < 0.05)** **Disease group:** **VSB 5 (-1.04, p < 0.0001)** **VSB 6 (1.65, p < 0.0001)** **VSB 19 (1.79, p < 0001)**
Measurement range		3.34	3.54
Targeting, difference between person & item means	<1.0 logits	0.29	0.30

VSB 5 = Distorted vision; VSB 6 = Loss of your peripheral vision; VSB 13 = Difficulty distinguishing colours; VSB 16 = Double vision; VSB 19 = Tunnel vision.
‡VSB 13 had poor discrimination (0.31); VSB 19 had very poor discrimination (-.05)
†Item 19 was retained as it was an important item
‖LID dealt with using the process outlined in the methods. LID item pairs; Final iteration: 6/19; 4/10; 6/7; 5/9; 2/3. Percentage refers to proportion of LID pairs of total number of correlated items.
**DIF was assessed for age group, gender, best eye visual acuity (BEVA), disease groups, and ocular comorbidity.
Number of participants responded to the items: VSB 5(n = 2); VSB 6(n = 46); VSB 13(n = 28); VSB 16(n = 1); VSB 19(n = 1)
Bolded values represent poor fit to the Rasch model.
VSB, visual symptoms bothersome; PCA, principal component analysis; MnSq, mean square; DIF, differential item functioning; LID, local item dependency

Item 19 was considered important item within the domain and hence, retained. When assessing the DIF for BEVA, item 16 had a contrast difference of 1.00 logit, indicating that people with visual acuity of 6/60 or better reported more of an impact of this item that people with visual acuity worse than 6/60. Items 5, 6 and 19 showed a contrast difference of -1.04, 1.65 and 1.79 logit respectively for RP and other hereditary retinal diseases indicating that

people with RP reported more of an impact of items 6 & 19 and people with other hereditary retinal diseases reported more of an impact of item 5. The response categories of the 20-item visual symptoms bothersome scale were ordered (Figure 5.18).

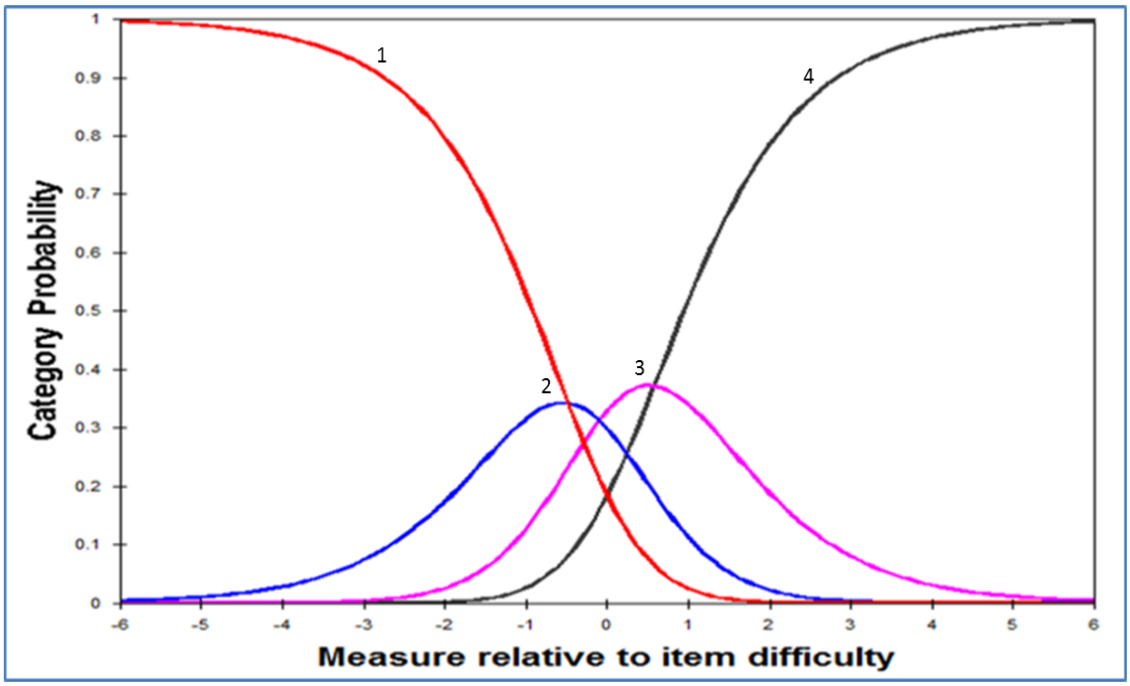

Figure 5.18 Category probability curves showing ordered thresholds for the four- response categories for the Visual Symptoms Bothersome scale

5.5.8.4 *Ocular Comfort Symptoms Frequency domain*

This 5-item scale had borderline precision (PSI = 1.80) and targeting (1.10) (Table 5.14). The explained variance of measure was 55.3% and the eigenvalue of the first contrast was 1.5, indicating that the scale is unidimensional. There were no misfitting items. The response categories of the 5-item ocular comfort symptoms frequency scale were ordered (Figure 5.19). DIF was absent for this scale. These items were not considered further for CAT calibration due to fewer number of items and lower precision.

Table 5.14. Psychometric properties of the Ocular Comfort Symptoms Frequency domain

Parameters	Rasch model expectations	First iteration	Final iteration
Disordered thresholds	No	No	No
Number of items	-	5	5
Person separation index	>2.0	**1.80**	**1.80**
Person reliability	> 0.8	**0.76**	**0.76**
PCA, variance by 1st factor	>50%	55.3%	55.3%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	1.5, **13.6%**	1.5, **13.6%**
PCA, % raw variance explained by items	-	19%	19%
Item fit (infit MnSq)	< 1.5	None	None
Item fit (outfit MnSq)	< 1.5	None	None
LID ‖	> 0.3	None	None
DIF**	<1.0 logits and p<0.05	None	None
Measurement range		1.66	1.66
Targeting, difference between person & item means	<1.0 logits	**1.10**	**1.10**

‖LID dealt with using the process outlined in the methods. LID item pairs: None. Percentage refers to proportion of LID pairs of total number of correlated items.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups and ocular comorbidity.
Bolded values represent poor fit to the Rasch model.
OSF, ocular comfort symptoms frequency; PCA, principal component analysis; MnSq, mean square; DIF, differential item functioning; LID, local item dependency

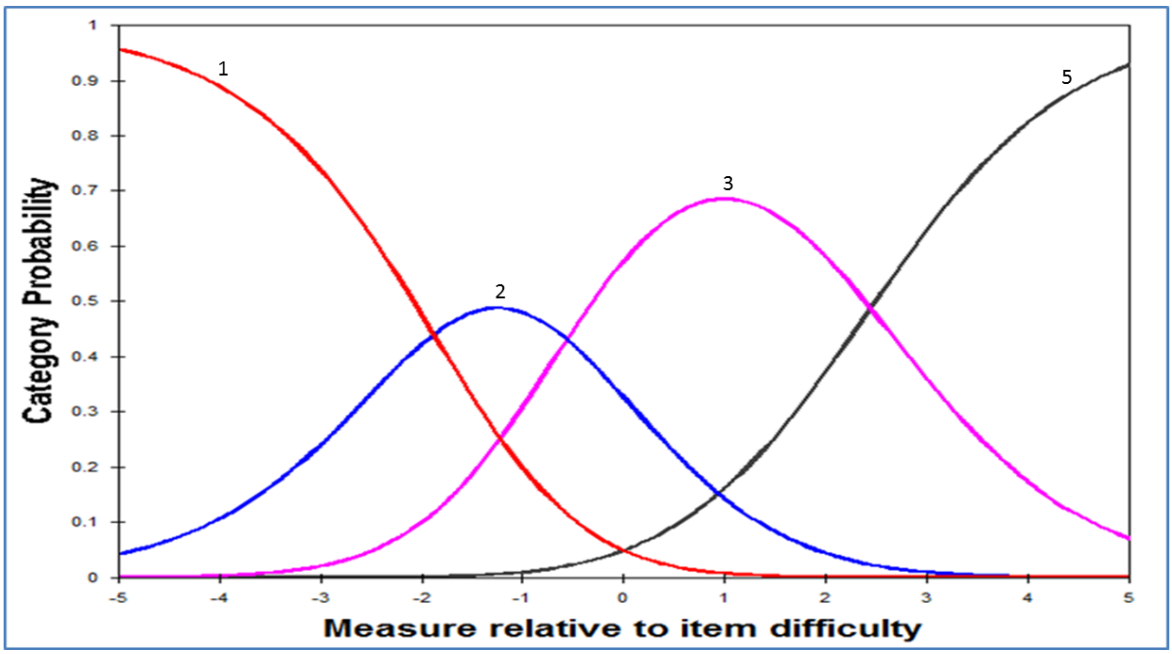

Figure 5.19 Category probability curves showing ordered thresholds for the four-response categories for the Ocular Comfort Symptoms Frequency scale

5.5.8.5 *Ocular Comfort Symptoms Severity scale*

This scale demonstrated borderline precision (PSI = 1.86) and targeting (1.20) (Table 5.15). The explained variance of the measure was 57.4% and the eigenvalue of the first contrast was 1.62 showing that the scale is unidimensional. All the 5 items showed good fit statistics. The response categories were ordered (Figure 5.20) and no items had notable DIF. As this domain had very few items that demonstrated sub-optimal psychometric properties, it was therefore not further tested for CAT simulation.

Table 5.15. Psychometric properties of Ocular Comfort Symptoms Severity domain

Parameters	**Rasch model expectations**	**First iteration**	**Final iteration**
Disordered thresholds	No	No	No
No. of items	-	5	5
Person separation index	>2.0	**1.86**	**1.86**
Person reliability	> 0.8	**0.78**	**0.78**
PCA, variance by 1st factor	>50%	57.4%	57.4%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	1.6, **13.8%**	1.6, **13.8%**
PCA, % raw variance explained by items	-	17.3%	17.3%
Item fit (infit MnSq)	< 1.5	None	None
Item fit (outfit MnSq)	< 1.5	None	None
LID ‖	> 0.3	None	None
DIF**	<1.0 logits and p<0.05	None	None
Measurement range		1.68	1.68
Targeting, difference between person & item means	<1.0 logits	**1.20**	**1.20**

‖LID dealt with using the process outlined in the methods. LID item pairs: None. Percentage refers to proportion of LID pairs of total number of correlated items.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups, and ocular comorbidity. Bolded values represent poor fit to the Rasch model.
OSS, ocular comfort symptoms severity; PCA, principal component analysis; MnSq, mean square; DIF, differential item functioning; LID, local item dependency

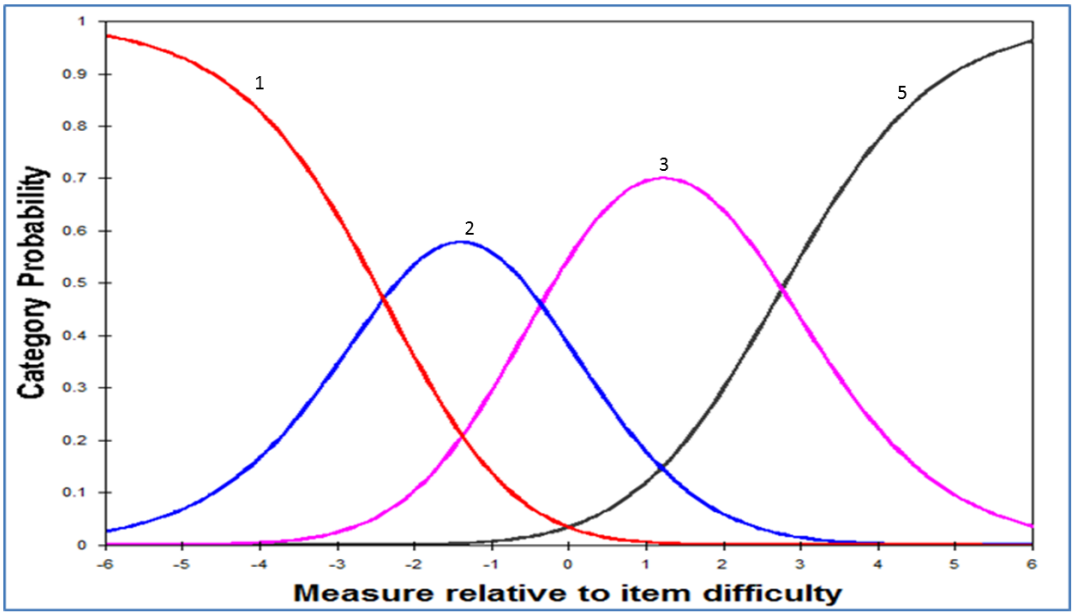

Figure 5.20 Category probability curves showing ordered thresholds for the four- response categories for the Ocular Comfort Symptoms Severity scale

5.5.8.6 *Ocular Comfort Symptoms Bothersome domain*

This scale showed borderline precision (PSI = 1.85) and targeting (1.79) (Table 5.16). The explained variance of the measure was 60.9% and the eigenvalue was 1.5, indicating that the scale is unidimensional. Only one item (item 2) showed misfit. There were no erratic responders for this item. This item was considered important and retained. The response categories were ordered (Figure 5.21) and no items had notable DIF. At this stage due to lower precision and a few number of items (less than 7) , this scale was not considered further for CAT calibration.

Table 5.16. Psychometric properties of the Ocular Comfort Symptoms Bothersome domain

Parameters	Rasch model expectations	First iteration	Final iteration
Disordered thresholds	No	No	No
Number of items	-	5	5
Person separation index	>2.0	**1.85**	**1.85**
Person reliability	> 0.8	**0.77**	**0.77**
PCA, variance by 1st factor	>50%	60.9%	60.9%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	1.5, **12.1%**	1.5, **12.1%**
PCA, % raw variance explained by items	-	18.2%	18.2%
Item fit (infit MnSq)	< 1.5	None	None
Item fit (outfit MnSq)	< 1.5	**OSB 2 (1.57) ‡**	**OSB 2 (1.57) ŧ**
LID ‖	> 0.3	None	None
DIF**	<1.0 logits and p<0.05	None	None
Measurement range		1.72	1.72
Targeting, difference between person & item means	<1.0 logits	**1.79**	**1.79**

OSB 2 = Watery eyes
‡OSB 2 had a poor discrimination (0.59)
ŧItem 2 was retained as it was an important item.
‖LID dealt with using the process outlined in the methods. LID item pairs: None. Percentage refers to proportion of LID pairs of total number of correlated items.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups and ocular comorbidity.
Bolded values represent poor fit to the Rasch model.
Number of participants responded to the items: OSB 2(n = 1)
OSB, ocular comfort symptoms bothersome; PCA, principal component analysis; MnSq, mean square; DIF, differential item functioning; LID, local item dependency

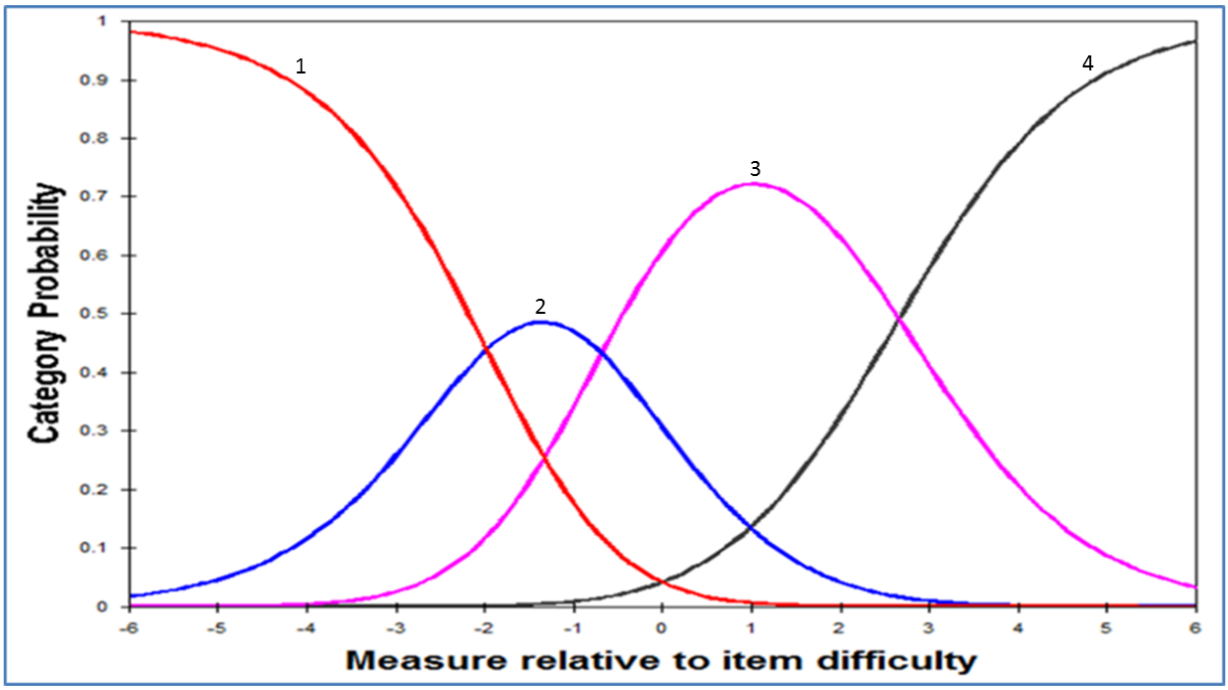

Figure 5.21 Category probability curves showing the ordered thresholds for the four-response categories for the Ocular Comfort Symptoms Bothersome scale

5.5.8.7 *General Symptoms Frequency domain*

This scale demonstrated poor precision (PSI = 1.63) and borderline targeting (1.37) (Table 5.17). The explained variance of the measure was 54.8% and the eigenvalue of the first contrast was 1.62, indicating that the scale is unidimensional. Of the 6 items, only one item (item 6) showed misfit (in-fit = 1.63; outfit = 1.77). After giving the errant responders a weighting of 0, it still showed misfit. However, this item was retained as it was considered an important item. The response categories were ordered (Figure 5.22). The items did not show any notable DIF. This domain was not considered for CAT calibrations due to fewer number of items and poor precision values.

Table 5.17. Psychometric properties of the General Symptoms Frequency domain

Parameters	Rasch model expectations	First iteration	Final iteration
Disordered thresholds	No	No	No
Number of items	-	6	6
Person separation index	>2.0	**1.63**	**1.66**
Person reliability	> 0.8	**0.73**	**0.73**
PCA, variance by 1st factor	>50%	54.8%	54.8%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	1.6, **12.2%**	1.6, **12.2%**
PCA, % raw variance explained by items		24.9%	24.8%
Item fit (infit MnSq)	< 1.5	**GSF 6 (1.62) ‡**	**GSF 6 (1.60) ŧ**
Item fit (outfit MnSq)	< 1.5	**GSF 6 (1.77) ‡**	None
LID ‖	> 0.3	None	None
DIF**	<1.0 logits and p<0.05	None	None
Measurement range		2.39	2.54
Targeting, difference between person & item means	<1.0 logits	**1.37**	**1.35**

GSF 6 = Hallucination/vivid dreams
‡GSF 6 had poor discrimination (0.41)
ŧItem 6 was retained as it was an important item.
‖LID dealt with using the process outlined in the methods. LID item pairs: None. Percentage refers to proportion of LID pairs of total number of correlated items.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups, and ocular comorbidity. Number of participants responded to the items: GSF 6(n = 0). Item 6 was extracted from the existing instruments and not form interviews
Bolded values represent poor fit to the Rasch model.
GSF, general symptoms frequency; PCA, principal component analysis; MnSq, mean square; DIF, differential item functioning; LID, local item dependency

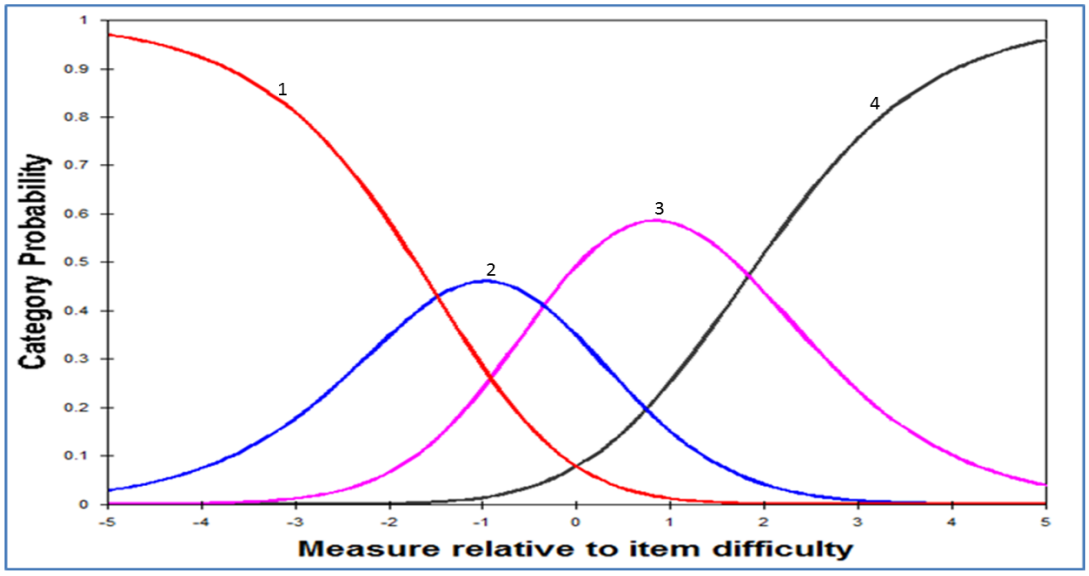

Figure 5.22 Category probability curves showing ordered thresholds for the four- response categories for the General Symptoms Frequency scale

5.5.8.8 *General Symptoms Severity scale*

The scale demonstrated borderline precision (PSI = 1.65) and targeting (1.60) (Table 5.18).

Table 5.18. Psychometric properties of the General Symptoms Severity domain

Parameters	Rasch model expectations	First iteration	Final iteration
Disordered thresholds	No	No	No
Number of items	-	6	6
Person separation index	>2.0	**1.65**	**1.73**
Person reliability	> 0.8	**0.73**	**0.75**
PCA, variance by 1st factor	>50%	54.7%	54.7%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	1.6, **12.3%**	1.6, **12.3%**
PCA, % raw variance explained by items		23.3%	22.9%
Item fit (infit MnSq)	< 1.5	**GSS 6 (1.57) ‡**	None
Item fit (outfit MnSq)	< 1.5	**GSS 6 (1.77) ‡** **GSS 1 (1.51) ‡**	**GSS 1 (1.62) ŧ**
LID ‖	> 0.3	None	None
DIF**	<1.0 logits and p<0.05	None	None
Measurement range		2.24	2.57
Targeting, difference between person & item means	<1.0 logits	**1.60**	**1.64**

GSS 1 =Headaches due to your vision; GSS 6 = Hallucinations/vivid dreams.
‡GSS 1 had poor discrimination (0.52); GSS 6 had poor discrimination (0.50)
ŧItem 1 was retained as it was important item.
‖LID dealt with using the process outlined in the methods. LID item pairs: None. Percentage refers to proportion of LID pairs of total number of correlated items.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups, and ocular comorbidity. Number of participants responded to the items: GSS 1 (n = 4); GSS 6(n = 0). Item 6 was extracted from existing instrument and not form interviews.
Bolded values represent poor fit to the Rasch model.
GSS, general symptoms severity; PCA, principal component analysis; MnSq, mean square; DIF, differential item functioning; LID, local item dependency

The explained variance of the measure was 54.7% and the eigenvalue of the first contrast was 1.6. Item 6 showed misfit. After giving the errant responders a weighting of 0, the fit statistics of item 6 improved, but item 1 showed slight misfit. Item 1 was retained as it was an important item. The response categories were ordered Figure (5.23). None of the items had notable DIF. This domain was not considered for CAT calibrations due to fewer number of items and poor precision.

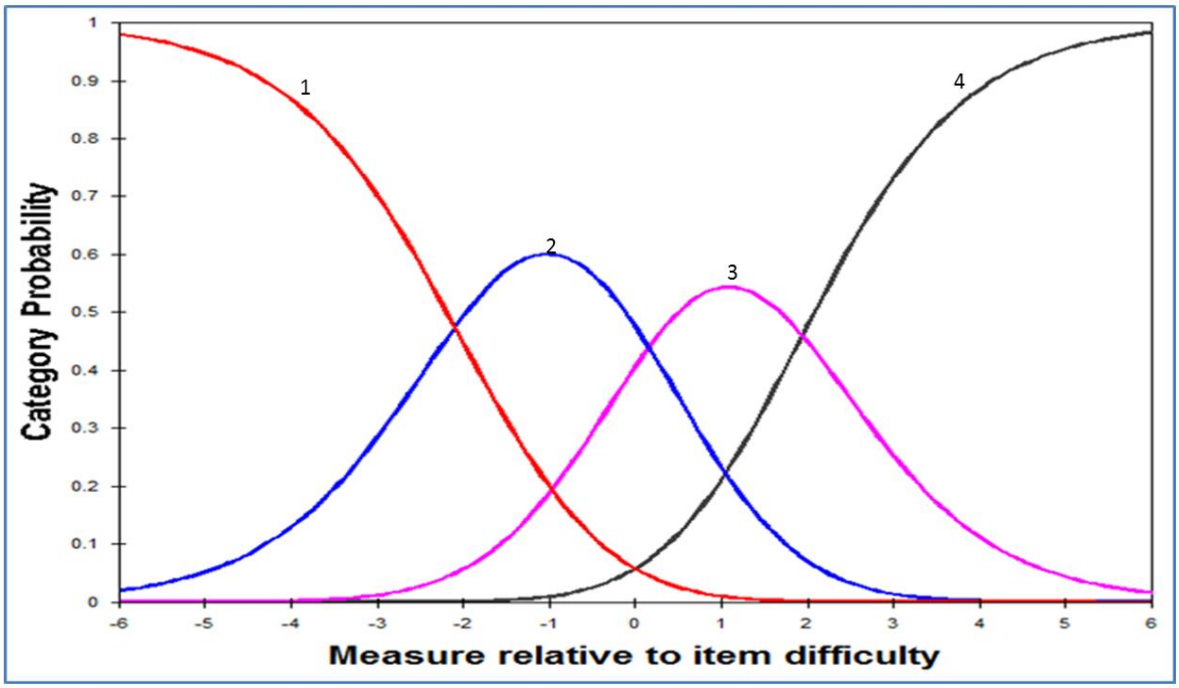

Figure 5.23 Category probability curves showing ordered thresholds for the four-response categories for the General Symptoms Severity scale

5.5.8.9 *General Symptoms Bothersome domain*

This scale demonstrated poor precision (PSI = 1.58) and poor targeting (2.10) (Table 5.19). The explained variance was 57.1% and the eigenvalue of the first contrast was 1.52. Item 6 showed misfit again. The fit statistics of item 6 showed improvement after giving the errant responders a weighting of 0, however, Item 1 showed slight misfit. Item 1 was retained as it was considered an important item. The response categories were ordered (Figure 5.24). There was no notable DIF for the items. These items showed sub-optimal Rasch properties and was not considered for CAT calibrations.

Table 5.19. Psychometric properties of the General Symptoms Bothersome domain

Parameters	Rasch model expectations	First iteration	Final iteration
Disordered thresholds	No	No	No
Number of items	-	6	6
Person separation index	>2.0	**1.58**	**1.62**
Person reliability	> 0.8	**0.71**	**0.72**
PCA, variance by 1st factor	>50%	57.1%	57.1%
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	1.5, **10.9%**	1.5, **10.9%**
PCA, % raw variance explained by items		21.9%	21.7 %
Item fit (infit MnSq)	< 1.5	**GSB 6 (1.52) ‡**	**None**
Item fit (outfit MnSq)	< 1.5	None	**GSB 1 (1.52) ŧ**
LIDǁ	> 0.3	None	None
DIF**	<1.0 logits and p<0.05	None	None
Measurement range		2.75	3.01
Targeting, difference between person & item means	<1.0 logits	**2.10**	**2.17**

GSB 1 = Headaches due to your vision; GSB 6 = Hallucinations/vivid dreams.
‡GSB 6 showed poor discrimination (0.74)
ŧItem 1 was retained as it was an important item.
ǁLID dealt with using the process outlined in the methods. LID item pairs: None. Percentage refers to proportion of LID pairs of total number of correlated items.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups, and ocular comorbidity. Number of participants responded to the items: GSB 1(n = 4); GSB 6(n = 0). Item 6 was extracted from existing interviews and not from interviews.
Bolded values represent poor fit to the Rasch model.
GSB, general symptoms bothersome; PCA, principal component analysis; MnSq, mean square; DIF, differential item functioning; LID, local item dependency

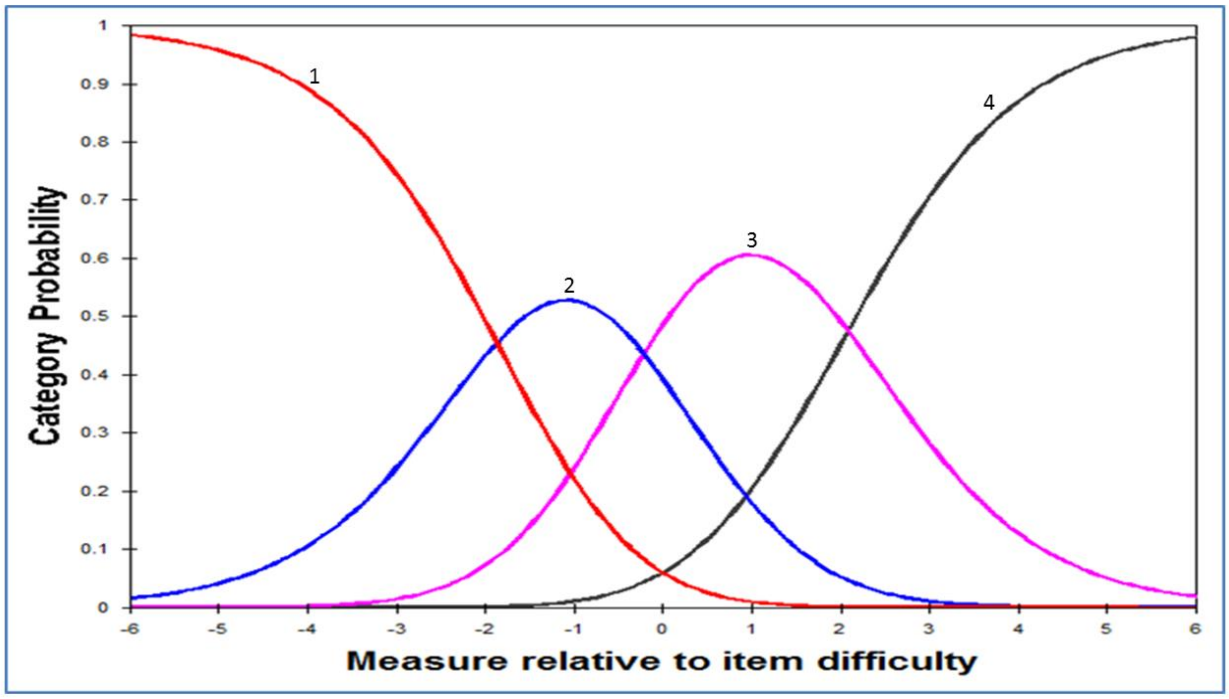

Figure 5.24 Category probability curves showing ordered thresholds for the four-response categories for the General Symptoms Bothersome scale

The ocular comfort symptoms and the general symptoms domains were not subjected to CAT simulations due to sub-optimal psychometric properties and very few number of items. The final HRD module had 13 item banks: activity limitation, reading, driving, lighting, mobility, negative emotional, positive emotional , general health concerns , concerns on the disease progression, convenience, social, economic, symptoms (Figure 5.25).

5.5.9 CAT simulation

CAT simulations were conducted for 1000 cases for the 13 final item banks (Table 5.20). When the standard error of measurement was set at 0.521, an average of 5 items were required across the item banks (range = 4 to 6). When the standard error of measurement was set to 0.387, an average of 10 items were required (range = 6 to 12). The activity limitation, convenience, social and driving item banks needed only 4 items to achieve a standard error of measurement of 0.52 and the positive emotional and the lighting item banks needed 6 items. Correlation between the 47-item activity limitation scale and the CAT theta was 0.96 for moderate precision and 0.98 for high precision. The correlation between the other item banks and the CAT theta ranged from 0.96 to 0.99 for moderate precision and 0.98 to 1 for high precision.

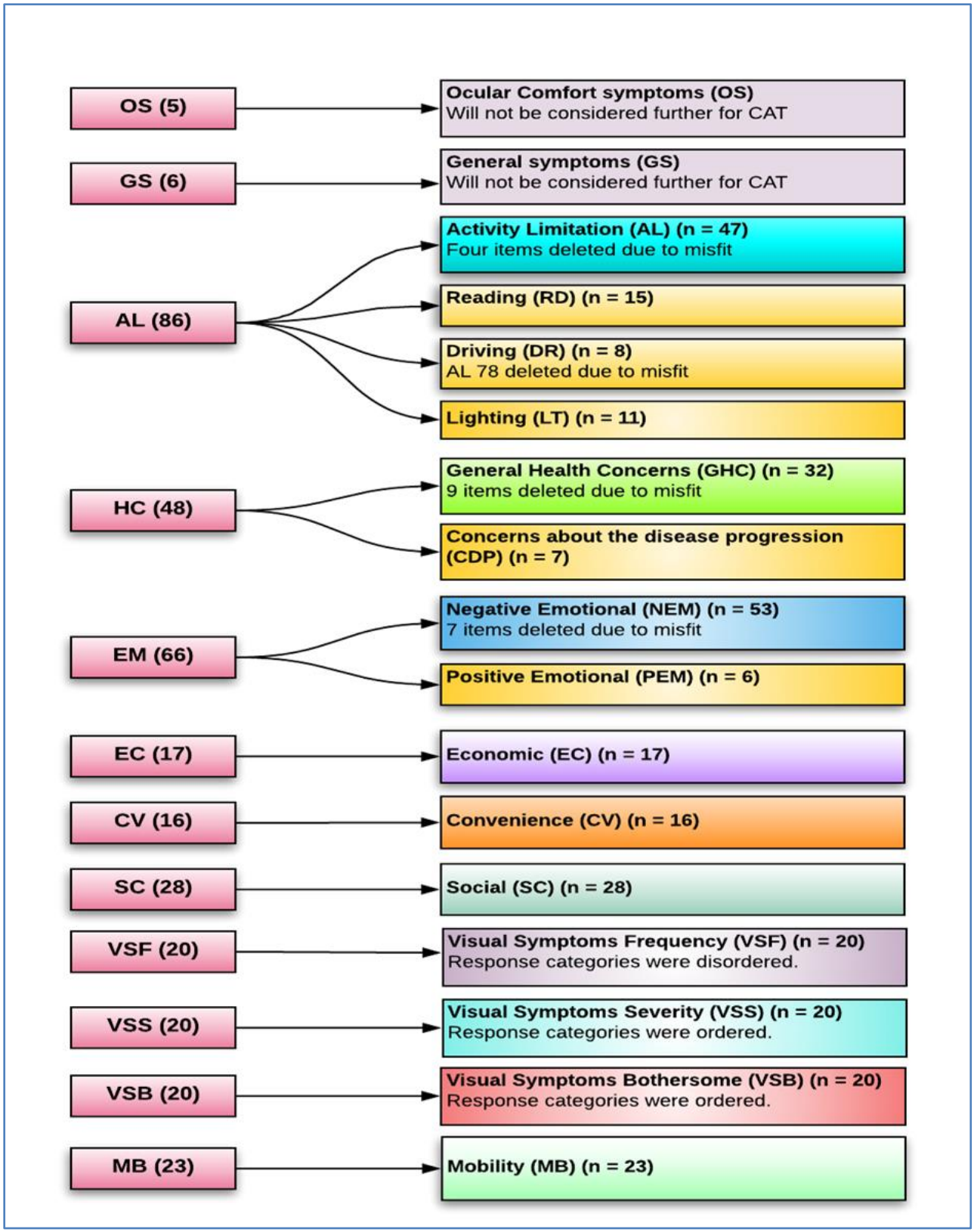

Figure 5.25 Flow chart showing the final item banks for hereditary retinal diseases (HRD). The boxes on the left show the original items banks and the boxes on the right show the final item banks. New domains identified is shown in yellow boxes

Table 5.20. Computer adaptive testing (CAT) simulation for the hereditary retinal diseases (HRD) item banks

Quality of life domains	Items available for CAT	Moderate precision (SEM = 0.521)		Higher precision (SEM = 0.387)	
		Average no of items used by CAT	Correlation CAT & Full item bank	Average no of items used by CAT	Correlation CAT and full item bank
Activity limitation	47	4	0.96	8	0.98
Mobility	23	5	0.96	11	0.99
Negative emotional	53	5	0.97	11	0.98
Positive emotional	6	6	0.99	6	1
Convenience	16	4	0.96	9	0.99
General health concerns	32	4	0.96	10	0.98
Social	28	4	0.96	9	0.98
Economic	17	5	0.96	10	0.98
Visual symptoms - frequency	20	5	0.97	11	0.99
Visual symptoms - severity	20	5	0.97	11	0.99
Visual symptoms - bothersome	20	5	0.97	11	0.99
Reading	15	5	0.97	12	0.99
Driving	8	4	0.98	8	1
Lighting	11	6	0.98	11	0.99
Concerns about the disease progression	7	5	0.99	7	1
Total	**323***	**72 (22.2%) †**		**145 (44.8%) †**	

* excludes the Ocular Comfort Symptoms 5-item scale, General symptoms 6-item scale and 21 other items from various scales that were deleted due to gross misfit, poor discrimination, or item wordings were confusing.
†Total number of items needed on average if all the 13 items banks are administered
SEM = Standard Error of Measurement; no = number.

5.6 Discussion

This is the first study to develop psychometrically valid item banks across 13 QoL domains specific to people with HRD. The currently existing PRO instruments for HRD were mostly developed for RP and they measure predominantly the mobility aspect of QoL.(254, 288, 307) Though the input for HRD item banks were predominantly from RP patients, the item banks with 13 QoL domains would provide a more comprehensive assessment of patient-reported outcomes. Understanding patients' perspective is very important as new treatment modalities such as gene therapy, cell transplantation, and retinal prostheses are fast emerging for this group of diseases.(66, 67, 382) One of the main advantages of CAT over the traditional paper-and-pencil based PRO instruments is that the CAT system requires fewer items to provide very precise and accurate assessment of patient-reported outcomes.(44, 383, 384) The CAT simulation test indicated that less than 10 items are required to gain precise measurement of each QoL item bank, providing a quicker assessment of PRO. This may be very valuable in a busy clinical setting where clinicians may have very little time to administer a PRO to quantify the patient's QoL. Moreover, availability of 13 QoL item banks provides an opportunity for the clinicians and researchers to choose the QoL domains relevant and sensitive to the treatments and /or intervention. Therefore, these items banks will have potential to revolutionize the way patient-reported outcome measures are used in clinical settings and research.

The framework of 13 QoL domains identified in this study are activity limitation, mobility, convenience, economic, social, symptoms, reading, driving, lighting, negative emotional, positive emotional, general health concerns and concerns about the disease progression. The QoL domains identified in this study was based on the ophthalmic QoL domains identified previously in other disease modules of the Eye-tem bank Project.(3, 45, 146)The DR-specific item banks had nine QoL domains(45, 146) and the glaucoma-specific module had 10 QoL domains. Again, the categorisation of the symptom domain into visual symptoms, ocular comfort symptoms and general symptoms was based on the previous studies. The DR module had only visual symptom and ocular comfort symptom domains, however, the glaucoma module had visual symptom, ocular comfort and general symptom domains.

Seven domains (activity limitation, general health concerns, convenience, social, visual symptoms, mobility, and negative emotional) demonstrated excellent precision and 2 domains (ocular comfort symptoms and general symptoms) showed borderline precision. The ocular comfort symptoms and the general symptoms domains had very few number of items (5 and 6) and demonstrated sub-optimal Rasch-based psychometric properties. Moreover, the items in the ocular comfort symptoms and the general symptoms domains were not relevant to people with HRD, who frequently experience visual symptoms. Ocular comfort and general symptoms are mostly related to eye treatment and they are uncommon in HRD as most of these diseases are incurable. As these items are not relevant to people with HRD, they were not considered further for CAT. Six domains (driving, negative emotional, social, ocular comfort symptoms, general symptoms, and lighting) showed poor targeting. The driving scale showed the worst targeting because more than two-thirds of the participants were not driving due to their visual loss. Despite the poor targeting the driving scale will be retained because these items will be relevant to people in the early stages of the disease, who are still able to drive. The mistargeting of the negative emotional domain is due to the relatively smaller number of participants who were emotionally affected. The mistargeting of the social domain is due to the relatively small number of participants who had less issues with social engagement. Targeting may improve by adding items relevant to those at the 'less impaired' end of the spectrum. This can be easily done in item banks where new uncalibrated items are added and their calibration is done using Rasch analysis.(385) Moreover, poor targeting is not a major concern in a CAT system, as the items are administered based on the participant's ability.

The response categories of all the domains, except for the visual symptoms domain were ordered. Only the frequency scale of the visual symptoms domain showed disordered categories, whereas the severity and bothersome scales showed ordered response categories. Disordering of the categories occurs when the number of categories exceeds what the respondents can distinguish, underutilisation of the categories or the categories are not well defined.(358) In the visual symptoms frequency domain the middle categories ('occasionally' and 'quite often') were underutilised. As most of the visual symptoms in the visual symptoms domain were on RP, it is likely that participants with RP have chosen the option 'very often' and the participants with other diseases have chosen the option 'never' for this domain. Disordered categories resulting due to underutilization of the category

thresholds may be addressed by collapsing the categories. However, collapsing the item categories in the visual symptoms frequency domain will further decrease the number of categories to 3, which might compromise the functioning of the CAT system. Moreover, the functioning of the response categories could be further tested by collecting more data and so it was decided not to alter the response categories at this stage.

Principal component analysis of the residuals demonstrated item grouping in activity limitation, health concerns, emotional, and mobility scales, indicating multidimensionality. The eigenvalue of the first contrast usually suggest the presence or absence of a second dimension. Given that as few as two items could form a valid functional scale, many studies use a cut-off value of > 2 as an evidence of a possible second dimension when developing a PRO instrument. (25, 386, 387) However, in this study a cut-off value of > 3 was used because when there are large number of items as in item banks items with similar content area tend to group together. Having a value > 3 will help to identify the item grouping for which item removal is not justified.

Multidimensionality was addressed by separating the suspect item clusters into independent scales. A series of post-hoc tests (dis-attenuated correlation & Bland and Altman test) were done before making a final decision to separate a scale. In the activity limitation domain, the standardised residual loadings for items revealed that the reading, driving, and lighting items grouped together. Removal of the reading, driving and lighting items reduced the precision of the remaining activity limitation scale, indicating that the items are adding more signal than noise. However, removal of these items significantly decreased the unexplained variance eigenvalues of the remaining activity limitation scale moving it closer to Rasch based criterion of unidimensionality. The driving and the lighting scales demonstrated poor agreement with the remaining activity limitation scale, indicating that they should become separate QoL measures. However, the reading items demonstrated only a moderate agreement with the remaining activity limitation scale. When the reading items were clubbed together with the remaining activity limitation items and analysed, the unexplained variance eigenvalue worsened to 8.2 and so, it was decided to separate the reading items from the remaining activity limitation scale to create unidimensional scales as much as possible. The reading, driving and the lighting scales formed unidimensional stand-alone measures with promising Rasch-based metric properties. Driving as a stand-alone measure was reported

in the glaucoma item bank study.(388) However, in the above study, the reading and lighting items showed only item grouping and did not form stand-alone measures.

The emotional domain had both positive and negative emotional items. When these items were analysed together, the positive items showed misfit and item grouping. However, removal of the positive items improved the eigenvalue of the new first contrast. The positive items also showed a poor correlation and a moderate agreement with the remaining emotional scale containing negative items. This shows that the positive and the negative emotional items measure different traits and so cannot be measured on the same scale. Some questionnaires use combined items (positive and negative) to reduce the acquiescence bias, but studies have shown that having combined items affects the internal consistency of the scale.(389) However, in this study the combined items affected the dimensionality of the scale. Hence, the positive and the negative items were separated into positive and negative emotional scales. Item 4 (‘feel surprised’) in the emotional scale showed misfit with both positive and negative items and was deleted.

Some of the domains (activity limitation, mobility, and negative emotional) had higher than satisfactory eigenvalues, even after the separation of reading, driving, lighting and positive emotional from the activity limitation and the emotional scales. Higher eigenvalues does not always suggest multidimensionality. Sometimes higher values can occur if the test has a broad dimension, like mathematics, which includes arithmetic, algebra, geometry and word problems.(390) Multidimensionality is a real concern only if the unexplained variance of the first contrast is very high and the suspect item cluster forms a meaningful construct. If the eigenvalue is borderline or if the suspect item clusters do not form meaningful constructs, then the multidimensionality can be ignored, especially in large item sets such as an item bank. The activity limitation and the emotional domains had lot of items measuring a range of activities and emotions and they demonstrated item grouping. In this situation, clusters that showed meaningful constructs were separated and clusters that did not form a meaningful clusters were left alone even though eigenvalues were higher than the acceptable criterion. In the activity limitation domain, 6 items (‘recognising someone across the street’, ‘recognising a friend up close’, ‘seeing facial expression’, ‘recognising traffic signals’, and ‘using a ruler or tape measure’) were grouping together. Some of the items had similar meanings, but overall these items did not form a meaningful construct and so these

items were not separated from the activity limitation scale. Similarly, in the emotional domain, 3 items ('feel depressed', 'feel unhappy', and 'feel sad or low') were grouping together. These 3 items had similar meanings, but again overall these items did not form a meaningful construct.

DIF evaluates the performance of an item across two groups. However, if DIF is present we should not draw the conclusion that the test is biased or unfair. Sometimes DIF may be statistically significant, but may not be clinically meaningful. So, we need to consider both the statistical significance and the substantive difference. Items that show DIF may be either discarded, revised, or left alone based on its content and its relevance to that construct. In the 13 QoL domains, only one item in the driving scale showed DIF for gender. Three items showed DIF for best corrected visual acuity and 6 items showed DIF for disease groups. Although the DIF was statistically significant in all the cases, it was not clinically meaningful and so all the items were retained. DIF is not a major concern in the CAT system because the item administration is based on the participant's response to previous items.

This study provides a superior method of assessing QoL impact in people with HRD using an item bank and CAT approach. These item banks can also provide solutions to the issues associated with traditional paper-and-pencil based PRO instruments. For example, the item calibration indicated that only 8 items are needed to measure the activity limitation of people affected with HRD with better precision. This is very valuable in a clinical setting where clinicians have very little time to quantify the patients' QoL using a PRO instrument. The automatic scoring in CAT enables frequent and real-time assessments and immediate feedback with minimal burden on respondents.(391) Because of these benefits, item banking and CAT is becoming more popular in health-related research. Item banks have been developed for spinal cord injury,(392) arthritis,(393) cancer-related fatigue (394) and paediatrics.(395) Currently items banks are under construction for other ocular eye diseases.(3, 45, 388) Our rigorous methodology used in the development and calibration of the HRD item banks was similar to that utilized in the Patient-Reported Outcomes Measurement Information System item bank study with some subtle differences.(396) Rasch analysis was used for item calibration in this study and a graded response model (GRM) was used in the Patient-Reported Outcomes Measurement Information System item bank study.

Some of the strengths of this study are relatively large number of participants, participants with different types of HRD, rigorous methodology used in the development of the item bank, and using sophisticated psychometric techniques to ensure local item dependency free items for calibration and address misfit items without having to remove items unnecessarily. Only 6 items showed DIF for disease groups, indicating that the rest of the items (98%) were perceived to have similar level of trait across people with different HRD. Hence, these item banks can be used to explore the impact of different HRD on QoL.

There were few limitations in this study. Most the participants were females. Most of the HRD do not have sexual predilections, but some of the X-linked diseases tend to occur more in males than in females. The larger number of female participants may be because women are more likely to participate in survey than men.(397, 398) Different modes of administration may affect the quality of the data, but only 19 questionnaires were interviewer-administered and the remaining were self-administered. Self-administered data may be nosier than interviewer-administered, which may be due to either loss of interest in answering the questions or due to the increase respondent burden. However, the online survey had an option where participants could answer the survey in multiple sessions to reduce respondents' burden. The majority of the paricipants had RP and only few patients with other HRD which may infer a disease bias in the results. However, when the sample was stratified by disease groups (RP = 165; other HRD = 68) the psychometric properties between the two groups were very similar between the two groups and no DIF for disease groups (Tables 5.2 to 5.18). Almost half of our study participants had other ocular comorbidities, mostly cataract, which could have added noise to the responses. HRD are bilateral progressive diseases which has an early onset than cataract. So, it is likely that most of the QoL issues in these participants were attributed to the HRD and not due to cataract. Moreover, there was no DIF for ocular comorbidities.

5.7 Conclusions

These item banks will enable clinicians and researchers to precisely measure the impact of different HRD on peoples' vision related QoL and are very sensitive to detect treatment outcomes. As recent advancements in treatments of RP such as stem cell transplantation, retinal prostheses, gene therapy, and neuroprotection continue to emerge from intensive research, a comprehensive PRO will be invaluable for use in clinical trials to compare the impact of new treatment strategies from the patients' perspective. The CAT simulation indicates that only a small number of items are needed to obtain a precise measurement of each QoL domain compared to the full item bank.

CHAPTER 6 DOES COPING FORM A MEASURABLE CONSTRUCT?

6.1 Introduction

Hereditary retinal diseases (HRD) cause a slowly progressive visual loss that ultimately result in blindness after several decades. This can cause a significant stress and anxiety to people with these retinal diseases.(2, 245, 351) Moreover, most of these people are aware that their disease is not curable which can affect their quality of life. Studies have also shown that HRD cause a substantial reduction in quality of life (QoL).(351) People with HRD respond to the stress of visual loss by adopting several coping strategies. Coping is a psychological mechanism for managing external stress. It acts as moderator between stress and health. Coping could either involve two dimensions (positive and passive). Coping that involves positive attitude (problem solving, planning, seeking emotional support) has shown to increase health related quality of life (354, 399) and coping that involves passive attitude (denial, behavioural disengagement, and alcohol/drug abuse) has shown to decrease the health related quality of life. Coping therefore plays an important role in preserving the health realted quality of life .(353) Hence understanding the coping responses in people with HRD can help us to understand their perception of stress and management. Moreover, there is currently no cure for these retinal diseases and clinicians and researchers can use this information to select the coping options that will work best for them. However, the coping strategies to manage the stress of visual loss in this group of retinal diseases is not very well understood due to lack of disease-specific coping questionnaires. There are several coping questionnaires developed for other medical conditions but none for eye diseases. Coping was identified as one of the major themes in the qualitative study (chapter 3). This chapter explored the psychometric properties of the coping domain in the HRD module to determine if it could form a meaningful construct. If the domain formed a measurable construct, then this could be used to understand and quantify how people with HRD cope with their eye condition.

6.2 Aims and objectives

1. To test the psychometric properties of the coping domain of the HRD module using Rasch analysis.

2. To calibrate the coping items using Rasch analysis to set up computer algorithm for the computer adaptive testing (CAT).

3. To assess the relationships between coping and other domains of the QoL.

6.3 Methods

Rasch analysis was used to assess the psychometric properties of the coping item bank and to establish item calibrations to develop computer algorithm for CAT. The Rasch parameters assessed were functioning of the response categories, measurement precision, unidimensionality, fit statistics, targeting of the scale to the study population, and differential item functioning (DIF). For details of these parameters please refer to 5.3.3 section in chapter 5. If the scale was found multidimensional, it was dealt by splitting the scale as described in 5. 3.3.3.2 in chapter 5. The coping item bank had 30 items. The coping domain was rated on a 5-point Likert scale ranging from 1 *not at all* to 5 *extremely.*

6.4 Statistical analyses

Rasch analysis was carried out using the Winsteps software (version 3.91.2) using the Andrich single rating scale model. The relationship between the coping and other the domains of QoL were assessed by estimating correlations (Spearman's Correlation co-efficient) using the IBM SPSS statistics software for windows, version 22 (SPSS Inc., Chicago, ill, USA). Bland and Altman test was done using the MedCalc software, version 17.2 (Ostend, Belgium, 2016) and CAT simulation was done using the Firestar-D software (version 1.3.2, Chicago IL, USA).

6.5 Results

One hundred and eighty-nine participants (median age = 58 years; range 19 to 87 years; RP, 77%; females, 55%) completed the coping domain items. The scale demonstrated good precision (PSI = 2.18) and good targeting (Table 6.1). The explained variance of the measure was 47.2%. The eigenvalue of the first contrast was 3.7, indicating that it had a strength of at least 4 items. Six items were grouping together to form a suspect item cluster with a loading > 0.4 to the first contrast. Removal of the 6 items reduced the precision of the remaining 24-item coping scale (PSI = 2.04).

Table 6.1. Psychometric properties of the Coping domain

Parameters	Rasch model expectations	First iteration	Final iteration
Disordered thresholds	No	No	No
No. of items	-	30	30
Person separation index	>2.0	2.18	2.32*
Person reliability	> 0.8	0.83	0.84
PCA, variance by 1st factor	>50%	**47.2%**	**47%**
PCA, Eigenvalue for 1st contrast & % unexplained variance in 1st contrast	<3.0, <5.0%	**3.7, 6.6%**	**3.7, 6.7%**
PCA, % raw variance explained by items	-	34.8%	33.2%
Item fit (infit MnSq)	< 1.5	**CP 22 (1.82)** **CP 16 (1.70)** **CP 6 (1.65)** **CP 19 (1.67)** **CP 8 (1.55)**	**CP 19 (1.54)** **CP 16 (1.53)**
Item fit (outfit MnSq)	< 1.5	**CP 22 (2.46)** **CP 16 (2.36)** **CP 6 (1.99)** **CP 19 (1.79)** **CP 8 (1.60)** **CP 30 (1.54)**	None #
LID ‖	> 0.3	9 pairs, 2 %	9 pairs, 2%
DIF**	<1.0 logits and p<0.05		**Age:** **CP 6 (1.14, p < 0.01)**
Measurement range		2.31	2.74
Targeting, difference between person & item means	<1.0 logits	0.37	0.36

CP 6 = Engaging in adventurous activities, e.g. SCUBA diving, Sky-diving, mount-climbing; CP 8 = Attributing your eye condition to ageing; CP 16 = Ignoring that you have an eye condition; CP 19 = Seeing your family members adapt to similar eye condition as yours; CP 22 = Thinking doctors will fix your eye condition; CP 30 = Engaging knowingly in unhealthy activities, e.g. smoking, drinking alcohol.
*Precision of the scale improved after fixing the misfitting items
#The misfit of the four items were resolved by diagnosing misfit through unpredictable individual responses (total n = 62, range 4-10 for each misfitting item) and giving errant responders a weighting of 0.
‖LID dealt with using the process outlined in the methods. LID item pairs: Final iteration: 1/2; 1/15; 2/15; 2/10; 4/26; 7/28; 9/16; 10/27; 15/18.Percentage refers to proportion of LID pairs of total number of correlated items.
**DIF was assessed for age, gender, best eye visual acuity (BEVA), disease groups and ocular comorbidity.
Bolded values represent poor fit to the Rasch model.
CP, coping; PCA, principal component analysis; LID, local item dependency; DIF, differential item functioning

The explained variance of the measure worsened to 40.8%, but the eigenvalue of the first contrast was dropped to 2.3. The 6-item scale formed a stand-alone unidimensional scale with promising Rasch based psychometric properties (Appendix 8). At this stage, post-hoc

tests were done to decide whether to separate or retain the 6 items from the main coping scale. The dis-attenuated correlation between the suspect item cluster and the main Rasch cluster was 0.8. Bland and Altman test showed that the 6-item scale had a moderate correlation (r = 0.40, 95% CI = 0.28 to 0.50) and a moderate agreement (mean bias, 1.5 logit, limits of agreement , -2.2 to 5.2) with the coping scale (Figure 6.1). Results of the post-hoc tests suggest that the 6-item scale forms a separate dimension. Even though the eigenvalue of the new first contrast improved after separating the 6 items, it was decided to retain them within the main coping scale because there was a significant loss in the measurement precision of the scale and worsening of the explained variance. Moreover, the 6 items were measuring coping like the main scale and did not form a meaningful construct.

Six items showed misfit (22, 16, 6, 19, 8 and 30). After fixing the item responses of the misfitting items, 4 items showed good fit statistics, but 2 items (item 19 and 16) still showed misfit. These two items were retained as the mean square (MNSQ) outfit values were within the recommended value of 1.5 and the MNSQ infit values were only slightly higher than the recommended value of 1.5. The response categories of the final 30-item coping scale were ordered (Figure 6.2). When assessing DIF for age, item 6 showed a contrast difference of 1.14 logit indicating that people above the age of 50 years perceived this item as difficult.

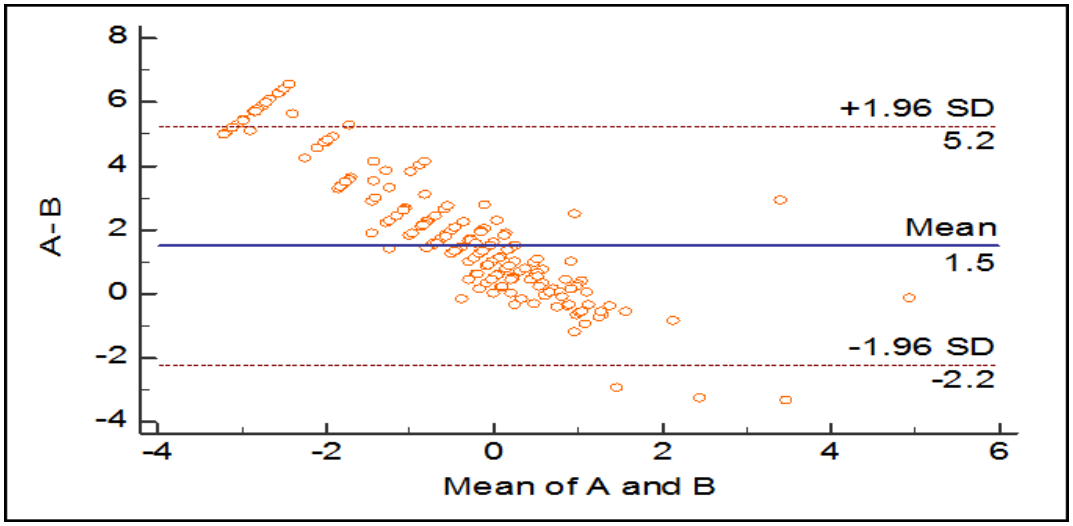

Figure 6.1 Bland & Altman plot showing limits of agreement between the Coping scale and the 6-item scale

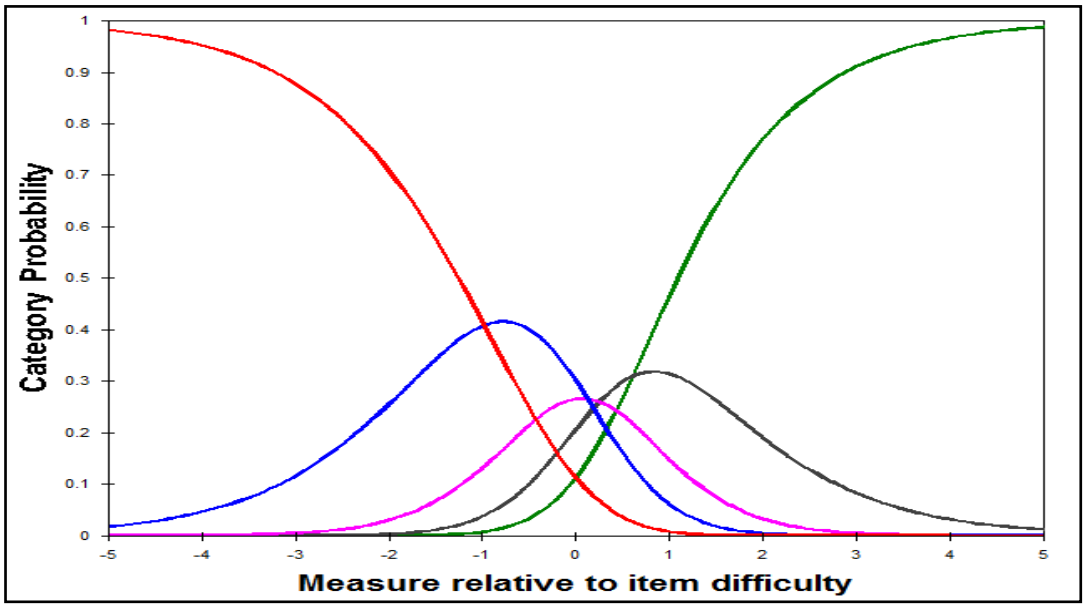

Figure 6.2 Category probability curves showing ordered thresholds for the five- response categories for the Coping scale

6.5.1 Relationship between coping and other quality of life domains

The relationship between the coping domain and the other QoL domains was determined by using the Spearman correlation test. The correlation between the person measures of the coping domain and the other QoL domains was poor (Table 6.2), suggesting that the coping domain was an independent measure.

Table 6.2 Correlation between the person measures of the coping domain and the other 13 quality of life (QoL) domains

Other quality of life domains	N	Correlation	*P*-value
Activity limitation	233	0.131	0.045
Reading	233	0.165	0.012
Driving	233	0.121	0.065
Lighting	233	0.116	0.077
Mobility	233	0.193	0.003
Positive emotional	233	-0.289	0.000
Negative emotional	233	0.038	0.561
Concerns about the disease progression	233	0.017	0.796
General health concerns	233	0.135	0.040
Social	233	0.1	0.126
Convenience	233	0.136	0.038
Economic	233	0.148	0.023
Visual symptoms frequency	233	0.101	0.126
Visual symptoms severity	233	0.136	0.038
Visual symptoms bothersome	233	0.149	0.023

6.5.2 CAT simulation

CAT simulations were conducted for 1000 cases for the coping item bank. When the standard error of measurement was set at 0.521, an average of 4 items were required and when the standard error of measurement was set to 0.387, an average of 9 items were required to gain precise measurement of coping. Correlation between the 30-item coping scale and the CAT theta was 0.96 for moderate precision and 0.98 for high precision.

6.6 Discussion

This study demonstrates that coping forms a valid and a psychometrically robust scale in the HRD module. Although multiple scales have been developed to assess coping in other medical conditions (400-402), none exists for eye health. This is the first study to develop a coping scale for eye disease. This will enable clinicians and researchers to better understand what coping strategies these people use to successfully manage their visual loss. This scale can also be used to explore the role of coping among people with same level of disease severity reporting different QoL impacts, which can facilitate better understanding of the dynamics of real world impact of the disease. The CAT simulation test indicated that less than 10 items are required to gain precise measurement of this domain, which may be valuable in a busy clinical setting where clinicians do not have much time to administer a questionnaire to assess patient-reported outcomes.

Coping with HRD is a major challenge not only for the affected individual but also for the entire family. People with HRD report difficulty in performing important day-day-activities such as reading, driving, shopping, playing sports and engaging in leisure activities.(351) They also report considerable uncertainty about their future, many disturbing visual symptoms and difficulty maintaining hope. They often report that their eye condition is not well understood by their eye specialist, friends and family members.(351) In spite of all these difficulties, little is known about how patients cope with visual loss of HRD and whether the use of certain coping strategies is related to higher health related quality of life. This is due to lack of a disease-specific coping questionnaire. The coping strategies used to manage stressful situations differs in different illness. Hence using a coping scale developed for a different disease will fail to provide information about how patients with HRD successfully manage their visual loss. Hence a multi-stage systematic process of item extraction and

item revision was used to develop a disease-specific coping scale for HRD. This coping scale can be used to understand the different coping strategies of people with different HRD.

To ensure that the questionnaire developed for a specific population is appropriate the content development should involve a comprehensive consultation with patients through focus groups or interviews. Researchers should address these challenges by using qualitative techniques to obtain information about patients' experiences and opinions and use this information to develop qualitative instruments. However, items of most of the existing coping questionnaires were developed based on theoretical assumptions and empirical basis and not from inputs from patients or participants experiencing the stressful events. So, these questionnaires may miss out important information that matters to patients. For example, the Brief Cope Questionnaire has been often used to determine the coping strategies associated with glaucoma.(403, 404) Although this questionnaire has 23 items about 14 different ways of coping, none of the 14 coping scales were associated with glaucoma progression. Hence this questionnaire may not be sensitive to determine the disease-specific coping strategies. However, items for the coping item bank were extracted from qualitative interviews and hence contain items from patients' perspective. Hence our coping scale is likely to be more sensitive than the existing questionnaires for use in patients with eye disease.

Coping is a very broad concept.(405) There are several ways of grouping or classifying coping responses. One recognised grouping includes; problem-focused (include active strategies to remove or change the stressful situation) and emotional focused (coping is focused on minimizing the emotional stress associated with the stressor).(406) The problem focused strategy is used when the stressful situation is controllable and changeable and emotion focused is used when the situation is uncontrollable. Younger individuals tend to use problem focused coping and older individuals use emotion focused coping more than the problem focused coping.(407) The difference may be due to functions of different types of stressors.(408) In our study also problem focused coping strategies were used commonly by younger people and emotional focused coping strategies were used by older individuals.

Coping scales are frequently used to assess coping in stressful situations such as pain, illness, injury, and disease diagnosis. The most frequently used coping scales in medicine,

nursing, psychology are the COPE, Ways of Coping questionnaire, Coping Strategies Questionnaire, Coping Inventory for Stressful Situations, Religious – COPE and Coping Response Inventory.(409) The COPE and the Ways of Coping were broadly applicable scales (i.e. coping in stressful situations/events), whereas Coping Strategies Questionnaire is a situation-specific scale (i.e. coping to specific stressor such as pain). Our coping scale is also applicable to specific situation (i.e. coping to visual loss). Our coping scale had 30 items on different coping strategies which included acceptance, active coping, denial, disengagement, humour, planning, positive reframing, self-distraction, substance use, using emotional support and venting. However, most of the items were on active coping which shows that people with HRD use coping strategies that involve positive attitude.

Coping was identified as one of the major themes in the qualitative study and Rasch analysis was used to test the psychometric properties of the domain to see if it forms a measurable trait. The coping scale demonstrated promising Rasch-based psychometric properties. However, PCA analysis showed multidimensionality. Six items ('accepting your eye condition', 'learning to live with your eye condition', 'trying to be positive', 'getting on with your eye condition', 'ignoring that you have an eye condition', and 'adapting to the eye condition or vision loss') grouped together with a loading of > 0.4 to the first contrast. Removal of these 6 items reduced the precision of the remaining coping scale, indicating that the 6-item scale was adding more signal than noise. Although, the 6 items were grouping together as a separate dimension, they were measuring coping like the remaining 24 items. Splitting the 6-item scale based on the psychometric analysis will unnecessarily create two scales measuring the same latent trait. Hence, the 6 items were not separated into a separate scale.

6.7 Conclusions

This study shows that coping item bank forms a measurable construct in this disease group. This item bank can be used by clinicians and researchers to better understand the coping responses of people with different HRD. Moreover, it can also assist in identifying people who do not cope well for timely referral for counselling and other intervention programs. The CAT simulation indicates that only less than 10 items are needed to obtain a precise measurement of this domain. A CAT system will be developed by professional software

designers to implement the coping item bank. The items that were calibrated in this study will be used to develop the computer algorithm for the CAT

CHAPTER 7 DISCUSSION AND FUTURE DIRECTIONS

The impact of other vitreoretinal diseases on peoples' quality of life (QoL) is mostly unexplored due to the lack of appropriate patient-reported outcome (PRO) measures. Non-disease-specific and generic PRO instruments are mostly used to study the impact of these retinal conditions. These existing PRO instruments are not comprehensive and their items are mostly not relevant to people with other vitreoretinal diseases and hence not sensitive enough to measure the disease-specific QoL impact. These diseases need specific PRO instruments that could accurately measure QoL impact and are also very sensitive to detect treatment outcomes. However, it may not be feasible to develop PROs for all the other vitreoretinal diseases that are uncommon. The best way forward is to group or split the other vitreoretinal diseases into groups and develop group-specific PRO instruments. Hence, the overall aim of this project was to develop comprehensive PRO instruments in the form of item banks implemented via computer adaptive testing (CAT) for other vitreoretinal diseases.

An extensive literature search was done to identify all the PRO instruments used in retinal diseases and to assess their content coverage of QoL and psychometric properties (chapter 2). The results of the literature review showed that the National Eye Institute Visual Function Questionnaire (NEI-VFQ) was the most commonly used PRO instrument to assess the QoL impacts on people with retinal diseases.(5) Assessment of the psychometric properties of this instrument showed that it is flawed and multidimensional.(25) Generic PRO instruments were used to assess the psychological well-being of people with retinal diseases, (163, 168, 250, 284) but these PRO instruments were not validated for use in this group of diseases. Of the 29 retina-specific PRO instruments that were developed for retinal diseases, 17 were specific for other vitreoretinal diseases. The content coverage of these PRO instruments was limited to measuring only few aspects of QoL. Of the 17 PRO instruments, only one PRO instrument; the independent mobility questionnaire (IMQ) was validated using the modern psychometric methods.(254) Although it was the highest quality instrument for retinitis pigmentosa with good validity and measurement precision, information on the dimensionality and reliability was missing.(5) The results of the literature review show that there are no comprehensive and psychometrically sound PRO instruments available for

other vitreoretinal diseases. Hence, there is a need to develop comprehensive PRO instruments in this group of diseases.

A qualitative approach was adopted to explore the QoL impacts of people with other vitreoretinal diseases (chapter 3). The other vitreoretinal diseases were grouped into hereditary retinal diseases (HRD) and acquired retinal diseases (ARD) for the qualitative study. Seventy-nine in-depth semi-structured interviews were done with people with different retinal diseases. Results of the qualitative study showed that people with HRD and ARD experience different QoL issues. Nine QoL themes were identified in both the disease groups. People with HRD reported more functional limitations (activity limitation) due to their eye condition than people with ARD. People with ARD expressed concerns about their treatment outcome (health concerns) and reported more inconveniences (convenience) associated with eye treatment than people with HRD. People with both HRD and ARD faced emotional and psychological challenges (emotional). People with HRD had more issues with social participation (social), mobility and orientation (mobility) and work and finance (economic) than people with ARD. However, people with HRD coped better than people with ARD (coping). The differences in the QoL issues is due to the differences in the disease, in terms of age of onset, duration of the disease, severity of visual loss and employment status. HRD tend have an early onset, involves both eyes and is progressive. ARD have a late onset, mostly unilateral and may be either progressive or stationary. Within the groups the QoL issues were similar and across the groups the QoL issues were different. This justifies the grouping of other vitreoretinal diseases into HRD and ARD. Based on the qualitative results, it was decided to develop separate questionnaires for HRD and ARD.

Development of the vitreoretinal-specific item banks involved a systematic multi-stage process of item extraction and item revision. Items were extracted from 17 PRO instruments, 4 qualitative studies and 79 semi-structured interviews (chapter 4). Item refinement and revision included three stages; binning and winnowing, expert panel opinion, and cognitive interviews. The content development yielded 1,217 unique items. Most of the items were from the qualitative interviews (70%). After 3 sessions of binning and winnowing, and one expert panel session, items were reduced to a minimally representative set (n = 411) across nine QoL domains namely; activity limitation, emotional, social, health concerns, symptoms, economic, mobility, convenience, and coping. Of the 411 items, 345 items were unique to

HRD and 257 were unique to ARD. After 22 cognitive interviews (HRD = 11 and ARD = 11) 29 items were amended resulting in a final set of 345 items in HRD and 3 items were amended resulting in a final set of 254 items in ARD. The domains activity limitation and emotional had the most number of items in both the disease groups. The HRD-specific and the ARD-specific item banks had 189 items in common. The HRD-specific item banks had more unique items (n = 155) than the ARD-specific item banks (n = 65). This study resulted in the development of two comprehensive QoL pilot item pools specific for HRD and ARD. Due to time constraint, it was decided to pilot test the HRD module alone.

The HRD item banks were pilot tested on 233 participants (chapter 5). The psychometric properties of the item banks were assessed using Rasch analysis and computer adaptive testing (CAT) simulations determined the average number of items administered at high and moderate precision levels. Five domains (mobility, convenience, economic, social, and visual symptoms) needed only minor modifications such as fixing the item responses of the misfitting items. Three domains (activity limitation, health concerns, and emotional) demonstrated multidimensionality and needed substantial modifications. Modifications of the activity limitation, health concerns and the emotional domains resulted in five new domains (reading, driving, lighting, positive emotional, and concerns on the disease progression). The main 'emotional' domain was renamed as 'negative emotional' and the main 'health concerns' domain was renamed as 'general health concerns'. Even though the mobility and the coping domains showed multidimensionality, the suspect item clusters were measuring the same underlying traits as the main scales. The 'ocular comfort symptoms' and 'general symptoms' domains were not considered for CAT simulation due to very few number of items and lower precision. Three domains (social, negative emotional, and driving) showed poor targeting. Poor targeting is not a real concern in the CAT system, because item administration in CAT is tailored to participants' ability levels. Overall twenty-one items were deleted due to either gross misfit or confusing item wordings. Eleven items showed DIF. Again, DIF is largely overcome by CAT as the test is tailored to individuals' impairment level. The item banks resulting from this work will provide psychometrically valid measurement of 13 areas of QoL specific to people with HRD.

The CAT simulation showed that on an average only 10 and 5 items were required to gain measurement at high and moderate precision. This will enable a quicker assessment of

patient-reported outcomes in clinics and research settings. With the availability of 13 item banks, clinicians and researches can now choose the constructs relevant to their patients and participants. The CAT simulation also showed that 145 items are required to gain precise measurement of the overall QoL. Approximately it would take 1 minute to answer 10 items and 14 to 15 minutes to answer 145 items.

Finally, the coping domain was tested using Rasch analysis to see if it forms a measurable construct (chapter 6). Psychometric analysis showed that it forms a measurable construct. This domain can provide clinicians and researchers an opportunity to explore the coping responses of people with different HRD. It can also assist identifying subgroups of people with poor perceived health for timely referral to counselling and other rehabilitative services.

7.1 Outcomes and significance

The development of the HRD item banks, for the first time, allows assessment of the impact of different HRD on all QoL domains. Currently HRD are not treatable and new treatment modalities such as gene therapy, retinal prostheses, cell transplantation, and neuroprotection are emerging fast from intensive research. In this situation, clinicians and researchers can use the HRD item banks to assess the impact of new interventions and therapies from the patients' perspective. It can also be used by policy makers to allocate resources for HRD. The application of Rasch scaling through item banking will solve the existing problems with the traditional paper-and-pencil based instruments by providing improved (1) measurement precision through interval-level scoring, (2) measurement accuracy by including only those items that measure the latent trait and (3) sensitivity of instruments to the target population. The CAT system needs only a few items to provide a precise and quick assessment of patient-reported outcomes. This can provide cost savings for outcome research by reducing the sample size required to detect differences in patient-centred outcomes. These item banks have the potential to revolutionize the measurement of vision-specific QoL in HRD.

7.2 Future directions of the research project

7.2.1 Other vitreoretinal diseases module

A CAT system will be developed by professional software designers to implement the HRD

item bank module. The items that were calibrated in this study will be used to develop the computer algorithm for the CAT. An initial set of items with calibration near the median person QoL scores on a Rasch based continuum scale will be chosen for the computer algorithm. The HRD module implemented via the CAT system will be subjected to a series of validity (construct validity, discriminant validity, convergent validity, and known group validity) and reliability tests (test-retest). The HRD module will be administered to participants in different stages of the disease (mild, moderate & severe), participants without disease and participants who have undergone different treatment modalities. Responses will be compared to demonstrate discriminant and known group validity. Convergent validity will be tested by comparing the responses against an existing PRO instrument such as IMQ. The test-retest reliability will be tested by repeating the test at an interval of one month to a group of participants with stable diseases. The validated HRD module will be interviewer administered to participants with different HRD. This data will be used to establish disease group normative data. The HRD module will also be used to test for responsiveness.

The ARD module will also be pilot tested on participants. Rasch analysis will be used to test the psychometric properties of the ARD item banks and to establish calibration for development of the CAT. The ARD module will be subjected to a series of validity and reliability tests and the validated ARD module will be administered to participants with different ARD to obtain normative data.

7.2.2 Other disease-specific modules

The Phase I has identified 3226 unique items for 7 modules (age related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma, cataract, uveitis, refractive error and strabismus and ambylopia) across 8 to 11 ophthalmic QoL domains (activity limitation, mobility, visual symptoms, ocular comfort symptoms, general symptoms, convenience, concerns, social, emotional, economic and coping). Overall 30 – 50% of the items are common between modules. Phase II has been completed for DR and glaucoma. Phase II is ongoing for AMD, strabismus and ambylopia and refractive error. Phase III is ongoing for DR. Comprehensive item banks for disease-specific QoL have been created. Disease-specificity is important as only one-third of items are common across disease modules. A core item set common to modules will be developed and tested.

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Appendix 1

List of generic, ophthalmic but non-disease-specific and retina-specific patient-reported outcome (PRO) instruments used in retinal diseases

Generic PRO instruments
CES-D, The Centre for Epidemiologic Studies Depression Scale; **PHQ**-**9**, Patient Health Questionnaire; **OPS**, Optimization in Primary and Secondary Control Scale ; **HADS**, Hospital Anxiety and Depression Scale; **SF-36**, 36-Item Short Form Health Survey; **GADS**, Goldberg Depression Scale; **IPAQ**, International Planned Activity Questionnaire scale; **HDRS**, Hamilton Depression Rating Scale; **GDS**, Geriatric Depression Scale ; **DSSI**, Duke Social Support Index; **SCID IV**, Structured Clinical Interview; **LOT-R**, Life Orientation Test Revised; **HIQ**, Health and Impact questionnaire; **SPSI**, Social Problem Solving Inventory; **SF-12**, 12-Item Short Form Health Survey; **POMS**, Profile of Mood States; **DHQ**, Driving Habits Questionnaire; **LSQ**, Life Space Questionnaire; **SIP**, Sickness Impact Profile; **SIPV**, Sickness Impact Profile Vision; **HAM-A**, Hamilton Rating Scale for Anxiety; **HAMD**, Hamilton Rating Scale for Depression; **TICS-m**, Telephone Interview for Cognitive Status; **IADL**, Instrumental Activities of Daily Living Questionnaire; **WMS**, Wechsler Memory Scale; **WHOQOL-BREF**, WHO Quality of Life Questionnaire; **GHQ**, General Health questionnaire; **STAI**, Spielberg trait anxiety and trait anger; **CBS**, Chronic Burden Scale; **CMHS**, Cook-Medley Hostility Scale; **CHD-SSI**, Coronary Heart Disease patients study Social Support Instrument; **DTSQ**, Diabetes Treatment Satisfaction Questionnaire; **IPQ-R**, Revised Illness Perception questionnaire; **SDSCA**, Summary of Diabetes Self Care Activities; **PTSD**, Post-Traumatic Stress Disorder; **PTDS,** Posttraumatic Diagnostic Scale; **MOS-HIV**, Medical Outcome Study-HIV Health Survey; **GHRQoL,** General Health Related Quality of Life Measures; **LAPAQ**, Longitudinal Aging Study Amsterdam Physical Activity Questionnaire; **MMSE,** Mini-Mental State Examination; **PSQI,** Pittsburgh Sleep Quality Index; **BDI,** Beck Depression Inventory; **SSS**, Stanford Sleepiness Scale; **ESS,** Epworth Sleepiness Scale; **PSS,** Perceived Stress Scale; **PANAS**, Positive and Negative Affect Schedules; **BSI,** Brief Symptom Inventory; **SCL-90-R**, Symptom Checklist; **MEL**, Munich Life Event List; **TAS -20**, Item Toronto Alexithymia Scale; **F-Sozu,K22**, Symptom List Questionnaire on Social Support; **SLQ**, Symptom List Questionnaire; **PFQ**, Personality Factor Questionnaire; **W-BQ12**, 12-Item well-being questionnaire; **ADDQoL**, Audit of Diabetes-Dependent Quality of Life; **WCS**, Weighted Co-morbidity Scale; **VPI**, Visual Phenomena Interview; **EPQ,** Eysenck Personality Questionnaire; **IQCODE**, Informant Questionnaire for Cognitive Decline; **ADL**, Activity of Daily Living; **PQ,** Pain Questionnaire.
Ophthalmic but non-disease-specific PRO instruments
NEI-VFQ, National Eye Institute Visual Function Questionnaire; **AI**, Activity Inventory; **VF -14**, Visual Function Index; **IVI,** Impact of Visual Impairment; **MLVAI**, Melbourne Low Vision Index; **AVL**, Adaptation to Vision Loss Scale; **EMQ,** Extended Mainz Questionnaire; **FVSQ**, Functional Vision Screening Questionnaire; **ADVS**, Activity of Daily Vision Scale; **MLVQ,** Manchester Low Vision Questionnaire; **VCM1**, Vision Core Measure; **NAS**, Nottingham Adaptation Scale; **VF-11**, Visual Function Index; **CLVQOL**, Chinese Low Vision Quality of Life; **PalmPilot VFQ**, PalmPilot Visual Function Questionnaire; **GAS**, Global Assessment Scores; **VSQ**, Vitrectomy Satisfaction Questionnaire; **VFQ,** Visual Function Questionnaire; **PSQ,** Patient Satisfaction Questionnaire.
Retina-specific PRO instruments
MacDQOL, Macular Disease-Dependent Quality of Life Scale; **DLTV,** Daily Living Tasks Dependent on Vision; **AMD-SEQ**, AMD Self-efficacy Questionnaire; **ALQ**, Activity Limitation Questionnaire; **AMD-HIQ**, Age Related Macular Degeneration Health Impact Questionnaire; **FRQ**, Face Recognition Questionnaire; **DAF**, Discomfort Anxiety Fear Questionnaire; **NVQ-10**, Night Vision Questionnaire; **EDTQ**, Everyday Mobility Difficulties Questionnaire; **VDQ**, Visual Disability Questionnaire; **DTPQ**, Daily Task Performance Questionnaire; **IMQ**, Independent Mobility Questionnaire; **ADVQ,** Activities of Daily Vision Questionnaire; **PVFQ**, Perceived Visual Function Questionnaire; **MDQ,** Mobility Difficulty Questionnaire; **NVQ-39**, Night Vision Questionnaire; **FEQ**, Field Expander Questionnaire; **V-ADL**, Vision Related Activities of Daily Living; **SMDVQ**, Stargardt's Macular Dystrophy Vision Questionnaire; **RetDQoL**, Retinopathy Dependent Quality of Life measure; **RetTSQ**, Retinopathy Treatment Satisfaction Questionnaire; **RDQ**, Retinal Detachment Questionnaire; **SVFQ**, Short Visual Function Questionnaire; **PMHQ**, Positioning for Macular Hole Questionnaire; **MPQ**, Metamorphopsia Questionnaire; **MDSQ**, Macular Disease Society Questionnaire; **CMVQ**, Cytomegalovirus Retinitis Questionnaire

Appendix 2

Semi-structured interview guide for hereditary retinal diseases / acquired retinal diseases

Introduction

Thank you very much for taking the time to participate in this interview. We are currently interested in finding out how having hereditary retinal diseases / acquired retinal diseases impacts on your life as a whole. This includes what you can do and can't do, how you feel, relationship with others and specific effects of the treatment you have had. We are basically interested in hearing your views, experiences and opinions. This will help us to better understand the needs of people who have hereditary retinal diseases / acquired retinal diseases.

My role here involves asking questions and listening. I won't actually be participating in the conversation, instead I would like you to feel free to talk as much as you like in response to the questions. I would like to stress that there are no right or wrong answers and we are most interested in your personal views, opinions and experiences. Therefore, whatever you say and share is right and is extremely important to us.

I'm audio recording this interview because I don't want to miss any of your comments. However, all the information you will provide will remain confidential. Your name will not be attached to any reports arising from this work.

Do you have any questions? Are we happy to move on?

Question route

Warm up questions

How long have you had hereditary retinal disease / acquired retinal diseases? Which eye is affected?

Symptoms

What sort of visual symptoms do you experience due to your eye condition? (E.g. difficulty in night vision, difficulty in seeing in bright light, distorted or tilted vision, difficult in focussing)

What other unwanted symptoms have you experienced because of your eye condition, for example any discomfort or eye strain?

Role Performance & Leisure

Has your eye condition affected your ability to do things in everyday life? (E.g. domestic work, personal care or community duties or employment? If so, how?

Has your ability to engage in leisure or social activities been impacted by your eye problem? If so, how?

Do you have less confidence in undertaking these duties/activities?

Relationships

Has your eye condition changed the way you interact with your partner, family and/or friends? In what ways?

OR *(following specific questions)*

Do you require greater assistance from family and/or friends because of your eye problem? With what sorts of things (e.g. help with mail, reading, chores, transport)

Do you feel other people understand your problem?

Do you feel your family & friends give you the support you need?

Do you feel you are a burden on family and/or friends due to your eye condition? If yes, in what way?

Concerns

Do you have any concerns due to your eye condition and its treatment? (E.g. effect of the disease on you and your family)

Do you have any other concerns? *Prompt each separately if not answered* –(such as about your eyesight, long term effect of the hereditary retinal disease / acquired retinal disease, personal safety, side effects of the treatment or losing your driver's licence, relationship with your partner, family members and friends)

What are your views on the quality of medical care received? Do you feel the advice or information received about your eye condition is adequate? Do the medical staffs communicate effectively? Do you feel your problems are understood?

Emotions

How did you feel when you were first diagnosed with hereditary retinal disease / acquired retinal disease?

How have the impacts of the symptoms and treatment of hereditary retinal disease / acquired retinal disease made you feel? (Feeling of reduced independence, loss of enjoyment, loss of identity or reduced self-esteem)

Do you have any fears and anxieties in relation to your eye condition? (E.g. disease progression, treatments, about the future?)

What are your feelings like in the lead up to appointments, during examination, measurements and treatments?

How do you feel after an appointment? Are you uncomfortable about hearing whether your eye condition is stable or getting worse?

How do you feel after finding your eye condition has become worse, if that has been the case?

How does the knowledge that hereditary retinal diseases / acquired retinal disease can potentially make you legally blind make you feel?

Do you feel depressed or unhappy at times because of your eye condition? If so, can you identify what triggers that make you feel depressed or unhappy?

What do you do to help cope with any negative feelings? Does this help?

Psychological

Has your eye condition altered the way you view yourself. If so, how has this changed?

Do you feel that you are in control of your life living with hereditary retinal disease / acquired retinal disease?

Have you had any issues with …….(prompt separately) because of you eye condition and its treatment/s?

- Identity, self-image
- Self-esteem, confidence
- Loneliness/ isolation
- Coping
- Others

Inconveniences

In your experience, what are the major inconveniences associated with having hereditary retinal disease / acquired retinal disease and its treatment? (Prompts: what about appointments, routine eye tests, instruments used to assess your eyes, time taken, travel, parking)

Costs

How does having hereditary retinal disease / acquired retinal disease and its treatment affect you financially?

Do you feel there have been direct or indirect costs associated with your eye condition and its treatment? (E.g. travel, health insurance, loss of income)

How does having hereditary retinal disease / acquired retinal disease affect your work life?

Treatment/Medical Care

What sort of treatments do you currently receive or have previously received for your eye condition? How have these treatments affected you? (E.g. day-to-day activities, emotionally, financially)

What are your expectations for your treatment? Do you find your expectations are met?

What are your views on the quality of medical care received? Do you feel the advice or information received about hereditary retinal diseases is adequate? Does the medical staff communicate effectively? Do you feel your problems are understood?

Everyday Tasks (Activity limitations)

Do you experience problems performing certain tasks? What are they? (E.g. reading at close/distance, writing, watching television, driving, recognising faces and objects, household chores)

Do you have trouble finding things in shops? Reading price tags?

Are you aware of any tasks you can no longer perform?

Mobility

Do you find that you have more difficulty getting around? What kind of difficulties have you experienced? (E.g. crossing roads, going up and down stairs, visiting friends or neighbours)

Do you feel you have more accidents or you bump into things more often? Can you describe such instances?

Is transportation an issue? If so, how?

Low vision aids

Do you use any visual aids? Do you mind using them? Do they help? (E.g. magnifying glasses, lamps, books with large print, audio books)

Summary

Thank you for your contribution to this project. I highly appreciate for your time and patience. Your experience will be very helpful to us in further understanding how hereditary retinal diseases / acquired retinal disease and its treatment impacts on patients' lives.

Appendix 3

Item modifications following the cognitive interviews for hereditary retinal diseases item bank (n=9)

Items identified as problematic	Comment	Changes made
Reading using low vision devices, e.g. CCTV, magnifiers	You can't blame not being able to use talking devices on sight as they are meant for those without sight.	Item deleted as this statement is already in the preamble (If you need reading glasses or distance glasses or contact lenses or low vision aids or environmental modifications (changes in lighting arrangements or modifications done in your home) please answer according to how you can manage when using them
Q3abc. How often do you feel you have deteriorating vision? 4abc. How often do you experience gradual loss of vision?	Q. 3abc and 4abc seem the same on page 4. Just asked differently	Items 4abc is deleted after referring to the content.
The original online survey has 406 questions	When I first read all the questions last night, it looked a bit overwhelming, but when I have gone through the questions again now, it wasn't so bad, but it may be too much for some people to go through the whole survey.	In addition to the original survey that contain all the questions, a short version of the survey will be developed by splitting the original survey into two surveys (A & B). Survey A will have 192 items and survey B will have 214 items.
Item stem for convenience is how much trouble is….?	On page 8, the questions start with "How much trouble" I don't really understand that line - perhaps something like How do you feel, or how much impact does ...."	The item stem for the domain convenience is changed to how much trouble is it…?
In coping	Page 10, you ask how do people cope with the diagnosis, perhaps do you self-medicate with smoking, drinking alcohol, taking drugs or pills, if people answer yes, this would be a big red flag for your computer system that someone is not coping.	An item 'do you cope by engaging knowingly in unhealthy habits such as smoking, drinking'? was added.
Non-specific	Do you need modification done in your home to make life a little bit easier - lights on in kitchen cupboards etc.	Changed made in the preamble to include a statement on this.
Non-specific	How would you cope in an emergency, thunderstorm, bushfire house fire if you were by yourself?	An item on this issue 'how concerned are you not being able to handle emergency situations, e.g. bushfire, thunderstorm? was added

In the preamble section….Please **only** consider your **hereditary retinal diseases and/or its treatment** when you answer these questions.	In the preambles, I would prefer 'consider only' as opposed to 'only consider'.	The statement in the preamble was modified accordingly.
Item stem for emotional well-being….In the past four weeks how often do you feel……?	In Section 3, there is a clash of tenses in the question. Perhaps the basic structure could read, "In a typical four-week period, how often do you feel...", or "Last month, how often did you feel ... ".	The item stem for the domain, emotional was changed to 'In the past four weeks how often do you feel….?'
Item…how often do you feel discriminating?	In Q 53, 'discriminated' is not an adjective. Perhaps it could read, "situations or people are discriminating against you", or "discriminated against".	Item 53 was changed to 'how often do you feel discriminated against?'
Item … how often do you feel overwhelming?	In Q 62, 'overwhelming' is not used properly. Perhaps it could read, "things are overwhelming", or "overwhelmed".	Item 62 was changed to 'how often do you feel things are overwhelming?'
In the preamble for symptoms…. The symptoms include ocular and general symptoms will be assessed in three different scales, namely frequency, severity and bothersome	In Section 4, I don't know about 'bothersome' in the preamble. Maybe 'to what extent' might be better?	The statement was modified …. The symptoms include ocular and general symptoms will be assessed in three different scales, namely frequency, severity and bothersome (to what extent is it a problem?).
Numbering for items in the domain, symptoms were numbered 1A, 1B and 1C.	When numbering the questions, please separate the number and the letter. 1A looks a lot like 14, and 25B looks a lot like 258.	The numbering 1A was changed to 1 A with space between 1 and A to make it clear.
In the preamble…If you need reading glasses or contact lenses or low vision aide or environmental modifications please answer according to how you can see when using them.	In Section 5, in the preamble, I would change 'how well you can see' to 'how well you can manage'. After all, a long (white) cane doesn't improve my vision, but it is invaluable in helping me manage the situations described in the questions.	The statement 'how you can see when using them' is modified to 'how you can manage when using them?'
How concerned are you about delay in getting diagnosis?	In Section 6, Q 16 should read 'a diagnosis' or 'diagnosed'.	Item 16 was changed to 'how concerned are you about delay in getting a diagnosis?'
Item....how concerned are you about people discriminating you?	Q 17 should read 'discriminating against'.	Item 17 was changed to 'how concerned are you about people discriminating you against?'
Item ----how concerned are you about your visual impairment?	In Q 18, visual impairment' should be 'vision impairment'.	Item 18 was changed to 'how concerned are you about your vision impairment?'
Item … how much of a problem do you have maintaining your friendship?	In Section 7, Q 3 should read 'friendships'.	The item 3 was changed to 'how much of a problem do you have maintaining your friendships?'
Item stem for the domain, convenience….how much of a trouble is…?	In Section 8, most of the questions should start with, 'How much trouble is it ...'	The item stem for the domain, convenience was changed to 'how much trouble is it…?'

How much trouble is having to plan and organize for the things you do beforehand?	Q 7 should read '... plan and organise the things ...'	Item 7 was changed to 'how much trouble is having to plan and organize for the things you do beforehand?'
Item…. Currently, how concerned are you about having to reduce the work hours?	In Section 9 Q8, I would prefer ' ...your work hours.'	Item 8 was changed to 'currently how concerned are about having to reduce your work hours?'
Currently how concerned are you about the cost of buying glasses or other visual aids?	In Q 17, I would prefer 'low vision aids'.	Item 17 was changed to 'currently how concerned are you about the cost of buying glasses or other low vision aids?'
Given that you know your eye condition, do you cope by engaging in adventurous activities, e.g. SCUBA diving, sky diving, mountain climbing?	In Section 10, Q 6 should read 'sky-diving, mountain-climbing'.	The word sky diving was changed to sky-diving.
Given that you know your eye condition, do you cope by attributing to ageing?	Regarding Q 8: 'attributing' what?	Item 8 was changed to 'do you cope by attributing your eye condition to ageing?'
Given that you know your eye condition, do you cope by trying to balance your life with positive and negative stuffs?	In Q 14, I'm sure you can do better than 'stuffs'. May I suggest 'thoughts'?	Item 14 was changed to 'do you cope by trying to balance your life with positive and negative thoughts?'
Given that you know your eye condition, do you cope by turning to work or other activities that take your mood off things, e.g. going for a walk, listening to music, reading books?	Q 17 would read better with 'taking your mind off things'.	Item 17 was changed to 'do you cope by turning to work or other activities that take your mind off things?'
Given that you know your eye condition, do you cope by having a peer support?	Q 28 should read 'peer' instead of 'a peer'.	Item 28 was changed to 'do you cope by having peer support?'
Response categories for the domains, mobility, and activity limitation	I would suggest having an option of 'Unable to do so without assistance/companion' or something similar for questions about difficulty going places, doing things, etc.	No changes made because getting assistance was included in the preamble.
How often do you feel you have gradual loss of vision?	I didn't fully understand Q4A (Symptoms)	Item removed
Management of hereditary retinal diseases • Low vision rehabilitation • None • Others (specify)	Management – low vision , ophthalmologist	Item removed
Low vision rehabilitation Yes No	13 what does this mean Rehab/aids?	Item 13 changed to 'Do you use low vision aids'
Response categories for the domain activity limitation	Activity limitation - Why have a refuse to answer box? Perhaps a box for comment? (not only this section, but all sections?)	Comment ignored as it is not possible to include a box for comment.

How much difficulty do you have reading sign posts, e.g. shop names?	5 reading signage (not posts!!)	Item 5 was changed to 'how much difficulty do you have reading signage, e.g. shop names?
How much difficulty do you have engaging in hobby or leisure activities, e.g. dancing, singing, and going to the beach?	36 e.g. walking	Item 36 was changed to 'how much difficulty do you have engaging in hobby or leisure activities, e.g. dancing, singing, walking'
How much difficulty do you have seeing things spilt on floor?	38 spilt or dropped on floor!	Item 38 is changed to 'how much difficulty do you have seeing things spilt or dropped on floor?'
How much difficulty do you have reading street signs during the day? How much difficulty do you have seeing road signs?	Are 39 & 14 the same?	Item 39 is dropped
How much difficulty do you have cutting your toenails safely?	61 and fingernails!	Item 61 was changed to 'how much difficulty do you have cutting your fingernails and toenails safely?'
How much difficulty do you have travelling overseas?	72 Travelling domestic and overseas!	Item 72 was changed to 'how much difficulty do you have travelling domestic and overseas?'
In the past four weeks how often do you feel shocked by what your eye specialist have told you about your eyes?	Emotional wellbeing _ - 16 Has!!	Item 16 was modified to 'how often do you feel shocked by what your eye specialist has told you about your eyes?'
In the past four weeks how often do you feel confronting?	21 Confronted	Item 21 changed to 'during the past four weeks how often do you feel confronted?'
In the past four weeks how often do you feel awkward?	56 Have you felt	Item 56 changed to 'during the past four weeks how have you felt awkward?'
How much difficulty do you have stepping on and off a train?	Mobility-Include tram	Item was changed to 'how much difficulty do you have stepping on and off a train or a tram?'
Given that you know your eye condition, do you cope by getting on with your eye condition?	Coping- 15 Getting on/coping!	Item deleted as item content was similar to another item ('accepting your eye condition')
How much difficulty do you have reading a book?	I 'd be a little uncertain how to answer these questions as I'm ok for say 5 - 10 mins of reading, but then it becomes more difficult the longer I try to read	Statement on this was included in the preamble.
How much difficulty do you have reading a menu in a dimly lit restaurant?	I'm a little unsure about these questions, as in many situations suggested, I'd be accompanied by my husband. If I were to answer as though I was alone, the answers would be quite different.	Getting assistance for doing day-to-day activities has been included in the preamble already.

How much difficulty do you have going to a sports event, e.g. cricket, tennis, football?	Question 38 Is that asking how difficult it is seeing what's going on at a sporting event? Rather than going to a sporting event.	It was decided to have two items ('difficulty going to a sporting event' and 'difficulty seeing the sporting event')
Response options for the domain activity limitation	Section 2 .I think add a selection: Varies. Or else add a little in the Notes – answer how you feel on the majority of days. I say this because my vision varies a lot. Some days I can hardly see a thing on sunny days, other days it's ok. Some days I can read the computer screen, other days even with the same settings it's really hard to see things.	The statement 'how you feel on the majority of the days' was added to the preamble.

Hereditary retinal degenerations/dystrophies item bank questionnaire

Appendix 4

Instructions

All the following questions are about the impact of hereditary retinal degenerations/dystrophies (HRD) and its treatment on your quality of life. By HRD, we mean eye conditions such as retinitis pigmentosa, cone dystrophy, congenital stationary night blindness, macular dystrophy, choroidal dystrophy etc. that affects the peripheral part or the central part or both peripheral and central part of your retina (i.e. back of your eye). I will read each question out to you. After each question, I will read you a list of possible answers. Please give me the answer that best applies to you.

Please take as much time as you need to answer each question.

Please answer every question unless you need to skip questions because they don't apply to you (select "not applicable"). All your answers and the information you have provided will be regarded as strictly confidential.

Please consider only your HRD and/or its treatment when you answer these questions. If you need reading glasses or distance glasses or contact lenses or low vision aids or environmental modifications (changes in lighting arrangements or modifications done in your home) or help and assistance please answer according to how you can see when using them.

Date: Time started: Time finished: Duration:	Name: ID: Interviewer: Mode: Face to face / Phone Combination

Hereditary retinal degenerations/dystrophies item bank questionnaire

Background Questionnaire

Name: _____ **DOB:** _ _/ _ _/ _ _ _ _

Gender: M / F **Postal code:** _____

Main language spoken at home: English/ Other *(If others specify)* _____

Marital status: Never married/ Married / De-facto / Divorced / Separated / Widowed
(Please circle)

Highest level of education: Primary – Incomplete / Complete
(Please circle) Secondary – Incomplete / Complete
TAFE / Uni – Incomplete / Complete

Current employment status: Retired/ Disability Pension/ Unemployed
(Please circle) Working / Volunteer Work

Diagnosis of your eye condition: _____

Eye/s involved: Right eye / Left eye / Both eyes

How many years have you had the eye condition for? _____

Other eye condition/s: Diabetic Retinopathy/ Cataract / Glaucoma/ Age related macular Degeneration / None
(Please circle) Other eye conditions *(specify)* _____

Do you use low visual aids? Yes / No

If yes, select all those apply to you:
Magnifiers (e.g. CCTV or digital magnifier)
Non-optical aids (e.g. typoscope)
Computer software
Changes to environment
Orientation and mobility training
Others (specify): _____
(Please circle)

Other medical condition/s: Diabetes mellitus/ Pulmonary disease/ Arthritis/ Hypertension/ Heart problems/ None/ others (specify)…….

Right eye visual acuity (if known) _____

Left eye visual acuity (if known) _____

Hereditary retinal degenerations/dystrophies item bank questionnaire

VISUAL SYMPTOMS															
How often do you experience…?		Never	Occasionally	Quite often	Very often	**How severe is/are the…?**	Not at all	Mild	Moderate	Severe	**How much of a problem is/are the…?**	None	A little	Quite a bit	A lot
VS1	Blurred vision	4	3	2	1	Blurred vision	4	3	2	1	Blurred vision	4	3	2	1
VS2	Poor vision in one or both eyes	4	3	2	1	Poor vision in one or both eyes	4	3	2	1	Poor vision in one or both eyes	4	3	2	1
VS3	**How often do you feel you have** deteriorating vision?	4	3	2	1	Deterioration of vision	4	3	2	1	Deterioration of vision	4	3	2	1
VS4	Floaters in your vision	4	3	2	1	Floaters in your vision	4	3	2	1	Floaters in your vision	4	3	2	1
VS5	Distorted vision (lines you know are straight appear curved or distorted)	4	3	2	1	Distorted vision (lines you know are straight appear curved or distorted)	4	3	2	1	Distorted vision (lines you know are straight appear curved or distorted	4	3	2	1
VS6	Loss of your peripheral vision	4	3	2	1	Loss of your peripheral vision	4	3	2	1	Loss of your peripheral vision	4	3	2	1
VS7	Difficulty seeing at night	4	3	2	1	Difficulty seeing at night	4	3	2	1	Difficulty seeing at night	4	3	2	1
VS8	Difficulty in depth perception	4	3	2	1	Depth perception	4	3	2	1	Depth perception	4	3	2	1
VS9	Spots in your vision	4	3	2	1	Spots in your vision	4	3	2	1	Spots in your vision	4	3	2	1
VS10	Flashes of light from within your eyes	4	3	2	1	Flashes of light from within your eyes	4	3	2	1	Flashes of light from within your eyes	4	3	2	1
VS11	Difficulty in light /dark adaptation	4	3	2	1	Difficulty in light /dark adaptation	4	3	2	1	Difficulty in light /dark adaptation	4	3	2	1

VS12	Difficulty focussing your eyes	4	3	2	1	Difficulty focussing your eyes	4	3	2	1	Difficulty focussing your eyes	4	3	2	1
VS13	Difficulty distinguishing colours	4	3	2	1	Difficulty distinguishing colours	4	3	2	1	Difficulty distinguishing colours	4	3	2	1
VS14	Glare from lights	4	3	2	1	Glare from lights	4	3	2	1	Glare from lights	4	3	2	1
VS15	Cloudy vision	4	3	2	1	Cloudy vision	4	3	2	1	Cloudy vision	4	3	2	1
VS16	Double vision	4	3	2	1	Double vision	4	3	2	1	Double vision	4	3	2	1
VS17	Difficulty distinguishing contrast	4	3	2	1	Difficulty distinguishing contrast	4	3	2	1	Difficulty distinguishing contrast	4	3	2	1
VS18	Patches of your vision missing	4	3	2	1	Patches of your vision missing	4	3	2	1	Patches of your vision missing	4	3	2	1
VS19	Tunnel vision	4	3	2	1	Tunnel vision	4	3	2	1	Tunnel vision	4	3	2	1
VS20	Day-to-day visual fluctuations	4	3	2	1	Day-to-day visual fluctuations	4	3	2	1	Day-to-day visual fluctuations	4	3	2	1

Hereditary retinal degenerations/dystrophies item bank questionnaire

OCULAR COMFORT SYMPTOMS														
How often do you experience…?		Never	Occasionally	Quite often	Very often	**How severe is/are the…?**	Not at all	Mild	Moderate	Severe	**How much of a problem is/are the…?**	None	A little	Quite a bit	A lot
OS1	Achy eyes	4	3	2	1	Achy eyes	4	3	2	1	Achy eyes	4	3	2	1
OS2	Watery eyes	4	3	2	1	Watery eyes	4	3	2	1	Watery eyes	4	3	2	1
OS3	Tired eyes	4	3	2	1	Tired eyes	4	3	2	1	Tired eyes	4	3	2	1
OS4	Eye strain	4	3	2	1	Eye strain	4	3	2	1	Eye strain	4	3	2	1
OS5	Discomfort in your eyes	4	3	2	1	Discomfort in your eyes	4	3	2	1	Discomfort in your eyes	4	3	2	1

Hereditary retinal degenerations/dystrophies item bank questionnaire

GENERAL SYMPTOMS

How often do you experience…?		Never	Occasionally	Quite often	Very often	**How severe is/are the…?**	Not at all	Mild	Moderate	Severe	**How much of a problem is/are the…?**	None	A little	Quite a bit	A lot
GS1	Headaches due to your vision	4	3	2	1	Headaches due to your vision	4	3	2	1	Headaches due to your vision	4	3	2	1
GS2	Body aches	4	3	2	1	Body aches	4	3	2	1	Body aches	4	3	2	1
GS3	Tiredness	4	3	2	1	Tiredness	4	3	2	1	Tiredness	4	3	2	1
GS4	Dizziness	4	3	2	1	Dizziness	4	3	2	1	Dizziness	4	3	2	1
GS5	Fatigue	4	3	2	1	Fatigue	4	3	2	1	Fatigue	4	3	2	1
GS6	Hallucinations/vivid dreams	4	3	2	1	Hallucinations/vivid dreams	4	3	2	1	Hallucinations/vivid dreams	4	3	2	1

Hereditary retinal degenerations/dystrophies item bank questionnaire

ACTIVITY LIMITATION								
How much difficulty do you have…?		**None**	**A little**	**Quite a bit**	**A lot**	**Unable to do because of my vision**	**This task is not relevant to me / don't do the task**	**Refuse to answer**
AL1	Reading book	5	4	3	2	1	9	8
AL2	Reading small print, e.g. the phone book, yellow pages	5	4	3	2	1	9	8
AL3	Reading a large print book	5	4	3	2	1	9	8
AL4	Reading the newspaper	5	4	3	2	1	9	8
AL5	Reading signage e.g. shop names	5	4	3	2	1	9	8
AL6	Reading in dim light conditions	5	4	3	2	1	9	8
AL7	Reading musical notes	5	4	3	2	1	9	8
AL8	Reading a menu in a dimly lit restaurant	5	4	3	2	1	9	8
AL9	Reading hand written documents	5	4	3	2	1	9	8
AL10	Reading text on your mobile phone screen	5	4	3	2	1	9	8
AL11	Reading from a portable screen, e.g. iPad, kindle book, iPhone	5	4	3	2	1	9	8
AL12	Reading street signs during the day	5	4	3	2	1	9	8
AL13	Reading street signs at night	5	4	3	2	1	9	8
AL14	Reading glossy and colourful prints, e.g. cook books, articles, magazines	5	4	3	2	1	9	8
AL15	Reading the numbers on the front of a bus	5	4	3	2	1	9	8
AL16	Reading price labels in shops	5	4	3	2	1	9	8
AL17	Reading the nutritional information or ingredients on food labels	5	4	3	2	1	9	8
AL18	Reading from a computer screen	5	4	3	2	1	9	8
AL19	Reading signs in supermarket	5	4	3	2	1	9	8
AL20	Doing any small, fiddly task	5	4	3	2	1	9	8
AL21	Using the computer	5	4	3	2	1	9	8
AL22	Using technology /gadgets, e.g. navigation devices, GPS	5	4	3	2	1	9	8
AL23	Researching things on the Internet	5	4	3	2	1	9	8
AL24	Recognising someone across the street	5	4	3	2	1	9	8
AL25	Recognising a friend up close	5	4	3	2	1	9	8
AL26	Seeing facial expressions	5	4	3	2	1	9	8

Hereditary retinal degenerations/dystrophies item bank questionnaire

How much difficulty do you have…?		None	A little	Quite a bit	A lot	Unable to do because of my vision	This task is not relevant to me / don't do the task	Refuse to answer
AL27	Cooking	5	4	3	2	1	9	8
AL28	Eating meals	5	4	3	2	1	9	8
AL29	Serving yourself food from the table	5	4	3	2	1	9	8
AL30	Cutting up food on your plate	5	4	3	2	1	9	8
AL31	Pouring a drink	5	4	3	2	1	9	8
AL32	Recognising traffic signals, e.g. the walk/don't walk light	5	4	3	2	1	9	8
AL33	Engaging in a hobby or leisure activity, e.g. dancing, singing, walking	5	4	3	2	1	9	8
AL34	Going out for entertainment, e.g. a movie, play or concert	5	4	3	2	1	9	8
AL35	Seeing things spilt or dropped on floor	5	4	3	2	1	9	8
AL36	Going to a sports event, e.g. cricket, tennis, football	5	4	3	2	1	9	8
AL37	Seeing what's going on at a sporting event, e.g. cricket, tennis, rugby	5	4	3	2	1	9	8
AL38	Taking part in recreational activities, e.g. bowling, fishing, shooting	5	4	3	2	1	9	8
AL39	Exercising and keeping fit	5	4	3	2	1	9	8
AL40	Finding something when it is surrounded by a lot of other things, e.g. on a crowded shelf or in a full drawer	5	4	3	2	1	9	8
AL41	Playing board games, e.g. Sudoku puzzles, bingo, cards, scrabble	5	4	3	2	1	9	8
AL42	Using hand tools, e.g. a screwdriver, hammer, chisel	5	4	3	2	1	9	8
AL43	Doing household chores e.g. cleaning, dusting, vacuuming	5	4	3	2	1	9	8
AL44	Hanging out the washing	5	4	3	2	1	9	8
AL45	Doing the ironing	5	4	3	2	1	9	8
AL46	Crocheting or knitting	5	4	3	2	1	9	8
AL47	Taking care of garden, e.g. weeding, pruning, mowing the lawn	5	4	3	2	1	9	8
AL48	Sewing	5	4	3	2	1	9	8
AL49	Seeing in poorly lit surroundings	5	4	3	2	1	9	8
AL50	Seeing at night	5	4	3	2	1	9	8
AL51	Seeing in the daytime	5	4	3	2	1	9	8
AL52	Seeing in bright sunlight	5	4	3	2	1	9	8
AL53	Seeing in glare conditions	5	4	3	2	1	9	8

AL54	Seeing in artificial lighting	5	4	3	2	1	9	8
AL55	Adjusting to bright light after the lighting has been rather dim	5	4	3	2	1	9	8
AL56	Adjusting to dark indoor lighting after being in bright light	5	4	3	2	1	9	8
AL57	Looking after your appearance, e.g. your face, hair, shaving	5	4	3	2	1	9	8
AL58	Cutting your fingernails and toenails safely	5	4	3	2	1	9	8
AL59	Putting on make-up	5	4	3	2	1	9	8
AL60	In dressing yourself	5	4	3	2	1	9	8
AL61	Finding things in shopping	5	4	3	2	1	9	8
AL62	Doing online shopping	5	4	3	2	1	9	8
AL63	Doing grocery shopping	5	4	3	2	1	9	8
AL64	Doing shopping other than grocery, e.g. clothes, jewellery	5	4	3	2	1	9	8
AL65	Judging the ball when playing ball sports, e.g. tennis, netball	5	4	3	2	1	9	8
AL66	Playing outdoor sports, e.g. golf, soccer, netball	5	4	3	2	1	9	8
AL67	Playing blind sports, e.g. blind cricket, blind tennis	5	4	3	2	1	9	8
AL68	Threading a needle	5	4	3	2	1	9	8
AL69	Travelling domestic and overseas	5	4	3	2	1	9	8
AL70	Watching TV	5	4	3	2	1	9	8
AL71	Writing on a card or a notebook	5	4	3	2	1	9	8
AL72	Writing and signing document	5	4	3	2	1	9	8
AL73	Telling the difference between coins or notes	5	4	3	2	1	9	8
AL74	Using a ruler or tape measure	5	4	3	2	1	9	8
AL75	Riding a bike in the daytime	5	4	3	2	1	9	8
AL76	Riding a bike in the dark (but with a flash light/bicycle light/headlight	5	4	3	2	1	9	8
AL77	Riding a bike in twilight or more than sufficient street light	5	4	3	2	1	9	8
AL78	Riding motorcycle/moped	5	4	3	2	1	9	8
AL79	Driving during the day	5	4	3	2	1	9	8
AL80	Driving in unfamiliar areas	5	4	3	2	1	9	8
AL81	Driving at night	5	4	3	2	1	9	8
AL82	Noticing when the car in front of you is speeding up or slowing down	5	4	3	2	1	9	8
AL83	Driving towards oncoming headlights	5	4	3	2	1	9	8
AL84	Changing lanes in traffic	5	4	3	2	1	9	8
AL85	Driving at dusk or dawn	5	4	3	2	1	9	8
AL86	Seeing road markings clearly when driving	5	4	3	2	1	9	8

Hereditary retinal degenerations/dystrophies item bank questionnaire

MOBILITY								
How much difficulty do you have…?		**None**	**A little**	**Quite a bit**	**A lot**	**Unable to do because of my vision**	**This task is not relevant to me / don't do the task**	**Refuse to answer**
MB1	Negotiating obstacles while walking, e. g. branches, poles, stones	5	4	3	2	1	9	8
MB2	Walking in crowded situations	5	4	3	2	1	9	8
MB3	Walking in a cluttered environment	5	4	3	2	1	9	8
MB4	Walking in dimly lit indoor areas	5	4	3	2	1	9	8
MB5	Walking around unfamiliar areas	5	4	3	2	1	9	8
MB6	Walking around your home	5	4	3	2	1	9	8
MB7	Walking during daytime	5	4	3	2	1	9	8
MB8	Walking around familiar areas	5	4	3	2	1	9	8
MB9	Walking around outdoors	5	4	3	2	1	9	8
MB10	Walking down a hallway	5	4	3	2	1	9	8
MB11	Walking in high-glare areas	5	4	3	2	1	9	8
MB12	Navigating in dim light	5	4	3	2	1	9	8
MB13	Crossing a street or road	5	4	3	2	1	9	8
MB14	Going down steps or stairs	5	4	3	2	1	9	8
MB15	Using steps/stairs in the daytime	5	4	3	2	1	9	8
MB16	Using escalators in busy places, e.g. train stations, shopping centres	5	4	3	2	1	9	8
MB17	Going up steps or stairs	5	4	3	2	1	9	8
MB18	Using unmarked steps or curbs, e.g. concrete curbs or steps that do not have a coloured strip	5	4	3	2	1	9	8
MB19	Using steps at night	5	4	3	2	1	9	8
MB20	Stepping on and off a train or a tram	5	4	3	2	1	9	8
MB21	Going on long journeys	5	4	3	2	1	9	8
MB22	Travelling somewhere independently	5	4	3	2	1	9	8
MB23	Using public transport	5	4	3	2	1	9	8

Hereditary retinal degenerations/dystrophies item bank questionnaire

EMOTIONAL							
During the past four weeks, how often do you…?		**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**	**Refuse to answer**
EM1	Feel hopeful	1	2	3	4	5	8
EM2	Feel encouraging	1	2	3	4	5	8
EM3	Feel appreciative	1	2	3	4	5	8
EM4	Feel surprised	1	2	3	4	5	8
EM5	Feel relieved	1	2	3	4	5	8
EM6	Feel fortunate	1	2	3	4	5	8
EM7	Feel grateful	1	2	3	4	5	8
EM8	Feel anxious	5	4	3	2	1	8
EM9	Feel like you've lost your confidence doing usual activities	5	4	3	2	1	8
EM10	Feel like a nuisance or a burden	5	4	3	2	1	8
EM11	Feel left out	5	4	3	2	1	8
EM12	Feel depressed	5	4	3	2	1	8
EM13	Feel gloomy	5	4	3	2	1	8
EM14	Feel upset	5	4	3	2	1	8
EM15	Feel lonely or isolated	5	4	3	2	1	8
EM16	Feel shocked by what your eye specialist have told you about your eyes	5	4	3	2	1	8
EM17	Feel worried	5	4	3	2	1	8
EM18	Feel reluctant to talk about your eye problem	5	4	3	2	1	8
EM19	Feel frustrated	5	4	3	2	1	8
EM20	Feel devastated	5	4	3	2	1	8
EM21	Feel confronted	5	4	3	2	1	8
EM22	Feel angry	5	4	3	2	1	8
EM23	Have trouble accepting that your eye problems are permanent	5	4	3	2	1	8
EM24	Feel like crying	5	4	3	2	1	8
EM25	Feel insecure	5	4	3	2	1	8
EM26	Feel stressed	5	4	3	2	1	8
EM27	Feel vulnerable	5	4	3	2	1	8
EM28	Feel humiliated	5	4	3	2	1	8
EM29	Feel traumatised	5	4	3	2	1	8
EM30	Feel terrible	5	4	3	2	1	8
EM31	Feel disoriented	5	4	3	2	1	8
EM32	Feel confused	5	4	3	2	1	8
EM33	Feel lost	5	4	3	2	1	8
EM34	Have a sudden feel of panic	5	4	3	2	1	8
EM35	Feel like you have lost your self-esteem	5	4	3	2	1	8
EM36	Feel disgusted	5	4	3	2	1	8

EM37	Feel unlucky	5	4	3	2	1	8
EM38	Feel sorry for yourself	5	4	3	2	1	8
EM39	Feel annoyed	5	4	3	2	1	8
EM40	Feel stupid	5	4	3	2	1	8
EM41	Feel dissatisfied	5	4	3	2	1	8
EM42	Feel cranky	5	4	3	2	1	8
EM43	Feel hurt	5	4	3	2	1	8
EM44	Feel unhappy	5	4	3	2	1	8
EM45	Feel fearful	5	4	3	2	1	8
EM46	Feel like 'why me'	5	4	3	2	1	8
EM47	Feel disappointed	5	4	3	2	1	8
EM48	Feel afraid	5	4	3	2	1	8
EM49	Feel sad or low	5	4	3	2	1	8
EM50	Feel nervous	5	4	3	2	1	8
EM51	Have suicidal thoughts	5	4	3	2	1	8
EM52	Feel discriminated against	5	4	3	2	1	8
EM53	Feel awful	5	4	3	2	1	8
EM54	Feel demeaning	5	4	3	2	1	8
EM55	During the past four weeks, how often have you felt awkward?	5	4	3	2	1	8
EM56	Feel like you've lost enjoyment in things	5	4	3	2	1	8
EM57	Feel terrified	5	4	3	2	1	8
EM58	Feel daunted	5	4	3	2	1	8
EM59	Feel subdued	5	4	3	2	1	8
EM60	Feel exhausted	5	4	3	2	1	8
EM61	Feel overwhelmed	5	4	3	2	1	8
EM62	Feel constrained	5	4	3	2	1	8
EM63	Feel inferior	5	4	3	2	1	8
EM64	Feel embarrassed	5	4	3	2	1	8
EM65	Feel life is so hard?	5	4	3	2	1	8
EM66	Feel stuck with your eye condition and treatment	5	4	3	2	1	8

HEALTH CONCERNS								
How concerned are you about…?		**Not at all**	**A little bit**	**A moderate amount**	**A lot**	**Extremely**	**This issue is not relevant to me**	**Refuse to answer**
HC1	Your eyesight getting worse	5	4	3	2	1		8
HC2	Going blind	5	4	3	2	1		8
HC3	Coping with things	5	4	3	2	1		8
HC4	Not being able to continue with your hobbies or leisure activities	5	4	3	2	1		8
HC5	Having to learn to do things in different ways.	5	4	3	2	1		8
HC6	Not knowing what's going to happen in the future	5	4	3	2	1		8
HC7	Falling	5	4	3	2	1		8
HC8	Tripping	5	4	3	2	1		8
HC9	Bumping into people or objects	5	4	3	2	1		8
HC10	Burning and scalding	5	4	3	2	1		8
HC11	Having accidents (motor vehicle related)	5	4	3	2	1		8
HC12	Having accidents (non-motor vehicle related)	5	4	3	2	1	9	8
HC13	The way how you do things	5	4	3	2	1	9	8
HC14	Not able to do things as before	5	4	3	2	1	9	8
HC15	Your disease progression	5	4	3	2	1	9	8
HC16	Delay in getting a diagnosis	5	4	3	2	1	9	8
HC17	People discriminating against	5	4	3	2	1	9	8
HC18	People not understanding your vision impairment	5	4	3	2	1	9	8
HC19	Maintaining your relationship with friends and family members	5	4	3	2	1	9	8
HC20	Not being able to make plans for the future because your vision keeps changing	5	4	3	2	1	9	8
HC21	Your family having to change the way they interact with you	5	4	3	2	1	9	8

HC22	Missing out on things	5	4	3	2	1	9	8
HC23	People not understanding the difficulties you face in day-to-day life	5	4	3	2	1	9	8
HC24	The way people react to you	5	4	3	2	1	9	8
HC25	What other people think of you	5	4	3	2	1	9	8
HC26	Losing your vision little by little all the time	5	4	3	2	1	9	8
HC27	The impact your vision loss has on your family members	5	4	3	2	1	9	8
HC28	Losing independence in the future	5	4	3	2	1	9	8
HC29	Losing your driver's license	5	4	3	2	1	9	8
HC30	The way you are treated by your eye care practitioner	5	4	3	2	1	9	8
HC31	How well your eye treatment is working	5	4	3	2	1	9	8
HC32	Not being able to keep up to date with things	5	4	3	2	1	9	8
HC33	Being able to access services, e.g. low vision service	5	4	3	2	1	9	8
HC34	Not getting enough information or explanation from medical staff	5	4	3	2	1	9	8
HC35	Not having enough support	5	4	3	2	1	9	8
HC36	Passing eye condition onto your children	5	4	3	2	1	9	8
HC37	Not being able to care for family	5	4	3	2	1	9	8
HC38	Starting a family or having more children	5	4	3	2	1	9	8
HC39	Vision not improving with glasses	5	4	3	2	1	9	8
HC40	Not being able to see the faces of your family members	5	4	3	2	1	9	8
HC41	Putting other people in danger by driving	5	4	3	2	1	9	8
HC42	People taking advantage of you	5	4	3	2	1	9	8
HC43	People judging you	5	4	3	2	1	9	8
HC44	Knowing that there is no or limited treatment options available for your eye condition	5	4	3	2	1	9	8

HC45	Becoming separated from the person you are with	5	4	3	2	1	9	8
HC46	Possibility of being rejected by friends/partners	5	4	3	2	1	9	8
HC47	Interacting with other people	5	4	3	2	1	9	8
HC48	Not being able to handle emergency situations, e.g. Bushfire, thunderstorm	5	4	3	2	1	9	8

Hereditary retinal degenerations/dystrophies item bank questionnaire

SOCIAL								
How much of a problem do you have…?		**None**	**A little**	**Quite a bit**	**A lot**	**Unable to do because of my vision**	**This task is not relevant to me / don't do the task**	**Refuse to answer**
SC1	Meeting friends and family socially	5	4	3	2	1		8
SC2	With family members or friends making an issue of your eye problem	5	4	3	2	1		8
SC3	Maintaining your friendships	5	4	3	2	1		8
SC4	Interacting socially with people	5	4	3	2	1		8
SC5	Maintaining your usual social activities or social life	5	4	3	2	1		8
SC6	Making new friends	5	4	3	2	1		8
SC7	Entertaining friends and family in your own home	5	4	3	2	1		8
SC8	Getting help and support from your family and friends	5	4	3	2	1	9	8
SC9	Being part of social activities/ games, e.g. parent groups, pubs, attending funeral	5	4	3	2	1	9	8
SC10	Attending organised social functions like weddings, parties, BBQ	5	4	3	2	1	9	8
SC11	Getting help or support from social welfare / government organisations	5	4	3	2	1	9	8
SC12	Engaging with your children or grandchildren	5	4	3	2	1	9	8
SC13	With strain in family relationships	5	4	3	2	1	9	8
SC14	Maintaining your close Personal relationship, e.g. marriage, partner, living companion, steady relationship	5	4	3	2	1	9	8
SC15	Maintaining your roles and responsibilities in the family	5	4	3	2	1	9	8
SC16	Chatting with people	5	4	3	2	1	9	8
SC17	Maintaining your roles and responsibilities in community organisations (e.g. church groups, volunteering, clubs)	5	4	3	2	1	9	8
SC18	Participating in social activities at night	5	4	3	2	1	9	8
SC19	Going out with family and friends	5	4	3	2	1	9	8

SC20	Doing things as a couple or friends e.g. going on holidays/ visiting places/doing recreational activities	5	4	3	2	1	9	8
SC21	With strain in your relationship with your partner	5	4	3	2	1	9	8
SC22	Engaging in social activities at or after work	5	4	3	2	1	9	8
SC23	Interacting with people at work	5	4	3	2	1	9	8
SC24	Interacting with people with similar eye condition	5	4	3	2	1	9	8
SC25	With family members getting annoyed at you when you can't do something or if you make a mistake	5	4	3	2	1	9	8
SC26	Eating out with your relatives or friends	5	4	3	2	1	9	8
SC27	With your family members being over protective	5	4	3	2	1	9	8
SC28	Not being aware of what other people around you are doing	5	4	3	2	1	9	8

Hereditary retinal degenerations/dystrophies item bank questionnaire

CONVENIENCE								
How much trouble is it…?		**None**	**A little bit**	**A moderate amount**	**Quite a lot**	**Extremely**	**This task is not relevant to me / don't do the task**	**Refuse to answer**
CV1	Not being able to do what you want to do	5	4	3	2	1		8
CV2	Not being able to do things as well as you used to	5	4	3	2	1		8
CV3	Having to use low vision aids for doing things, e.g. reading	5	4	3	2	1		8
CV4	Having to concentrate harder on things	5	4	3	2	1		8
CV5	Needing longer to do things	5	4	3	2	1		8
CV6	Having to rely on others for help	5	4	3	2	1		8
CV7	Having to plan and organise for the things you do beforehand	5	4	3	2	1		8
CV8	Losing or misplacing things	5	4	3	2	1		8
CV9	The amount of time needed when attending your eye appointment	5	4	3	2	1	9	8
CV10	Having to travel a long way to attend your eye appointment	5	4	3	2	1	9	8
CV11	Having to rely on public transport to do day to day tasks, e.g. shopping	5	4	3	2	1	9	8
CV12	Having to drive slower and more carefully	5	4	3	2	1	9	8
CV13	Having to allow a bit of extra leeway when going to unfamiliar places	5	4	3	2	1	9	8
CV14	Having to rely on computers and technology	5	4	3	2	1	9	8
CV15	Having to adopt unusual head or body posture	5	4	3	2	1	9	8
CV16	Having more complicated travel plans (because of driving limitations, e.g. at night-time)	5	4	3	2	1	9	8

Hereditary retinal degenerations/dystrophies item bank questionnaire

ECONOMIC								
Currently, how concerned are you about...?		**Not at all**	**A little bit**	**A moderate amount**	**Quite a bit**	**Extremely**	**This issue is not relevant to me**	**Refuse to answer**
EC1	Your ability to find employment or get a new job	5	4	3	2	1	9	8
EC2	Limitation on the types of jobs you can do e.g. jobs that require a driving licence, lots of reading or computer work	5	4	3	2	1	9	8
EC3	Not being able to work	5	4	3	2	1	9	8
EC4	Losing your job	5	4	3	2	1	9	8
EC5	Being able to access work-related opportunities, such as promotions or training	5	4	3	2	1	9	8
EC6	Your career being compromised	5	4	3	2	1	9	8
EC7	Having to change career due to losing sight	5	4	3	2	1	9	8
EC8	Having to reduce the work hours	5	4	3	2	1	9	8
EC9	The financial impact from loss of income	5	4	3	2	1	9	8
EC10	The cost associated with upgrading computer and technology	5	4	3	2	1	9	8
EC11	The cost associated with seeing your eye specialist	5	4	3	2	1	9	8
EC12	The cost associated with looking after guide dog, e.g. food, vet bills	5	4	3	2	1	9	8
EC13	The cost associated with accessing private health care	5	4	3	2	1	9	8
EC14	The cost associated with taking care of children affected with similar eye condition as yours	5	4	3	2	1	9	8
EC15	The cost associated with travel, e.g. taxis, bus	5	4	3	2	1	9	8
EC16	The costs associated with Leisure activities, e.g. gymnastics	5	4	3	2	1	9	8
EC17	The cost of buying glasses or other visual aids	5	4	3	2	1	9	8

Hereditary retinal degenerations/dystrophies item bank questionnaire

COPING							
Given that you know your eye condition, do you cope by……..?		**Not at all**	**A little bit**	**A moderate amount**	**A lot**	**Extremely**	**Refuse to answer**
CP1	Accepting your eye condition	1	2	3	4	5	8
CP2	Learning to live with your eye condition	1	2	3	4	5	8
CP3	Communicating with people about your eye condition	1	2	3	4	5	8
CP4	Thinking that there are people much worse than you	1	2	3	4	5	8
CP5	Learning to do things in a different way than you used to do before	1	2	3	4	5	8
CP6	Engaging in adventurous activities, e.g. SCUBA diving, Sky-diving, mount-climbing	1	2	3	4	5	8
CP7	Getting professional support	1	2	3	4	5	8
CP8	Attributing you eye condition to ageing	1	2	3	4	5	8
CP9	Trying not to think about it	1	2	3	4	5	8
CP10	Trying to be positive	1	2	3	4	5	8
CP11	Trying to be more independent	1	2	3	4	5	8
CP12	Learning to deal with frustrations	1	2	3	4	5	8
CP13	Keeping yourself busy	1	2	3	4	5	8
CP14	Trying to balance your life with positive and negative thoughts	1	2	3	4	5	8
CP15	Getting on with your eye condition	1	2	3	4	5	8
CP16	Ignoring that you have an eye condition	1	2	3	4	5	8
CP17	Turning to work or other activities that take your mind off things, e.g. Going for a walk, listening to music, reading books etc.	1	2	3	4	5	8
CP18	Adapt to the eye condition or vision loss	1	2	3	4	5	8
CP19	Seeing your family members adapt to similar eye condition as yours	1	2	3	4	5	8
CP20	Try not to feel sorry for yourself	1	2	3	4	5	8
CP21	Focussing on your daily routines	1	2	3	4	5	8
CP22	Thinking doctors will fix your eye condition	1	2	3	4	5	8
CP23	Trying to see your life in a different light	1	2	3	4	5	8
CP24	Thinking that your eye condition is not life threatening	1	2	3	4	5	8

CP25	Doing things to let your unpleasant feelings escape, e.g. crying, screaming	1	2	3	4	5	8
CP26	Thinking that much worse things could happen to you	1	2	3	4	5	8
CP27	Enjoying your life and appreciating it	1	2	3	4	5	8
CP28	Having peer support	1	2	3	4	5	8
CP29	Using humour	1	2	3	4	5	8
CP30	Engaging knowingly in unhealthy activities, e.g. smoking, drinking alcohol	1	2	3	4	5	8

Acquired retinal diseases item bank questionnaire

Appendix 5

Instructions

All the following questions are about the impact of acquired retinal diseases (ARD) such as macular hole (MH), epiretinal membrane (ERM), vascular occlusion, retinal infections and others and its treatment on your quality of life. By acquired retinal diseases, we mean your eye condition that affects the central part or the peripheral art or both central and peripheral part of your retina (i.e. back of your eye) and by treatment we include laser or surgery or anti-VEGF (vascular Endothelial Growth Factor) injections.

I will read each question out to you. After each question, I will read you a list of possible answers. Please give me the answer that best applies to you.

Please take as much time as you need to answer each question.

Please answer every question unless you need to skip questions because they don't apply to you (select "not applicable"). All your answers and the information you have provided will be regarded as strictly confidential.

Please consider only your retinal diseases and/or its treatment when you answer these questions. For example, if you need reading glasses or distance glasses or contact lenses or low vision aids or environmental modifications (changes in lighting arrangements or modifications done in your home) please answer according to how you can manage when using them.

Date:
Time started:
Time finished:
Duration:

Name:
ID:
Interviewer:
Mode: Face to face / Phone / Combination

Acquired retinal diseases item bank questionnaire

Background Questionnaire

Name: _____ **DOB:** _ _/ _ _/ _ _ _ _

Gender: M / F **Post code:** _____

Main language spoken at home: English/ Other *(If others specify)* _____

Marital status: Never married/ Married / De-facto / Divorced / Separated / Widowed
(Please circle)

Highest level of education: Primary – Incomplete / Complete
(Please circle) Secondary – Incomplete / Complete
TAFE / Uni – Incomplete / Complete

Current employment status: Retired/ Disability Pension/ Unemployed
(Please circle) Working / Volunteer Work

How many years have you had the eye condition? _____

Eye/s involved: Right eye / Left eye / Both eyes
(Please circle)

Other eye condition/s: Diabetic Retinopathy/ Cataract / Glaucoma/
(Please circle) Age related macular Degeneration / None
Other eye conditions *(specify)* _____

Treatment for retinal condition: Injection/ Laser / Surgery / None
(Please circle) Others (*specify*): _____

Other medical condition/s: Diabetes mellitus/ Pulmonary disease/ Arthritis/
(Please circle) Hypertension/ Heart problems/ None
Others conditions (*specify*)_____

Right eye visual acuity (If known only): _____

Left eye visual acuity (if known only):_____

Acquired retinal diseases item bank questionnaire

VISUAL SYMPTOMS															
How often do you experience…?		**Never**	**Occasionally**	**Quite often**	**Very often**	**How severe is/are the…?**	**Not at all**	**Mild**	**Moderate**	**Severe**	**How much of a problem is/are the…?**	**None**	**A little**	**Quite a bit**	**A lot**
VS1	Blurred vision	4	3	2	1	Blurred vision	4	3	2	1	Blurred vision	4	3	2	1
VS2	Difficulty seeing at night	4	3	2	1	difficulty seeing at night	4	3	2	1	difficulty seeing at night	4	3	2	1
VS3	Loss of your peripheral vision	4	3	2	1	Loss of your peripheral vision	4	3	2	1	Loss of your peripheral vision	4	3	2	1
VS4	Floaters in your vision	4	3	2	1	Floaters in your vision	4	3	2	1	Floaters in your vision	4	3	2	1
VS5	Distorted vision (lines you know are straight appear curved or distorted)	4	3	2	1	Distorted vision (lines you know are straight appear curved or distorted)	4	3	2	1	Distorted vision (lines you know are straight appear curved or distorted)	4	3	2	1
VS6	**How often do you feel you have** deteriorating vision?	4	3	2	1	Deterioration of vision	4	3	2	1	Deterioration of vision	4	3	2	1
VS7	A grey/dark patch in the centre of your vision	4	3	2	1	A grey/dark patch in the centre of your vision	4	3	2	1	A grey/dark patch in the centre of your vision	4	3	2	1
VS8	Spots in your vision	4	3	2	1	Spots in your vision	4	3	2	1	Spots in your vision	4	3	2	1
VS9	Flashes of light from within your eyes	4	3	2	1	Flashes of light from within your eyes	4	3	2	1	Flashes of light from within your eyes	4	3	2	1
VS10	Difficulty in depth perception	4	3	2	1	Difficulty in depth perception	4	3	2	1	Difficulty in depth perception	4	3	2	1
VS11	Difficulty focussing your eyes	4	3	2	1	Difficulty focussing your eyes	4	3	2	1	Difficulty focussing your eyes	4	3	2	1

VS12	Difficulty distinguishing colours	4	3	2	1	Difficulty distinguishing colours	4	3	2	1	Difficulty distinguishing colours	4	3	2	1
VS13	Glare from lights	4	3	2	1	Glare from lights	4	3	2	1	Glare from lights	4	3	2	1
VS14	Cloudy vision	4	3	2	1	Cloudy vision	4	3	2	1	Cloudy vision	4	3	2	1
VS15	Double vision	4	3	2	1	Double vision	4	3	2	1	Double vision	4	3	2	1
VS16	Difficulty with light/dark adaptation	4	3	2	1	Difficulty with light/dark adaptation	4	3	2	1	Difficulty with light/dark adaptation	4	3	2	1
VS17	Patches of your vision missing	4	3	2	1	Patches of your vision missing	4	3	2	1	Patches of your vision missing	4	3	2	1
VS18	Tunnel vision	4	3	2	1	Tunnel vision	4	3	2	1	Tunnel vision	4	3	2	1
VS19	Temporary periods of blindness	4	3	2	1	Temporary periods of blindness	4	3	2	1	Temporary periods of blindness	4	3	2	1
VS20	Golden floaters inside your eyes	4	3	2	1	Golden floaters inside your eyes	4	3	2	1	Golden floaters inside your eyes	4	3	2	1

Acquired retinal diseases item bank questionnaire

OCULAR COMFORT SYMPTOMS															
How often do you experience…?		Never	Occasionally	Quite often	Very often	**How severe is/are the…?**	Not at all	Mild	Moderate	Severe	**How much of a problem is/are the…?**	None	A little	Quite a bit	A lot
OS1	Achy eyes	4	3	2	1	Achy eyes	4	3	2	1	Achy eyes	4	3	2	1
OS2	Tired eyes	4	3	2	1	Tired eyes	4	3	2	1	Tired eyes	4	3	2	1
OS3	Stinging in your eyes	4	3	2	1	Stinging in your eyes	4	3	2	1	Stinging in your eyes	4	3	2	1
OS4	Discomfort in your eyes	4	3	2	1	Discomfort in your eyes	4	3	2	1	Discomfort in your eyes	4	3	2	1
OS5	Burning in your eyes	4	3	2	1	Burning in your eyes	4	3	2	1	Burning in your eyes	4	3	2	1
OS6	Bloodshot eye, e.g. after having injection	4	3	2	1	Bloodshot eye, e.g. after having injection	4	3	2	1	Bloodshot eye, e.g. after having injection	4	3	2	1
OS7	Eye strain	4	3	2	1	Eye strain	4	3	2	1	Eye strain	4	3	2	1
OS8	Pain in your eyes	4	3	2	1	Pain in your eyes	4	3	2	1	Pain in your eyes	4	3	2	1

Acquired retinal diseases item bank questionnaire

GENERAL SYMPTOMS																
How often do you experience…?		Never	Occasionally	Quite often	Very often	**Not relevant**	**How severe is/are the…?**	Not at all	Mild	Moderate	Severe	**How much of a problem is/are the…?**	None	A little	Quite a bit	A lot
GS1	Headaches due to your vision	4	3	2	1	9	Headaches due to your vision	4	3	2	1	Headaches due to your vision	4	3	2	1
GS2	Tiredness from having to lie face down after the eye procedure	4	3	2	1	9	Tiredness from having to lie face down after the eye procedure	4	3	2	1	Tiredness from having to lie face down after the eye procedure	4	3	2	1
GS3	Tiredness after sitting for long to see the specialist	4	3	2	1	9	Tiredness after sitting for long to see the specialist	4	3	2	1	Tiredness after sitting for long to see the specialist	4	3	2	1
GS4	Lethargy after an eye operation	4	3	2	1	9	Lethargy after an eye operation	4	3	2	1	Lethargy after an eye operation	4	3	2	1

Acquired retinal diseases item bank questionnaire

ACTIVITY LIMITATION								
How much difficulty do you have…?		**None**	**A little**	**Quite a bit**	**A lot**	**Unable to do because of my vision**	**This task is not relevant to me / don't do the task**	**Refuse to answer**
AL1	Reading a book	5	4	3	2	1	9	8
AL2	Reading small print, e.g. the phone book, yellow page	5	4	3	2	1	9	8
AL3	Reading a large print book	5	4	3	2	1	9	8
AL4	Reading newspaper	5	4	3	2	1	9	8
AL5	Reading signage, e.g. shop names, charts, etc.	5	4	3	2	1	9	8
AL6	Reading in dim light conditions	5	4	3	2	1	9	8
AL7	Reading musical notes	5	4	3	2	1	9	8
AL8	Reading hand written documents	5	4	3	2	1	9	8
AL9	Reading text on your mobile phone screen	5	4	3	2	1	9	8
AL10	Reading from a portable screen, e.g. iPad, kindle book, iPhone	5	4	3	2	1	9	8
AL11	Reading street signs during the day	5	4	3	2	1	9	8
AL12	Reading street signs at night	5	4	3	2	1	9	8
AL13	Reading glossy and colourful prints, e.g. cook books, articles, magazines	5	4	3	2	1	9	8
AL14	Reading the numbers on the front of a bus	5	4	3	2	1	9	8
AL15	Reading price labels in shops	5	4	3	2	1	9	8
AL16	Reading the numbers on the front of a bus	5	4	3	2	1	9	8
AL17	Reading a street directory or map	5	4	3	2	1	9	8
AL18	Reading the signs in the supermarket	5	4	3	2	1	9	8
AL19	Reading from a computer screen	5	4	3	2	1	9	8
AL20	Reading the nutritional information or ingredients on food labels	5	4	3	2	1	9	8

Acquired retinal diseases item bank questionnaire

How much difficulty do you have…?		None	A little	Quite a bit	A lot	Unable to do because of my vision	This task is not relevant to me / don't do the task	Refuse to answer
AL21	Judging how close or far are things from you	5	4	3	2	1	9	8
AL22	Judging the ball when playing ball sports, e.g. tennis, netball	5	4	3	2	1	9	8
AL23	Recognising someone across the street	5	4	3	2	1	9	8
AL24	Using the computer	5	4	3	2	1	9	8
AL25	Cooking	5	4	3	2	1	9	8
AL26	Eating meals	5	4	3	2	1	9	8
AL27	Telling the time from a clock	5	4	3	2	1	9	8
AL28	Engaging in a hobby or leisure activity, e.g. walking, dancing, singing	5	4	3	2	1	9	8
AL29	Going out for entertainment, e.g. a movie, play or concert	5	4	3	2	1	9	8
AL30	Seeing road signs	5	4	3	2	1	9	8
AL31	Going to a sports event, e.g. cricket, tennis, football	5	4	3	2	1	9	8
AL32	Taking part in recreational activities, e.g. bowling, fishing, shooting	5	4	3	2	1	9	8
AL33	Exercising and keeping fit	5	4	3	2	1	9	8
AL34	Playing board games, e.g. cards, scrabble, soduku puzzles	5	4	3	2	1	9	8
AL35	Using hand tools, e.g. a screwdriver, hammer, chisel	5	4	3	2	1	9	8
AL36	Doing household chores e.g. cleaning, dusting, vacuuming	5	4	3	2	1	9	8
AL37	Crocheting or knitting	5	4	3	2	1	9	8
AL38	Take care of garden, e.g. weeding, pruning, mowing the lawn	5	4	3	2	1	9	8
AL39	Sewing	5	4	3	2	1	9	8
AL40	Seeing in poorly lit surroundings	5	4	3	2	1	9	8
AL41	Seeing at night	5	4	3	2	1	9	8
AL42	Seeing in the daytime	5	4	3	2	1	9	8
AL43	Seeing in glare conditions	5	4	3	2	1	9	8
AL44	Adjusting to bright light after the lighting has been rather dim	5	4	3	2	1	9	8
AL45	Adjusting to dark indoor lighting after being in bright light	5	4	3	2	1	9	8
AL46	Doing any small, fiddly task	5	4	3	2	1	9	8

AL47	Looking after your appearance, e.g. your face, hair, shaving	5	4	3	2	1	9	8
AL48	Cutting your fingernails and toenails safely	5	4	3	2	1	9	8
AL49	Bathing or showering	5	4	3	2	1	9	8
AL50	Doing online shopping	5	4	3	2	1	9	8
AL51	Doing grocery shopping	5	4	3	2	1	9	8
AL52	Playing outdoor sports, e.g. golf, soccer, netball	5	4	3	2	1	9	8
AL53	Threading a needle	5	4	3	2	1	9	8
AL54	Travelling domestic and overseas	5	4	3	2	1	9	8
AL55	Watching TV	5	4	3	2	1	9	8
AL56	Writing on a card or a book	5	4	3	2	1	9	8
AL57	Writing and signing documents	5	4	3	2	1	9	8
AL58	Riding a bike in the daytime	5	4	3	2	1	9	8
AL59	Driving during the day	5	4	3	2	1	9	8
AL60	Driving at night	5	4	3	2	1	9	8
AL61	Parking	5	4	3	2	1	9	8
AL62	Noticing when the car in front of you is speeding up or slowing down	5	4	3	2	1	9	8

Acquired retinal diseases item bank questionnaire

MOBILITY								
How much difficulty do you have…?		**None**	**A little**	**Quite a bit**	**A lot**	**Unable to do because of my vision**	**This task is not relevant to me / don't do the task**	**Refuse to answer**
MB1	Navigating in dim light	5	4	3	2	1	9	8
MB2	Crossing a street or road	5	4	3	2	1	9	8
MB3	Noticing things to the left or right of you while you are walking	5	4	3	2	1	9	8
MB4	Walking in dimly lit indoor areas	5	4	3	2	1	9	8
MB5	Walking around unfamiliar areas	5	4	3	2	1	9	8
MB6	Walking on uneven ground and negotiating bumps or cracks in your path	5	4	3	2	1	9	8
MB7	Walking around outdoors	5	4	3	2	1	9	8
MB8	Using stairs	5	4	3	2	1	9	8
MB9	Travelling somewhere independently	5	4	3	2	1	9	8
MB10	Travelling by public transport	5	4	3	2	1	9	8

Acquired retinal diseases item bank questionnaire

EMOTIONAL							
During the past four weeks, how often do you….?		**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**	**Refuse to answer**
EM1	Feel hopeful	1	2	3	4	5	8
EM2	Feel appreciative	1	2	3	4	5	8
EM3	Feel surprised	1	2	3	4	5	8
EM4	Feel relieved	1	2	3	4	5	8
EM5	Feel fortunate	1	2	3	4	5	8
EM6	Feel grateful	1	2	3	4	5	8
EM7	Feel amazing	1	2	3	4	5	8
EM8	Feel anxious	5	4	3	2	1	8
EM9	Feel like you've lost your confidence doing usual activities	5	4	3	2	1	8
EM10	Feel like a nuisance or a burden	5	4	3	2	1	8
EM11	Feel depressed	5	4	3	2	1	8
EM12	Feel upset	5	4	3	2	1	8
EM13	Feel lonely or isolated	5	4	3	2	1	8
EM14	Feel shocked by what your eye specialist has told you about your eyes	5	4	3	2	1	8
EM15	Feel worried	5	4	3	2	1	8
EM16	Feel frustrated	5	4	3	2	1	8
EM17	Feel devastated	5	4	3	2	1	8
EM18	Feel angry	5	4	3	2	1	8
EM19	Feel like crying	5	4	3	2	1	8
EM20	Feel insecure	5	4	3	2	1	8
EM21	Feel stressed	5	4	3	2	1	8
EM22	Feel vulnerable	5	4	3	2	1	8
EM23	Feel terrible	5	4	3	2	1	8
EM24	Feel disheartening	5	4	3	2	1	8
EM25	Feel confused	5	4	3	2	1	8
EM26	Have a sudden feel of panic	5	4	3	2	1	8
EM27	Feel unlucky	5	4	3	2	1	8
EM28	Feel staggered	5	4	3	2	1	8
EM29	Feel sorry for yourself	5	4	3	2	1	8
EM30	Feel annoyed	5	4	3	2	1	8

EM31	Feel stupid	5	4	3	2	1	8
EM32	Feel inadequate	5	4	3	2	1	8
EM33	Feel dissatisfied	5	4	3	2	1	8
EM34	Feel hurt	5	4	3	2	1	8
EM35	Feel fed up	5	4	3	2	1	8
EM36	Feel unhappy	5	4	3	2	1	8
EM37	Feel fearful	5	4	3	2	1	8
EM38	Feel like 'why me'	5	4	3	2	1	8
EM39	Feel disappointed	5	4	3	2	1	8
EM40	Feel afraid	5	4	3	2	1	8
EM41	Feel sad or low	5	4	3	2	1	8
EM42	Feel nervous	5	4	3	2	1	8
EM43	Feel irritated	5	4	3	2	1	8
EM44	Have suicidal thoughts	5	4	3	2	1	8
EM45	Feel awful	5	4	3	2	1	8
EM46	Feel restricted	5	4	3	2	1	8
EM47	Felt awkward	5	4	3	2	1	8
EM48	Grieve for the loss of your vision	5	4	3	2	1	8
EM49	Feel agitated	5	4	3	2	1	8
EM50	I am stuck with my eye condition and treatment	5	4	3	2	1	8

Acquired retinal diseases item bank questionnaire

HEALTH CONCERNS								
How concerned are you about…?		**Not at all**	**A little bit**	**A moderate amount**	**A lot**	**Extremely**	**This issue is not relevant to me**	**Refuse to answer**
HC1	Your eyesight getting worse	5	4	3	2	1		8
HC2	Going blind	5	4	3	2	1		8
HC3	Having to learn to do things in different ways	5	4	3	2	1		8
HC4	Not knowing what's going to happen in the future	5	4	3	2	1		8
HC5	Falling	5	4	3	2	1		8
HC6	Tripping	5	4	3	2	1		8
HC7	Bumping into people or objects	5	4	3	2	1		8
HC8	Having accidents (motor vehicle related)	5	4	3	2	1		8
HC9	Having accidents (non-motor vehicle related)	5	4	3	2	1		8
HC10	Not able to do things as before	5	4	3	2	1		8
HC11	Your disease progression	5	4	3	2	1		8
HC12	People not understanding your vision impairment	5	4	3	2	1		8
HC13	Your current eye management	5	4	3	2	1		8
HC14	Having to live with eye disease	5	4	3	2	1		8
HC15	Being able to access services, e.g. low vision service	5	4	3	2	1		8
HC16	Knowing that your eye condition cannot be treated (if that is the case)	5	4	3	2	1		8
HC17	How well your eye treatment is working	5	4	3	2	1	9	8
HC18	The way you are treated by your eye care practitioner	5	4	3	2	1	9	8
HC19	Losing your driver's license	5	4	3	2	1	9	8

HC20	Not getting enough information or explanation from medical staff	5	4	3	2	1	9	8
HC21	Getting the eye disease in the other eye	5	4	3	2	1	9	8
HC22	Having injections /needles in your eye	5	4	3	2	1	9	8
HC23	Passing eye condition onto your children	5	4	3	2	1	9	8
HC24	Having to undergo laser treatment for eye condition	5	4	3	2	1	9	8
HC25	Vision not improving with glasses	5	4	3	2	1	9	8
HC26	Putting other people in danger by driving	5	4	3	2	1	9	8
HC27	Side effects from your eye treatment	5	4	3	2	1	9	8

Acquired retinal diseases item bank questionnaire

SOCIAL								
How much of a problem do you have…?		**None**	**A little**	**Quite a bit**	**A lot**	**Unable to do because of my vision**	**This task is not relevant to me / don't do the task**	**Refuse to answer**
SC1	Meeting friends and family socially	5	4	3	2	1		8
SC2	Maintaining your usual social activities or social life	5	4	3	2	1		8
SC3	Maintaining your friendships	5	4	3	2	1		8
SC4	Entertaining friends and family in your own home	5	4	3	2	1		8
SC5	Interacting socially with people	5	4	3	2	1		8
SC6	With family members or friends making an issue of your eye problems	5	4	3	2	1		8
SC7	Getting help and support from your family and friends	5	4	3	2	1	9	8
SC8	Being part of social activities/ games, e.g. parent groups, pubs, attending funeral	5	4	3	2	1	9	8
SC9	Getting help or support from social welfare / government organizations	5	4	3	2	1	9	8
SC10	Engaging with your children or grandchildren	5	4	3	2	1	9	8
SC11	Maintaining your roles and responsibilities in the family	5	4	3	2	1	9	8
SC12	Maintaining your roles and responsibilities in community organisations (e.g. church groups, volunteering, clubs)	5	4	3	2	1	9	8
SC13	Going out with family and friends	5	4	3	2	1	9	8
SC14	Doing things as a couple, e.g. going on holidays/visiting places/doing recreational activities	5	4	3	2	1	9	8
SC15	Engaging in social activities at or after work	5	4	3	2	1	9	8
SC16	Interacting with people with similar eye condition	5	4	3	2	1	9	8
SC17	Eating out with your relatives or friends	5	4	3	2	1	9	8
SC18	Talking about your eye condition to friends and family members	5	4	3	2	1	9	8

Acquired retinal diseases item bank questionnaire

CONVENIENCE								
How much trouble is it…?		**None**	**A little bit**	**A moderate amount**	**Quite a lot**	**Extremely**	**This task is not relevant to me / don't do the task**	**Refuse to answer**
CV1	Having to concentrate harder on things	5	4	3	2	1	9	8
CV2	Having to rely on others for help	5	4	3	2	1	9	8
CV3	Having to travel a long way to attend your eye appointment	5	4	3	2	1	9	8
CV4	The amount of time needed when attending your eye appointment	5	4	3	2	1	9	8
CV5	Having to rely on public transport to do day to day tasks, e.g. shopping	5	4	3	2	1	9	8
CV6	Having to drive slower and more carefully	5	4	3	2	1	9	8
CV7	Having to turn or tilt your head to see better	5	4	3	2	1	9	8
CV8	Having to attend frequent appointments	5	4	3	2	1	9	8
CV9	Having to change plans or put off things to attend your eye appointment	5	4	3	2	1	9	8
CV10	Having to depend on others for instilling eye drops	5	4	3	2	1	9	8
CV11	Having to lie face down after the eye procedure	5	4	3	2	1	9	8
CV12	Having travel restrictions after eye procedures	5	4	3	2	1	9	8
CV13	Taking your glasses when you are travelling	5	4	3	2	1	9	8
CV14	Having to maintain head or face positioning in the waiting room	5	4	3	2	1	9	8
CV15	Having more complicated travel plans (because of driving limitations, e.g. at night-time)	5	4	3	2	1	9	8
CV16	Inability to see clearly after instilling dilating eye drops	5	4	3	2	1	9	8
CV17	Having dilating drops every time you have an appointment for you eye condition	5	4	3	2	1	9	8
CV18	Having to undergo routine eye tests at every eye appointment, e.g. OCT, fundus examination, dilating drops	5	4	3	2	1	9	8
CV19	Having to maintain head/face positioning while travelling after an eye procedure	5	4	3	2	1	9	8

CV20	Having to adopt unusual head or body posture	5	4	3	2	1	9	8
CV21	Having to wait for the surgery	5	4	3	2	1	9	8

Acquired retinal diseases item bank questionnaire

ECONOMIC								
Currently, how concerned are you about...?		**Not at all**	**A little bit**	**A moderate amount**	**Quite a bit**	**Extremely**	**This issue is not relevant to me**	**Refuse to answer**
EC1	Your ability to find employment or get a new job	5	4	3	2	1	9	8
EC2	Limitation on the types of jobs you can do e.g. jobs that require a driving licence, lots of reading or computer work	5	4	3	2	1	9	8
EC3	Not being able to work	5	4	3	2	1	9	8
EC4	Losing your job	5	4	3	2	1	9	8
EC5	The financial impact from loss of income	5	4	3	2	1	9	8
EC6	The cost associated with seeing your eye specialist	5	4	3	2	1	9	8
EC7	The cost of buying glasses or other vision aids	5	4	3	2	1	9	8
EC8	The costs associated with attending eye appointments, e.g. parking, travel cost, loss of income	5	4	3	2	1	9	8
EC9	The cost associated with accessing private health care	5	4	3	2	1	9	8
EC10	The cost of treatment for your eye condition, e.g. eye injections, vitamin tablets, laser treatment	5	4	3	2	1	9	8

Acquired retinal diseases item bank questionnaire

COPING						
Given that you know your eye condition, do you cope by……?		**Not at all**	**A little bit**	**A moderate amount**	**Quite a bit**	**Extremely**
CP1	Accepting your eye condition	1	2	3	4	5
CP2	Thinking that there are people much worse than you	1	2	3	4	5
CP3	Learning to live with your eye condition	1	2	3	4	5
CP4	Attributing your eye condition to ageing	1	2	3	4	5
CP5	Trying not to think about it	1	2	3	4	5
CP6	Trying to be positive	1	2	3	4	5
CP7	Trying to be more independent	1	2	3	4	5
CP8	Getting on with your eye condition	1	2	3	4	5
CP9	Dealing with other significant medical condition/s that you have	1	2	3	4	5
CP10	Not worrying about your eye condition	1	2	3	4	5
CP11	Taking things easily	1	2	3	4	5
CP12	Being more resilient	1	2	3	4	5
CP13	Turning to work or other activities that take your mind off things, e.g. going for a walk, listening to music, reading books	1	2	3	4	5
CP14	Adapting to the eye condition or vision loss	1	2	3	4	5
CP15	Focussing on your daily routines	1	2	3	4	5
CP16	Being patient	1	2	3	4	5
CP17	Thinking doctors will fix your eye condition	1	2	3	4	5
CP18	Trying to see your life in a different light	1	2	3	4	5
CP19	Praying or meditating	1	2	3	4	5
CP20	Thinking that your eye condition is not life threatening	1	2	3	4	5
CP21	Doing things to let your unpleasant feelings escape, e.g. crying, screaming	1	2	3	4	5
CP22	Trying to be more rational or practical	1	2	3	4	5
CP23	Reassuring that things will get better	1	2	3	4	5
CP24	Using humour	1	2	3	4	5

Appendix 6

Psychometric properties of 6-item scale in the Mobility (MB) domain

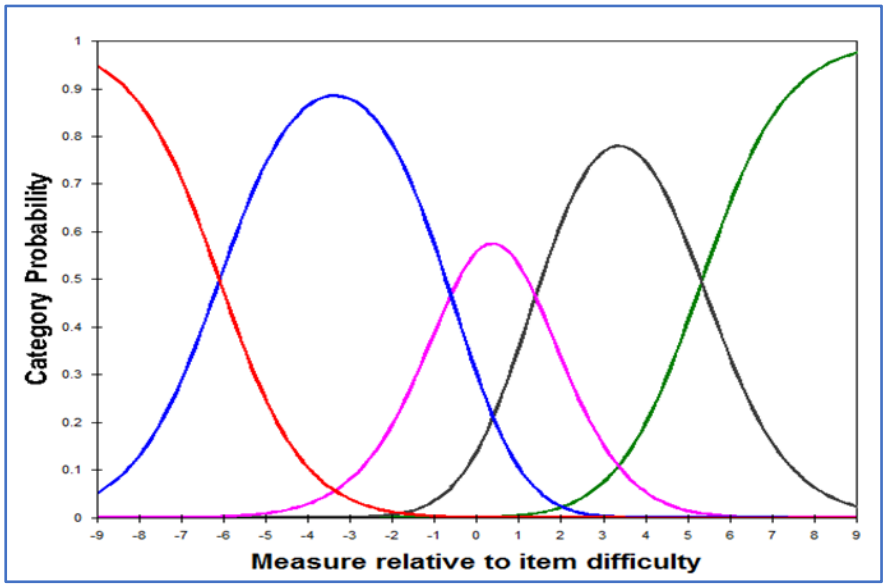
1. Measurement precision

Person separation index = 3.45; Person separation reliability = 0.92; Targeting = -0.25

```
Processing Table 0
\\userOP\P\prem0013\prefs\Desktop\Rasch analysis\Phase II- Rasch analysis vr 1
-------------------------------------------------------------------------------
| PERSON     233 INPUT     195 MEASURED                INFIT         OUTFIT   |
|           TOTAL     COUNT     MEASURE  REALSE     IMNSQ   ZSTD  OMNSQ   ZSTD|
| MEAN       17.1       6.0        -.25    1.01       .92    -.4    .91    -.4|
| P.SD        6.2         .1        3.90     .40      1.27    1.5   1.30    1.4|
| REAL RMSE   1.08 TRUE SD    3.75  SEPARATION  3.45  PERSON RELIABILITY  .92|
|-----------------------------------------------------------------------------|
| ITEM       6 INPUT       6 MEASURED                INFIT         OUTFIT   |
|           TOTAL     COUNT     MEASURE  REALSE     IMNSQ   ZSTD  OMNSQ   ZSTD|
| MEAN     555.5     194.3         .00     .15       .99    -.3    .95    -.5|
| P.SD      24.9         .7         .51     .01       .25    2.3    .28    2.2|
| REAL RMSE    .15 TRUE SD     .49  SEPARATION  3.17  ITEM   RELIABILITY  .91|
-------------------------------------------------------------------------------
```

2. Category threshold order

Category probability curves showing the five category response categories for the 6-item scale



SUMMARY OF CATEGORY STRUCTURE. Model="R"

CATEGORY LABEL	SCORE	OBSERVED COUNT	%	OBSVD AVRGE	SAMPLE EXPECT	INFIT MNSQ	OUTFIT MNSQ	ANDRICH THRESHOLD	CATEGORY MEASURE
1	1	78	7	-5.39	-5.49	1.33	1.04	NONE	(-7.20)
2	2	498	43	-2.79	-2.77	.97	.99	-6.10	-3.37
3	3	242	21	-.02	-.02	.78	.69	-.62	.38
4	4	207	18	2.67	2.64	1.00	1.18	1.39	3.38
5	5	141	12	5.58	5.58	1.08	1.01	5.33	(6.44)

3. Dimensionality

Principal component analysis = 76.9%

Unexplained variance eigenvalues = 2.3

4. Fit statistics

No misfitting items

ENTRY NUMBER	TOTAL SCORE	TOTAL COUNT	MEASURE	MODEL S.E.	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMEASUR-AL CORR.	PTMEASUR-AL EXP.	EXACT MATCH OBS%	EXACT MATCH EXP%	ITEM
6	539	193	.29	.15	1.37	3.0	1.43	2.9	A .87	.90	69.4	69.0	MB12
5	547	194	.12	.15	1.14	1.3	1.05	.4	B .89	.90	66.3	68.7	MB5
4	524	195	.72	.15	1.13	1.1	1.08	.7	C .88	.90	75.3	69.0	MB4
1	602	195	-.94	.14	.89	-1.0	.90	-.8	c .89	.89	76.4	69.2	MB1
2	570	195	-.27	.15	.74	-2.5	.69	-2.6	b .91	.89	76.4	68.9	MB2
3	551	194	.07	.15	.65	-3.5	.56	-3.8	a .93	.90	79.0	68.7	MB3

5. **Differential Item functioning**

(i) DIF class specification is DIF = Gender

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
0	-.01	-.90	.19	1	.01	-1.00	.22	.10	.29	.34	168	.7329	.4311	.5114	.27	20	1	MB1
0	-.04	-.13	.19	1	.05	-.46	.22	.33	.29	1.14	168	.2572	.7159	.3975	.36	20	2	MB2
0	-.05	.25	.20	1	.06	-.16	.22	.42	.30	1.40	168	.1628	1.1136	.2913	.47	20	3	MB3
0	.06	.48	.20	1	-.08	1.06	.23	-.58	.30	-1.94	166	.0542	3.0596	.0803	-.65	20	4	MB4
0	.00	.12	.19	1	.00	.12	.22	.00	.30	.00	167	1.000	.1408	.7075	.13	20	5	MB5
0	.03	.17	.19	1	-.04	.45	.23	-.28	.30	-.92	162	.3599	.4414	.5064	-.28	20	6	MB12

(ii) DIF class specification is: DIF= Age

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
1	.07	-1.23	.27	2	-.03	-.83	.17	-.40	.32	-1.26	98	.2115	.9561	.3282	-.44	18	1	MB1
1	-.02	-.19	.27	2	.01	-.30	.17	.11	.32	.35	98	.7304	.0984	.7537	.16	18	2	MB2
1	.05	-.11	.27	2	-.02	.15	.17	-.26	.33	-.81	99	.4204	1.2250	.2684	-.58	18	3	MB3
1	-.03	.87	.27	2	.01	.67	.18	.20	.33	.60	100	.5492	.0021	.9634	.02	18	4	MB4
1	.00	.12	.27	2	.00	.12	.17	.00	.32	.00	99	1.000	.3245	.5689	.22	18	5	MB5
1	-.07	.56	.27	2	.03	.18	.18	.39	.33	1.18	99	.2389	.5074	.4763	.35	18	6	MB12

(iii) DIF class specification is: DIF=Best eye visual acuity

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
1	.04	-1.09	.19	2	-.15	-.38	.31	-.71	.36	-1.96	68	.0544	2.3990	.1214	-.78	14	1	MB1
1	.01	-.33	.19	2	.03	-.38	.31	.05	.36	.15	69	.8812	.0214	.8838	.08	14	2	MB2
1	.03	-.03	.19	2	-.01	.11	.32	-.14	.37	-.37	66	.7159	.0634	.8012	-.17	14	3	MB3
1	-.01	.75	.19	2	.06	.49	.31	.26	.37	.71	68	.4802	.0033	.9542	-.03	14	4	MB4
1	.03	-.02	.19	2	-.25	1.10	.32	-1.11	.38	-2.96	67	.0042	2.6296	.1049	-.85	14	5	MB5
1	-.11	.72	.19	2	.33	-.95	.31	1.66	.37	4.50	67	.0000	6.8068	.0091	1.37	14	6	MB12

(iv) DIF class specification is: DIF= Disease groups

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
1	.05	-1.11	.17	2	-.15	-.38	.29	-.73	.33	-2.19	77	.0313	4.8372	.0279	-1.05	17	1	MB1
1	.00	-.27	.17	2	-.04	-.13	.29	-.14	.33	-.42	78	.6741	3.9368	.0472	-1.02	17	2	MB2
1	.00	.07	.17	2	-.01	.12	.29	-.05	.33	-.14	80	.8890	1.5542	.2125	-.75	17	3	MB3
1	-.01	.78	.18	2	.07	.45	.29	.34	.34	1.00	81	.3183	4.8219	.0281	.96	17	4	MB4
1	.00	.12	.17	2	.01	.07	.29	.05	.34	.16	77	.8766	.3154	.5744	-.24	17	5	MB5
1	-.03	.42	.18	2	.11	-.13	.29	.55	.34	1.64	80	.1056	6.6073	.0102	1.37	17	6	MB12

(v) DIF class specification is: DIF= Ocular comorbidity

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
0	.04	-1.09	.22	1	-.03	-.83	.19	-.25	.29	-.87	165	.3856	.5790	.4467	-.31	20	1	MB1
0	.06	-.49	.22	1	-.04	-.10	.19	-.39	.30	-1.31	168	.1923	.3411	.5592	-.26	20	2	MB2
0	.07	-.20	.22	1	-.05	.28	.20	-.47	.30	-1.59	167	.1146	1.0504	.3054	-.47	20	3	MB3
0	-.11	1.14	.22	1	.08	.39	.20	.75	.30	2.51	169	.0130	5.0702	.0243	.96	20	4	MB4
0	-.05	.32	.22	1	.04	-.03	.19	.35	.30	1.19	166	.2365	.3626	.5471	.23	20	5	MB5
0	.00	.29	.23	1	.00	.29	.20	.00	.30	.00	165	1.000	.6632	.4154	-.38	20	6	MB12

Appendix 7

Psychometric properties of the 5-item scale in the Health concerns (HC) domain

1. Measurement precision

Person separation index = 3.09; Person separation reliability = 0.91; Targeting = 0.75

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Processing Table 0
\\userOP\P\prem0013\prefs\Desktop\Rasch analysis\Phase II- Rasch analysis vr 1
-------------------------------------------------------------------------------
| PERSON     233 INPUT     213 MEASURED              INFIT         OUTFIT    |
|          TOTAL     COUNT     MEASURE  REALSE     IMNSQ   ZSTD  OMNSQ   ZSTD|
| MEAN      16.2       4.9         .75    1.06       .95    -.2    .95    -.2|
| P.SD       6.3        .4        3.73     .44       .91    1.3    .94    1.3|
| REAL RMSE   1.15 TRUE SD    3.55  SEPARATION  3.09  PERSON RELIABILITY  .91|
|-----------------------------------------------------------------------------|
| ITEM       5 INPUT       5 MEASURED              INFIT         OUTFIT    |
|          TOTAL     COUNT     MEASURE  REALSE     IMNSQ   ZSTD  OMNSQ   ZSTD|
| MEAN     688.6     210.2         .00     .14      1.00    -.3    .96    -.7|
| P.SD      43.5       1.9         .72     .01       .30    2.9    .29    2.8|
| REAL RMSE    .14 TRUE SD     .71  SEPARATION  5.13  ITEM   RELIABILITY  .96|
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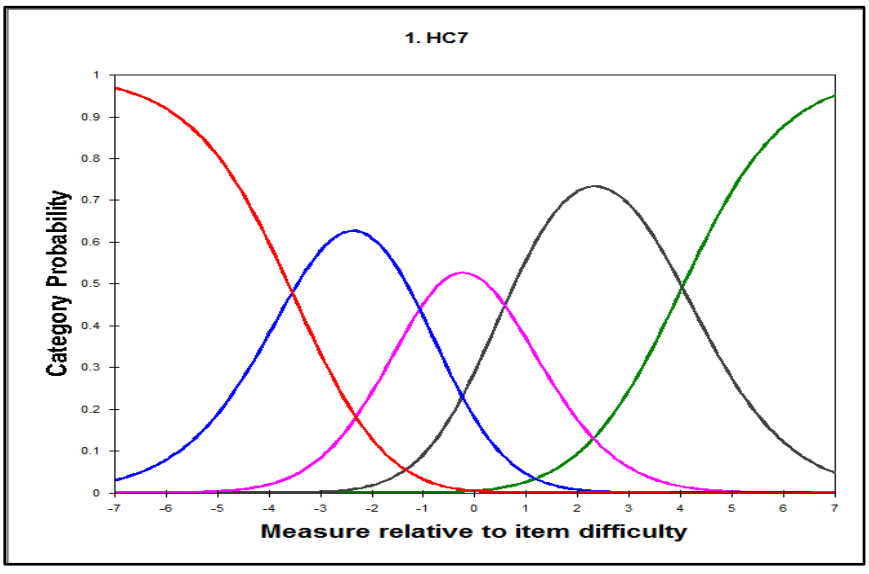
2. Category threshold order

Category probability curves showing the five category response categories for the 5-item scale



SUMMARY OF CATEGORY STRUCTURE. Model="R"

CATEGORY LABEL	SCORE	OBSERVED COUNT	%	OBSVD AVRGE	SAMPLE EXPECT	INFIT MNSQ	OUTFIT MNSQ	ANDRICH THRESHOLD	CATEGORY MEASURE
1	1	159	15	-3.75	-3.89	1.33	1.25	NONE	(-4.71)
2	2	166	16	-2.06	-1.92	.78	.75	-3.55	-2.36
3	3	188	18	-.01	.03	.77	.72	-1.07	-.22
4	4	302	29	2.21	2.09	.94	1.00	.58	2.34
5	5	236	22	3.93	4.08	1.41	1.20	4.03	(5.15)

3. Fit statistics

There were no misfitting items

ENTRY NUMBER	TOTAL SCORE	TOTAL COUNT	MEASURE	MODEL S.E.	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMEASUR-AL CORR.	PTMEASUR-AL EXP.	EXACT MATCH OBS%	EXACT MATCH EXP%	ITEM
5	693	207	-.30	.13	1.29	2.5	1.25	2.1	A .88	.91	63.9	61.3	HC12
3	648	209	.64	.13	1.25	2.2	1.24	2.0	B .89	.91	58.7	61.0	HC9
4	769	211	-1.25	.13	1.17	1.5	1.06	.6	C .88	.89	60.1	61.6	HC10
1	680	212	.23	.13	.69	-3.1	.67	-3.3	b .93	.91	67.1	61.4	HC7
2	653	212	.68	.13	.58	-4.5	.55	-4.7	a .94	.91	77.0	61.1	HC8

4. Dimensionality

Principal component analysis = 75.9%

Unexplained variance eigen value = 1.9

5. Differential item functioning

(i) DIF class specification is: DIF= GENDER

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
0	-.08	.45	.17	1	.11	-.08	.20	.53	.26	2.05	155	.0419	2.1896	.1389	.58	18	1	HC7
0	-.01	.71	.17	1	.01	.64	.19	.06	.26	.24	158	.8094	.1194	.7297	-.13	18	2	HC8
0	.05	.50	.17	1	-.07	.83	.19	-.33	.26	-1.28	158	.2014	.5624	.4533	-.26	18	3	HC9
0	-.02	-1.18	.17	1	.03	-1.36	.21	.18	.27	.67	152	.5008	.6126	.4338	.29	18	4	HC10
0	.07	-.48	.17	1	-.09	-.05	.20	-.44	.26	-1.67	153	.0968	.8283	.3628	-.32	18	5	HC12

(ii) DIF class specification is: DIF= Age

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
1	.08	-.03	.24	2	-.04	.33	.15	-.36	.29	-1.25	89	.2133	.7229	.3952	-.38	17	1	HC7
1	.10	.39	.24	2	-.05	.80	.15	-.41	.29	-1.45	89	.1510	3.0084	.0828	-.90	17	2	HC8
1	-.05	.80	.24	2	.02	.60	.15	.20	.28	.71	90	.4769	.0147	.9034	-.05	17	3	HC9
1	.02	-1.32	.25	2	.00	-1.25	.16	-.07	.30	-.22	89	.8226	.0052	.9427	.03	17	4	HC10
1	-.15	.15	.24	2	.07	-.49	.15	.64	.29	2.23	91	.0283	2.8886	.0892	.75	17	5	HC12

(iii) DIF class specification is: DIF= Best eye visual acuity

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
1	-.01	.26	.18	2	-.08	.44	.29	-.18	.34	-.54	59	.5932	.2546	.6138	-.25	13	1	HC7
1	-.02	.72	.17	2	.00	.68	.28	.04	.33	.13	59	.8959	.0399	.8417	.11	13	2	HC8
1	.01	.64	.18	2	.07	.44	.29	.20	.34	.61	59	.5456	.0088	.9253	.05	13	3	HC9
1	.03	-1.34	.19	2	-.12	-.90	.30	-.43	.35	-1.24	61	.2185	.3137	.5754	-.28	13	4	HC10
1	.00	-.30	.18	2	.13	-.66	.30	.36	.35	1.05	57	.2995	.4061	.5240	.31	13	5	HC12

(IV) DIF class specification is: DIF= Disease groups

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
1	.02	.17	.15	2	-.06	.41	.26	-.25	.30	-.82	68	.4158	.0351	.8513	-.08	18	1	HC7
1	.03	.59	.14	2	-.10	.97	.26	-.38	.30	-1.25	67	.2163	1.0519	.3051	-.48	18	2	HC8
1	.00	.64	.15	2	-.01	.68	.27	-.04	.30	-.13	65	.8991	.2672	.6052	-.21	18	3	HC9
1	-.01	-1.23	.15	2	.03	-1.36	.27	.13	.31	.42	67	.6792	.0472	.8280	.10	18	4	HC10
1	-.05	-.16	.15	2	.15	-.73	.27	.57	.31	1.85	66	.0685	1.2264	.2681	.49	18	5	HC12

(V) DIF class specification is: DIF= Ocular comorbidity

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
0	.00	.23	.20	1	.00	.23	.17	.00	.26	.00	153	1.000	.2511	.6163	.19	18	1	HC7
0	.01	.68	.20	1	.00	.68	.17	.00	.26	.00	153	1.000	1.0720	.3005	-.44	18	2	HC8
0	.05	.50	.20	1	-.04	.75	.17	-.24	.26	-.93	151	.3518	.4951	.4816	-.26	18	3	HC9
0	.02	-1.33	.21	1	-.02	-1.21	.17	-.12	.27	-.46	147	.6449	.0033	.9544	.02	18	4	HC10
0	-.07	-.09	.20	1	.05	-.46	.17	.37	.26	1.41	151	.1615	.8480	.3571	.33	18	5	HC12

Appendix 8

Psychometric properties of the 6-item scale in the Coping (CP) domain

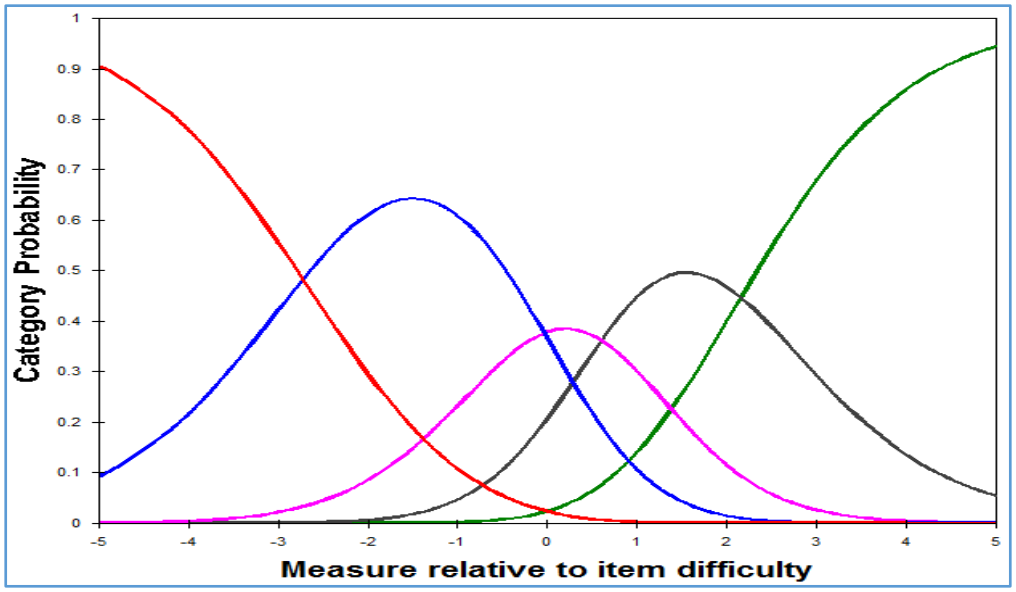
1. Measurement precision

Person separation Index = 2.15; Person reliability = 0.82; Targeting = -1.30

PERSON	233 INPUT	190 MEASURED		INFIT		OUTFIT	
	TOTAL	COUNT	MEASURE	REALSE	IMNSQ	ZSTD	OMNSQ	ZSTD
MEAN	13.5	5.8	-1.30	.83	1.00	-.2	1.00	-.2
P.SD	5.3	.6	2.22	.44	.95	1.4	.96	1.4
REAL RMSE	.94	TRUE SD	2.01	SEPARATION	2.15	PERSON RELIABILITY		.82
ITEM	30 INPUT	6 MEASURED		INFIT		OUTFIT	
	TOTAL	COUNT	MEASURE	REALSE	IMNSQ	ZSTD	OMNSQ	ZSTD
MEAN	428.3	184.5	.00	.11	.99	-.1	.98	-.2
P.SD	14.4	5.6	.22	.00	.16	1.5	.18	1.6
REAL RMSE	.11	TRUE SD	.19	SEPARATION	1.67	ITEM RELIABILITY		.74

2. Category threshold order

Category probability curves showing the five category response categories for the 6-item Coping (CP) scale



SUMMARY OF CATEGORY STRUCTURE. Model="R"

CATEGORY LABEL	SCORE	OBSERVED COUNT	%	OBSVD AVRGE	SAMPLE EXPECT	INFIT MNSQ	OUTFIT MNSQ	ANDRICH THRESHOLD	CATEGORY MEASURE
1	1	303	27	-2.62	-2.71	1.32	1.23	NONE	(-3.87)
2	2	400	36	-1.33	-1.26	.89	.91	-2.73	-1.49
3	3	206	19	-.21	-.20	.82	.79	-.04	.21
4	4	141	13	.75	.63	.83	.82	.60	1.55
5	5	57	5	1.17	1.29	1.18	1.23	2.16	(3.40)

3. Fit statistics

All items showed good fit statistics

ENTRY NUMBER	TOTAL SCORE	TOTAL COUNT	MEASURE	MODEL S.E.	INFIT MNSQ	INFIT ZSTD	OUTFIT MNSQ	OUTFIT ZSTD	PTMEASUR-AL CORR.	PTMEASUR-AL EXP.	EXACT MATCH OBS%	EXACT MATCH EXP%	ITEM
27	425	185	.05	.11	1.21	1.8	1.29	2.4	A .74	.77	45.1	52.8	CP27
18	446	183	-.26	.11	1.12	1.1	1.11	1.0	B .75	.78	54.6	51.5	CP18
10	414	188	.27	.11	1.04	.3	.98	-.2	C .75	.76	57.8	54.4	CP10
1	450	189	-.09	.11	.97	-.2	.98	-.1	c .78	.78	59.0	51.4	CP1
15	416	173	-.25	.11	.88	-1.0	.81	-1.7	b .80	.78	55.6	51.8	CP15
2	419	189	.27	.11	.72	-2.7	.74	-2.5	a .81	.76	60.2	54.4	CP2

4. Dimensionality

Principal component analysis = 55.8%

Unexplained variance eigenvalue = 1.7

4. Differential item functioning

(i) DIF class specification is: DIF= Age

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
1	-.05	.00	.18	2	.03	-.14	.13	.13	.23	.60	102	.5526	.2553	.6133	.18	20	1	CP1
1	.04	.20	.19	2	-.02	.30	.14	-.10	.23	-.44	106	.6616	.0500	.8230	.08	20	2	CP2
1	.02	.24	.19	2	-.03	.32	.14	-.09	.23	-.37	106	.7139	.0005	.9819	-.01	20	10	CP10
1	.03	-.30	.19	2	-.01	-.25	.13	-.06	.24	-.24	90	.8115	.0224	.8809	-.06	18	15	CP15
1	-.09	-.11	.18	2	.04	-.34	.13	.23	.22	1.04	102	.3007	.2411	.6234	.18	19	18	CP18
1	.05	-.04	.18	2	-.02	.10	.13	-.13	.23	-.58	106	.5615	.8220	.3646	-.35	19	27	CP27

(ii) DIF class specification is: DIF= Best eye visual acuity

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
1	-.06	.02	.14	2	.07	-.21	.21	.23	.26	.90	70	.3695	.2731	.6012	.24	17	1	CP1
1	.00	.27	.15	2	-.13	.52	.23	-.25	.27	-.92	66	.3598	.0089	.9249	-.04	17	2	CP2
1	.01	.27	.15	2	-.05	.37	.23	-.10	.27	-.36	67	.7232	.0023	.9615	-.02	17	10	CP10
1	.05	-.34	.14	2	.09	-.40	.23	.05	.27	.19	56	.8513	.2043	.6513	.22	17	15	CP15
1	-.03	-.20	.14	2	-.09	-.10	.22	-.10	.26	-.38	62	.7068	1.0060	.3159	-.49	16	18	CP18
1	.03	-.01	.14	2	.12	-.16	.21	.15	.26	.60	70	.5521	.0411	.8393	.08	17	27	CP27

(iii) DIF class specification is: DIF= Gender

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
0	.08	-.23	.14	1	-.10	.12	.17	-.35	.22	-1.59	146	.1149	.3236	.5695	-.21	17	1	CP1
0	-.03	.33	.14	1	.04	.18	.17	.16	.22	.71	149	.4798	1.1045	.2933	.40	17	2	CP2
0	-.08	.42	.14	1	.10	.06	.17	.36	.22	1.60	151	.1111	2.9184	.0876	.59	17	10	CP10
0	.06	-.35	.14	1	-.08	-.09	.18	-.26	.23	-1.15	131	.2542	1.8645	.1721	-.54	16	15	CP15
0	.00	-.26	.14	1	.00	-.26	.16	.00	.22	.00	147	1.000	.0156	.9007	-.04	17	18	CP18
0	-.02	.09	.14	1	.02	.00	.17	.08	.22	.37	149	.7096	.3203	.5714	-.23	17	27	CP27

(iv) DIF class specification is: DIF= Ocular comorbidity

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
0	-.08	.05	.15	1	.07	-.22	.14	.27	.21	1.26	159	.2093	.3496	.5543	.21	18	1	CP1
0	-.01	.29	.16	1	.01	.25	.15	.05	.22	.21	161	.8320	1.0417	.3074	.40	18	2	CP2
0	-.08	.42	.16	1	.07	.13	.15	.29	.22	1.31	160	.1925	.5772	.4474	.30	18	10	CP10
0	.03	-.31	.16	1	-.03	-.19	.15	-.11	.22	-.51	143	.6129	.0070	.9335	-.03	17	15	CP15
0	.04	-.33	.15	1	-.03	-.19	.15	-.14	.21	-.66	157	.5080	.1295	.7190	-.13	18	18	CP18
0	.10	-.13	.16	1	-.08	.22	.15	-.36	.22	-1.64	159	.1024	2.2055	.1375	-.54	18	27	CP27

(v) DIF class specification is: DIF = Disease groups

PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	PERSON CLASS	Obs-Exp Average	DIF MEASURE	DIF S.E.	DIF CONTRAST	JOINT S.E.	Rasch-Welch t	d.f.	Prob.	Mantel Chi-squ	Prob.	Size CUMLOR	Active Slices	ITEM Number	Name
1	.06	-.19	.12	2	-.14	.19	.22	-.38	.25	-1.52	69	.1327	.0655	.7981	.11	17	1	CP1
1	-.02	.30	.13	2	.04	.19	.22	.11	.25	.43	71	.6666	.6932	.4051	.33	17	2	CP2
1	.01	.27	.13	2	-.06	.39	.23	-.12	.26	-.47	70	.6431	.4462	.5042	-.28	17	10	CP10
1	-.02	-.22	.13	2	.06	-.36	.22	.14	.25	.57	68	.5694	.1281	.7204	.15	15	15	CP15
1	-.02	-.22	.12	2	.06	-.38	.21	.16	.25	.64	67	.5264	.0069	.9336	-.04	15	18	CP18
1	-.02	.08	.12	2	.04	-.03	.22	.11	.25	.43	66	.6660	.2397	.6244	-.20	16	27	CP27

Appendix 9: Publications

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Survey of Ophthalmology

Public health and the eye

Assessment of patient-reported outcomes in retinal diseases: a systematic review

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ABSTRACT

Advances in the understanding of the genetic, molecular, and cellular biology of retinal diseases have led to the development of new treatments. These expanding treatment options demand appropriate outcome measures for studies of treatment benefit including patient-reported outcomes (PROs). A plethora of PRO instruments assess impacts of retinal diseases from the patients' perspectives. We review all the studies that implemented PRO assessment in retinal diseases and also discuss quality assessment of the PRO instruments. We also include qualitative studies that explored quality of life impact on people with retinal diseases. Most studies used PRO instruments not specifically developed for retinal diseases (non–disease specific), nor have they undergone comprehensive validation in this disease group. A few retina-specific PRO instruments are available, but they suffer from limited content coverage of quality of life. Finally, we discuss the need for a new comprehensive and technologically advanced PRO instrument to assess quality of life impacts in retinal diseases.

1. Background

Patient-reported outcome (PRO) is increasingly accepted as a necessary outcome measure in clinical practice, audits, clinical trials, and economic evaluation.[A] This has resulted in the development of a large number of PRO measures across all health care fields.[4,74] To our knowledge, in ophthalmology alone, there are over 150 PRO instruments developed to assess the patient's perspectives of the disease impact and treatment outcomes. We undertook a systematic review which determined that most of these PRO instruments were developed for cataract, glaucoma, and low vision.[101,121] In terms of retina-specific PRO instruments, only a few disease-specific instruments exist.[101,48] We discuss the extent to which the instruments measure quality of life (QoL) and provide a quality assessment of the PRO instruments in terms of their measurement properties.

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1.1. *Patient-reported outcome measures*

A PRO measure captures information on the health from the patient's perspectives without the interpretation by a clinician or a researcher.[52] The application of PRO measures in health services research, health policy, and clinical practice dates back to the 1950s.[136] PRO instruments were initially intended to supplement the physiological measures to better understand treatment effectiveness. Currently, a plethora of PRO instruments exists in all health care fields.[101,136] Grossly, PRO instruments can be defined as generic or disease specific. Generic PRO instruments (e.g., 36-Item Short Form Health Survey [SF-36]) measure a broad spectrum of health concepts and are potentially suitable for a wide range of patient groups suffering from different types of diseases. The disease-specific PRO instruments (e.g., Macular Disease Dependent Quality of Life [MacDQoL]) are designed to be used in patients with a specific disease health problem and are intended to measure the impact of that specific disease on the person. Of course, there are many different eye diseases, so a PRO instrument developed for one eye disease, but then used in a different eye disease, ceases to be disease specific, but could be called an ophthalmic PRO instrument. In this study, we considered disease-specific instruments as those originally developed for the specific retinal disease (e.g., specifically for age-related macular degeneration [AMD]). Ophthalmic, but non-–disease-specific instruments, are instruments that were originally developed for eye disease/s other than the retinal disease under consideration and generic instruments developed for nonophthalmic diseases to measure broad concepts of health outcomes.

PRO instruments are basically developed or validated using 2 different approaches: the Classic Test Theory (CTT) or the Item Response Theory approaches.[150,167,174,240] The CTT and the Item Response Theory approaches have differences in terms of scoring and the assessment of the psychometric properties of the instrument. In CTT, the PRO instruments are scored by simple algebraic sum of the raw rank values assigned to the response categories across all the items.[128] Such scores, however, do not provide true interval-level measurement (i.e., the steps along the measurement continuum are not the same size). The summary scores obtained in this way introduce noise that damages the sensitivity of the PRO instrument to make meaningful comparisons between patients or between clinical outcomes. Moreover, summary scores are problematic when there is a ceiling (i.e., the items in a PRO instruments are too easy for the study population) or floor (i.e., the items in a PRO are too difficult for the study population) effect. On the other hand, the Item Response Theory models such as the Rasch analysis model provide advantages in terms of instrument scoring and more in-depth assessment of psychometric properties, including the test of dimensionality and the measurement precision. The Rasch model is a probabilistic mathematical model that assumes that the probability of a respondent to choose a particular response category for an item is a logistic function of the relative distance between the item's location (i.e., difficulty) and the respondent's location (i.e., ability) on a single linear continuum scale.[124] The advantage of Rasch analysis is that it estimates interval-level scoring for both the items' difficulty and respondents' ability from the PRO raw data. The interval-level scores of the respondent ability and the item difficulty on the same underlying trait makes the Rasch model a powerful method for estimating health outcome measures.[101]

1.2. *Quality of life*

The World Health Organization defines QoL as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns.[B] Basically, QoL is a very broad concept that fundamentally encompasses every impact that health or disease has on a person. It is a multidimensional construct affected by the person's physical health, psychological state, personal beliefs, and social relationships. In eye diseases, a set of 10 QoL domains are identified as important to people.[63,100,134] The ophthalmic QoL domains are activity limitation, mobility, visual symptoms, ocular surface symptoms, general symptoms, emotional well-being, social participation, economic, health concerns, and convenience.[64,100] For a complete assessment of QoL impact, all these QoL domains have to be included and assessed separately.

We provide a systematic review of the status of PRO measures in retinal diseases. For this, we set out 3 aims: 1) to identify all the PRO instruments used in retinal diseases and to determine to what extent they measure QoL; 2) to retrieve information including validity, reliability, and responsiveness of the PRO instruments to assess their quality; and 3) to identify gaps between known QoL impacts of retinal diseases and QoL measured by the existing PRO instruments.

2. Methods

To address aim 1, we grouped the retrieved articles together by disease (AMD, diabetic retinopathy [DR], retinal vascular conditions, hereditary retinal conditions, retinal infection, macular disease, and others) and further subgrouped them based on types of PRO instruments used (i.e., disease specific, ophthalmic but non–disease specific, and generic). Similarly, we grouped the articles on qualitative studies separately. We identified the content coverage of all the PRO instruments (disease specific, ophthalmic but non–disease specific, and generic) across the 10 ophthalmic QoL domains identified by our group based on extensive qualitative consultations with patients living with AMD and DR.[63,134] The QoL domains are activity limitation, mobility, general symptoms, visual symptoms, ocular surface symptoms, social participation, emotional well-being, economic, health concerns, and convenience. A few PRO instruments used in retinal diseases have content that target construct/s other than identified 10 ophthalmic QoL domains. The other constructs, coping, general health, problem solving, memory, general vision, environment, quality of sleep, and cognition did not qualify as ophthalmic QoL domains. These concepts based on the content review were also identified and listed as concepts/constructs being measured.

Next, we grouped the PRO instruments based on a series of quality criteria (aim 2) that include steps taken in the development and identification of the initial content through to testing the validity and reliability (see Table 1 for the definition and assessment of the quality criteria). Patients' reported outcomes instruments that were summary scored were assessed using CTT-based psychometric properties, namely acceptability, targeting, and internal consistency (see Table 1 for definition of these quality criteria), and Rasch scaled PRO instruments were assessed using Rasch-based psychometric properties, namely response categories, dimensionality, measurement precision, item-fit statistics, differential item functioning (DIF), and targeting (see Table 1 for definition of these quality criteria).

The quality criteria we used in this study are based on the US Food and Drug Administration guidelines and framework proposed by Pesudovs and colleagues and Lundstrom and Pesudovs.[121,177,225,234] Similarly, a standardized scoring system for assessing the quality of PRO instruments using 9 metric properties has been put forward by an international initiative (Consensus-based Standards for the selection of health status Measurement Instruments).[153,154] Our assessment criteria are similar to the quality criteria proposed by the Consensus-based Standards for the selection of health status Measurement Instruments group with a slight modification (Table 1). We have also used the same criteria in a major systematic review which explored quality of all the ophthalmic instruments tested with Rasch analysis.[101] The assessment criteria broadly assessed robustness in the content development, thorough psychometric assessment, and evidence of validity, reliability, and responsiveness. The aim was to identify the highest quality existing instrument for retinal diseases. We assessed each PRO instrument against the following criteria: content quality (item identification and item selection), psychometric assessment based on CTT (acceptability, targeting of the items, and internal consistency) and Rasch analysis (response categories, dimensionality, measurement precision, item-fit statistics, DIF, and targeting), validity (concurrent validity, convergent validity, discriminant validity, and known group validity) reliability (test-retest reliability), and responsiveness (Table 1). Each of the criterion is assessed differently based on the definition given in Table 1 for a grade assignment of A/B/C. Each PRO was given specific grades across all the criteria based on the available information and metrics. For example, the 7-item Near and Distance Vision subscale of the Daily Living Task Dependent on Vision (DLTV) was graded "A" for "measurement precision" because its person reliability value was high (i.e., 0.89, according to our definition grade "A" for any value $\geq$ 0.85; Table 1). The PRO instruments with the highest number of "grade A" across the criteria are considered to have superior quality.

For aim 3, we explored how the QoL issues expressed in qualitative studies across the 10 QoL domains compared with the content of the existing PRO instruments. This was done to identify the gaps in the known QoL impacts of retinal diseases and QoL measured by the existing PRO instruments.

3. Results

A total of 2,042 articles were identified from the initial search (Fig. 1). After reading the abstracts of the articles, 1,461 were excluded. The remaining 581 were matched with the selection criteria, and a further 376 articles were excluded as they did not meet the selection criteria. The final phase yielded 205 articles for analysis to which 12 articles were added in the review by cross checking the references. Analysis was carried on these final 217 articles (Fig. 1). Most articles were on AMD (n = 108) followed by DR (n = 31), hereditary retinal degenerations/dystrophies (n = 29), macular hole (MH; n = 9), retinal vascular conditions (n = 6), retinal detachment (RD; n = 5), retinal infections (n = 8), central serous retinopathy (CSR; n = 2), epiretinal membrane (ERM; n = 3) and studies on populations with mixed retinal diseases (n = 16). Of 217, 17 qualitative studies were identified, and these studies were on AMD (n = 8), DR (n = 5), hereditary retinal diseases (n = 3), and MH (n = 1). Among 200 articles reporting PRO measurement, we identified 110 different PRO instruments. More than half of these PRO instruments are generic instruments (n = 62) followed by disease-specific instruments (n = 29) and ophthalmic but non–retina-specific instruments (n = 19; Supplementary Table 1). Seventy studies used more than one PRO instrument.

Among the ophthalmic but non–retina-specific PRO instruments, the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ) was the most frequently used (n = 104 studies) followed by the Visual Function Index (VF-14; n = 10 studies). The DLTV (n = 8 studies) was the commonly used retina-specific PRO instrument. Among the generic PRO instruments, the SF-36 (n = 24 studies) and the Hospital Anxiety and Depression Scale (n = 11 studies) were the commonly used instruments. Most of the studies used summative scores for analysis, and only 13 studies used Rasch analysis–validated PRO instruments and interval-level scoring. Only 52 studies of 200 articles used disease-specific PRO instruments.

In the following section, we describe the types of PRO instruments used for each retinal disease. We assessed the quality of PRO instruments based on a series of quality criteria (Table 1) including the extent of their content coverage for each retinal disease. We also included qualitative studies that reported the impact of the disease on QoL from the patient's perspectives.

3.1. *Age-related macular degeneration*

We identified 108 studies on AMD in total. Of the 108 studies, 100 studies used PRO instruments, and the remaining were qualitative studies (Table 2).

3.1.1. *Disease-specific PRO instruments for AMD*

We identified 9 disease-specific PRO instruments for AMD. These included the MacDQoL,[147] the DLTV,[80] the Age-related Macular Degeneration Self-Efficacy Questionnaire,[25] the Activity Limitation Questionnaire (ALQ),[159] the Night Vision Questionnaire (NVQ-10),[243] the Face Recognition

Table 1 – Criteria used to assess quality of PRO instruments[48,121,173,177,225,234]

Property	Definition/assessment	Grade	Quality criteria
Content development			
Item identification	Identification of the initial item content.	A	Comprehensive consultation with patients and literature review for that particular disease group.
		B	Minimal consultation with the appropriate patients and expert opinion and literature review for that particular disease group.
		C	No consultation with patients/developed for other disease group.
Item selection	Selection of the items included in the final instrument.	A	A pilot instrument developed and tested with Rasch or factor analysis, statistical justification was provided for removing items, plus items with floor and ceiling effects were removed, and the amount of missing data was considered to obtain the final set of items.
		B	Only some of the previously mentioned techniques were used.
		C	No pilot instrument or no statistical justification of items was included in the final instrument.
Classic Test Theory (CTT)–based psychometric properties			
Acceptability	The percentage of missing data for each item and the percentage of people for whom a PRO instrument score can be computed.	A	$\leq 5\%$
		B	5% to $\leq 40\%$
		C	$> 40\%$
Targeting of the items	PRO instrument scores should span the entire range; floor (proportion of the sample at the maximum score) and ceiling (proportion of the sample at the minimum score effects should be low).	A	Either floor or ceiling effect $\leq 5\%$
		B	Either floor or ceiling effect 5% to $\leq 40\%$
		C	Either floor or ceiling effect $> 40\%$
Internal consistency	The extent to which all the items of a test measure the same latent variable. Internal consistency is usually measured with Cronbach's alpha, a statistic calculated from the pairwise correlations between items. Internal consistency ranges between negative infinity and one.	A	≥ 0.7 to ≤ 0.95
		B	≥ 0.6 to < 0.7
		C	< 0.6
Rasch-based psychometric properties			
Response categories	The extent to which the categories used to rate the items are chosen in a logical order (ordered categories). Evenly spaced categories (distance between category thresholds are expected to be between $\geq$1.4 and $<$5.00 logits).	A	All the categories were ordered or ordering of the categories was obtained after repairing disordered categories and evenly spaced categories.
		B	All the categories were ordered or ordering of the categories were obtained after repairing disordered categories and categories were not evenly spaced.
		C	Unrepairable disordered categories.
Dimensionality	The extent to which the instrument measures a single underlying construct. Principal components analysis (PCA) of the residuals based on 2 parameters: the amount of raw variance explained by the measure and eigenvalue of the unexplained variance in the first contrast or PCA/t-test protocol: % of t-tests of person measures obtained from the 2 item sets grouped based on PCA guided residual loading (first set $= \geq +0.3$ and second set $= \leq -0.3$) significantly different/% of t-tests falling outside the range $\pm$1.96 (95% CI).	A	Variance explained by the measure $\geq 60\%$ and eigenvalue of the first contrast $< 2.0/\leq 5\%$ of the person estimates are significantly different/% of t-tests falling outside 95% CI is $\leq 5\%$.
		B	Variance explained by the measure $\geq 50\%$ to $< 60\%$ and eigenvalue $< 2.0/> 5\% \leq 10\%$ of the person estimates are significantly different/% of t-tests falling outside 95% CI is $> 5\% \leq 10\%$.
		C	Variance explained by the measure $< 50\%$, eigenvalue ≥ 2.0, indication of subsets of items (this indicates unidimensionality)/$>$10% of the person estimates are significantly different/the lower bound of a Binomial 95% CI of the observed proportion overlaps $>$10%.
Measurement precision	The extent to which an instrument distinguishes between different levels of participants' abilities. Represented by person separation index or reliability coefficient (minimum acceptable value, separation $= 2.00$, or reliability $\alpha = 0.80$)	A	≥ 2.50, $\alpha \geq 0.85$
		B	2.0 to 2.49, $\alpha \geq 0.80$ to < 8.50
		C	< 2.0, $\alpha < 0.80$

(*continued on next page*)

Table 1 – (*continued*)

Property	Definition/assessment	Grade	Quality criteria
Item fit statistics	The extent to which the items in the instrument fit with the Rasch model expectation.	A	All items with infit and outfit mean square between 0.7 and 1.3 (or) infit and outfit standardized residuals < 2.
	Two fit statistics: infit and outfit mean square. Both fit statistics should have a value of 1 (acceptable range, 0.50–1.5).	B	One or 2 items within the 0.5 and 1.5 (or) infit and outfit standardized residuals ≥ 2 to < 2.5.
		C	More than 2 items outside the 0.5 and 1.5 limit (or) infit and outfit standardized residuals ≥ 2.5.
Differential item functioning (DIF)	The extent to which the levels of response ability of different subgroups of the same study population differ to an item (magnitude, <0.50 logits: insignificant, 0.50–1.0 logits: mild, >1.0 logit: notable).	A	All items with DIF < 0.50 logits
		B	Some items 0.50 to 1.0 logits and one at the most >1.0 logits
		C	More than one item >1.0 logits DIF.
Targeting	The extent to which item difficulty matches with the level of participants' visual abilities. It is the difference between item and person means (difference of >1 logit indicates significant mistargeting).	A	≤ 1 logits
		B	>1 to ≤ 2 logits
		C	>2 logits
Validity			
Concurrent validity	The extent to which the instrument score correlates with the score of the clinical measure (e.g., visual acuity, contrast sensitivity, visual field, and so forth).	A	Tested against appropriate clinical measures and correlates between 0.3 and 0.9
		B	Tested against debatable clinical measures and correlates between 0.3 and 0.9
		C	Correlates < 0.3 and > 0.9
Convergent validity	The extent to which the instrument correlates with the existing instrument measuring similar instrument.	A	Tested against appropriate instrument and correlates between 0.3 and 0.9
		B	Tested against debatable instrument and correlates between 0.3 and 0.9
		C	Tested and correlation < 0.3 or > 0.9
Discriminant validity	The extent to which the instrument correlates with the existing instrument measuring a different construct.	A	Tested against appropriate instrument and correlates < 0.3
		B	Tested against debatable instrument and correlates < 0.3
		C	Tested and poor correlation > 0.3
Known group validity	The extent to which the instrument can discriminate between clinically distinct groups.	A	Tested in appropriate groups and significant difference between groups
		B	Tested in debatable groups and significant difference between groups
		C	Tested and nonsignificant differences between groups
Reliability			
Test-retest reliability	The extent to which the instrument demonstrated temporal stability when administered in 2 different periods.	A	ICC ≥ 0.8
	Intraclass correlation (ICC) > 0.8 is considered good reliability.	B	ICC 0.79 to ≤ 0.60
		C	ICC < 0.60
Responsiveness			
Responsiveness	The extent to which the instrument can detect clinically important changes over time (minimal importance difference [MID] is the smallest difference in score, which a patient perceives as beneficial).	A	Change in score shown (increase or decrease) to have statistical significance
		B	Instrument tested for responsiveness, but statistical significance not reported
		C	No change in the PRO instrument score from baseline or statistically insignificant

A, high; B, medium; C, low; NR, not reported.

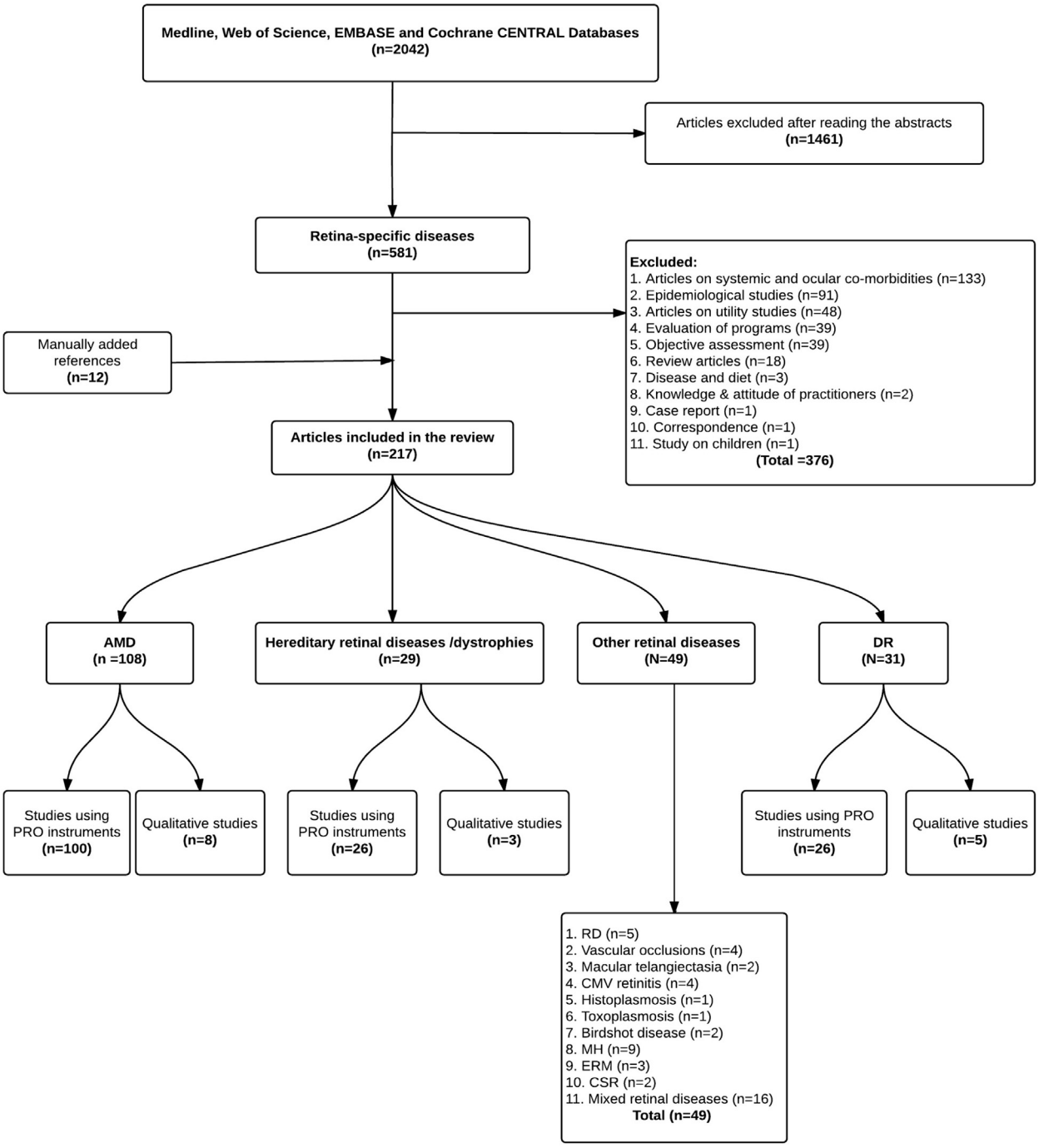

Fig. 1 – Steps taken for this review. AMD, age-related macular degeneration; CMV, cytomegalovirus; CSR, central serous retinopathy; DR, diabetic retinopathy; ERM, epiretinal membrane; RD, retinal detachment; MH, macular hole.

Questionnaire (FRQ),[224] the Low Luminance Questionnaire,[167] the Age-related Macular Degeneration Health Impact Questionnaire,[196] and the Discomfort Anxiety Fear Questionnaire.[38] The DLTV (n = 8 studies) was the most frequently used AMD-specific questionnaire.[53,80,81,135,195,196,214] Most of the AMD-specific PRO instruments cover activity limitation and emotional well-being domains of QoL. The DLTV and Age-related Macular Degeneration Health Impact Questionnaire covers a single domain. The DLTV covers activity limitation and the Age-related Macular Degeneration Health Impact Questionnaire covers social participation. The ALQ, Age-related Macular Degeneration Self-Efficacy Questionnaire, FRQ, Discomfort Anxiety Fear Questionnaire, and NVQ-10 cover 2 QoL domains. The ALQ covers activity limitation and health concerns; Discomfort Anxiety Fear Questionnaire, ocular symptoms and emotional well-being; Age-related Macular Degeneration Self-Efficacy Questionnaire, the NVQ-10; and the FRQ covers, activity limitation and emotional

Table 2 – The patient-reported outcome instruments used and their content coverage (concepts/domains being measured) as suggested by item content in age-related macular degeneration (AMD)

Study	Ophthalmic PRO instruments/population developed for/types of PRO instruments	Age (years)/target population/country/sample size	Concepts/domains being measured	Generic PRO instruments	Concepts/domains being measured
Mitchell (2013)[149]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/AMD/Australia, Canada, and Europe/345	AL, EM, and SC		
Parravano (2013)[170]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/Italy/12	AL, EM, and SC		
Jivraj (2013)[96]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease-specific	≥ 65/AMD/Canada/101	AL, EM, and SC	CES-D	EM
Menon (2013)[137]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥ 60/AMD/UK/99	AL, EM, and SC		
Rovner (2013)[187]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific AI/general ophthalmic population/ophthalmic but non–disease specific	≥ 65/AMD/US/241	AL, EM, and SC AL	PHQ-9 OPS	EM CP and SC
Finger (2013)[67]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/Germany/3470	AL, EM, and SC		
Bressler (2013)[19]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/US/1126	AL, EM & SC		
Finger (2012)[66]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/Germany/55	AL, EM, and SC		
Parodi (2012)[169]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/Italy/28	AL, EM, and SC		
Šiaudvytytė (2012)[205]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/Lithuania/140	AL, EM, and SC	HADS	EM
Mettu (2011)[139]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥55/AMD/US/55	AL, EM, and SC		
Rovner (2011)[190]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥65/AMD/US/241	AL, EM, and SC	PHQ-9 OPS	EM CP and SC
Sørensen (2011)[210]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/Denmark/120	AL, EM, and SC		
Orr (2011)[165]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/US/92	AL, EM, and SC		
Coleman (2010)[41]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥65/AMD/US/1674	AL, EM, and SC		
Berdeaux (2011)[10]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific MacDQoL/AMD/retina specific	≥50/AMD/France, Canada, US, Italy, Germany, the Netherlands, Spain, Australia, Belgium, and Israel/797	AL, EM, and SC AL, SC, EM, and MB		
Piermarocchi (2011)[178]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/Italy/293	AL, EM & SC		
Frennesson (2010)[68]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥ 60/AMD/Sweden//30	AL, EM, and SC		
Cruess (2007)[45]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/Canada/166	AL, EM, and SC	HADS	EM
Soubrane (2007)[211]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/Canada, France, Germany, Spain, and UK/401	AL, EM, and SC	HADS	EM

Leys (2008)[112]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/US and Canada/569	AL, EM, and SC		
Lotery (2007)[118]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/UK/75	AL, EM, and SC	HADS	EM
Lüke (2007)[120]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥65/AMD/Germany/50	AL, EM, and SC		
Rovner (2007)[186]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥64/AMD/US/206	AL, EM, and SC	HDRS	GS and EM
Hudson (2006)[93]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥55/AMD/US/217	AL, EM, and SC	ADL	AL
Tranos (2006)[227]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/UK/38	AL, EM, and SC		
Lindblad (2005)[113]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥55/AMD/US/4119	AL, EM, and SC		
Berdeaux (2005)[11]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/US and Europe/114	AL, EM, and SC		
Cahill (2005)[31]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥55/AMD/US/70	AL, EM, and SC	SF-12	GH, AL, GS, EM, and SC
Cahill (2005)[32]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥55/AMD/US/50	AL, EM, and SC	SF-12	GH, AL, GS, EM, and SC
Bass (2004)[9]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/US/996	AL, EM, and SC	SF-36 HADS	GH, AL, GS, EM, and SC EM
Childs (2004)[37]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/US/336	AL, EM, and SC	SF-36 HADS	GH, AL, GS, EM, and SC EM
Miskala (2004)[142]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/US/454	AL, EM, and SC	SF-36 HADS	GH, AL, GS, EM, and SC EM
Maguire (2004)[123]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/US/1052	AL, EM, and SC		
Miskala (2004)[143]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/US/120	AL, EM, and SC	SF-36	GH, AL, GS, EM, and SC
DeCarlo (2003)[51]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/US/126	AL, EM, and SC	DHQ LSQ	AL MB
Brody (2001)[21]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥60/AMD/US/151	AL, EM, and SC	SCID-IV GDS SIPV SIP HIQ	EM EM MB, EM, AL, and SC MB, EM, AL, and SC GH and SC
Dong (2004)[56]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/US/789	AL, EM, and SC	SF-36 HADS	GH, AL, GS, EM, and SC EM
Whitson (2013)[237]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥65/AMD/US/12	AL, EM, and SC	TICS – m IADL - C WMS –R GDS	CG AL MM EM
DeCarlo (2012)[50]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/US/199	AL, EM, and SC	CES-D	EM
Scilley (2004)[199]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥55//AMD/US/195	AL, EM, and SC		

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Table 2 – (*continued*)

Study	Ophthalmic PRO instruments/population developed for/types of PRO instruments	Age (years)/target population/country/sample size	Concepts/domains being measured	Generic PRO instruments	Concepts/domains being measured
Odergren (2010)[160]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/Sweden/98	AL, EM, and SC		
Bressler (2010)[18]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/US/1025	AL, EM, and SC		
Reeves (2009)[183]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/UK/1829	AL, EM, and SC	SF-36	GH, AL, GS, EM, and SC
Revicki (2010)[184]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥52/AMD/US/1134	AL, EM, and SC	SF-36	GH, AL, GS, EM, and SC
Suner (2009)[220]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥52/AMD/US/1139	AL, EM, and SC		
Bressler (2009)[17]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥52/AMD/US/418	AL, EM, and SC		
Chang (2007)[35]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥52/AMD/US/716	AL, EM, and SC		
Marback (2007)[126]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/Brazil/108	AL, EM, and SC		
Submacular Surgery Trials Research Group (2007)[216]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/US/828	AL, EM, and SC		
Miskala (2004)[144]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/US/120	AL, EM, and SC	SF-36	GH, AL, GS, EM, and SC
Casten (2010)[33]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	AMD/US/51	AL, EM, and SC	PHQ-9	
Brody (2006)[23]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific AMD – SEQ/AMD/retina specific	≥60/AMD/US/32	AL, EM, and SC AL and EM	GDS DSSI SCID – IV LOT-R HIQ	EM SC EM CP GH and SC
Rovner (2006)[188]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific MLVAI/general ophthalmic population/ophthalmic but non–disease specific	≥65/AMD/US/160	AL, EM, and SC AL	HDRS SPSI (SF)	GS and EM PS
Brody (2002)[22]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific AMD –SEQ/AMD/retina specific	≥60/AMD/US/231	AL, EM, and SC AL and EM	POMS DSSI LOT-R SCID HIQ	EM SC EM EM GH and SC
Brody (2005)[24]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific AMD-SEQ/AMD/retina specific	≥60/AMD/US/214	AL, EM, and SC AL and EM	POMS DSSI SCID HIQ	EM SC EM GH and SC
Brody (2011)[20]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific AMD-SEQ/AMD/retina specific	AMD/US/16	AL, EM, and SC AL and EM	HAM – A HAMD HIQ	GS and EM EM GH and SC

Smith (2005)[208]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific MLVQ/general ophthalmic population/ophthalmic but non–disease specific MLVAI/general ophthalmic population/ophthalmic but non–disease specific	AMD/UK/225	AL, EM, and SC AL, EM, and HC AL		
Sahel (2007)[192]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific MacDQoL/AMD/retina specific	≥50/AMD/France, Germany and Italy/360	AL, EM, and SC AL, SC, EM, and MB		
Ying (2008)[243]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific NVQ-10/AMD/retina specific	AMD/US/1052	AL, EM, and SC AL and EM		
Denny (2007)[53]	DLTV/AMD/retina specific	AMD/UK/186	AL		
Schmier (2006)[195]	DLTV/AMD/retina specific	AMD/US/802	AL		
Hart (2005)[81]	DLTV/AMD/retina specific	≥50/AMD/UK/235	AL		
Stevenson (2005)[213]	DLTV/AMD/retina specific	≥60/AMD/UK/199	AL	SF-36	GH, AL, GS, EM, and SC
Stevenson (2004)[214]	DLTV/AMD/retina specific	≥50/AMD/UK/199	AL	SF-36	GH, AL, GS, EM, and SC
McClure (2000)[135]	DLTV/AMD/retina specific	≥45/AMD/UK/100	AL		
Hart (1999)[80]	DLTV/AMD/retina specific	≥55/AMD/UK/103	AL		
Schmier (2006)[196]	DLTV/AMD/retina specific AMD-HIQ/AMD/retina specific	≥18/AMD/US/803	AL SC		
Mozaffarieh (2008)[158]	VF-14/cataract/ophthalmic but non–disease specific	AMD/Austria/90	AL	HADS	EM
Bansback (2007)[8]	VF-14/cataract/ophthalmic but non–disease specific	≥40/AMD/UK/209	AL		
Hewitt (2006)[89]	VF-14/cataract/ophthalmic but non–disease specific	AMD/Australia/82	AL		
Armbrecht (2004)[3]	VF-14/cataract/ophthalmic but non–disease specific	≥50/AMD/UK/48	AL		
Riusala (2003)[185]	VF-14/cataract/ophthalmic but non–disease specific GAS/no information/ophthalmic but non–disease specific	≥55/AMD/Finland/62	AL VS		
Espallargues (2005)[59]	VF-14/cataract/ophthalmic but non–disease specific	≥40/AMD/UK/209	AL		
Dubuc (2009)[57]	VF-14/cataract/ophthalmic but non–disease specific	≥50/AMD/Canada/46	AL		
Mackenzie (2002)[122]	VF-14/cataract/ophthalmic but non–disease specific GAS/no information/ophthalmic but non–disease specific	AMD/Canada/159	AL VS	SF-36	GH, AL, GS, EM, and SC
Finger (2012)[65]	MacDQoL/AMD/retina specific	AMD/Germany/108	AL, SC, EM, and MB		
Mitchell (2008)[151]	MacDQoL/AMD/retina specific	AMD/UK/135	AL, SC, EM, and MB		
Mitchell (2005)[150]	MacDQoL/AMD/retina specific	AMD/UK/171	AL, SC, EM, and MB		
Lamoureux (2008)[108]	IVI/general ophthalmic population/ophthalmic but non–disease specific	≥18/AMD/Australia/219	AL, EM, and MB		
Hassell (2006)[84]	IVI/general ophthalmic population/ophthalmic but non–disease specific	≥60/AMD/Australia/106	AL, EM, and MB	SF-12	GH, AL, GS, EM, and SC
Mathew (2011)[130]		≥55/AMD/Australia/145		SF-36 GADS IPAQ	GH, AL, GS, EM, and SC EM AL
Nguyen (2007)[159]	ALQ/AMD/retina specific	AMD/Germany/15	AL and HC		
Owsley (2006)[166]	LLQ/AMD/retina specific	≥50/AMD/US/104	AL and EM		
Owsley (2006)[167]	LLQ/AMD/retina specific	AMD/US/125	AL and EM		
Tolman (2005)[226]	AVL/general ophthalmic population/ophthalmic but non–disease specific	≥65/AMD/US/144	EM	GDS-SF	EM

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Table 2 – (*continued*)

Study	Ophthalmic PRO instruments/population developed for/types of PRO instruments	Age (years)/target population/ country/sample size	Concepts/domains being measured	Generic PRO instruments	Concepts/domains being measured
Krummenauer (2005)[104]	EMQ/cataract/vision specific	≥70/AMD/Germany/84	AL, MB, and EM		
Childs (2004)[36]		AMD/US/196		SF-36	GH, AL, GS, EM, and SC
Tejeria (2002)[224]	FRQ/AMD/retina specific	≥65/AMD/UK/30	AL and EM		
Rovner (2002)[191]	FVSQ/general ophthalmic population/ophthalmic but non–disease specific	≥64/AMD/US/51	AL	CES-D CDS	EM AL and MB
Scilley (2002)[200]	ADVS/cataract/ophthalmic but non–disease specific	≥50/AMD/US/92	AL		
Bailie (2013)[7]	MLVQ/general ophthalmic diseases/ophthalmic but non–disease specific	≥50/AMD/Ireland/39	AL, EM, and HC		
Coco-Martin (2013)[40]		≥60/AMD/Spain/41		WHOQOL-BREF	AL, MB, GS, EM, SC, and EV
Reeves (2004)[182]	VCM1/general ophthalmic population/ophthalmic but non–disease specific MLVQ/general ophthalmic population/ophthalmic but non–disease specific NAS/general ophthalmic population/ophthalmic but non–disease specific	AMD/UK/226	AL and EM AL, EM, and HC EM	SF-36	GH, AL, GS, EM, and SC
Haymes (2001)[87]	MLVAI/general ophthalmic population/ophthalmic but non–disease specific	≥60/AMD/Australia/22	AL		
Harper (1999)[79]	MLVQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/AMD/UK/56	AL, EM, and HC		
Chua (2009)[38]	DAF/AMD/retina specific	AMD/UK/100	EM and OS		
Rovner (2009)[189]		≥65/AMD/US/160		GDS IQCODE	EM MM & CG
Mangione (1999)[125]	ADVS/cataract/ophthalmic but non–disease specific	≥45/AMD/US/201	AL	SF-36	GH, AL, GS, EM, and SC
Submacular surgery trials pilot study investigators (2000)[215]		AMD/US/54		SF-36	GH, AL, GS, EM, and SC

ADVS, Activity of Daily Vision Scale; ADL, Activities of Daily Living Scale; AI, activity inventory; AL, activity limitation; ALQ, Activity Limitation Questionnaire; AMD-SEQ, Age-related Macular Degeneration Self-Efficacy Questionnaire; AMD-HIQ, Age-related Macular Degeneration Health Impact Questionnaire; AVL, Adaptation to Vision Loss Scale; CDS, Community Disability Scale; CES-D, the Centre for Epidemiologic Studies Depression Scale; CP, coping; CV, convenience; CG, cognition; DAF, Discomfort Anxiety Fear Questionnaire; DHQ, Driving Habits Questionnaire; DSSI, Duke Social Support Index; DLTV, Daily Living Tasks Dependent on Vision; EC, economic; EM, emotional well-being; EMQ, Extended Mainz Questionnaire; EV, environment; FRQ, Face Recognition Questionnaire; FVSQ, Functional Vision Screening Questionnaire; GAS, Global Assessment Scores; GADS, Geriatric Depression Scale; GDS, Goldberg Depression Scale; GH, general health; GHQ, General Health Questionnaire; GS, general symptoms; GV, general vision; HAM-A, Hamilton Rating Scale for Anxiety; HADS, Hospital Anxiety and Depression Scale; HAMD, Hamilton Rating Scale for Depression; HC, health concerns; HDRS, Hamilton Depression Rating Scale; HIQ, Health and Impact Questionnaire; IADL, Instrumental Activities of Daily Living Questionnaire; IPAQ, International Planned Activity Questionnaire scale; IQCODE, Informant Questionnaire for Cognitive Decline; IVI, Impact of Visual Impairment; LLQ, Low Luminance Questionnaire; LOT-R, Life Orientation Test Revised; LSQ, Life Space Questionnaire; MacDQoL, Macular Disease Dependent Quality of Life scale; MB, mobility; MM, memory; MLVQ, Manchester Low Vision Questionnaire; MLVAI, Melbourne Low Vision Index; NAS, Nottingham Adaptation Scale; NEI-VFQ, National Eye Institute Visual Function Questionnaire; NVQ-10, Night Vision Questionnaire (10 items); OPS, Optimization in Primary and Secondary Control Scale; OS, ocular comfort symptoms; PHQ-9, Patient Health Questionnaire; POMS, Profile of Mood States; PS, problem solving; SC, social participation; SCID-IV, Structured Clinical Interview; SF-36, 36-Item Short Form Health Survey; SF-12, 12-Item Short Form Health Survey; SIP, Sickness Impact Profile; SIPV, Sickness Impact Profile Vision; SPSI, Social Problem Solving Inventory; TICS–m, the Modified Telephone Interview for Cognitive Status; VCM1, Vision Core Measure 1; VF-14, Visual Function Index (14 questions); VS, visual symptoms; WHOQOL-BREF, WHO Quality of Life Questionnaire; WMS-R, Wechsler Memory Scale.

well-being. The Low Luminance Questionnaire covers 3 domains: activity limitation, mobility, and emotional well-being. Among all the PRO instruments, the MacDQoL seems more comprehensive in terms of the content coverage (activity limitation, socioemotional well-being, health concerns, and economic);[65] however, it has limited number of items representing those domains.[65]

Among the 9 AMD-specific PRO instruments, 7 instruments were summary scored, and 2 were Rasch scaled. The 7 PRO instruments (ALQ, FRQ, Low Luminance Questionnaire, Age-related Macular Degeneration Health Impact Questionnaire, Discomfort Anxiety Fear Questionnaire, and NVQ-10) performed poorly against our quality criteria. Only the MacDQoL and the DLTV were assessed with Rasch analysis.[53,65] The original version of the MacDQoL is flawed owing to its complex multiplicative rating scale and multidimensionality; however, after several revisions, 2 of its subscales (activity limitation and mobility and socioemotional well-being) are recommended for use in AMD.[65] The DLTV was also assessed with Rasch analysis as a legacy instrument.[53] Both the native and the Rasch scaled versions violated unidimensionality, and only the revised scale consisting of 11 items on activity limitation and the subscale near and distance vision consisting of 7 items has been recommended for use in AMD.[53] Although these are valid instruments, their QoL coverage is limited to measuring only activity limitation.

3.1.2. *Ophthalmic, but non–disease-specific, PRO instruments in AMD*

Overall 13 non-AMD–specific but ophthalmic PRO instruments were used in AMD (Table 2). These are the NEI-VFQ, the Activity Inventory (AI), VF-14, Impact of Visual Impairment (IVI), Melbourne Low Vision Index (MLVAI), Adaptation to Vision Loss Scale, Global Assessment Scores, Functional Vision Screening Questionnaire, Activity of Daily Vision Scale, Manchester Low Vision Questionnaire, Vision Core Measure 1, Nottingham Adaptation Scale, and Extended Mainz Questionnaire. The NEI-VFQ (n = 60 studies) was the most commonly used PRO instrument followed by the VF-14 (n = 8 studies), Manchester Low Vision Questionnaire (n = 4), MLVAI (n = 3), Activity of Daily Vision Scale (n = 2), IVI (n = 2), AI (n = 1), ADL (n = 1), Vision Core Measure 1 (n = 1), and Extended Mainz Questionnaire (n = 1). The AI, VF-14, MLVAI, Functional Vision Screening Questionnaire, Adaptation to Vision Loss Scale, Nottingham Adaptation Scale, Global Assessment Scores, and Activity of Daily Vision Scale cover only a single QoL domain. The AI, VF-14, MLVAI, Activity of Daily Vision Scale, and Functional Vision Screening Questionnaire cover activity limitation; Adaptation to Vision Loss Scale, Nottingham Adaptation Scale, emotional well-being; and Global Assessment Scores, visual symptoms. The Vision Core Measure 1 covers 2 domains, activity limitation and emotional well-being. The Extended Mainz Questionnaire, Manchester Low Vision Questionnaire, and IVI cover 3 domains. The Extended Mainz Questionnaire covers activity limitation, mobility, and emotional well-being; the Manchester Low Vision Questionnaire covers activity limitation, emotional well-being, and health concerns; and the IVI covers activity limitation, mobility, and emotional well-being. Most of the ophthalmic but non–retinal-specific PRO instruments again are limited in measuring few QoL domains.

Among the 13 PRO instruments, 9 were summary scored, and only 4 (NEI-VFQ, MLVAI, IVI, and VF-14) were Rasch scaled.[66,89,108,178,208] The NEI-VFQ compared with other vision-specific PRO instruments appears more comprehensive, purporting to measure 6 domains, but suffers from inadequate number of items across domains except for activity limitation and the socioemotional well-being. Similarly, Rasch analysis of the instrument revealed that the NEI-VFQ has problems with the item construction and response categories, and it is multidimensional.[175] The Rasch analysis revised NEI-VFQ have 2 valid measures of QoL: visual functioning and socioemotional aspects of QoL only.[66] The revised scale of IVI consisting of 3 scales (emotional well-being, reading and accessing information, and mobility and independence) was found to be a valid measure in AMD.[108] Although the VF-14 was assessed with Rasch analysis, the authors provided limited information on the metric properties to determine its suitability in patients with AMD.[89] The 9 PRO instruments that were validated using the CTT showed poor performance in AMD.

3.1.3. *Generic PRO instruments in AMD*

A total of 28 generic PRO instruments were used in AMD (Table 2). Among these, the SF-36 (n = 16 studies) and the Hospital Anxiety and Depression Scale (n=9 studies) were the most commonly used. The SF-36 covers general health, activity limitation, general symptoms, emotional well-being, and social participation, and the Hospital Anxiety and Depression Scale covers emotional well-being. All these generic PRO instruments were developed for nonocular conditions. All these PRO instruments were validated by CTT and performed poorly against our quality criteria.

3.1.4. *Qualitative studies in AMD*

Our search found 8 qualitative studies. The methods of data collection in these studies were either semistructured interviews (n = 4) and/or focus groups (n = 2) or both (n = 2). The sociodemographics of the population of these qualitative studies is given in Table 3.

Patients with unilateral disease have little or no debilitating difficulties in daily living compared with patients with bilateral AMD.[239] People with AMD frequently experience difficulties carrying out important activities requiring central vision such as reading, driving, recognizing faces, watching television, and manual work (activity limitation).[13] The biggest issue raised is losing the ability to drive and its effect on patients' independence (health concerns).[239] Ivanoff and colleagues[94] report that patients with AMD usually feel incompetent at performing activities of daily living and therefore adopt strategies such as changing how the activity is performed, modification of the environment (doing things more in daytime than at night), using other senses, avoidance, and asking for help. Wong and colleagues[239] in their study involving 15 patients with AMD report that patients with bilateral disease required greater concentration, planning, recall capabilities, and coordination of sensory modalities like hearing and touching even to perform simple daily activities (convenience).

Table 3 – Description of the qualitative studies in retinal diseases

Study	Data collection	Sample size	Age (years)	Gender, M = male; F = female	Country	Population
Age-related macular degeneration (AMD)						
McCloud (2014)[134]	Semistructured interviews and focus groups	34	≥ 56	M = 15; F = 19	Australia	Geographic type = 6 Exudative type = 6
Wong (2004)[239]	Semistructured interviews	15	≥ 60	M = 7; F = 8	Australia	Mild-to-severe AMD
Moore (2003)[156]	Interviews	8	≥ 65	M = 8	US	Severe AMD
Moore (2000)[155]	Interviews	8	≥ 60	F = 8	US	Severe AMD
Owsley (2006)[168]	Focus groups	53	≥ 45	F = 28; M = 25	US	Mild to severe AMD
Mogk (2008)[152]	Semistructured interviews	12	≥ 75	NR	US	Mild to severe AMD
Feely (2007)[61]	Interviews	7	≥ 60	NR	UK	Moderate to severe AMD
Ivanoff (1996)[94]	Focus groups	25	≥ 65	M = 10; F = 15	Sweden	NR
Diabetic retinopathy (DR)						
Coyne (2004)[44]	Focus groups	15	≥ 18	M = 5; F = 7	US	NPDR and PDR
Devenney (2011)[55]	Semistructured interviews	10	≥ 18	M = 4; F = 6	Ireland	Moderate and severe DR
Fenwick (2012)[63]	Semistructured interviews and focus groups	57	≥ 18	M =39; F = 18	Australia	Mild, moderate, and severe NPDR and PDR
Fenwick (2013)[62]	Semistructured interviews and focus groups	57	≥ 18	M =39; F = 18	Australia	Mild, moderate and severe NPDR & PDR
Scanlon (2006)[193]	Interviews	227	≥ 18	NR	UK	DME and PDR
Hereditary retinal degenerations/dystrophies						
Bittner (2010)[14]	Focus groups	8	≥ 18	M = 2; F = 6	US	RP
Combs (2013)[42]	Semistructured interviews	25	NR	NR	UK	RP Sorsby fundus dystrophy Cone-rod dystrophy Retinoschisis Choroideremia Cone dystrophy Leber congenital amaurosis and unspecified retinal or macular dystrophy
Hayeems (2005)[86]	Semistructured interviews and focus groups	43	≥ 18	M = 24; F = 19	US	RP
Macular hole (MH)						
Wittich (2008)[238]	Dairy content	1	≥ 60	F = 1	Canada	MH

AMD, age-related macular degeneration; DME, diabetic macular edema; MN, macular hole; NR, not reported; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; RP, retinitis pigmentosa.

People with AMD have a higher risk of emotional distress, depression, and social isolation. AMD patients express more negative emotional comments such as frustration/bothered, sadness, fear, and inadequacy compared with the positive comments like hope and optimism (emotional well-being).[168] The lack of understanding about AMD causes psychological problems such as depression, loss of personal control, and powerlessness (emotional well-being). Loss of independence and loss of meaningful leisure time were found to contribute to loneliness, isolation, and inactivity among AMD patients (social participation).[94] McCloud and colleagues[134] report that inability to recognize faces often led to social isolation (social participation). Social isolation also leads to suicidal tendencies (emotional well-being).[239]

Fear of blindness, uncertainty about the future, and cost of the treatment relative to the improvement are some of the health concerns.[134,156] McCloud and colleagues[134] report that loss of work and cost for frequent injections led to financial constraints (economic). Most of the patients in the study by Wong and colleagues expressed dissatisfaction, anger, or resentment toward their eye care providers as a result of lack of knowledge of AMD (health concerns).[239] An underlying fear that treatment would only work for a while and that eventually they would slide into blindness was expressed by AMD patients on anti-vascular endothelial growth factor treatment (emotional well-being and health concerns).[134] Relative newness of the treatment and disease progression form one eye to both the eyes also frequently caused anxiety (emotional well-being and health concerns).[134]

AMD patients also frequently expressed hope and optimism (emotional well-being).[155,156] Patients who participate in rehabilitation programs and those who use assistive devices for their visual impairment are optimistic and hopeful (emotional well-being) compared with older adults who were socially isolated.[239] AMD patients responding to treatment and those with stable disease feel optimistic, whereas people in whom the treatment has failed and those with geographic atrophy are usually subjected to more emotional impact (emotional well-being).[134] McCloud and colleagues[134] report that painful injections, bloodshot eyes, and physical difficulties associated with monthly treatments or visits are some of the inconveniences (visual symptoms and convenience).

The major QoL issues among AMD patients seem to be activity limitations because of loss of central vision. Inability to perform important activities requiring central vision frequently result in emotional impact such as frustration, anger, and depression. Other major QoL issue is health concerns among AMD patients which include their concerns about future, possibilities of losing vision, uncertainty of treatments outcomes, current level of eye care, and so forth.

3.1.5. *QoL impact versus QoL measured in AMD*

The qualitative studies highlight a broader QoL issues in people with AMD; however, none of the existing PRO instruments provide comprehensive QoL measure and valid QoL score (Table 2). Most of the PRO instruments primarily assess only one or few aspects of QoL (such as activity limitation and emotional well-being) and do not provide a comprehensive assessment of QoL (Table 2). There are other QoL issues such as social well-being, financial implication, issues related to inconvenience, and health concerns not well represented in the existing PRO instruments.[134,156,239]

3.1.6. *The highest quality existing PRO instruments for AMD*

The PRO instruments with the highest quality criteria (Table 4) for AMD are the IVI with its 3 scales (emotional well-being, reading and accessing information, and mobility and independence) and the Rasch modified version of the MacDQoL with 2 scales (socioemotional well-being and activity limitation and mobility). All 3 scales of the IVI were graded "A" for measurement precision (i.e., person separation reliability was > 0.90, according to our definition grade "A" for any value ≥ 0.85), item fit (i.e., fit residuals < 2.5, according to our definition grade "A" for any value < 2), response categories, dimensionality, targeting, and DIF. The 2 scales of MacDQoL were graded "A" for item identification (i.e., focus group sessions with patients with macular diseases and literature review was done for the identification of the initial item content of the questionnaire, according to our definition grade "A" if identification of the initial item content involved comprehensive consultation with patients and literature review for that particular disease group), item selection, response categories (i.e., no disordered response categories, according to our definition grade "A" if all the categories were ordered), item fit, and targeting.

3.2. *Diabetic retinopathy (DR)*

We identified 31 studies on DR. Of the 31 studies, 26 studies used PRO assessments (Table 5), and 5 were qualitative studies.

3.2.1. *Disease-specific PRO instruments in DR*

Only 5 studies of the 26 studies used DR-specific PRO instruments.[26,27,46,240,241] The Retinopathy Dependent Quality of Life (RetDQoL) and the Retinopathy Satisfaction Treatment Questionnaires are the only 2 PRO instruments developed for DR.[240,241] The QoL domains covered by the RetDQoL are activity limitation, socioemotional well-being, economic, and health concerns, and the Retinopathy Satisfaction Treatment Questionnaires claims to measure ocular symptoms, emotional well-being, and health concerns. Neither of the instruments was tested with Rasch analysis. The RetDQoL and the MacDQoL are almost identical. They have similar items (except for 2 items: 1) the way society at large reacts to me would be and 2) my enjoyment of food would be), few items within domains (e.g., emotional well-being has 2 items) and the same multiplicative rating scale and scoring schema. The original version of the MacDQoL is flawed because of its complex multiplicative scoring and multidimensionality.[65] We speculate that the same holds for the RetDQoL.[65]

3.2.2. *Ophthalmic but non–disease-specific PRO instruments in DR*

The ophthalmic but non–disease-specific PRO instruments used were the NEI-VFQ, AI, VF-11, and IVI. Again the NEI-VFQ ($n = 12$ studies) was the most frequently used PRO instrument.[71,78,90,110,115,117,132,133,161,230,231,236] The VF-11 is derived from VF-14 and measures activity limitation. The AI and the VF-11 PRO instruments were tested with Rasch analysis. The

Table 4 – Quality of patient-reported outcome measures in retinal diseases

Study	Name of the PRO	Content development	Type of PRO instruments	CTT-based psychometric properties	Rasch-based psychometric properties	Validity	Reliability/ responsiveness
Age-related macular degeneration							
Finger (2012)[66]	10-item visual functioning scale (derived from NEI-VFQ-25)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = B Measurement precision = B Dimensionality = B Item fit = A DIF = NR Targeting = B	Concurrent = C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = A
Finger (2012)[66]	8-item socioemotional scale (derived from NEI-VFQ-25)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = B Measurement precision = C Dimensionality = A Item fit = A DIF = NR Targeting = C	Concurrent = C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Piermarocchi (2011)[178]	NEI-VFQ-39	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = B Measurement precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = A	Concurrent = C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Smith (2005)[208]	9-Item self-assessed Visual Functioning Scale (derived from NEI-VFQ)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement precision = NR Item fit = A Dimensionality = NR DIF = NR Targeting = NR	Concurrent = NR Known group = NR Convergent = NR Discriminant =NR	ICC = NR Responsiveness = C
Smith (2005)[208]	9-item observed performance on tasks dependent on vision scale (derived from MLVAI)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement precision = NR Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = C
Smith (2005)[208]	7-item self-assessed ADL scale (derived form MLVAI)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement precision = NR Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = C
Lamoureux (2008)[108]		Item identification = C Item selection = B	Ophthalmic but non–disease specific		Response categories = A Measurement precision = A	Concurrent = NR Known group = A	ICC = NR Responsiveness = NR

	Emotional well-being scale (derived from IVI)			Acceptability = NR Targeting = NR Internal consistency = NR	Dimensionality = A Item fit = A DIF = NR Targeting = A	Convergent = NR Discriminant = NR	
Lamoureux (2008)[108]	Reading and accessing information scale (derived from IVI)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = A Measurement precision = A Dimensionality = A Item fit = A DIF = NR Targeting = A	Concurrent = NR Known group = A Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Lamoureux (2008)[108]	Mobility and independence scale (derived from IVI)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = A Measurement precision = A Dimensionality =A Item fit = A DIF = NR Targeting = A	Concurrent = NR Known group = A Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Hewitt (2006)[89]	12-item modified version of the VF-14	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement precision = NR Dimensionality = NR Item fit = NR DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = A
Finger (2012)[65]	Activity limitation and mobility scale (derived from MacDQoL)	Item identification = A Item selection = A	Retina specific	Acceptability = NR Targeting = NR Internal consistency= NR	Response categories = A Measurement precision = B Dimensionality = B Item fit = A DIF = B Targeting = A	Concurrent = C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Finger (2012)[65]	Socioemotional well-being scale (derived from MacDQoL)	Item identification = A Item selection = A	Retina specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = A Dimensionality = A Measurement precision = B Item fit = A DIF = B Targeting = A	Concurrent = C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Denny (2007)[53]	11-item activity limitation scale (derived from DLTV)	Item identification = B Item selection = A	Retina specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = B Dimensionality = NR Measurement precision = B Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Denny (2007)[53]	7-item near and distance vision subscale (derived from DLTV)	Item identification = B Item selection = A	Retina specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = B Measurement precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR

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Table 4 – (*continued*)

Study	Name of the PRO	Content development	Type of PRO instruments	CTT-based psychometric properties	Rasch-based psychometric properties	Validity	Reliability/ responsiveness
Diabetic retinopathy							
Ahmadian (2008)[1]	AI All items	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency= NR	Response categories = NR Measurement precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Ahmadian (2008)[1]	Goals scale (derived from AI)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Ahmadian (2008)[1]	Reading scale (derived from AI)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Ahmadian (2008)[1]	Visual information scale (derived from AI)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Accepting = NR Targeting =NR Internal consistency = NR	Response categories = NR Measurement precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Ahmadian (2008)[1]	Visual motor scale (derived from AI)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Ahmadian (2008)[1]	Mobility scale (derived from AI)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement precision = B Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = NR Known group = C Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Lamoureux (2010)[109]	VF-11	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency= NR	Response categories = NR Measurement precision = B Dimensionality = NR Targeting = NR DIF = NR Item fit = NR	Concurrent = A Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR

Matza (2008)[132]	NEI-VFQ	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = A to B	NR	Concurrent = A Known group = A Convergent = NR Discriminant = NR	ICC = NR Responsiveness = A
Lloyd (2013)[115]	NEI-VFQ	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = A	NR	Concurrent = C Known group = A Convergent = NR Discriminant = NR	ICC = NR Responsiveness = A
Tranos (2004)[230]	NEI-VFQ	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	NR	Concurrent = A Known group = NR Convergent = NR Discriminant = NR	ICC = A to B Responsiveness = A
Macular telangiectasia							
Lamoureux (2011)[107]	Mobility and independence scale (derived from IVI)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement precision = A to C Dimensionality = NR Item fit = NR DIF = NR Targeting = C	Concurrent = B Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = C
Lamoureux (2011)[107]	Emotional well-being scale (derived from IVI)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement Precision = A to C Dimensionality = NR Item fit = NR DIF = NR Targeting = C	Concurrent = C Known group = NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = C
Lamoureux (2011)[107]	Reading and accessing information scale (derived from IVI)	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Accepting = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement precision-PSR = A to C Dimensionality = NR Item fit = NR DIF = NR Targeting = C	Concurrent = A Known group =NR Convergent = NR Discriminant = NR	ICC = NR Responsiveness = C
Hereditary retinal degenerations/dystrophies							
Turano (1999)[232]	IMQ	Item identification = C Item selection = B	Retina specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = NR Measurement precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = NR	Concurrent = A Known group = A Convergent = NR Discriminant = NR	ICC = NR Responsiveness = NR
Mixed retinal diseases							
Arimura (2011)[2]	MPQ	Item identification = C Item selection = B	Retina specific	Acceptability = NR Targeting = NR Internal consistency = NR	Response categories = A Measurement precision = A Dimensionality = NR	Concurrent = A to C Known group = NR	ICC = NR Responsiveness = NR

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Table 4 — (continued)

Study	Name of the PRO	Content development	Type of PRO instruments	CTT-based psychometric properties	Rasch-based psychometric properties	Validity	Reliability/ responsiveness
Unver (2009)[233]	PalmPilot-VFQ	Item identification = C Item selection = B	Ophthalmic but non–disease specific	Acceptability = NR Targeting = NR Internal consistency = A	Item fit = A DIF = B Targeting = NR Response categories = NR Measurement precision = A Dimensionality = NR Item fit = A DIF = NR Targeting = B	Convergent = NR Discriminant = NR Concurrent = A Known group = NR Convergent = A Discriminant = NR	ICC = C Responsiveness = NR

ADL, Activity of Daily Living; AI, activity inventory; CTT, Classic Test Theory; DIF, Differential Item Functioning; DLTV, Daily Living Tasks Dependent on Vision; ICC, intraclass correlation; IMQ, Independent Mobility Questionnaire; IVI, impact of visual impairment; MacDQoL, Macular Disease Dependent Quality of Life; MLVAI, Melbourne Low Vision Index; MPQ, Metamorphopsia Questionnaire; NEI-VFQ, National Eye Institute Visual Function Questionnaire; NR, not reported; PalmPilot-VFQ, PalmPilot Visual Function Questionnaire; PRO, patient-reported outcome; VF-14, Visual Function Index (14 questions); VF-11, Visual Function Index (11 questions).

AI shows good measurement precision and item fit; however, most of the information on the metric properties of the VF-11 is not available (Table 4). The NEI-VFQ and the IVI showed poor performance in DR.

3.2.3. *Generic PRO instruments in DR*

A total of 14 PRO instruments were used in DR (Table 5). Nine of them assessed the emotional well-being aspect of QoL. The 12-Item Short Form Health Survey was the frequently used generic instrument among them and QoL domains it covers are similar to the SF-36. None of these PRO instruments contain items related to vision, and none of them were validated in this disease.

3.2.4. *Qualitative studies in DR*

There were 5 qualitative studies. The methods of data collection in these studies were focus groups (n = 1 study), interviews (n = 1 study), and both focus groups and interviews (n = 3 studies). The sociodemographics of the population of these qualitative studies are given in Table 3.

Patients with DR, like AMD, also frequently report difficulties in executing day-to-day tasks such as reading, watching TV, cooking, housekeeping, sewing, gardening, recognizing faces, hobbies, and getting dressed (activity limitation).[44,63] Vision loss in DR also affects the individual's diabetic care activities such as reading labels on the food items, insulin injections, blood testing, and exercise (activity limitation).[44] They also experience a variety of visual symptoms such as blurry, wavy, hazy or distorted vision, trouble with bright lights, flashes, floaters, and temporary blackness due to retinal hemorrhage (visual symptoms).[63] The possibility of going blind is a major concern for those with moderate and severe form of DR (health concerns).[44] Visual loss due to DR has been associated with loss of ability to perform important occupational and family roles such as working, driving, or caring for the family (social participation).[55] Driving, especially at night, was the most frequently affected activity among the DR patients (activity limitation) that frequently resulted in loss of mobility and independence (mobility).[44] DR has also been shown to cause emotional distress and depression (emotional well-being).[63] They also have substantial reduction in their social well-being (social participation).[63]

Poor diabetes control was the most commonly reported risk factor for DR. Poor eating habits, smoking, lack of exercise, lack of awareness, delay in the diagnosis, genetics, and environmental factors were the other perceived risk factors for DR.[62] As DR affects younger patients compared with AMD, the visual loss has financial implications from loss of employment or restricted work hours, cost of purchasing visual aids, and the cost of treatment (economic).[63] Most patients with DR also have limited understanding about laser treatment and believe that laser or related treatments made their vision worse.[62] DR patients also experience lot of inconveniences such as having to depend on others for transport during clinic visits, having multiple treatments, and having to undergo frequent dilatations at every clinic appointment (convenience).[63] Unlike AMD, patients with DR are more likely to have multiple comorbidities and the presence of renal or neurological comorbidities may compromise QoL further.

Table 5 – The patient-reported outcome instruments used and their content coverage in diabetic retinopathy, other retinal vascular diseases, retinal detachment, and retinal infections

Study	Ophthalmic PRO instruments/population developed for/types of PRO instruments	Age (years)/target population/country/sample size	Concepts/domains being measured	Generic PRO instruments	Concepts/domains being measured
Diabetic retinopathy (DR)					
Hirai (2011)[90]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	DR/US/471	AL, EM, and SC		
Hariprasad (2008)[78]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥16/DR/US/33	AL, EM, and SC		
Lang (2013)[110]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/DR/Australia, Belgium, Canada, France, Germany, Greece, Hungary, UK, Spain, Switzerland, Italy, and the Netherlands/240	AL, EM, and SC		
Loftus (2011)[117]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/DR/Australia, Europe, India, North America and South America/260	AL, EM, and SC		
Matza (2008)[132]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	DR/US/535	AL, OS, EM, and SC	SF-36	GH, AL, GS, EM, and SC
Mazhar (2011)[133]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥40/DR/US/1064	AL, EM, and SC	SF-12	GH, AL, GS, EM, and SC
Okamoto (2008)[161]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	DR/Japan/51	AL, EM, and SC		
Tsilimbaris (2013)[231]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	DR/Greece/20	AL, EM, and SC		
Warrian (2010)[236]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	DR/US/91	AL, EM, and SC		
Tranos (2004)[230]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥17/DR/UK/55	AL, EM, and SC		
Lloyd (2013)[115]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/DR/Australia, Canada, Europe, India, South Africa and South America/235	AL, EM, and SC		
Gabrielian (2010)[71]	NEI-VFQ/general ophthalmic population /ophthalmic but non–disease specific	DR/US/104	AL, EM, and SC		
Ahmadian (2008)[1]	AI/general ophthalmic disease/ophthalmic but non–disease specific	≥18/DR/US/114	AL and SC		
Brose (2010)[27]	RetDQOL/DR/retina specific RetTSQ/DR/retina specific	≥19/DR/Germany/207	AL, EM, EC, SC, and HC HC, OS, and EM	SF-12	GH, AL, GS, EM, and SC
Davidov (2009)[46]	RetDQOL/DR/retina specific RetTSQ/DR/retina specific	≥18/DR/Germany/207	AL, EM, EC, SC, and HC HC, OS, and EM	SF-12	GH, AL, GS, EM, and SC
Hirai (2012)[91]		DR/US/484		CES-D	EM
Jensen (2010)[95]		≥45/DR/US/6417		CES-D	EM
				STAI	EM
				CBS	EM
				CMHS	EM
				CHD-SSI	SC

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Table 5 – (*continued*)

Study	Ophthalmic PRO instruments/population developed for/types of PRO instruments	Age (years)/target population/ country/sample size	Concepts/domains being measured	Generic PRO instruments	Concepts/domains being measured
Lamoureux (2010)[109]	VF-11/cataract/ophthalmic but non–disease specific	≥40/DR/Singapore/357	AL		
Mirshahi (2013)[141]		DR/Iran/66		PQ	OS
Mozaffarieh (2005)[157]		≥35/DR/Austria/123		DTSQ	SF
Rees (2012)[181]		≥18/DR/Australia/400		IPQ-R	GS, OS, HC and EM and
				SDSCA	CP
				HADS	AL
					EM
Sieu (2011)[206]		DR/US/2359		PHQ-9	EM
Woodcock (2004)[240]	RetDQOL/DR/retina specific	≥18/DR/UK and Germany/44	AL, EM, EC, SC, and HC		
Woodcock (2005)[241]	RetSTQ/DR/retina specific	≥25/DR/UK and Germany/44	HC, OS, and EM		
Brose (2009)[26]	RetTSQ/DR/retina specific	≥18/DR/Germany/207	HC, OS, and EM	SF-36	GH, AL, GS, EM, and SC
	RetDQOL/DR/retina specific		AL, EM, EC, SC, and HC		
Lamoureux (2004)[106]	IVI/general ophthalmic population/ophthalmic but non–disease specific	≥18/DR/Australia/45	AL, MB, and EM	SF-12	GH, AL, GS, EM, and SC
Retinal detachment (RD)					
Fabian (2013)[60]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/RD/Israel/366	AL, EM, and SC	PTSD	EM
				PTDS	EM
Koriyama (2007)[103]	RDQ/RD/retina specific	≥50/RD/Japan/46	OS and HC		
Okamoto (2008)[163]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	RD/Japan/51	AL, EM, and SC		
Zou (2008)[244]	CLVQOL/general ophthalmic population/ophthalmic but non–disease specific	≥18/RD/China/163	MB, AL, and EM		
			VS		
	GAS/no information/ophthalmic but non–disease specific				
Zou (2011)[245]	CLVQOL/general ophthalmic population/vision specific	≥18/RD/China/92	MB, AL, and EM		
			VS		
	GAS/no information/ophthalmic but non–disease specific				
Vascular occlusion (VO)					
Brown (2013)[28]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/VO/US, Canada, Columbia, India, and Israel/189	AL, EM, and SC		
Deramo (2003)[54]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/VO/US/51	AL, EM, and SC		
Awdeh (2010)[6]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/VO/US/46	AL, EM, and SC		
Varma (2012)[235]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/VO/US/789	AL, EM, and SC		
Macular telangiectasia (MT)					
Clemons (2008)[39]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/MT//France, Australia, US, Germany, Israel, India, and UK/222	AL, EM, and SC		
Lamoureux (2011)[107]	IVI/general ophthalmic population/ophthalmic but non–disease specific	≥45/MT/France, Australia, US, Germany, Israel, India, and UK/22	AL, MB, and EM		

Cytomegalovirus (CMV) retinitis					
Kempen (2003)[98]	CMVQ/CMV/retina specific	≥13/CMV/US/971	AL, VS, HC, and EM	MOS-HIV	AL, GS, EM, and SC
Martin (2001)[127]	CMVQ/CMV/retina specific	CMV/US/279	AL, VS, HC, and EM	GHRQoL	GH, AL, GS, EM, MB, and SC
Matheï (2011)[129]		≥80/CMV/Belgium/567		ADL	AL
				LAPAQ	AL
				GDS	EM
				MMSE	MM and CG
Wu (1996)[242]	CMVQ/CMV/retina specific	CMV/US/26	AL, VS, HC, and EM		
Histoplasmosis (HS)					
Hawkins (2004)[85]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/HS/US/225	AL, EM, and SC	SF-36	GH, AL, GS, EM, and SC
				HADS	EM
Birdshot retinopathy (BDR)					
Kuiper (2013)[105]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥25/BR/the Netherlands/127	AL, EM, and SC		
Levinson (2009)[111]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	BR/France/80	AL, EM, and SC		
Toxoplasmosis (TS)					
de-la-Torre (2011)[47]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥15/TP/South America/29	AL, EM, and SC		

ADL, Activities of Daily Living; AI, activity inventory; AL, activity limitation; CBS, Chronic Burden Scale; CES-D, the Centre for Epidemiologic Studies Depression Scale; CG, cognition; CHD-SSI, Coronary Heart Disease patients study Social Support Instrument; CLVQOL, Chinese Low Vision Quality of Life questionnaire; CMHS, Cook-Medley Hostility Scale; CMVQ, Cytomegalovirus Retinitis Questionnaire; CP, coping; CV, convenience; DTSQ, Diabetes Treatment Satisfaction Questionnaire; EC, economic; EM, emotional well-being; GAS, Global Assessment Score; GDS, Goldberg Depression Scale; GH, general health; GHRQoL, General Health Related Quality of Life Measures; GS, general symptoms; GV, general vision; HADS, Hospital Anxiety and Depression Scale; HC, health concerns; HDRS, Hamilton Depression Rating Scale; IVI, Impact of Visual Impairment; IPAQ, International Planned Activity Questionnaire scale; LAPAQ, Longitudinal Aging Study Amsterdam Physical Activity Questionnaire; MB, mobility; MM, memory; MOS-HIV, Medical Outcome Study–HIV Health Survey; MMSE, Mini-Mental State Examination; NEI-VFQ, National Eye Institute Visual Function Questionnaire; OS, ocular comfort symptoms; PQ, Pain Questionnaire; PHQ-9, Patient Health Questionnaire; PTDS, Posttraumatic Diagnostic Scale; PTSD, Post-Traumatic Stress Disorder; RDQ, Retinal Detachment Questionnaire; RetDQOL, Retinopathy Dependent Quality of Life measure; RetSTQ, Retinopathy Satisfaction Treatment Questionnaire; SC, social participation; SDSCA, Summary of Diabetes Self Care Activities; SF-12, 12-Item Short Form Health Survey; SF-36, 36-Item Short Form Health Survey; STAI, Spielberg Trait Anxiety and Trait Anger; VF-11, Visual Function Index (11 questions); VS, visual symptoms.

3.2.5. *QoL impacts versus QoL measured in DR*

Similar to the AMD, the content coverage of the retina-specific, ophthalmic but non–disease-specific and the generic PRO instruments used in DR is limited to activity limitation and emotional well-being (Table 5). Qualitative studies in DR, however, show that these patients have issues with social participation, finance, health concern, and conveniences, which are not covered in the existing PRO instruments.[44,55,63]

3.2.6. *The highest quality existing PRO instruments for DR*

All the DR-specific PRO instruments have limited validation so score poorly on quality assessment. The highest quality PRO instruments available for DR is the AI (its subscales reading, goals, visual information, visual motor, and mobility; Table 4).[1] The subscales of AI (reading, goals, visual information, and visual motor) were graded "A" for measurement precision (i.e., person separation reliability was > 0.88, according to our definition grade "A" for any value ≥ 0.85) and item fit (i.e., all items with infit mean square between 0.99 and 1.09, according to our definition grade "A" for any value between 0.7 and 1.3).

3.3. *Retinal vascular diseases*

There were only 6 studies on retinal vascular diseases, and these included 4 studies on vascular occlusions and 2 on macular telangiectasia (Table 5). There were no qualitative studies in this group. Only ophthalmic but non–disease-specific PRO instruments were used, and there were no retina-specific PRO instrument developed in this group of retinal diseases.

3.3.1. *Ophthalmic, but non–disease-specific, PRO instruments in retinal vascular diseases*

Only 2 PRO instruments were used which were the NEI-VFQ and the IVI. Of 6 studies, the NEI-VFQ was used in 5 studies.[6,28,39,54,235] The IVI was tested with Rasch analysis in retinal vascular diseases.[107] Three scales derived from the IVI were used and scored separately; however, information on the dimensionality, item fit, and DIF was not reported (Table 4).[107] The NEI-VFQ showed poor performance in retinal vascular diseases.

3.3.2. *QoL impacts versus QoL measured in retinal vascular conditions*

Only ophthalmic but non–disease-specific PRO instruments were used to assess QoL impacts in these patients. The content coverage of these PRO instruments is limited to activity limitation and emotional well-being. Moreover, there is no qualitative study found for this group of retinal diseases.

3.3.3. *The highest quality existing PRO instruments for retinal vascular conditions*

The IVI and subscales (reading and accessing information, mobility and independence, and emotional well-being) have the highest score on quality assessment (Table 4).

3.4. *Retinal detachment (RD)*

Only 5 studies on RD were identified (Table 5). All the studies used PRO instruments, and there is no qualitative study found in RD.

3.4.1. *Disease-specific PRO instruments in RD*

A single PRO instrument, the Retinal Detachment Questionnaire for the subjective assessment of the RD surgery and recovery was originally developed for RD.[103] The instrument covers ocular symptoms and health concerns; however, it has few items in each of these domains. Moreover, the instrument was not validated for use in RD.

3.4.2. *Ophthalmic, but non–disease-specific, PRO instruments in RD*

Three PRO instruments, the NEI-VFQ, Global Assessment Scores, and Chinese version of the Low Vision Quality of Life Questionnaire were used. The Chinese version of the Low Vision Quality of Life Questionnaire covers general vision, mobility, activity limitation, and emotional well-being. The Chinese version of the Low Vision Quality of Life Questionnaire was used in 2 studies,[244,245] and the NEI-VFQ was used in 2 studies.[60,163] All these 3 instruments performed poorly in RD.

3.4.3. *Generic PRO instruments in RD*

The Post-traumatic Distress Stress Disorder and Post-traumatic Depressive Scale PRO instruments were used to assess the stress related to RD.[60] These 2 instruments performed poorly against our quality criteria.

3.4.4. *QoL impacts versus QoL measured in RD*

Only one retina-specific PRO instrument was developed for RD, and its content coverage is limited to ocular symptoms and health concerns (Table 5). The content coverage of the ophthalmic, but non–disease-specific, PRO instruments is limited to activity limitation, emotional well-being, and mobility, and the content coverage of the generic PRO instruments was limited to measuring emotional well-being (Table 5). None of the PRO instrument are validated in RD.

3.5. *Retinal infections*

There were 8 studies identified, 4 on cytomegalovirus retinitis, 2 on histoplasmosis, and 1 each on birdshot chorioretinopathy and toxoplasmosis (Table 5). There were no qualitative studies in this group of retinal diseases.

3.5.1. *Disease-specific PRO instruments in retinal infections*

The Cytomegalovirus Retinitis Questionnaire is the only cytomegalovirus-specific PRO instrument. Of the 4 studies, 3 used the Cytomegalovirus Retinitis Questionnaire.[98,127,242] The Cytomegalovirus Retinitis Questionnaire covers activity limitation, visual symptoms, health concerns, and emotional well-being. The Cytomegalovirus Retinitis Questionnaire was assessed by CTT methods, and it showed a poor performance in retinal infection.

3.5.2. *Ophthalmic, but non–disease-specific, PRO instruments in retinal infections*

The NEI-VFQ was the only PRO instrument used in this group of retinal diseases (4 studies).[47,85,105,111] It has not, however, been validated in this disease group.

3.5.3. *Generic PRO instruments in retinal infections*

We identified 8 generic PRO instruments that were used in retinal infections (Table 5). They were the Medical outcome Study-HIV, General Health Related Quality of Life Measures, Amsterdam Physical Activity Questionnaire, Mini-Mental State Examination, Goldberg Depression Scale, SF-36, ADL, and Hospital Anxiety and Depression Scale. These PRO instruments were used to assess emotional impact only (Table 5). None of these PRO instruments were valid for use in retinal infections.

3.5.4. *QoL impacts versus QoL measured in retinal infections*

The content coverage of the PRO instruments used in retinal infections is limited to 2 QoL domains (activity limitation and emotional well-being). None of these instruments are validated in this group of diseases.

3.6. *Hereditary retinal degenerations/dystrophies*

There were 29 studies identified in total; 26 studies with PRO instruments and 3 qualitative studies. Most of the studies were on RP (n = 23) followed by 2 on macular dystrophies and 1 on congenital stationary night blindness (Table 6). Of the 3 qualitative studies, 2 were on RP and 1 on mixed retinal dystrophies.

3.6.1. *Disease-specific PRO instruments in hereditary retinal degenerations/dystrophies*

Eleven disease-specific PRO instruments were developed to be used in hereditary retinal diseases (Table 6). They were the Independent Mobility Questionnaire (IMQ),[232] Mobility Difficulties Questionnaire,[72] Field Expander Questionnaire,[99] Perceived Visual Function Questionnaire,[116] Activities of Daily Vision Questionnaire,[221] Vision-Related Activity of Daily Living,[209] Daily Task Performance Questionnaire,[223] Night Vision Questionnaire (NVQ-39),[12] Visual Disability Questionnaire,[219] Everyday Task Questionnaire[119] and Stargardt's Macular dystrophy Vision Questionnaire.[140] Of the 11 PRO instruments, 9 were developed for RP and 1 for congenital stationary night blindness and 1 for Stargardt disease (Stargardt Macular dystrophy Vision Questionnaire). The PRO instruments, Mobility Difficulties Questionnaire, Everyday Task Questionnaire, Field Expander Questionnaire, and IMQ cover a single domain. The Mobility Difficulties Questionnaire and IMQ cover mobility; the Everyday Task Questionnaire covers activity limitation; and the Field Expander Questionnaire covers health concerns. The Perceived Visual Function Questionnaire, Activities of Daily Vision Questionnaire, Daily Task Performance Questionnaire, Visual Disability Questionnaire, NVQ-39, and Stargardt Macular dystrophy Vision Questionnaire cover 2 domains—activity limitation and mobility. The IMQ was the only PRO instrument to be Rasch analyzed; it has good measurement precision, item fit, and validity; however, other important psychometric information such as dimensionality, DIF, and targeting were not reported. The other PRO instruments performed poorly against our quality criteria.

3.6.2. *Ophthalmic, but non–disease-specific, PRO instruments in hereditary retinal degenerations/dystrophies*

The NEI-VFQ was the only PRO instrument used in 8 studies.[29,30,77,97,138,203,217,218] Validity assessment of the NEI-VFQ was not carried out in any of these studies.

3.6.3. *Generic PRO instruments in hereditary retinal degenerations/dystrophies*

Eight PRO instruments were used: the Pittsburgh Sleep Quality Index, Beck Depression Inventory, Stanford Sleepiness Scale, Epworth Sleepiness Scale, Perceived Stress Scale, Positive and Negative Affect Schedules, Brief Symptom Inventory, and SF-36 (Table 6). Emotional well-being domain was the most frequently tested QoL issue among these patients. None of these instruments is validated in this disease group.

3.6.4. *Qualitative studies and quality of life in patients with hereditary retinal degenerations/dystrophies*

The mode of data collection was focus groups (n = 1 study), interviews (n = 1 study), and both (n = 1 study). The sociodemographics of the population of these studies are given in Table 3.

In contrast to AMD and DR, RP causes untreatable progressive loss of peripheral vision and involves relatively young people in the prime of their education and professional career. Therefore, people with RP have functional and psychological challenges as they need to adjust to the progressive loss of vision in their lives.[86] RP patients experience a variety of visual symptoms such as day-to-day fluctuation in vision, intermittent diplopia, photopsias, visual hallucinations, high glare, and time-of-day effects (visual symptoms). The challenge to maintain independence in the face of worsening vision is a major issue (health concerns). The chronic nature of the condition has often made people with RP more resilient and coping with the difficulties better with time.[14] The arduous and grueling path and time taken to obtain a proper diagnosis has left many people frustrated (health concerns and emotional well-being). Inadequate communication and information supplied by their doctors about the diagnosis and prognosis was also caused frustrations among people with hereditary retinal diseases (health concerns and emotional well-being).[42]

On the positive note, patients with RP frequently adopt coping strategies to manage the stress of visual loss and humor was the frequently discussed strategy for coping.[14] Social support and communicating with other patients who have RP are important part of coping process among RP patients (social participation).[14] Unlike other retinal conditions, in hereditary retinal diseases the unaffected relatives also experienced difficulties like feeling guilty, especially the parents (health concerns).[42] RP patients also adopt several strategies to cope with their visual fluctuations such as scheduling important activities later in the morning or waking up early to allow adequate time to adjust to their vision.[14]

Table 6 – The patient-reported outcome instruments used and their content coverage in hereditary retinal degenerations/dystrophies, macular disorders, and other retinal conditions

Study	Ophthalmic PRO instruments/population developed for/types of PRO instruments	Age (year)/target population/country/sample size	Concepts/domains being measured	Generic PRO instruments	Concepts/domains being measured
Hereditary retinal degenerations/dystrophies (HRD)					
Burstedt (2005)[30]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥5/RP/Sweden/49	AL, EM, and SC		
Burstedt (2010)[29]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥5/RP/Sweden/49	AL, EM, and SC		
Jonsson (2007)[97]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥20/RP/Sweden/12	AL, EM, and SC		
Hahm (2008)[77]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	RP/Korea/144	AL, EM, and SC	BDI	EM
Seo (2009)[203]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥15/RP/Korea/108	AL, EM, and SC		
Sugawara (2010)[217]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥20/RP/Japan/40	AL, EM, and SC		
Sugawara (2011)[218]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥20/RP/Japan/30	AL, EM, and SC		
Menzel-Severing (2012)[138]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥35/RP/Germany/5	AL, OS, EM, and SC		
Geruschat (1998)[72]	MDQ/RP/retina specific	RP/US/22	MB		
Gordo (2001)[76]		≥10/RP/Spain/177		PSQI	Pattern and quality of sleep
Hartong (2006)[83]	IMQ/RP/retina specific	≥25/RP/the Netherlands/11	MB		
Hartong (2004)[82]	IMQ/RP/retina specific	≥20/RP/the Netherlands/20	MB		
Turano (1999)[232]	IMQ/RP/retina specific	RP/US/145	MB		
Kennedy (1977)[99]	FEQ/RP/retina specific	≥20/RP/US/10	HC (limited information on questionnaire)		
Lodha (2003)[116]	PVFQ/RP/retina specific	≥10/RP/Canada/68	AL and MB		
Lowe (1992)[119]	EDTQ/RP/retina specific	≥10/RP/UK/48	AL		
Somani (2006)[209]	V-ADL/RP/retina specific	≥30/RP/Canada/16	AL		
Szlyk (1998)[222]	ADVQ/RP/retina specific	≥10/RP/US/72	AL and MB		
Szlyk (2001)[223]	DTPQ/RP/retina specific	≥10/RP/US/62	AL and MB		
Szlyk (1997)[221]	ADVQ/RP/retina specific	≥10/RP/US/167	AL and MB		
Bijveld (2013)[12]	NVQ-39/CSNB/retina specific	≥12/RP/the Netherlands/20	MB and AL		
Bittner (2013)[15]		≥20/RP/US/37		SSS	GS
				ESS	GS
				PSS	EM
				PANAS	EM
Peters (2013)[176]		≥25/RP/Germany/9		BSI	GS and EM
Bittner (2011)[16]		≥ 18/RP/US/27		SSS	GS
				ESS	GS
				PSS	EM
				PANAS	EM
				SF-36	GH, AL, GS, EM, and SC
				BDI	EM
				PSQI	Pattern and quality of sleep

Sumi (2000)[219]	VDQ/RP/retina specific	RP/Japan/93	AL and MB		
Miedziak (2000)[140]	SMDVQ/Stargardt disease/retina specific	≥8/SD/US/203	AL and MB		
Macular hole (MH)					
Pearce (1998)[171]	SVFQ/MH/retina specific	≥55/MH/UK/30	HC		
Tranos 2004[228]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥17/MH/UK/30	AL, EM, and SC	SF-36	GH, AL, GS, EM, and SC
Fukuda (2009)[70]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	MH/Japan/32	AL, EM, and SC		
Rayat (2011)[180]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/MH/Canada/20	AL, EM, and SC		
Tranos (2007)[229]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/MH/UK/41	AL, EM, and SC		
Ellis (2000)[58]	PMHQ/MH/retina specific	MH/UK/38	HC		
Hirneiss (2007)[92]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥50/MH/Germany/59	AL, EM, and SC		
Singh (2011)[207]	MHTSQ/MH/retina specific	MH/UK/53	HC		
Epiretinal membrane (ERM)					
Matsuoka (2012)[131]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥55/ERM/Japan/26	AL, EM, and SC		
Ghazi-Nouri (2006)[73]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥25/ERM/UK/20	AL, EM, and SC	SF-36	GH, AL, GS, EM, and SC
Okamoto (2009)[164]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	ERM/Japan/28	AL, EM, and SC		
Central serous retinopathy (CSR)					
Conrad (2007)[43]		CSR/Germany/31		SCL–90-R	EM
				TAS–20	EM
Spahn (2003)[212]		CSR/Germany/24		SCL-90-R	GS and EM
				F-Sozu, K-22	SC
				SLQ	GS
				PFQ	EM
Mixed retinal diseases (MRD)					
Arimura (2011)[2]	MPQ/MD/retina specific	MRD/Japan/131	VS		
Mitchell (2002)[148]	MDSQ/MD/retina specific	≥18/MRD/UK/1411	HC and EM		
Hazel (2000)[88]	VCM1/general ophthalmic population/ophthalmic but non–disease specific	≥20/MRD/UK/28	AL and EM		
Mitchell (2001)[146]	MDSQ/MD/retina specific	≥18/MRD/UK/1421	HC and EM	W-BQ12	EM
				ADDQoL	FC, SC, AL, HC, EM, and MB
Unver (2009)[233]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific PalmPilot-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥18/MRD/US/135	AL, EM, and SC GH and AL		
Linder (1999)[114]	VF-14/cataract/ophthalmic but non–disease specific GAS/no information/ophthalmic but non–disease specific	≥15/MRD/Canada/546	AL VS	SF-36 WCS	GH, AL, GS, EM, and SC AL

(*continued on next page*)

Table 6 – (*continued*)

Study	Ophthalmic PRO instruments/population developed for/types of PRO instruments	Age (year)/target population/ country/sample size	Concepts/domains being measured	Generic PRO instruments	Concepts/domains being measured
Scott (2001)[201]				SIP	AL, MB, SC, and EM
				CDS	AL and MB
				GHQ	GS and EM
				VPI	VS
				EPQ	EM & SC
				TICS	EM
Scott (2001)[202]		MRD/US/86		CDS	AL and MB
				GHQ	GH and EM
Globe (2002)[75]		≥15/MRD/Canada/1081		SF-36	GH, AL, GS, EM, and SC
				SF-12	GH, AL, GS, EM, and SC
Okamoto (2010)[162]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	MRD/Japan/299	AL, EM, and SC		
Schiff (2000)[194]	NEI-VFQ/general ophthalmic population/ophthalmic but non-disease-specific VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥55/MRD/US/5	AL, EM, and SC HC		
Schulz-Key (2011)[197]	VSQ/general ophthalmic population/ophthalmic but non–disease specific	≥30/MRD/Sweden/61	AL and HC		
Sharma (2002)[204]	VF – 14/cataract/ophthalmic but non–disease specific	MRD/US/323	AL		
Miskala (2003)[145]	NEI-VFQ/general ophthalmic population/vision specific	≥18/MRD/US/483	AL, EM, and SC		
Schweitzer (2011)[198]	NEI-VFQ/general ophthalmic population/ophthalmic but non–disease specific	≥40/MRD/Canada/84	AL, EM, and SC		
de Nie (2013)[49]	PSQ/general ophthalmic population/ophthalmic but non–disease specific	MRD/the Netherlands/110	GH, AL, HC, and EM		

ADVQ, Activities of Daily Vision Questionnairse; ADDQoL, Audit of Diabetes-Dependent Quality of Life; AL, activity limitation; BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory; CDS, Community Disability Scale; CSNB, Congenital Stationary Night Blindness; CV, convenience; DTPQ, Daily Task Performance Questionnaire; EC, economic; EM, emotional well-being; EPQ, Eysenck Personality Questionnaire; ESS, Epworth Sleepiness Scale; FEQ, Field Expander Questionnaire; F-Sozu, K-22, Symptom List Questionnaire on Social Support; GAS, Global Assessment Scores; GH, general health; GHQ, General Health Questionnaire; GS, general symptoms; GV, general vision; HC, health concerns; IMQ, Independent Mobility Questionnaire; LLQ, Low Luminance Questionnaire; MB, mobility; MD, macular diseases; MDSQ, Macular Disease Society Questionnaire; MDQ, Mobility Difficulties Questionnaire; MEL, Munich Life Event List; MHTSQ, Macular Hole Treatment Satisfaction Questionnaire; MPQ, Metamorphopsia Questionnaire; NEI-VFQ, National Eye Institute Visual Function Questionnaire; NVQ-39, Night Vision Questionnaire (39 Questions); OS, ocular comfort symptoms; PANAS, Positive and Negative Affect Schedules; PFQ, Personality Factor Questionnaire; PMHQ, Positioning for Macular Hole Questionnaire; PSS, Perceived Stress Scale; PSQ, Patient Satisfaction Questionnaire; PSQI, Pittsburgh Sleep Quality Index; PVFQ, Perceived Visual Function Questionnaire; RP, retinitis pigmentosa; SC, social participation; SCL-90-R, Symptom Checklist; SD, Stargardt disease; SF-12, 12-Item Short Form Health Survey; SF-36, 36-Item Short Form Health Survey; SIP, Sickness Impact Profile; SLQ, Symptom List Questionnaire; SMDVQ, Stargardt Macular Dystrophy Vision Questionnaire; SSS, Stanford Sleepiness Scale; SVFQ, Short Visual Function Questionnaire; TAS-20, 20-Item Toronto Alexithymia Scale; TICS, Telephone Interview for Cognitive Status; V-ADL, Vision-Related Activity of Daily Living; VCM1, Vision Core Measure 1; VF-14, Visual Function Index (14 questions); VDQ, Visual Disability Questionnaire; VFQ, Visual Function Questionnaire; VPI, Visual Phenomenon Interview; VS, visual symptoms; VSQ, Vitrectomy Satisfaction Questionnaire; W-BQ12, 12-Item Well-Being Questionnaire; WCS, Weighted Co-morbidity Scale.

3.6.5. *QoL impacts versus QoL measured in hereditary retinal degenerations/dystrophies*

Most of the disease-specific PRO instruments in this disease group are developed for RP; however, the content coverage of most of these instruments is only mobility (Table 6). The content coverage of the ophthalmic but non–disease-specific and the generic PRO instruments is limited to activity limitation and emotional well-being. Patients with RP also have a myriad of QoL issues as suggested in the qualitative studies[14,42,86]; however, these issues are not well represented in the content of the existing PRO instruments (Table 6). Of the 11 retina-specific PRO instruments used in this group of diseases only the IMQ was assessed with Rasch analysis. It was shown to have good validity and measurement precision, but information on the dimensionality and reliability is missing.

3.6.6. *The highest quality existing PRO instruments for hereditary retinal degenerations/dystrophies*

The IMQ is the highest quality instrument available for RP, although it is limited to measuring mobility. The IMQ was graded "A" for measurement precision (i.e., person separation reliability was 0.95, according to our definition grade "A" for any value $\geq$ 0.85), item fit (i.e., infit and outfit mean squares was between 0.98 and 1.01, according to our definition grade "A" for any value between 0.7 and 1.3), concurrent and known group validity.

3.7. *Macular hole (MH)*

A total of 9 studies were identified on MH (Table 6). Among the 9 studies, 8 used PRO instruments, and only 1 was a qualitative study.

3.7.1. *Disease-specific PRO instruments in MH*

Three disease-specific PRO instruments to assess the patient's satisfaction following MH surgery were developed. These were the Short Visual Function Questionnaire,[171] Macular Hole Treatment Satisfaction Questionnaire,[207] and Posturing for Macular Hole surgery questionnaire.[58] The Short Visual Function Questionnaire, Macular Hole Treatment Satisfaction Questionnaire, and Posturing for Macular Hole surgery questionnaire cover a single domain, health concerns. None of these instruments were validated for use in MH.

3.7.2. *Ophthalmic, but non–disease-specific, PRO instruments in MH*

The NEI-VFQ was the only PRO used in 5 studies. No validation was performed in this disease group.[70,92,180,228,229]

3.7.3. *Generic PRO instruments in MH*

Only one study used a generic PRO instrument, the SF-36.[228] No validation was performed in this disease group.

3.7.4. *Qualitative studies and quality of life in MH*

Only one qualitative study was identified. This study was based on the qualitative analysis of the content of a diary of a single patient who has undergone MH surgery.

Wittich and colleagues report that coping with extended face down positioning after MH surgery caused both physical and psychological challenges.[238] Wittich and colleagues also report that emotional instability from prolonged rehabilitation, frustration with slow visual recovery, and lack of sleep are some of the frequent psychological challenges (emotional well-being and convenience).[238] Extended treatment and rehabilitation are health concerns. Support from family members and peers who have undergone similar treatments often help in coping with emotional instability (social participation).[238]

3.7.5. *QoL impacts versus QoL measured in MH*

The content coverage of the retina-specific PRO instruments developed for MH is mostly restricted to health concerns, and the content coverage of the ophthalmic but non–disease-specific and generic PRO instruments is restricted to activity limitation and socioemotional well-being (Table 6). Qualitative studies, however, show that these patients have issues with convenience, which is not covered in the existing PRO instruments. None of the PRO instruments used in MH were validated in this disease group.[58,70,92,171,180,207,228,229]

3.8. *Epiretinal membrane (ERM)*

There were 3 studies in ERM and all of them were on PRO instruments (Table 6). There were no qualitative studies in ERM. There is no retina-specific PRO instrument developed for ERM.

3.8.1. *Ophthalmic, but non–disease-specific, PRO instruments in ERM*

The NEI-VFQ was the only PRO instrument used in all the studies.[73,131,164] It has not been validated in ERM.

3.8.2. *Generic PRO instruments in ERM*

The SF-36 was used in one study, and it has not been validated in ERM.[73]

3.8.3. *QoL impacts versus QoL measured in ERM*

Only ophthalmic, but non–disease-specific, PRO instruments were used to assess the QoL impacts in ERM (Table 6). The content coverage of these PRO instruments was limited to measuring activity limitation, emotional well-being, and social participation.

3.9. *Central serous retinopathy (CSR)*

We identified 2 studies on CSR (Table 6), and both the studies used generic PRO instruments. We did not identify any qualitative study on CSR. There were no disease-specific PRO instruments developed for CSR.

3.9.1. *Generic PRO instruments in CSR*

Five PRO instruments were used in these 2 studies (Table 6). The PRO instruments are the Symptom Checklist 90-R, 20-item Toronto Alexithymia Scale, Symptom List questionnaire on Social Support (F-Sozu, K-22), Symptom List Questionnaire, and Personality Factor Questionnaire. The Symptom Checklist 90-R, 20-item Toronto Alexithymia Scale, and Personality Factor Questionnaire cover emotional well-being; the F-Sozu-K-22 covers social participation; and

the Symptom List Questionnaire covers general symptoms of QoL. No validation was performed in this disease group.

3.9.2. *QoL impacts versus QoL measured in CSR*

The QoL impact in this disease group was assessed using generic instruments, and the content coverage of these generic PRO instruments is limited to emotional well-being and general symptoms (Table 6).

3.10. *Studies in population with mixed retinal diseases*

We identified 16 studies on mixed retinal conditions such as macular disease, vitreous floaters, and posterior vitreous detachment (Table 6). We did not identify any qualitative study in this group of retinal diseases.

3.10.1. *Disease-specific PRO instruments in mixed retinal diseases*

The 2 disease-specific PRO instruments used in studies in population with mixed retinal diseases were the Metamorphopsia Questionnaire (MPQ)[2] and Macular Disease Society Questionnaire.[148] The MPQ covers visual symptoms, and the Macular Disease Society Questionnaire covers health concerns and emotional well-being. The MPQ was assessed using Rasch analysis. It has good measurement precision, response categories, and item fit; however, information on the dimensionality and targeting is not available (Table 4).

3.10.2. *Ophthalmic but non–disease-specific PRO instruments in mixed retinal diseases*

Seven ophthalmic but non–disease-specific PRO instruments were used that included the NEI-VFQ,[145,162,194,198,233] PalmPilot-VFQ,[233] VF-14,[114] Vision Core Measure 1,[88] Visual Function Questionnaire (VFQ),[194] Vitrectomy Satisfaction Questionnaire,[197] and Patient Satisfaction Questionnaire.[49] The VFQ covers a single domain, health concerns. The PalmPilot-VFQ and Vitrectomy Satisfaction Questionnaire cover 2 domains. The PalmPilot-VFQ covers general vision and activity limitation, and the Vitrectomy Satisfaction Questionnaire covers activity limitation and health concerns. The Patient Satisfaction Questionnaire covers 4 domains—general health, activity limitation, emotional well-being, and health concerns. The PalmPilot-VFQ was tested using Rasch analysis and showed good measurement precision and item fit. Information about the dimensionality and DIF was not reported (Table 4).

3.10.3. *Generic PRO instruments in mixed retinal diseases*

Eleven PRO instruments were used (Table 6). They were the 12-Item Well-Being Questionnaire, Audit of Diabetes-Dependent Quality of Life, SF-36, Weighted Co-morbidity Scale, Sickness Impact Profile, Community Disability Scale, General Health Questionnaire, Visual Phenomenon Interview, Eysenck Personality Questionnaire, Telephone Interview for Cognitive Status, and 12-Item Short Form Health Survey. Most of these instruments measured emotional well-being and activity limitation. No validation was performed in this disease group.

3.10.4. *QoL impacts versus QoL measured in mixed retinal diseases*

The content coverage of the PRO instruments used in this group of retinal diseases is limited to 2 QoL domains only (emotional well-being and activity limitation; Table 6).

3.10.5. *The highest quality existing PRO instruments for mixed retinal diseases*

The MPQ and the PalmPilot-VFQ instruments have the highest quality assessments (Table 4). The MPQ was graded "A" for response categories (i.e., no disordered response categories, according to our definition grade "A" if all the response categories were ordered), measurement precision (i.e., person separation reliability was 0.97, according to our definition grade "A" for any value $\geq$ 0.85) and item fit, and the PalmPilot-VFQ was graded "A" for measurement precision (i.e., person separation index was 3.79, according to our definition grade "A" for any value $\geq$ 2.50), item fit (i.e., infit and outfit mean square were between 0.98 and 0.99, according to our definition grade "A" for any value between 0.7 and 1.3), concurrent and convergent validity. The MPQ is the best retina-specific PRO instrument available for general macular diseases, and the PalmPilot–VFQ is the highest quality ophthalmic but non–disease-specific PRO instrument in this group of retinal diseases.

4. Discussion

There is a growing consensus that PRO measurement should be comprehensive to assess a holistic impact in QoL. QoL, however, is a multidimensional construct. It includes, but is not limited to, activity limitation, symptoms, emotional well-being, socioemotional impact, and so forth. These are basically component constructs or domains of QoL which deserves separate assessment. All the PRO instruments used to assess the QoL impact in patients with retinal diseases in this study are limited in measuring certain domain/s of QoL, e.g., activity limitation, mobility, emotional-well-being, or combinations of these. Most of the retina-specific PRO instruments used in AMD and DR predominantly measure activity limitation (MacDQoL, DLTV, ALQ, Low Luminance Questionnaire, FRQ, NVQ-10, and RetDQoL), and most of the retina-specific PRO instruments used in RP predominantly measure mobility (IMQ, NVQ-39, Mobility Difficulties Questionnaire, Perceived Visual Function Questionnaire, and Everyday Task Questionnaire) aspect of QoL. Therefore, the existing retina-specific PRO instruments are less comprehensive and fail to cover all the aspects of QoL.

Most of the PRO instruments were summary scored, and only 11 PRO instruments were Rasch scaled. Despite its popularity CTT suffers 2 major limitations, lack of an explicit ordered continuum of items that represent a unidimensional construct, and lack of equal interval scaling both of which increase noise and reduce the statistical power thereby preventing a precise and accurate measurement of PROs. In contrast to the CTT approach, the Rasch model provides an interval-level scoring that enables the examination of the hierarchical structure and unidimensionality of the PRO

measure.[179] Rasch analysis is important for achieving the most extensive validation of PRO instruments. Of all the retina-specific PRO instruments used in this study, only 3 (2 in AMD and 1 in RP) were subjected to Rasch analysis. None of the retina-specific PRO instruments as a whole were found to be valid for use in any retinal diseases; however, 2 of the subscales (socioemotional well-being and activity limitation and mobility) of the AMD-specific PRO instrument, the MacDQoL were found to be valid for use in AMD.[65] Interestingly, 3 scales (emotional well-being, reading and accessing information, and mobility and independence) of the PRO instrument, the IVI which was originally developed for low vision were also found to be valid measures for AMD[108]; however, for other retinal diseases, there are no valid PRO instruments available.

Comparing the findings of the qualitative studies in AMD, DR, and RP and the content coverage of the PRO instruments used in this study, we found that there is clearly a gap between known QoL impacts of retinal diseases and QoL measured by the existing PRO instruments. Qualitative studies are vital to understand a patient's experience of living with a disease, and therefore, qualitative consultation with patients is important in the content development of any PRO instrument. A PRO instrument developed without a qualitative consultation will miss out important aspects of QoL issue that matters to the patients. Qualitative studies were done only for AMD, DR, and RP.[14,44,55,63,86,94,134,155,156,239] There are no qualitative studies done for other less common retinal diseases such as RD, ERM, MH, CSR, vascular occlusive diseases, retinal infections, and so forth. Moreover, the QoL impact of these retinal diseases are measured using PRO instruments either developed for ocular diseases other than retinal diseases (ophthalmic but non–disease specific) or other medical diseases (generic).[43,54,60,73,131,161,228] As these PRO instruments contain items/questions that are not relevant to retinal diseases, they are likely not sensitive enough in measuring the QoL impact in these retinal diseases. Hence, there is a need to develop comprehensive retina-specific PRO instruments that are capable of measuring all relevant QoL domains.

5. Conclusions

We found that all the currently existing retina-specific PRO instruments are limited in their content coverage of QoL and also their psychometric properties are not scientifically sound to assess the PROs. There is a need to develop a new comprehensive and technologically advanced PRO instruments to assess QoL impacts in retinal diseases.

6. Future research and developments

Considering the number of retinal diseases/conditions in ophthalmology and the emergence of new treatment interventions for these conditions, there exists a need for comprehensive and psychometrically robust retina-specific PRO instruments that are capable of measuring all relevant QoL domains. It is difficult to achieve this with the existing PRO instruments. New instruments with a wider coverage of QoL domains and good psychometric qualities are required. A new generation PRO measurement approach in the form of item banking (third generation PROs) implemented via Computer Adaptive Testing can provide solutions to the issues associated with the existing PRO instruments. The first step to developing such instruments is to comprehensively understand QoL impacts from patients' perspectives through well designed and executed qualitative studies. Work is ongoing in this area.[63,134]

An item bank is simply a pool of a large number of items that measure a unidimensional construct (e.g., activity limitation, symptoms, emotional well-being, and so forth).[172] The Computer Adaptive Testing system is an iterative algorithm that chooses items from the available pool of items to measure the underlying trait for an individual.[5] The items are chosen based on the individual's ability which is based on the respondent's answer to previous items. Because the item administration is predominantly based on the patient's response to an initial question, it is fast and needs only a few items to complete measurement. The third-generation PROs are successfully developed and implemented in other health care fields[34,69,102] and are currently under construction for eye diseases.[100]

7. Method of literature search

We conducted a systematic review to identify all the published articles that reported QoL assessment or PRO measurements or qualitative reports of patient's perspectives in patients with retinal diseases. We carried out the literature search using the Medline, Web of Science, EMBASE, and Cochrane CENTRAL databases. The following are the key words used for the search: vitreoretinal OR macula OR retina* OR retinitis OR maculopathy OR retinopathy AND quality of life OR questionnaire OR focus groups OR qualitative OR patient perspectives OR patient-reported outcomes.

The search was carried out on April 17, 2014, and it was not limited to any preceding dates. Two authors (M.P. and J.K.) conducted the search and the data abstraction. All the authors reviewed the abstracted data, and any disagreement aroused was solved by discussion. We identified all the articles on retina-specific diseases and QoL issues.

Our exclusion criteria were studies on children of age <18 years and articles not written in English. Types of studies excluded were epidemiological studies, studies on systemic and ocular co-morbidities, studies on health valuation methods (preference-based or utility measures), studies on evaluation of health programs, studies on objective ocular assessments, articles on nutrition and diet, articles on knowledge and attitude of practitioners, review articles, case reports, and letters to the editors. Figure 1 summarizes the review process and the number of articles included in this study.

8. Disclosures

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Supplementary data

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Title page:

Full title: **Seeing through their eyes: lived experiences of people with retinitis pigmentosa**

Running title: **Quality of life impact in retinitis pigmentosa**

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Abstract

Aims: Retinitis pigmentosa (RP) is the most common retinal degeneration causing blindness. Although their clinical problems are amenable for the clinical diagnosis, their day-to-day problems for having to live with the disease are mostly unexplored. This study aims to explore and understand the issues and impact of people with RP on quality of life (QoL).

Methods: A qualitative research methodology to facilitate the understanding of the experiences of people with RP was carried out. Data were collected through audio-recorded semi-structured interviews. Thematic analysis occurred through the process of line-by-line coding, aggregation, and theme development using the NVivo -10 software.

Results: Twenty-three interviews were conducted (mean age = 56 years; females, 14). We identified five major QoL themes: (1) struggle to perform important day-to-day tasks; (2) concerns about disease progression, disease outcome and personal safety; (3) facing a lot of emotional and psychological challenges. ; (4) experiencing a myriad of visual symptoms and (5) adopting different strategies to cope and manage stressful circumstances. Difficulty in performing important day-to-day tasks was the most prominent QoL issue among these people. Their major concerns were going blind and uncertainties about their future. They face a lot of emotional and psychological challenges to adapt to the physiological stress associated with the progressive vision loss. However, they adopt several coping strategies to manage the stressful circumstances. C**onclusions:** People with RP experience a myriad of QoL issues. Despite all the hardship, they remain optimistic and learn to accept their eye condition and move on in life.

Key words: Retinitis pigmentosa; quality of life; qualitative; interviews; patient-reported outcomes

Introduction

Retinitis pigmentosa is a group of inherited retinal disorders that affects the photoreceptors and the retinal pigmentary epithelium.[1] In some disorders the rods are affected first and the cones later (termed rod-cone dystrophy) or the reverse (cone-rod dystrophy). Rod-cone dystrophy is the most common form of RP, in which the first manifestation is night blindness, followed by decreasing visual fields and eventually leading to blindness after several decades. The prevalence of RP is 1 in 3000 to 1 in 5000.[2] Majority of the disorders have a genetic basis [3] and involve photoreceptor cell death by apoptosis. Retinitis pigmentosa can be inherited as autosomal-dominant (30-40%), autosomal-recessive (50-60%) or X-liked recessive (5-15%) fashion.[3-6] The role of oral vitamin A and docosahexaenoic acid (DHA) in slowing down the degenerative process in typical RP is not well established.[7] However, dietary modification and nutritional supplements may be beneficial for rare syndromic forms of RP.[8, 9] Newer therapeutic modalities for RP include gene therapy, cell transplantation, neuroprotection and hyperbaric oxygen.[10, 11]

Retinitis pigmentosa is a disabling disease that is currently incurable. It typically starts at the early teenage years and progresses to severe visual impairment during the 4th and the 5th decade. The classical symptoms of RP include nyctalopia (night blindness), peripheral visual loss and in advanced cases central visual loss and photopsia (seeing flashes of light). Apart from the classical symptoms, people with RP exhibit difficulty adjusting to changing levels of illumination, difficulty seeing in poor contrast,[12] abnormal temporal processing,[13, 14] and motion perception anomalies.[15] All these difficulties along with the progressive visual loss can have a serious impact on quality of life (QoL) of an individual with RP. Even though these problems are identified clinically, limited research has been conducted to understand the impact on day-to-day life of people with RP from their perspectives. A well conducted qualitative study is essential to understand the patient's experience of living with RP. Hence the aim of this study was to explore the issues and impact of people with RP on QoL.

Methodology

Twenty-three participants with RP were recruited through a nonprobability, convenience sampling techniques. Participants were recruited from the Royal Society for the Blind (Adelaide) and Retina Australia Society (Queensland, Western Australia, Victoria, New South Wales, and Canberra) through emails and flyers. Participants who responded to the email

request and the flyers were sent out a research pack consisting of an invitation letter, participant information sheet, consent form and demographic form in the post. Upon receiving the consent form, participants were contacted through telephone to organise a date and time for an interview. A semi-structured interview guide was developed from existing literature and expert consultation and it was validated by a panel of experts. The interviews were carried out over the telephone. All the interviews occurred between August 2014 and June 2015. All interviews were audio recorded and transcribed. Interviews were carried out till thematic saturation (no additional new information arising) was obtained.

An ethical approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee and the corresponding ethics committees at health care facilities and the study adheres to the Tenets of Declaration of Helsinki.

Data analysis

We used an inductive approach where the content of the data directed the coding and the theme development (data-driven).[16] Nodes (words or phrases) to code text segments were generated after scan reading individual transcripts. The nodes bear meaning of the text segments to be coded by them as close as possible. For this, we carried out an open coding strategy which entailed line-by-line coding approach. Each transcript was coded using the nodes in its entirety. Once the coding was complete, individual nodes were reorganized by assimilating them into different categories (i.e. nodes of similar concept were brought under the umbrella of a mother node (potential major theme)). The mother nodes with component child nodes (potential sub-themes) were explored to identify linkage between similar patterns across the transcripts. [17]This exercise helped us to identify key threads. These key threads were then re-assessed by the authors to come to a decision whether they qualify to form a theme. Any discrepancies between the authors were resolved by discussion. New or improved themes that emerged from later transcripts were incorporated into the coding hierarchy, and earlier transcripts were updated to reflect the modification. The computer program QSR NVivo 10 (QSR International Pty Ltd) was used to code the transcripts systematically.

Rigor

Several identified strategies were used to enhance the trustworthiness of this study including credibility, transferability, dependability and confirmability. Credibility was achieved through

adoption of systematic, in-depth field work and triangulation of time and space (various times of the day, week and year were used in the collection of the data and use of multi-sites for participant recruitments). Transferability was achieved through description of the clinical context of the study and description of the demographics of the participants. Dependability was achieved through in-depth description of the methodology and confirmability was achieved through the recognition of shortcomings in study's method and their potential effects.

Results

A total of 23 interviews were conducted (mean age = 55.6 years (*SD* =14.3); range = 28 to 81 years; females, 14). Two-thirds of the participants were above the age of 50 years and all the participants had bilateral disease (Table 1). The mean age of onset of the disease was 18.8 years (*SD* =11.8) and the mean duration of the disease was 38.9 years (*SD* = 14.7). We identified five major QoL themes: (1) struggle to perform important day-to-day tasks (activity limitation); (2) concerns about disease progression disease outcome and personal safety (health concerns); (3) facing a lot of emotional and psychological challenges (emotional well-being); (4) experiencing a myriad of visual symptoms (symptoms) and (5) adopting different strategies to manage stressful circumstances (coping) (Figure 1)

1. Struggle to perform important day-to-day tasks (activity limitation)

Participants with RP frequently reported difficulty in performing important day-to-day tasks such as reading, seeing in changing light conditions, shopping, driving, playing sports, taking part in leisure activities and doing household chores (Table 2). They reported difficulty in reading books, menu cards, magazines and newspapers.

"My biggest loss for my own self is reading a novel. I used to love to sit down and read a novel and I can't do that now. I can read still but only for very short periods."

They often reported missing out the fun of reading and had to rely on low vision assistive devices such as closed circuit television (CCTV), iPhone, kindle, computers and talking books for reading. Poor or too bright lighting conditions are also reported to be a challenge. They eloquently mentioned various situations where they faced difficulties in seeing under different light conditions such as in dark, dim-lights and bright lights. They were comfortable doing online shopping as they could avoid relying on others for transport. Participants had difficulty in driving both during the day and the night and not being able to drive and associated loss of

independence by some has tormented as regret in life. They had difficulty playing sports due to poor hand-eye coordination. Cleaning was the most difficult household chore reported. Other difficulties reported were engaging in leisure activities such as knitting, gardening and playing lawn-bowls and self-grooming.

They experienced difficulties when walking in unfamiliar places, crowded places and using steps. Navigation in unfamiliar places was the most frequent mobility difficulty reported. Being in unfamiliar surrounding caused anxiety and stress. Using a white cane or a guide dog or asking for assistance were some of the methods used by RP people to navigate in such difficult situations. However, they were quite confident walking and navigating in familiar surroundings. They also struggle in confined places and busy places such as shopping malls and airports and generally tried to avoid going to such places. They also expressed dislike for crowds and steps. Going downstairs was reported as a more difficult task than going upstairs.

"I avoid supermarkets or big shops or department stores; I find them very overwhelming and difficult to get around."

2. Concerns about disease progression, disease outcome and personal safety (health concerns)

People with RP expressed lots of concern about their health, disease outcome and personal safety. One of the major health concerns was having frequent accidents such as falls and bumping into things.

"The other fear is that I keep bashing into things and falling over things and hurting myself and getting bruises and scrapes and stuff like that."

Having to rely on others for reading, shopping, transport and getting around in darkness was again a major concern. They generally expressed dissatisfaction towards the medical service providers as they felt that the information provided by them was inadequate. The prospect of losing eye sight completely or going blind early was also the biggest concern. The uncertainty of their future as a result of the visual loss, life and career was one of the pressing concerns mentioned. Learning new ways to do everything was challenging for them. They also raised concerns about handling emergency situations such as bushfire, house fire and thunder storms.

"There's fear of being in a place, that if it catches fire or in an accident or something and not being able to get yourself to safety because you can't see, so that's quite frightening."

3. Facing a lot of emotional and psychological challenges (emotional well-being)

Participants with RP face a lot of emotional and psychological challenges due to their progressive visual loss. Frustration, worry, shock, anxiety and feel as a burden were the commonly expressed emotions. They frequently expressed frustrations which results from myriad of reasons such as not knowing what to do when being diagnosed with RP, having to learn different ways of doing things, inability to participate in sports and having to depend on people, technology etc.

"It was frustrating because when they give you the diagnosis that you've got this eye condition and you're going to go blind you're in so much shock and you don't really know what to do."

They worried about their future, their employability, their eye condition, and their coping skills. Unfamiliar surroundings, uncertainties about the progression of the eye condition and inability to identify social cues when in a group caused anxiety. They also go through bouts of depression that is sparked by some kind of life event such as people getting married or people having children that reminded them that life is different to everybody else's. They felt embarrassed and didn't want to associate with being a disabled person or being a blind person. Fear of being left on their own, fear of rejection by people or partner and fear of having accidents were often reported.

"Probably being left on my own would be the biggest fear."

4. Experiencing a myriad of symptoms (symptoms)

The commonly cited symptoms were night blindness, restricted visual fields, difficulty in discriminating colours, difficulty in adjusting to different light conditions and poor contrast vision (Figure 2). Night blindness was the most common symptom.

"I've always had the night blindness but when I was about 15, I suppose, was when it really got to the point where it was difficult to get around."

Restriction of the peripheral visual field caused depth perception issues resulting in frequent

tripping and bumping into things. Limitation of the visual fields was also associated with difficulty in working with computer screens and watching movies. These people had trouble discerning colours that are of a similar spectrum such as yellow and white or blue and green. Adjusting to different lighting condition was also a big issue. People with macular oedema reported worsening of their central vision. They also reported that they have difficulty in seeing things that are of poor contrast.

"My contrast, it depends on the colours. If they're very light colours, no, I don't have any contrast."

5. Adopting different strategies to manage stressful circumstances (coping)

Coping strategies were commonly discussed by all the participants. They expressed their resilience in facing the nature of their eye condition. Some of the commonly reported coping strategies were trying to be optimistic, accepting their eye condition/visual loss and learning to live with the eye condition.

"It has taken a lot of work to become more comfortable and accepting of it and I've got a lot less angst now, but I have had to go to counselling and there's been a lot of tears and reliance on people for support."

Trying to be optimistic and thinking that there are people much worse than them helped them to cope better. Accepting their eye condition and learning to do things in a different ways was also a common coping mechanism among these people. They tried to get away with their frustrations by listening to books, playing sports and travelling to places to meet people. Interacting with people with similar eye condition was also an important way of coping. Thinking that their eye condition was not life threatening helped them to move on. They also learned to enjoy life and appreciate it.

"I work very hard to have a good life despite my vision loss and as long as I can have a good meal a couple of times a week and a couple of glasses of wine that'll do."

6. Other QoL issues

People with RP had difficulty interacting with their friends and family members. Difficulty in identifying social cues and inability to participate in social events in the evenings made social life a bit harder for them. Their progressive visual loss was not well understood by their family

members and friends that affected their long term relationship with them. Despite these hardships majority of the participants were very independent. Early onset of the disease affected their career development and progress in life. Difficulty in finding suitable jobs and reduced job opportunities were frequently reported. They had to frequently change jobs to suit their abilities due to the progressive worsening of their eye condition and majority of them had to give up work and retrain into something else. Loss of income associated with loss of job caused financial constraints.

"I was earning a very good income and that was cut completely. Well now, as a remedial massage therapist I do have an income but it's still very small at the early stages of my practice but it will grow, I know over time."

Inconveniences ensued in day-to-day life for having to live with RP and the subsequent vision loss was commonly discussed. Lack of independence and having to rely on others was reported as one of the major inconvenience. Having to plan and organize for the things beforehand was also a major inconvenience. Most of them depended on gadgets for doing most of the things such as reading, shopping, moving around etc. Having more complicated travel plans because of driving limitations, having to allow a bit of extra leeway when going to unfamiliar places, having to concentrate on things harder, having to be slower and more careful, and having limitations on where you can go were the other inconveniences.

"I still go places I don't know but I do allow – I must admit I do allow either extra time or extra awareness because it's unfamiliar and I know I'm not going to recognise things so I have to allow myself a bit of extra leeway."

Discussion

This study systematically explored the overall impact of RP on quality of life. The participants of this study described emotional impacts and adaptation to their visual disability that were consistent with previous qualitative research. [18, 19]Our study shows that people with RP experience a myriad of QoL issues. We identified five major QoL themes (activity limitation, health concerns, emotional well-being, symptoms and coping). This information may be used to help inform the eye care providers, who should take such perspectives into consideration when evaluating and managing their patients with RP. Moreover, understanding the extent of the QoL impact of these people can help identify subgroups with relatively poor perceived health and help guide interventions to improve their situations and avert more serious consequences.

Activity limitation was the major QoL issue among people with RP. The greater functional limitations experienced by the people with RP may be due to bilateral involvement, severe visual impairment and the progressive nature of the eye condition. Participants expressed a series of concerns because of uncertainty surrounding their eye condition which is progressive and incurable. Similar health concerns were reported in previous qualitative studies.[19, 20]People with RP face a lot of emotional and psychological challenges due to the physiological stress associated with the vision loss. Studies show that vison loss, from any eye disease has been linked with a range of emotional and social issues.[21, 22] People with vision loss may experience emotional reactions like fear, anxieties, frustration, depression and embarrassment. [23, 24]In fact, the most common psychological comorbidity in vision loss is depression and it has been shown that people with visual impairment have high incidence of depression. [25-27] People with RP also expressed a lot of emotional reactions such as frustration, anxiety, depression, shock, worry and fear. Social manifestations of vision loss include increased social isolation, family problems, and divorce. [23, 28, 29] Similar social issues were reported by people with RP. Progressive loss of the photoreceptors causes a myriad of visual symptoms in RP. The common visual symptoms among our participants were night blindness, progressive visual field loss, and difficulty in light adaptation. In contrast, a previous study has reported a different set of symptoms (day-to-day visual fluctuations, intermittent diplopia, photopsia, high glare and visual hallucinations).[18]

Individuals with RP experience different levels of stress. It could be due to uncertainty to their

ability to perform different activities, lack of independence, increased fear of falling due to difficulties with mobility and increased mental effort and information processing required to compensate for the limited visual information.[30, 31] However, most people with RP are able to cope with their visual loss by adopting several coping strategies. Trying to be optimistic and accepting their eye condition/visual loss were the common coping strategies adopted by our participants. Similar coping strategies were reported in previous studies.[18, 19]

People with RP have greater functional limitations compared to people with major blinding retinal conditions such as age related macular degeneration (AMD) and diabetic retinopathy (DR), because in these major blinding conditions the visual disability is mostly due to the loss of central vision [24, 32, 33], whereas in RP the visual disability is due to the loss of both the peripheral and the central vision. Retinitis pigmentosa also causes a greater emotional and psychological impact on the individuals than AMD and DR because RP is not treatable, whereas AMD and DR are mostly treatable. The major health concern among people with RP was going blind, whereas the major concern among people with AMD and DR was mostly related to the treatment outcomes.[24, 32]Early onset of the eye disease affects the career development and progress in life of people with RP which is not the case in AMD which typically has a late onset.

There are currently nine RP-specific PRO instruments.[31, 34-41] The motive behind our endeavor to develop a comprehensive RP-specific PRO is that none of the existing PRO instrument has undergone comprehensive validation in this disease group and their content coverage is limited to measuring only a few QoL domains (predominantly mobility).[42-44] Lack of an appropriate RP-specific PRO measure restricts the understanding of the full impact of RP on QoL. Understanding patients' perspective is also critical as newer treatment modalities such as gene therapy, cell transplantation, retinal prosthesis and neuroprotection are fast emerging. Moreover, the US Food and Drug Administration (FDA) and most funding organisations now insist on using PRO instruments in clinical trials to assess the intervention/treatment outcomes. Hence there is also a need for developing comprehensive and psychometrically sound RP-specific PRO instrument. The findings of this study will guide us to develop the content (items) of a comprehensive RP-specific PRO instrument, which will be technologically advanced in the form of item banking implemented via computer adaptive testing (CAT). An item bank is simply a large collection of items/questions that measure a unidimensional construct such as activity limitation, emotional well-being, social participation, etc.[45]A disease-

specific item bank will have a series of calibrated item pools covering important domains of QoL.[44] The CAT system choses the best and highly informative items from the available item pool that closely match with the participant's ability. As the item administration is based on the participant's response to previous items, the CAT provides an effective, quick and precise measurement of QoL.[46, 47] Item banks have been developed and implemented in other fields of health care[48, 49] and is currently under construction for eye diseases such as glaucoma, DR and AMD. [24, 50, 51]

One of the limitations of this study was the small sample size. Unlike a quantitative study where the statistical power of the study depends on an adequate sample size, in a qualitative study the sample size should be adequate enough to assure that most of the perceptions that might be important are uncovered, but at the same time should not be too large to become repetitive. The sample size in a qualitative data should follow the concept of saturation when the collection of new data does not shed any further light on the issue under investigation. Our sample size for this study was based on the information saturation. The other limitation of this study was that our cohort had predominantly people with late stages of RP and we did not have a broad spectrum of people with RP. This is because our cohort was selected from charity organizations. People who suffer more from the disease are more likely to join organizations to seek more information and support. These people are also more likely to take part in research. This could have resulted in selection bias. Ideal would be to have even distribution of people with different disease severity and age distribution in the cohort. However, we had five individuals (22% of participants) who were younger than 40 years and their perspectives were also obtained. The youngest participant we had was 28 years old. Moreover, RP is a heterogeneous disease and our finding may not be generalized to all the people living with RP. The other limitation of this study was that greater number of our participants were females. Retinitis pigmentosa has no racial, ethnic or sexual predilection. However, the X-linked type is more prevalent in males. More number of female participants may be because women are more likely to participate in surveys than men.[52, 53]

Disclosure

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Conflict of interest

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

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Titles and legends to figures

Figure 1. Major quality of life (QoL) themes in people with retinitis pigmentosa (RP). X-axis: codes = number of times the attribute was discussed across all the transcripts analysed. Y-axis: QoL themes. Theme 1, struggle to perform important day-to-day tasks; Theme 2, concerns about disease progression, disease outcome and personal safety; Theme 3, facing a lot of emotional and psychological challenges; Theme 4, experiencing a myriad of visual symptoms; Theme 5, adopting different strategies to manage stressful circumstances

Figure 2. Common visual symptoms reported by people with retinitis pigmentosa (RP). X-axis: symptoms. Y-axis: codes = number of times the attribute was discussed across all the transcripts analysed.

The Association for Research in Vision and Ophthalmology Conference (ARVO), abstract 2018 (Oral presentation)

Title: **Developing a sophisticated instrument to measure the coping strategies of people with hereditary retinal diseases**

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Conflict of interest: None

Purpose: Our understanding of the coping strategies used by people with visual impairment to manage stress related to visual loss is limited. There are several coping questionnaires developed for medical conditions but none for eye diseases. This study aims to develop a sophisticated coping instrument in the form of an item bank implemented via computerized adaptive testing (CAT) for hereditary retinal diseases. As CAT system iteratively presents items based on a patient's response to previous items, we hypothesize that fewer items will be required to gain a precise measurement of the coping compared to the full item bank.

Methods: Items on coping were extracted from qualitative interviews with patients with hereditary retinal diseases which were supplemented by items from a literature review. A systematic multi-stage process of item refinement was carried out followed by expert panel discussion and cognitive interviews with patients with hereditary retinal diseases. The final coping item bank had 30 items. Rasch analysis was used to assess the psychometric properties of the coping item bank. A CAT simulation was carried out to estimate an average number of items required to gain precise measurement of hereditary retinal diseases-related coping.

Results: The coping item bank was answered by189 participants (median age = 58 years; range = 19 to 87 years; retinitis pigmentosa; 77%, females, 55%). The coping scale demonstrated good precision and targeting. The standardized residual loadings for items revealed that six items related to active coping grouped together. Removal of the six items reduced the precision of the main coping scale and worsened the variance explained by the measure. Therefore, the six items were retained within the main coping scale. Our CAT simulation indicated that, on average, less than 10 items are required to gain a precise measurement of coping.

Conclusions: This is the first study to develop a psychometrically robust coping instrument for hereditary retinal diseases. Our CAT simulation indicated that on an average, only 4 and 9 items were required to gain measurement at moderate and high precision, respectively. The coping item bank can be used by clinicians and researchers to better understand the coping responses of people with hereditary retinal diseases.

Key words: Coping, hereditary retinal diseases, item bank, computerized adaptive testing, Rasch analysis, psychometric properties.

Character count: 2438 (2500 characters and spaces for the title, abstract body text, and image captions)

Layman Abstract (optional)

Hereditary retinal diseases cause progressive visual loss that ultimately results in blindness after several decades. Moreover, people with hereditary retina diseases are aware that their eye condition is incurable which can cause a significant stress and anxiety. People with hereditary retinal diseases been found to respond to the stress of visual loss by adopting several coping strategies. The coping responses of people with hereditary retinal diseases have been explored only through qualitative studies and there are no coping questionnaires developed for hereditary retinal diseases. Hence, there is a need to develop a new measure of coping for this disease group. As the traditional paper-pencil based questionnaires have several limitations (static and often burdensome to complete and often fail to cover all aspects of the construct under measure) this study aimed to develop a smart coping instrument in the form of an item bank implemented via computerized adaptive testing (CAT) for hereditary retinal diseases. This study provides an evidence that the CAT system requires a fewer items to gain a precise measurement of coping. This item bank can be used by clinicians and researchers to better understand the coping responses of people with hereditary retinal diseases.

South Adelaide Local Health network (SALHN) Research week, abstract 2017 (Oral presentation)

Title: Psychometric assessment of the hereditary retinal diseases item banks

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Background: The existing questionnaires in ophthalmology are static (paper-and-pencil based), limited in their content, not comprehensive enough to measure quality of life (QoL), and outdated. Therefore, a project is designed to develop and validate technologically advanced questionnaires in the form of item bank (a long questionnaire) implemented via computer adapting testing (CAT) which can precisely measure ophthalmic QoL. This study aims to develop comprehensive item banks for hereditary retinal diseases (HRD).

Methods: Items were generated from 11 pre-existing questionnaires, 3 qualitative studies and 32 interviews. Item revision and refinement were done during three stages, namely binning and winnowing, expert panel discussion and cognitive interviews. At the end of the content development, the HRD item banks had 345 items across ten QoL domains (activity limitation, mobility, social, emotional, economic, symptoms, health concerns and coping). Rasch analysis was used to assess the psychometric properties of the item banks and to establish item calibration for CAT.

Results: The item banks were administered to 233 participants (mean age 56 years; females, 59%). Five domains (activity limitation, emotional, social, mobility, convenience and symptoms) required minor modifications. Three domains (activity limitation, emotional and health concerns) demonstrated multidimensionality, requiring substantial modifications. Our CAT simulations indicated that only 5 items were needed to gain precise measurement of each QoL domain.

Conclusion: These item banks will enable clinicians and researchers to comprehensively explore the impact of HRD from the patients' perspective. Our CAT system is likely to be time efficient modality for use in clinics and research settings.

Key words: Quality of life, hereditary retinal diseases, item bank, computer adaptive testing, Rasch analysis, psychometric properties.

Australian Society for Medical Research Conference (ASMR), abstract 2017 (Oral presentation)

Development of comprehensive quality of life item banks for retinal diseases

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Background: Lack of an appropriate retina-specific patient-reported outcome measure (questionnaire) restricts the understanding of the full impact of hereditary retinal diseases (HRD) and other less common but potentially blinding acquired retinal disease (ARD) such as vascular occlusions, macular hole, central serous retinopathy, and the others on quality of life (QoL). This study aims to develop a comprehensive QoL item bank (a large collection of questions) for HRD and ARD. As HRD differ from ARD in terms of the nature of onset, presentation, and manifestation, we hypothesize that these two disease groups would need separate item banks for assessing QoL impact.

Methods: Development of an item bank involved two phases: item extraction and item evaluation. The items were extracted from three sources: (1)17 pre-existing questionnaires; (2) 4 qualitative studies and (3) 79 semi-structured interviews with patients. The item evaluation involved three stages namely, binning (grouping) and winnowing (refining to unique sets of items); expert panel opinion and cognitive interviews with patients.

Results: The content development yielded 1,217 unique items. Most of the items were from the semi-structured interviews (70%). After 3 sessions of binning and winnowing, and one session of expert panel discussion, items were reduced to a minimally representative set (n=411) across nine QoL domains namely, activity limitation, emotional, social, health concerns, symptoms, economic, mobility, convenience, and coping. After 22 cognitive interviews 29 items were amended resulting in a final set of 345 items in HRD and 3 items were amended resulting in a final set of 254 items in ARD. Overall across all the QoL domains, only 45% of the items were common between the disease groups. Activity limitation domain had the maximum number of common items and convenience domain had the fewer number of common items between the disease groups.

Conclusion: As the majority of the items were unique to the disease groups separate item banks are required to capture QoL impacts for HRD and ARD. A core item pool with common set of items could be used to study QoL impact in mixed population with HRD and ARD.

The Association for Research in Vision and Ophthalmology (ARVO – Asia) Conference, abstract 2017 (Oral presentation)

Control ID: 2599593

Development of a comprehensive quality of life item bank for retinal diseases

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Conflict of interest: None

Purpose: Lack of an appropriate retina-specific patient-reported outcome measure restricts the understanding of the full impact of hereditary retinal diseases (HRD) and other less common but potentially blinding acquired retinal diseases (ARD) such as vascular occlusions, epiretinal membrane, macular hole, central serous retinopathy, retinal infection etc. on quality of life (QoL). This study aims to develop a comprehensive QoL item banks (a long questionnaire) for other vitreoretinal diseases. As, HRD differ from ARD in terms of the nature of onset, presentation and manifestations, we hypothesize that these two diseases groups would need separate item bank for assessing the QoL impact of these diseases.

Methods: Development of an item bank involved two phases: item extraction and item evaluation. The items were extracted from three sources: (1)17 pre-existing patient-reported outcome measures; (2) 4 qualitative studies and (3) 79 semi-structured interviews with patients. The item evaluation involved three stages namely, binning (grouping) and winnowing (refining to unique sets of items); expert panel discussion and cognitive interviews with patients.

Results: The content development yielded 1,217 unique items. Majority of the items were from the interviews (70%). After 3 sessions of binning and winnowing, items were reduced to a minimally representative set (n=411) across nine QoL domains namely, activity limitation, emotional, social, health concerns, symptoms, economic, mobility, convenience, and coping. Of the 411 items, 344 items were unique to HRD and 257 items were unique to ARD. After 22 cognitive interviews 29 items were amended resulting in a final set of 345 items in HRD and 3 items were amended resulting in a final set of 254 items in ARD. Overall across all the QoL domains, only 45% of the items were common between these two disease groups. The QoL domain activity limitation had the maximum number of common items (59%) and the QoL domain convenience had fewer number of common items between the disease groups (16%).

Conclusions: As majority of the items were unique to the disease groups separate item banks are required to capture the QoL impacts for HRD and ARD. A core item pool with common set of item items could be used to study QoL impact in mixed population with ARD and HRD.

Key words: Quality of life; hereditary retinal diseases; acquired retinal conditions; patient-reported outcome; item bank.

Character count: 2327 (2500 characters and spaces for the title, abstract body text, and image captions)

Lay abstract

Quality of life (QoL) has been shown to be severely compromised in people with hereditary (HRD) and other less common but potentially blinding acquired retinal diseases (ARD). However, only a very few patient-reported outcome (PRO) instruments are developed for these diseases which are limited to measuring visual disability than a comprehensive QoL impact. There are no PRO instruments developed for vascular occlusions, epiretinal membrane, central serous retinopathy etc. This study aimed to develop comprehensive QoL item banks (a long comprehensive QoL questionnaire) for other vitreoretinal diseases. This study provides an evidence that there is a need for the development of separate item banks for HRD and ARD. Using the findings of this study we have developed comprehensive item banks for theses disease groups.

Support: ARVO-Asia Travel grant 2017 and Flinders University Student Travel Grant

Report to the National Disability Scheme (NDS), 2015

Seeing through their eyes: lived experiences of people with hereditary and acquired retinal diseases

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Background

World Health Organization (WHO) defines quality of life (QoL) as individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. [1] Therefore, QoL is a broad ranging concept that includes but not limited to an individual's physical health, psychological state, level of independence, personal and social relationship, personal beliefs and their relationship to their environment. Studies have reported that quality of life has been reported to be severely affected in many eye conditions; including major blinding eye diseases that affect retina (back of the eyes) which are age related macular degeneration (AMD) and diabetic retinopathy. [2; 3] There are anecdotal reports that QoL affected in less common but potentially blinding retinal conditions such as hereditary retinal conditions (e.g. retinitis pigmentosa) and other acquired retinal conditions (e.g. vascular eye diseases, epiretinal membrane and macular hole).[4; 5] Moreover, a very little is known about the QoL impacts in people with hereditary retinal conditions and other acquired retinal conditions.

Aim: The purpose of this study was to (1) qualitatively explore and understand the issues and impact of hereditary retinal condition and acquired retinal conditions on QoL and (2) to compare the QoL issues between the hereditary retinal diseases and acquired retinal diseases.

The overarching aims of this study is to develop comprehensive QoL measuring survey questionnaires to be use in clinical, research and rehabilitation evaluation. This study has explored how similar or different is QoL impacts in hereditary and acquired retinal diseases. The findings will inform us whether single or separate questionnaires are required to capture QoL impact in these two disease groups.

Methodology: An interpretive qualitative methodology was used to facilitate the understanding of the lived experiences of people with different retinal conditions and rich in-depth data were collected through semi-structured interviews. Thematic analysis of the data

was carried out by line-by-line coding, aggregation and theme development using the NVivo software.

Results: A total of 79 semi-structured interviews were conducted. The total number of participants in the hereditary retinal diseases group was 32 (median age = 57 years; range 28 to 81 years; 21 females) and the total number of participants in the acquired retinal diseases group was 47 (median age 73 years; range = 54 to 90 years, 32 females). Hereditary retinal diseases included people with retinitis pigmentosa (RP) (n=23), cone dystrophy (CD) (n=2) and macular dystrophy (MD) (n=7) and acquired retinal diseases included people with vascular occlusions (VD) (n=18), epiretinal membrane (ERM) (n=20) and macular hole (MH) (n=9).
Extensive QoL impacts in both disease groups were found. Nine QoL issues were explored. We categorised them into five major and four minor QoL issues. The 5 major QoL issues were: difficulty in performing day-to-day activities (activity limitation), facing emotional and psychological challenges (emotional well-being), struggle with social participation (social participation), concern about health, disease outcome and personal safety (health concerns) and symptoms (ocular and general symptoms) and the 4 minor QoL issues were: problem with orientation and mobility (mobility), effect on work & finance (economic), inconveniences in day-to- day life and coping with the disease (convenience & coping). The prominent QoL issues among people with hereditary and acquired retinal diseases are listed in Table 1.

Table 1. QoL issues among people with hereditary and acquired retinal diseases by importance and hierarchy

Hereditary retinal diseases	**Acquired retinal diseases**
Activity limitation	Health concern
Social participation	Emotional well-being
Mobility	Symptoms
Work & finance	Convenience
	Coping

1. Difficulties in performing day-to-day activities (Activity limitation)

Participants with both hereditary retinal diseases and acquired retinal diseases reported difficulty in performing important day-to-day activities. However, activity limitation was the major QoL issue among people with hereditary retinal diseases. This could be because of early onset of the disease, bilateral occurrence and progressive nature of the disease. The major activity limitation reported among people with hereditary retinal diseases were difficulty in reading, seeing in the dark/night, shopping, driving and playing outdoor games, especially ball games. The major activity limitation among people with acquired retinal diseases were difficulty in driving, reading, watching TV, using public transport and playing indoor games such as board games.

2. Facing emotional and psychological challenges (Emotional well-being)

Participants with both hereditary retinal diseases and acquired retinal diseases faced emotional and psychological challenges. However, participants with hereditary retinal diseases expressed more negative emotional comments compared to people with acquired retinal diseases. Participants with hereditary retinal diseases frequently expressed frustrations. Inability to do things like other people, everything needs planning and organization, inability to read, inability to drive, inability to play sports and inability to find a suitable job were the reasons behind their frustrations. Unfamiliar surroundings and generally not knowing how the eye condition is going to progress frequently caused anxiety among people with hereditary retinal diseases. Inability to drive and having to rely on others made them feel as a burden. They also expressed shock when they were told by their specialist that they would ultimately go blind. In contrast, people with acquired retinal diseases were found to be optimistic and hopeful. They hoped that treatment would improve their eye condition. Some of them worried about the disease recurrence and involvement of the other eye. Frequent hospital appointments for injections and laser treatment caused frustrations among this group of participants.

3. Struggle in social participation (Social participation)

Social participation was a major issue among people with hereditary retinal diseases. They experienced more difficulty in getting help and support from friends and family members compared to people with acquired retinal conditions. People with hereditary retinal diseases reported strain in personal relationship especially with their partners, but despite that majority of the participants in this group were found to be very independent. Maintaining

roles and responsibility in organizations and societies, being part of social groups like book clubs, church groups and interacting with people with similar eye condition was the way of socializing among this group of participants. People with acquired retinal diseases did not rely on the family and friends for support, because in majority of them the eye condition was unilateral and did not hinder the performance of their day-to-day activities.

4. Concern about health, disease outcome and personal safety (Health concerns)

Health concern was a major issue among people with acquired retinal diseases. Majority of the participants with hereditary retinal diseases reported that the information that they received from the specialist or the optometrist was inadequate and that they had to do their own research for more information. The other major concern among people with hereditary retinal diseases was accidents. Participants frequently reported having falls, injuries, tripping and bumping/knocking things or people. Going blind early was another concern among this group of participants. The major concern among people with acquired retinal diseases was the treatment outcome. Similar to people with hereditary retinal diseases, most people with acquired retinal diseases were unaware of their eye condition and expressed unhappiness with the services of the medical provider.

5. Symptoms (Ocular and General symptoms)

The prominent symptoms among people with hereditary retinal diseases were difficulty in seeing in the dark/night or night blindness, difficulties with peripheral vision, progressive loss of vision, difficulty in colour discrimination and problems with light adaptation. The prominent symptoms among people with acquired retinal diseases were blurred vision, distorted vision, difficulty in focussing and seeing floaters in the vision.

6. Problem in orientation and mobility (Mobility)

Difficulty with orientation and mobility was a major issue among people with hereditary retinal disease. This is because of the degeneration of the photoreceptors especially rods which are responsible for orientation. Walking outdoors, navigation in unfamiliar places, walking in crowded places and using steps/stairs were the frequent challenges encountered by these participants. Crossing a street/road, walking in the dark and walking on uneven grounds were the frequent challenges encountered among people with acquired retinal diseases.

7. Effect on work and finance

Work and finance was a major issue among people with hereditary retina diseases, because of the early onset of the disease and progressive nature of the condition interfering with the career development and progress. Majority of the participants with hereditary retinal diseases were worried about the economic and financial impact. Participants in this group reported difficulty or reduced opportunities in finding a job. Not being able to continue their job and loss of income associated with loss of job contributed to the financial impact in this group. The financial impact among people with acquired retinal conditions was less because majority of them were retired. Costs associated with seeing a specialist, buying medication and costs associated with eye procedure were some of the financial impacts among this group of participants.

8. Inconvenience in day-to-day life

People with both hereditary and acquired retinal diseases reported inconveniences associated with their eye condition. Not being able to drive, having to rely on others and having to rely on public transport were some of the major inconveniences reported by people with hereditary retinal diseases and having to do positioning after surgery, having to attend frequent appointments and having to wait for hours in the clinic were some of the inconveniences reported by people with acquired retinal diseases.

9. Coping with the disease

Generally people with acquired retinal diseases coped better. This could be due to the late onset of the disease and unilateral involvement. Participants in both the disease groups adopted coping strategies to cope with their eye condition. Trying to be positive, accepting the eye condition/visual loss and engaging in some useful activities such as travelling to meet people, engaging in sports and other adventurous activities were some of the coping strategies adopted by people with hereditary retinal diseases. Attributing the visual loss to ageing, trying not to think about the eye condition and trusting the doctors were some of the coping strategies adopted by people with acquired retinal diseases.

Comparison of the QoL issues between the disease groups

Majority of the QoL issues were unique to the disease group. The maximum overlap in QoL occurred in activity limitation, about 44% and the minimum overlap occurred in health concern about 16%. Overall the overlap of the QoL was less than 30%.

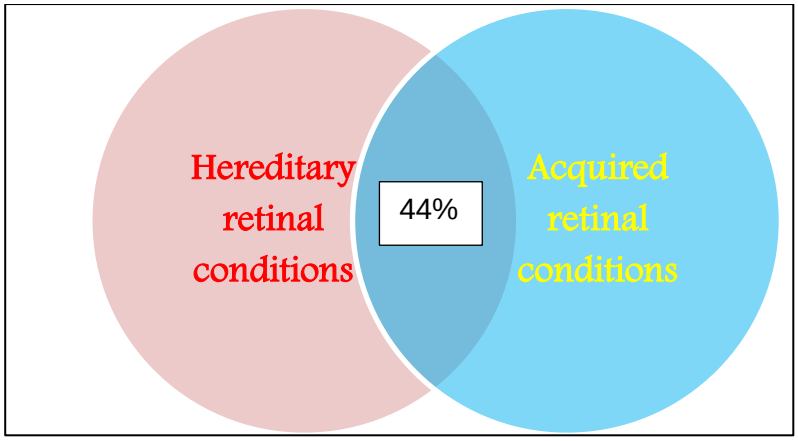

Figure 1. Percentage of overlap of QoL in social well-being

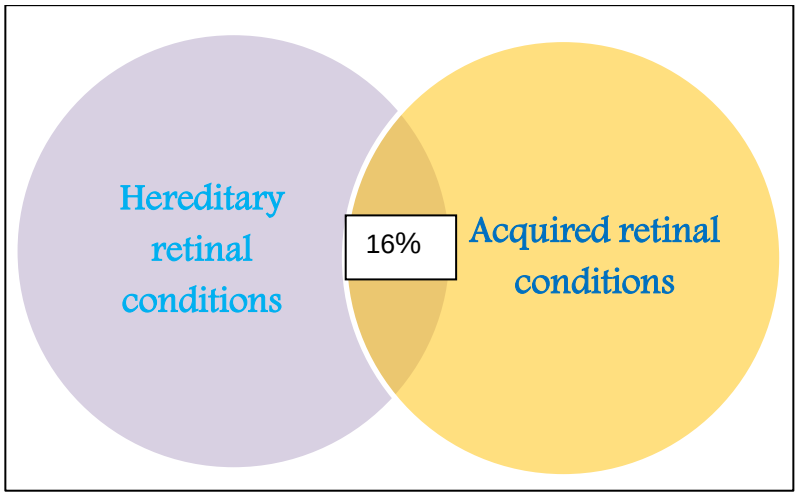

Figure 2. Percentage of overlap of QoL in health concern

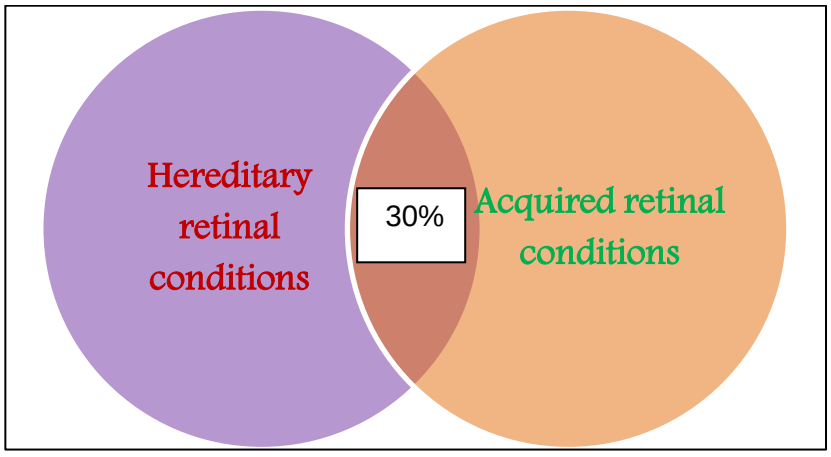

Figure 3. Percentage of overall overlap of QoL issues

Conclusion

People with hereditary retinal diseases reported more QoL issues compared to people with acquired retinal diseases. The major QoL issue in people with hereditary retinal diseases was difficulty in performing day-to-day activities (activity limitation) and the major QoL issue in people with acquired retinal diseases was concerns about health, disease outcome and personal safety (health concern). The overlap of QoL issues between the disease groups was less than one third and the QoL issues were unique to the disease groups.

Future directions

1. This study is part of a big study called the Eye-tem bank project, where we are developing QoL survey questionnaires in the form of item banking implemented via computer adaptive testing (CAT) for all eye diseases. Item banks are nothing but a pool of large number of items across several QoL issues/domains and when implemented via CAT would need only few items to measure the QoL impact precisely and accurately. We are developing these QoL survey questionnaires because the currently existing questionnaires in ophthalmology measure only a few aspect of the QoL and do not provide a comprehensive assessment of the QoL. For example the currently available questionnaires in retinitis pigmentosa measure only the mobility aspect of the QoL and do not measure the socio-emotional or the financial impact of the disease. Moreover, all the existing questionnaires are traditional paper-pencil based. These paper-pencil based questionnaires are static, out-dated, limited in their item content, poorly targeted to patients and do not provide a holistic measurement of QoL. A superior strategy is to develop item banks (a large number of items pooled across different domains of QoL implemented via a CAT.
2. Majority of the QoL issues in our study were unique to the disease group and hence we would have to develop separate questionnaires to measure the QoL impacts in patients with hereditary and acquired retinal conditions.
3. The QoL issues identified in this study will be used to develop items for these questionnaires.

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Research

Phase 2 study – Can you help?

Editors note: It's not often we get the chance to be a part of research studies and even less often do we get our mates across the ditch asking for our help! Researcher Dr.Mallika Prem Senthil is looking for about 100 more participants to take part in an online questionnaire ...

Developing a technologically advanced Quality of Life questionnaire for hereditary retinal diseases.

Quality of life has been shown to be severely compromised in people with major blinding retinal diseases such as Age-related Macular Degeneration [AMD] and Diabetic Retinopathy.

However, very little is known about quality of life impact of people with hereditary retinal diseases such as Retinitis Pigmentosa [RP].

Studies exploring impact of hereditary retinal diseases on quality of life have been restricted by the lack of appropriate survey questionnaires.

To date, only a few questionnaires are available for hereditary retinal diseases. Moreover, all the existing questionnaires are traditional paper-and-pencil based and mostly not validated. These paper-pencil based questionnaires are static, out-dated, and do not provide a holistic measurement of quality of life.

A superior strategy is to develop item banks [a large number of questions] implemented via a computer adaptive testing [CAT] system. The CAT system iteratively presents questions based on a patient's response to previous questions. Thus, the item bank implemented via the CAT system requires fewer questions to provide precise and accurate assessment of quality of life impact.

Therefore, a project [The Eye-tem bank] has been designed to develop an item bank for hereditary retinal diseases. This technologically advanced survey questionnaire will revolutionise the way questionnaires are used in ophthalmic research and clinical practice.

The Eye-tem Bank project is a collaborative study carried out at Flinders University as a lead organisation and three centres: The Queen Elizabeth Hospital, SA, The Royal Adelaide Hospital, SA, and the Royal Victorian Eye and Ear Hospital, VIC. The study started in 2014 and is ongoing.

The Phase 1 study which has now been completed, involved consultation with people who have hereditary retinal conditions through in-depth interviews from all over Australia.

The qualitative interviews were done to explore the influence and impact of hereditary retinal diseases on patient's overall quality of life.

The results of our Phase I study shows that people with hereditary retinal diseases experience a myriad of QoL issues such as difficulty in performing important day-to-day activities such as reading, seeing under different

light conditions, driving, shopping, playing sports and using a computer; facing lots of emotional and psychological challenges; concerns about disease progression, outcome and personal safety; experiencing a myriad of visual symptoms; problems with socialisation and interaction with others; problems with mobility and orientation and effect on work and finance.

We also found that people with hereditary retinal diseases experience far greater quality of life issues compared to other retinal diseases.

The Phase I study results were presented at the National Retina Congress in 2015 at Melbourne.

Using phase I data we have developed a pilot survey questionnaire which we are currently pilot testing on people with hereditary retinal diseases using an online survey.

This part of the study [Phase 2] has started in July 2016 and is currently ongoing. This study involves answering an online survey about how your eye disease/s and its treatment are affecting you and your life.

We are currently looking for participants with hereditary retinal diseases [e.g. Retinitis Pigmentosa, Usher syndrome, Bardet-Biedl syndrome, Rod dystrophies, Cone dystrophies, Stargardt's disease, Best disease, Fundus Flavimaculatus, Juvenile Retinschisis, vitelliform macular dystrophy, Choroideremia, etc.] to take part in this online survey.

People with hereditary retinal diseases are kindly requested to take part in the online survey and help us in this research. People who wish to participate in this survey or who need further information on this please contact: Dr Mallika Prem Senthil, Optometry and Vision Science, Flinders University, [Australia]
Phone: +61 8 7221 8708
Mobile: +61 450 755338
email: prem0013@flinders.edu.au

Editors note: I've just completed the survey. It takes a couple of hours but its possible to do it in multiple sessions if need be. Its done through Survey Monkey so its fully accessible.

Retina NZ – Research Grant Update:

In recent years, Retina New Zealand has granted a summer studentship of $5000 from the proceeds of its Research Fund. For the financial year 2016/17 it was decided by the Executive Committee, to instead support an honours student with a $7000 Honours Scholarship, to undertake a low vision related research project over the course of the 2017 Tertiary year. Its still too early to publicly announce the details yet, but it will be a really interesting and exciting project within the world of low vision. Look out for the full story in the February 2017 issue.

Newsletter for Retina NZ, 2017

People don't see the way I do! Quality of life impact of retinitis pigmentosa.

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Introduction

Retinitis pigmentosa (RP) is a disabling disease that is currently incurable. It typically starts at the early teenage years and progresses to severe visual impairment during the 4th and 5th decade. The classical symptoms of RP include night blindness, peripheral visual loss and in advanced cases central visual loss. Apart from the classical symptoms, people with RP exhibit difficulty adjusting to changing levels of illumination, difficulty seeing in poor contrast, processing auditory information and perception of moving objects in the environment. All these difficulties along with the progressive visual loss can have a serious impact on quality of life of an individual with RP. Even though these problems are identified clinically, limited research has been conducted to understand the impact on day-to-day life of people with RP from their perspective. Hence the aim of this study was to explore the issues and impact of people with RP on quality of life.

Methods

Twenty-three participants with RP were recruited from charity and welfare organisations through emails and flyers. The lived experiences of people with RP were explored using semi-structured interviews.

Results

A total of 23 interviews were carried out (mean age = 56 years; range 28 to 81 years; females, 14). Two-third participants were above the age of 50 years. We identified five major quality of life themes: (1) struggle to perform important day-to-day tasks (activity limitation), (2) concerns about disease progression, disease outcome and personal safety (health concerns), (3) facing emotional and psychological challenges (emotional well-being), (4) experiencing a myriad of symptoms (symptoms) and (5) adopting different strategies to manage stressful circumstances (coping).

1. Struggle to perform important day-to-day tasks (activity limitation)

Participants frequently reported difficulty in performing important day-to-day tasks such as reading, seeing in changing light conditions, shopping, driving, playing sports, taking part in leisure activities and doing household chores. They reported difficulty in reading books, menu cards, magazines, and newspaper. They had difficulty driving both during the day and the night. Cleaning was the most difficult household chore reported. Other difficulties reported were engaging in leisure activities such as knitting, gardening and playing lawn-bowls. The following quotation exemplifies the difficulties one of the participants facing whilst reading.

"You know I used to love to curl up in bed and read a book, well now I have to sit at a reading machine and it's so slow and you're trying to follow the line across and the whole enjoyment of that is gone because of the way that you have to do it."

They experienced difficulties when walking in unfamiliar places, crowded places and using steps. They also struggle in confined places and busy places such as shopping malls and airports.

2. Concerns about disease progression, disease outcome and personal safety (health concerns)

One of the major health concern was having frequent accidents such as falls and bumping into things. Having to rely on others for reading, shopping, transport and getting around in darkness was again a major concern. They generally expressed dissatisfaction towards the medical service providers as they felt that the information provided by them was inadequate. The prospect of losing eye sight completely or going blind early was also the biggest concern.

'My biggest fear is that perhaps I will lose it all. I've been fighting all these years to retain my vision and my biggest fear is losing it all."

3. Facing a lot of emotional and psychological challenges (emotional well-being)

Participants with RP face a lot of emotional and psychological challenges due to their progressive visual loss. Frustration, worry, shock, anxiety and feel as a burden were the commonly expressed emotions. They frequently expressed frustrations which results from myriad of reasons such as not knowing what to do when being diagnosed with RP, having to learn different ways of doing things, inability to participate in sports and having to depend on people.

"It was frustrating because when they give you the diagnosis that you've got this eye condition and you're going to go blind you're in so much shock and you don't really know what to do."

4. Experiencing a myriad of symptoms (symptoms)

The commonly cited symptoms were night blindness, restricted visual fields, difficulty in discriminating colours and difficulty in adjusting to different light conditions. Restriction of the peripheral visual field caused depth perception issues resulting in frequent tripping and bumping into things. Gradual or progressive loss of vision over a period of time is one of the commonly uttered symptoms.

"*Gradually not being able to see things when I was out at night*."

5. Adopting different strategies to manage stressful circumstances (coping)

Coping strategies were commonly discussed by all the participants. They expressed their resilience in facing the nature of their eye condition. Some of the commonly reported coping strategies were trying to be optimistic, accepting their eye condition/visual loss and learning to live with the eye condition.

"Cry and then pull myself up by my socks and get on with it."

Other quality of life issues

Participants with RP had difficulty interacting with their friends and family. Their progressive visual loss was not well understood by their family members and friends that affected their long term relationship with them. Despite these hardships the majority of the participants were very independent. Difficulty in finding suitable jobs and reduced job opportunities were frequently reported. Loss of income was associated with financial constraints.

"The rest of my brothers and sisters don't understand it and they call me a liar and a cheat and I've been sort of disconnected from that side of the family, which also broke my heart."

Discussion

This study shows that people with RP experience a myriad of quality of life issues. This information may be used to inform eye care providers, who should take such perspectives into consideration when evaluating and managing their patients with RP. Moreover, understanding the extent of the quality of life impact of these people can help identify subgroups with relatively poor perceived health and help guide interventions to improve their situations and avert more serious consequences.

The currently existing questionnaires in RP are limited to measuring only a few aspects of quality of life (mostly activity limitation) and do not capture the socio-emotional and financial implications of the disease. This restricts the understanding of the full impact of RP on quality of life. Understanding patients' perspective is critical as newer treatment modalities such as gene therapy, cell transplantation, retinal prosthesis and neuroprotection are gaining momentum. Hence there is a need for developing comprehensive and psychometrically sound RP-specific questionnaire. The findings of this study will guide us to develop the content (questions) of a comprehensive RP-specific questionnaire, which will be technologically advanced in the form of item banking implemented via computer adaptive testing (CAT). An item bank is a repository of items that measure a latent construct such as activity limitation, emotional well-being, social well-being, and so on. The CAT system choses the best and highly informative items from the available item pool that closely matches with the participant's ability. As the item administration is based on the participant's response to previous items, the CAT provides an effective, quick and precise measurement of quality of life. Item banks have been developed and implemented in other fields of health care and is currently under construction for eye diseases such as glaucoma, diabetic retinopathy and age related macular degeneration.

Note: A detailed result of this study has been published in a peer review scientific journal. Please refer to the following citation for detail.
Prem Senthil M *et al*. Seeing through their eyes: lived experiences of people with retinitis pigmentosa. *Eye (London)* 2017 31(5):741-48.

Quality of life impact in people with hereditary and acquired retinal diseases

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Flinders UNIVERSITY inspiring achievement

BACKGROUND

- Quality of life (QoL) is **severely** compromised in people with **major** blinding retinal conditions such as age related macular degeneration (AMD) and diabetic retinopathy (DR).[1,2] However, **very little** is know about the QoL impact in less common but potentially blinding other vitreo-retinal diseases.
- This study aimed to **explore** and **compare** QoL issues between people with hereditary retinal diseases (HRD) and other less common acquired retinal diseases (ARD).

METHODS

- Data were collected through semi-structured **interviews.**
- We carried out an **open coding strategy** whereby nodes (words or phrases were generated by scan reading the transcripts. Each transcript was coded using the nodes in its entirety using the NVivo software (QSR International Pty Ltd. Version 10, 2014).
- Individual nodes were then reorganized by assimilating them into different **categories** (i.e. nodes of similar concept were brought under the umbrella of a mother node (potential major theme).
- The mother nodes with component child nodes (potential sub-themes) were explored to identify linkage between **similar patterns** across the transcripts.

RESULTS

- **79** (females, n=53) interviews were conducted with people with HRD (n=32; range 28 to 81 years; median age = 57 years) and ARD (n=47; range 54 to 90 years; median age=72 years).
- **HRD:** Retinitis pigmentosa (n=23), cone dystrophy (n=2) and macular dystrophy (n=7).
- **ARD:** Vascular occlusions (n=18), macular hole (n=9) and epiretinal membrane (n=20).
- We identified **9 QoL themes** relevant to people with retinal diseases (Figure 1).
- Difficulty in performing important day-to day activities (**Activity limitation**) was the most prominent QoL issue among people with HRD (Figure 1).
- People with ARD reported '**reading**' was affected significantly whereas '**reading**' and '**seeing in the dark**' were significantly affected in HRD (Figure 2).
- Concerns about health, disease outcome and personal safety (**Health concerns**) was the most prominent QoL issue in the ARD group (Figure 1).
- People with HRD & ARD both faced many emotional and psychological challenges (**Emotional well-being**) (Figure 1, 3).
- People with HRD had more issues with social participation (**Social well-being**), problems with orientation and mobility (**Mobility**) and effect on work and finance (**Economic**) (e.g. finding a suitable job) compared to the people with ARD (Figure 1).
- People with HRD also reported more ocular and visual symptoms (**Symptoms**) (e.g. night blindness) (Figure 1).
- People with ARD reported more inconveniences due to their eye condition (**Convenience**) (e.g. to attend frequent eye appointments).
- People with HRD were coping better compared to people with ARD (**Coping**) (e.g. accepting your eye condition/vision loss).
- Overall **less** than **30%** of QoL issues were common between the two disease groups (Figure 4).

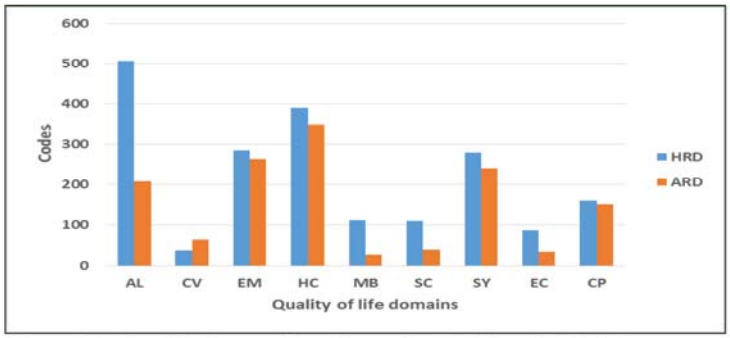


Figure 1. Quality of life themes affected in people with HRD and ARD. Codes = number of times the issue was discussed. Note: AL, activity limitation; CV, convenience; EM, emotional well-being; HC, health concerns; MB, mobility; SC, social participation; SY, symptoms; EC, economic; CP, coping.

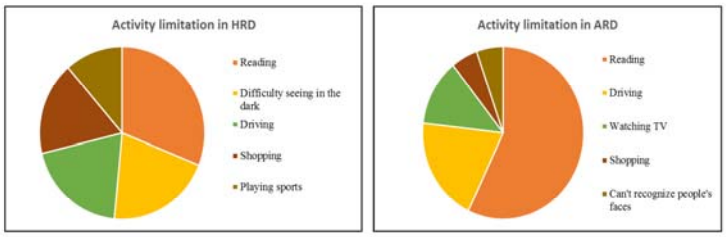


Figure 2. Major activity limitations in people with HRD and ARD

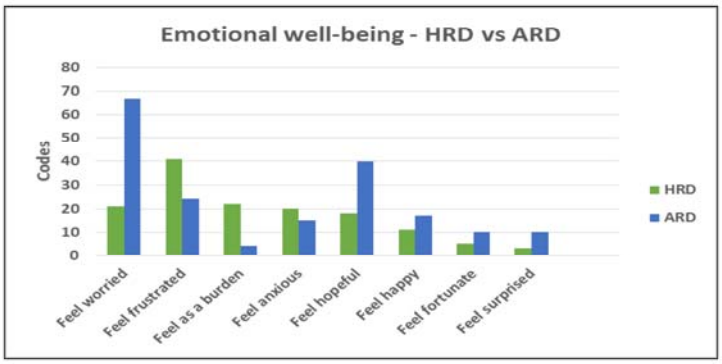


Figure 3. Negative and positive emotional comments expressed by people with HRD and ARD. Codes = Number of times the issue was discussed.

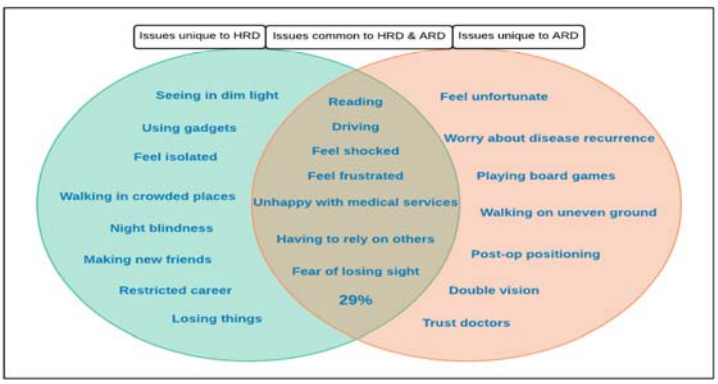


Figure 4. Unique and common QoL issues between HRD and ARD

CONCLUSIONS

- **Both** groups of retinal conditions had to live with myriad of QoL issues.
- However, people with **HRD** experience **more** QoL issues but coped well with their diseases and day-to-day lives.
- Some of the issues were common to the disease groups, but **most** of the QoL issues were unique to the disease groups.

References

1. McCloud C, Khadka J, Gilhotra JS, Pesudovs K: Divergence in the lived experience of people with macular degeneration. Optom Vis Sci 91:966-974, 2014.
2. Fenwick EK, Pesudovs K, Khadka J, et al.: The impact of diabetic retinopathy on quality of life: qualitative findings from an item bank development project. Qual Life Res 21:1771-1782, 2012

Contact email: prem0013@flinders.edu.au

Listening to the voices of people with retinal conditions: a qualitative study

Mallika Prem Senthil MS, Jyoti Khadka PhD, Konrad Pesudovs PhD

Discipline of Optometry and Vision Science, Flinders University, Bedford Park, South Australia, 5042, Australia

Flinders UNIVERSITY inspiring achievement

BACKGROUND

- Difference in quality of life (QoL) impact in people with hereditary retinal (HD) and other less common, but potentially blinding acquired (AD) retinal conditions has not been explored before.[1,2]
- We aim to explore the issues and impact of HD and AD on QoL.

METHODS

- Qualitative methodology was undertaken.
- Data were collected through semi-structured interviews.
- Thematic analysis done by line-by-line coding, aggregation, and theme development using the NVivo software (QSR International Pty Ltd. Version 10, 2014).

RESULTS

- **79** semi-structured interviews were conducted. HD (n=**32**; median age = 57 yrs; range = 28 to 81yrs; 21 females) and AD (n=**47**; median age = 72 yrs; range = 54 to 90 yrs; 32 females).
- **HD:** retinitis pigmentosa (n=23), cone dystrophy (n=2) and macular dystrophy (n=7).
- **AD:** vascular diseases (n=18), macular hole (n=9) and epiretinal membrane (n=20).
- We identified **5 major** QoL themes : activity limitation, emotional well-being, social well-being, concern about health and well-being and symptoms and **4 minor** QoL themes: mobility, coping, economic and convenience.
- **'Activity limitation'** was the major theme in **HD group**, whereas in **AD group** was '**Concern about health and well-being**.'
- Overall only 30% QoL issues were common between HD and AD.
- Among 5 major QoL themes (Figures 1 to 5):**'Social well-being'** had the maximum overlap (44%) followed by '**Symptoms**' (30%) and **'Concern about health and well-being'** had the minimum overlap (16%) between HD and AD.
- All minor QoL themes had less than 40% overlap.

CONCLUSION

- People with HD reported more QoL impact than people with AD.
- Majority of QoL issues were group specific, hence two separate questionnaires would be required to capture QoL impact between AD and HD.
- QoL issues identified will be used to develop items (questions) for these questionnaires.

References

1. McCloud C, Khadka J, Gilhotra JS, Pesudovs K: Divergence in the lived experience of people with macular degeneration. Optom Vis Sci 91:966-974, 2014.
2. Fenwick EK, Pesudovs K, Khadka J, et al.: The impact of diabetic retinopathy on quality of life: qualitative findings from an item bank development project. Qual Life Res 21:1771-1782, 2012

SOCIAL WELL-BEING (SC)

HD – Hereditary diseases
AD – Acquired diseases

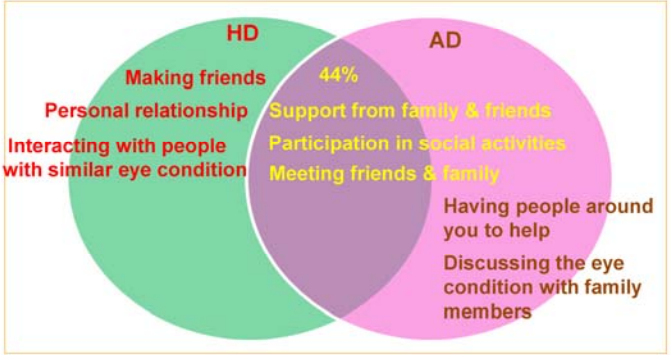


Figure 1. Percentage of common and unique issues in SC

SYMPTOMS (SY)

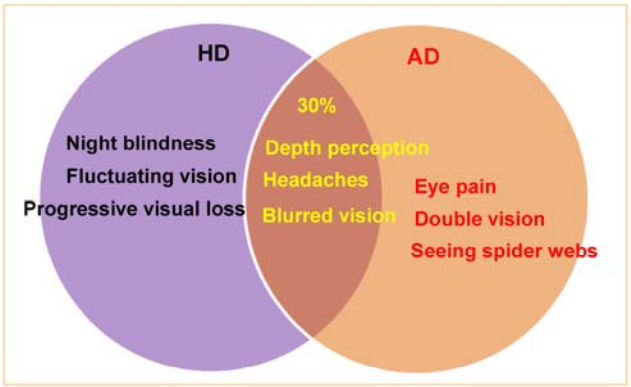


Figure 2. Percentage of common and unique issues in SY

EMOTIONAL WELL-BEING (EM)

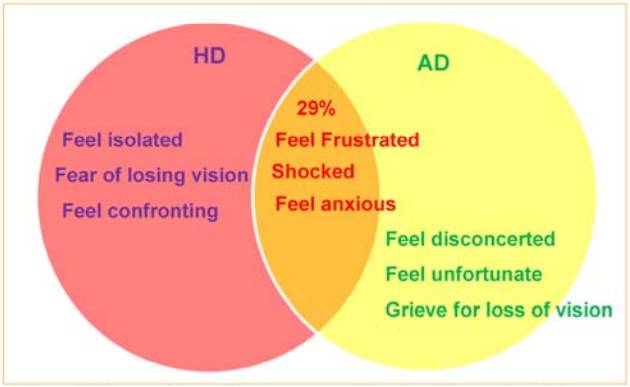


Figure 3. Percentage of common and unique issues in EM

ACTIVITY LIMITATION (AL)

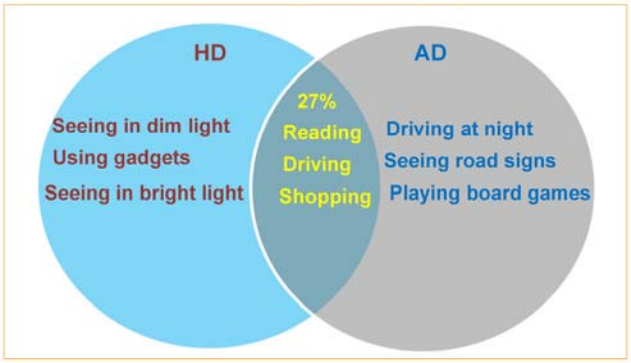


Figure 4. Percentage of common and unique issues in AL

CONCERN ABOUT HEALTH AND WELL-BEING (HC)

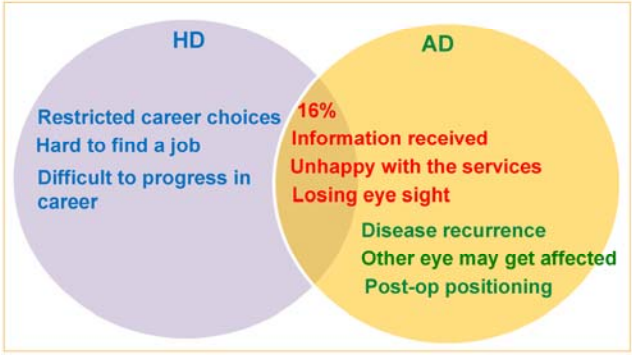


Figure 5. Percentage of common and unique issues in HC

Seeing through their eyes: lived experiences of people with retinal diseases

Mallika Prem Senthil MS, Jyoti Khadka PhD, Konrad Pesudovs PhD
Discipline of Optometry and Vision Science, Flinders University of South Australia, Bedford Park, South Australia, 5042, Australia

BACKGROUND

- Quality of life (QoL) is severely compromised in people with major blinding retinal diseases such as age related macular degeneration & diabetic retinopathy.[1,2]
- Very little is known about QoL impact in people with hereditary retinal diseases (HD) and other less common but potentially blinding diseases such as vascular diseases (VD), macular hole (MH) and epiretinal membrane (ERM).
- The main aim of this study was to qualitatively explore and understand the issues and impact of HD on QoL and compare it with people with acquired retinal diseases.
- This study is conducted as a part of a major study (The Eye-tem Bank project), which aims to develop QoL measuring questionnaires in the form of item banking implemented via computer adaptive testing system for all eye diseases.[3,4]

METHODS

- Data was collected through semi-structured interviews.
- All interviews were recorded and transcribed verbatim word by word.
- Interviews were carried out until thematic saturation was obtained.
- The coding, aggregation and theme development were carried out using the NVivo software (QSR International Pty Ltd. Version 10, 2014).

RESULTS

- A total of 61 semi-structured interviews were conducted (median age = 69 years; range 28 to 90 years; 39 females).
- Hereditary diseases (n=18): retinitis pigmentosa (RP) (n=13), cone dystrophy (CD) (n=1) and macular dystrophy (MD) (n=4).
- Acquired diseases (n=43): VD (n=17), MH (n=9) and ERM (n=17).
- Ten major themes emerged from the qualitative analysis (Table 1).
- People with HD have significantly more issues in all the aspects of QoL when compared to people with acquired retinal diseases (Figure 1).
- Among acquired retinal diseases, people with VD had more emotional and health concerns (Figure 1).
- Within each major theme, many sub-themes were identified. E.g. driving (AL), help and family support (SC), job loss or stopped working (EC) (Table 2).

CONCLUSION

- People with HD were found to have more QoL impact than people with acquired retinal diseases.
- Major themes identified in this study will form the QoL domains for the new questionnaire.
- QoL issues identified in this study will be used to develop items for QoL questionnaire.

References

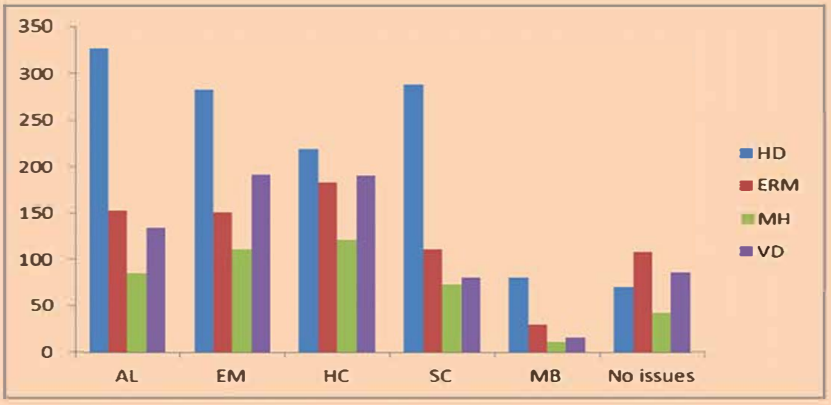
1. Wong EYH, Guymer RH, Hassell JB, Keeffe JE: The experience of age-related macular degeneration. Journal of Visual Impairment & Blindness 98:629-640, 2004.
2. Fenwick EK, Pesudovs K, Khadka J, et al.: The impact of diabetic retinopathy on quality of life: qualitative findings from an item bank development project. Qual Life Res 21:1771-1782, 2012.
3. McCloud C, Khadka J, Gilhotra JS, Pesudovs K: Divergence in the lived experience of people with macular degeneration. Optom Vis Sci 91:966-974, 2014.
4. Fenwick EK, Pesudovs K, Khadka J, et al.: Evaluation of item candidates for a diabetic retinopathy quality of life item bank. Qual Life Res 22:1851-1858, 2013.

Contact email: prem0013@flinders.edu.au

Table 1. Major QoL themes identified among people with retinal diseases

Major themes	No. of Coded segments	Quotes
Emotional well-being (EM)	763	*"it looked like it was the end of the world so I found that very, very **confronting and I was very angry.** I think I took a lot of risks, like risky behaviour, and **I was in denial and felt very hard done by "**..... (RP)*
Health concern (HC)	722	*"I've always had **lots of accidents and bumping into stuff "**..... (CD)*
Activity limitation (AL)	703	*"I **couldn't read small letters like newspaper letters** and things like that"..... (MH)*
Social participation (SC)	554	*"I was 31 when I was actually diagnosed with RP ... **my marriage had just broken up** and I had two children who were seven and nine"..... (RP)*
Visual symptoms (VS)	384	*"it's like **looking through a window when it's raining"**..... (VD)*
No issues and concerns	309	*"Yeah **I do everything**. I was just reading before you came. I play on the computer, I sew"..... (ERM)*
Positive attitude (PA)	284	*"Well after a **while I just grew out of it and I'm back to normal"**.... (ERM)*
Mobility (MB)	143	*"I only **go somewhere I'm very familiar** with on my own at night"..... (RP)*
Economic (EC)	135	*"**I can't do the job** I was doing in the police force before so now" ... (VD)*

Figure 1. Comparison of QoL issues between hereditary and acquired retinal diseases



Note: AL – Activity limitation; EM – Emotional well-being; HC – Health concern; SC – Social participation; MB – Mobility; No issues – No QoL issues.

Table 2. Sub-themes identified within the major themes

Emotional well-being (763)	Health concern (722)	Activity limitation (703)	Social participation (554)	Symptoms (384)	Mobility (143)	Work & Finance (135)
Negative comments (614)	Health service-Unsatisfactory (106)	Driving (203)	Help & Family support (550)	Poor night vision (47)	Walking (72)	Job loss or stopped work (21)
Positive comments (227)	Treatment outcome (95)	Reading (202)	Relationship break up (3)	Blurry vision (45)	Navigation in unfamiliar places (20)	Finance-Buying reading glasses (6)
	Information about eye condition (93)	Lighting related activities (89)	Support services (3)	Restricted field of vision (38)	Moving around (15)	Finance-Loss of income (5)
	Information provided by specialist/s (45)	Leisure (79)		Distorted vision (24)	Walking in crowded places (10)	Reduced job opportunities (5)

Note : (Number in the parenthesis represents number of coded segments)

Appendix 10: Ethics submission and documents

Southern Adelaide Clinical Human Research Ethics Committee

Government of South Australia
Southern Adelaide Health Service

26 May 2014

Dear Mr Pesudovs

This is a formal correspondence from the Southern Adelaide Clinical Human Research Ethics Committee. Whilst this official title of the committee has changed the committee is still properly constituted under AHEC requirements with the registration number EC00188. This committee operates in accordance with the "National Statement on Ethical Conduct in Human Research (2007)." This department only uses email correspondence for all documents unless prior arrangements have been made with the manager. No hard copy correspondence will be issued.

Application Number: 469.11

Title: A system for measurement of vision-specific quality of life using item banking and computer adaptive testing (Eye item bank)

Chief Investigator: Konrad Pesudovs

The Issue: The Southern Adelaide Health Service / Flinders University Human Research Ethics Committee (SAFUHREC) have approved the above project amendment. Your project may now incorporate these amendments into your research. The approval extends to the following documents/changes:

- Project amendment application form
- Cover letter.
- SAC HREC general research application V6.0 dated May 2014. (tracked)
- Transcript for macular disorders focus group V1.0 dated May 2014.
- Transcript for hereditary retinal degenerations/dystrophies focus group V1.0 dated May 2014.
- Transcript for retinal vascular disorders focus group V1.0 dated May 2014.
- Transcript for macular disorders semi-structured interview V1.0 dated May 2014.
- Transcript for hereditary retinal degenerations /dystrophies semi-structured interview V1.0 dated May 2014.
- Transcript for retinal vascular disorders semi-structured interview V1.0 dated May 2014.

This amendment approval does not alter the current SAC HREC approval period for the study: 20 January 2015

Please read the terms and conditions of ethical approval below, as researchers have a significant responsibility to comply with reporting requirements and the other stated conditions.

For example, the implications of not providing annual reports and requesting an extension for research prior to approval expiring could lead to the suspension of the research, and has further serious consequences.

Please retain a copy of this approval for your records.

Flinders Medical Centre

The Flats G5 – Rooms 3 and 4

Flinders Drive, Bedford Park SA 5042

T: 08 8204 6453

E:Research.ethics @health.sa.gov.au

TERMS AND CONDITIONS OF ETHICAL APPROVAL
Final ethical approval is granted subject to the researcher agreeing to meet the following terms and conditions.

As part of the Institution's responsibilities in monitoring research and complying with audit requirements, it is essential that researchers adhere to the conditions below.

Researchers have a significant responsibility to comply with the *National Statement 5.5.* in providing the SAC HREC with the required information and reporting as detailed below:

1. **Compliance** with the *National Statement on Ethical Conduct in Human Research* (2007) & the *Australian Code for the Responsible Conduct of Research* (2007).
2. To **immediately report to SAC HREC** anything that may change the ethical or scientific integrity of the project.
3. **If University personnel are involved in this project,** the Principal Investigator should notify the University before commencing their research to ensure compliance with University requirements including any insurance and indemnification requirements.
4. **It is the policy of the SAC HREC not to provide signed hardcopy or signed electronic approval letters**, as our office is moving to electronic documentation. The SAC HREC office provides an unsigned electronic PDF version of the study approval letter to the Chief Investigator/Study Manager via email. These email approvals are generated via the email address research.ethics@health.sa.gov.au which can be linked back to the SAC HREC.
5. **Report Significant Adverse events (SAE's)** as per SAE requirements available at our website.
6. **Submit an annual report on each anniversary of the date of final approval** and in the correct template from the SAC HREC website.
7. **Confidentiality** of research participants MUST be maintained at all times.
8. A copy of the **signed consent form** must be given to the participant unless the project is an audit.
9. Any **reports or publications derived from the research** should be submitted to the Committee at the completion of the project.
10. All requests for **access to medical records** at any SAHS site must be accompanied by this approval email.
11. To **regularly review the SAC HREC website** and comply with all submission requirements, as they change from time to time.
12. The researchers agree to use **electronic format** for all correspondence with this department.
13. Researchers are reminded that **all advertisements/flyers** need to be approved by the committee, and that no promotion of a study can commence until final ethics and executive approval has been obtained. In addition, all media contract should be coordinated through the FMC media unit.

Yours sincerely

Rhiannon Kitik
Administration Officer
SAC HREC

Government of South Australia
SA Health

Flinders UNIVERSITY

PARTICIPANT INFORMATION SHEET

Title of the project: Questionnaire Study – Phase I
A system for measurement of vision-specific quality of life using item banking and computer adaptive testing (Eye-tem Bank): Phase I- Item identification

Name of organizations:
This is a collaborative study carried out at Flinders University as a lead organization and three centres: The Queen Elizabeth Hospital, SA, The Royal Adelaide Hospital, SA, and the Royal Victorian Eye and Ear Hospital, VIC.

This is a research project and you do not have to be involved. If you do not wish to participate, your medical care will not be affected in any way.

You are invited to take part in Phase I of a research study conducted by the Discipline of Optometry and Vision Science at Flinders University. This study is being conducted to explore how eye problems affect people's lives. The information obtained will be used to develop a comprehensive bank of items (questions) for the assessment of quality of life. This item bank will assist eye doctors and researchers to better evaluate the impact of an eye problem on each patient and determine the appropriate course for treatment.

If you choose to participate, you may be invited to attend a focus group discussion or one-on-one interview (face-to-face or telephone), in which you will be asked to talk about how your eye problem is affecting you and your life. The focus group/ face-to-face interviews will take place in one of four settings (Flinders University/Flinders Medical Centre, Bedford Park, SA, The Queen Elizabeth Hospital, Woodville West, SA, the Royal Adelaide Hospital, Adelaide, SA, and the Royal Victorian Eye and Ear Hospital, East Melbourne, VIC), wherever is most convenient for you. A facilitator will be present to guide the discussion/interviews, which will last around 1-2 hours. If you instead prefer a telephone interview, one of our staff will contact you at your preferred time and will guide the telephone interview. The focus group discussion and interviews will be audiotaped, but your identity and what you say will remain confidential. Apart from attending a discussion group /interview you will not be asked to attend any special visits. You will receive a flat rate of $20 to assist with transport and parking costs. Refreshments will also be provided during the focus group/ face-to-face interviews.

You will need to fill out the demographic form and sign the consent (attached) before participating in the study, this should only take few minutes. If you agree to participate, we will acquire measurements of your vision and diagnosis from your clinical file. If you do not consent, we will not access your clinical file.

There are no direct benefits to you from being associated with this study. However, your input may help eye doctors and researchers in being better able to assess how these eye problems affect quality of life in future patients.

Your involvement in this study will not affect your treatment in any way. Your participation in the study is entirely voluntary and you have the right to withdraw at any time. If you decide not to participate in this study or if you withdraw, you may do this freely without prejudice to any treatment.

If you suffer injury as a result of participation in this research or study, compensation might be paid without litigation. However, such compensation is not automatic and you may have to take legal action to determine whether you should be paid.

All records containing personal information will remain confidential and no information that could lead to your identification will be released. Records will be kept in a securely locked filing cabinet and in a password protected computer located in room 4E 432, Flinders Medical Centre. The audio recording of the focus groups and interviews will be transcribed for analytic purposes only. Data will be deleted and destroyed 5 years after the study is completed. We expect that once the study is completed, the results will be published in a scientific journal. All patient responses will be de-identified and then collated, so that your identity and any personal information will remain completely confidential.

Please note, if you do not want to be identified by name during the focus group session, you can use a different name. In order to respect the privacy of other participants, we request that you do not share what has been discussed in the focus group or divulge the identity of fellow participants to anybody outside the group.

Should you require further details about the project, either before, during or after the study, you may contact the research higher degree student, Mallika Prem Senthil, on telephone (08) 8204 6122 (Discipline of Optometry and Vision Science, Flinders University).

This study has been reviewed by the Southern Adelaide Clinical Human Research Ethics Committee. If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the executive officer on 8204 4507 or email research.ethics@health.sa.gov.au

Government of South Australia
SA Health

Flinders UNIVERSITY

SOUTHERN ADELAIDE CLINICAL HUMAN RESEARCH ETHICS COMMITTEE / FLINDERS UNIVERSITY

CONSENT TO PARTICIPATION IN RESEARCH

I, ... request and give
(first or given names) *(last name)*

consent to my involvement in the research project: Questionnaire Study – Phase I
A system for measurement of vision-specific quality of life using item banking and computer adaptive testing (Eye-tem Bank) Phase I: Item identification

I acknowledge the nature, purpose and contemplated effects of the research project, especially as far as they affect me, have been fully explained to my satisfaction by.....and my consent is given voluntarily
(first or given names) *(last name)*.

I acknowledge that the detail(s) of the following has/have been explained to me, including indications of risks, any discomfort involved, anticipation of length of time, and the frequency with which they will be performed.

Joining a focus group/one-on-one interviews to talk about how my eye condition affects me (approx. 1-2 hours duration)

I have understood and am satisfied with the explanations that I have been given.

I have been provided with a written information sheet.

I understand that my involvement in this research project may not be of any direct benefit to me and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the researchers in any respect.

I understand that my medical records may be accessed to confirm my diagnosis.

I declare that I am over the age of 18 years.

I also consent to extracting my clinical details (measurements of vision and diagnosis) from my clinical file for this research *(please tick)* ☐ Yes ☐ No

I acknowledge that I have been informed that should I receive an injury as a result of taking part in this study, I may need to start legal action to determine whether I should be paid.

Signature of Research Participant : ..... Date:…….

I, …….have described to ……
the research project and nature and effects of procedure(s) involved. In my opinion he/she understands the explanation and has freely given his/her consent.

Signature: ..... Date:…….

Status in Project: …….

This study study is a joint collaboration between:

Discipline of Optometry and Vision Science
Flinders University
South Australia

The Queen Elizabeth Hopital
Adelaide University
South Australia

The Royal Adelaide Hospital
Adelaide University
South Australia

The Royal Victorian Eye and Ear Hospital
Melbourne University
Victoria

DEMOGRAPHIC FORM

DEMOGRAPHIC DETAILS - please print or circle options			
Title *(please circle):*	Mr / Ms / Mrs / Miss / Dr		Date:
Surname:			
First & Second Names:			
Address:			
			Postcode:
Telephone Number:	Home:	Work:	Mobile:
Date of Birth:			Sex: Male / Female
Ocular Diagnosis:			
Age at diagnosis OR Year of Diagnosis:			
Other eye disease:			
Other medical conditions or diagnoses			
Habitual Visual Acuity:	RE:		LE:
Do you wear:	Glasses ☐		Contact Lenses (CL) ☐ ?
How often do you wear your Glasses / CL ?	All of the time ☐	Most of the time ☐	Rarely ☐ For reading ☐

DEMOGRAPHIC QUESTIONNAIRE - please print or circle options

(This information will be used to compare participants' demographic characteristics with people in the Australian population using the National Health Survey (ABS) data.)

1.	In general, how would you **describe your overall health**? *(please circle):*	Excellent(1) / Very good(2) / Good(3) / Fair(4) / Poor(5)
2.	What is your **country of birth**? *(please circle):*	Australia(1) / Other(2) (specify):
3.	Are you of **Aboriginal or Torres Strait Islander** origin? *(please circle):*	No(1) / Aboriginal(2) / Torres Strait Islander(3) / Both(4)
4.	Do you speak a **language other than English**, at home? *(please circle):*	No, English only(1) Yes(2) (specify):
5.	What is the **highest year of school completed**? *(please circle):*	Year 12 or equivalent(1) / Year 11(2) / Year 10(3) / Year 9(4) / Year 8 or lower(5) / Never attended school(6) / Other(7) (specify):
6.	What is the **highest level of post-school education** you have achieved? *(please circle):*	Higher degree or postgraduate diploma(1) / Bachelor degree(2) / Undergraduate diploma or associate diploma(3) / Vocational qualification, i.e. TAFE or trade certificate(4) / No post-school qualification(5) / Other qualification(6) (specify):
7.	What is your **marital status**? *(please circle):* *(Note: '**Married'** indicates registered marriage only)*	Married(1) / De Facto(2) / Widowed(3) / Divorced(4) / Separated but not divorced(5) / Never married(6)

8.	What **type of accommodation** do you live in? *(please circle):* *(Note: **'Private accommodation'** includes house, unit, caravan, or boat. **'Non-private accommodation'** includes boarding house, disabled hostel, nursing home or aged care*)	Private accommodation(1) Non-private accommodation (2)
9.	What is your **gross weekly household income**? *(please circle):* *(Note: '**Gross weekly household income'** is the income of all people in the household, before tax is taken out. This includes pensions, superannuation and all other types of income)*	Less than $200, including no income and negative income(1) $200 to $399(2) $400 to $599(3) $600 to $799(4) $800 to $999(5) $1,000 to $1,499(6) $1,500 to $1,999(7) $2,000 to $2,499(8) $2,500 or more than(9) Don't know(10)

Thank you for completing this demographic questionnaire.
All information provided will remain confidential and will be used only for the purposes of this study.

OFFICE USE ONLY		
URN:	Focus group date:	Focus group Id:
GL Type:		

Optometry and Vision Science

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inspiring achievement

Have you been diagnosed with Hereditary Retinal degenerations/dystrophies?

Volunteers are needed to help us understand the impact of eye problems on quality of life. This will allow us to develop specific and accurate survey questionnaires for use in clinical and research settings.

We would appreciate if you would share your thoughts and opinions about how having been diagnosed with hereditary retinal degenerations/dystrophies has influenced and affected your life.

If you would like to participate, or require any further information regarding the study, please contact me:

Phone: Mallika Prem Senthil on 08 7221 8708 / 0450755338

Email: prem0013@flinders.edu.au

Office for Research

Flinders Medical Centre / The Flats F6/F8
Flinders Drive, Bedford Park SA 5042
Tel: (08) 8204 6453
E: Health.SALHNOfficeforResearch@sa.gov.au

Government of South Australia
SA Health
Southern Adelaide Local Health Network

Amendment to ethics application approved

You are reminded that this letter constitutes ethical approval only for this amendment. If you are waiting on Site Specific Assessment (SSA) authorisation for your study, you must not commence this research project at any public Health site until separate authorisation from the Chief Executive or delegate of that site has been obtained.

09 June 2016

Professor Konrad Pesudovs
Optometry and Vision Science
Flinders University
BEDFORD PARK SA 5042

Dear Professor Konrad Pesudovs

The Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188) have reviewed and provided ethical approval for this amendment which appears to meet the requirements of the *National Statement on Ethical Conduct in Human Research.*

Application Number: OFR # 469.11

Title: A system of measurement of vision-specific quality of life using item banking and computer adaptive testing (Eye-tem bank)

Chief Investigator: Professor Konrad Pesudovs

Approval date: 08 June 2016

This amendment approval does not alter the current SAC HREC approval period for the study: 20 January 2016 to 20 January 2017

The below documents have been reviewed and approved:

- Cover Letter
- Project Amendment Application form dated 23 May 2016
- General Research Application form vs10 dated April 2016
- Acquired Retinal Diseases Item Bank Questionnaire vs1 dated April 2016
- Hereditary Retinal Degenerations/Dystrophies Item Bank Questionnaire vs 1 dated April 2016
- Statement of Privacy and Security email dated 16 April 2016
- Hereditary Retinal Diseases – Specific Item Bank Questionnaire

TERMS AND CONDITIONS OF ETHICAL APPROVAL
As part of the Institution's responsibilities in monitoring research and complying with audit requirements, it is essential that researchers adhere to the conditions below and with the *National Statement chapter 5.5.*

Final ethical approval is granted subject to the researcher agreeing to meet the following terms and conditions:

1. The approval covers the ethics component of the application. Please submit a copy of the approved amendment to the local RGO for acknowledgement
2. If University personnel are involved in this project, the Principal Investigator should notify the University before commencing their research to ensure compliance with University requirements including any insurance and indemnification requirements.

3. Compliance with the *National Statement on Ethical Conduct in Human Research* (2007) & the *Australian Code for the Responsible Conduct of Research* (2007).
4. To immediately report to SAC HREC anything that may change the ethical or scientific integrity of the project.
5. Report Significant Adverse events (SAE's) as per SAE requirements available at our website.
6. Submit an annual report on each anniversary of the date of final approval and in the correct template from the SAC HREC website.
7. Confidentiality of research participants MUST be maintained at all times.
8. A copy of the signed consent form must be given to the participant unless the project is an audit.
9. Any reports or publications derived from the research should be submitted to the Committee at the completion of the project.
10. All requests for access to medical records at any SALHN site must be accompanied by this approval email.
11. To regularly review the SAC HREC website and comply with all submission requirements, as they change from time to time.
12. Once your research project has concluded, any new product/procedure/intervention cannot be conducted in the SALHN as standard practice without the approval of the SALHN New Medical Products and Standardisation Committee or the SALHN New Health Technology and Clinical Practice Innovation Committee (as applicable) Please refer to the relevant committee link on the SALHN intranet for further information.
13. Researchers are reminded that all advertisements/flyers need to be approved by the committee, and that no promotion of a study can commence until final ethics and executive approval has been obtained. In addition, all media contact should be coordinated through the FMC media unit.

Yours sincerely

pp **Paula Davies**
Manager, Office for Research

PARTICIPANT INFORMATION SHEET- PHASE II

Quality of life in herediatry retinal diseases

Development of a novel testing system to measure the impact of hereditary retinal diseases on quality of life

Name of organizations:
This is a collaborative study carried out between Flinders University as a lead orgnization and Queen Elizabeth Hospital, SA; Royal Adelaide Hospital, SA and Royal Victorian Eye and Ear Hospital, VIC)

This is a research project, and you do not have to be involved. If you do not wish to participate, your medical care will not be affected in any way.

You are invited to take part in a research study conducted by the Discipline of Optometry and Vision Science at Flinders University. This study aims to develop and refine banks of items (questions) that will be used for the assessment of quality of life in patients with hereditary retinal diseases. The item bank will assist eye doctors and researchers to gain a better understanding of the impact of eye problems on each patient and determine the appropriate course for treatment.

If you choose to participate, we will mail you a survey questionnaire in which you will be asked a set of questions about how your eye problem (hereditary retinal diseases) and its treatments are affecting you and your quality of life. After each question, there will be a list of possible answers (options) and please record the option that best describes your situation.

There are no direct benefits to you from being associated with this study. However, the information obtained from your interview will help us refine our item banks. Therefore, your input may help eye doctors and researchers in being better able to assess how these eye problems affect quality of life in future patients.

Your involvement in this study will not affect your treatment in any way. Your participation in the study is entirely voluntary and you have the right to withdraw at any time. If you decide not to participate in this study or if you withdraw, you may do this freely without prejudice to any treatment.

All records containing personal information will remain confidential and no information that could lead to your identification will be released. Records will be kept in a securely locked filing cabinet and in a password protected computer. Data will be deleted and destroyed 5 years after the study is completed.. We expect that once the study is completed, the results will be published in a scientific journal. However, all your answers will be de-identified and then collated so that your identity and any personal information will remain completely confidential.

Should you require further details about the project, either before, during or after the study, you may contact the researcher, Ms Mallika Prem Senthil, on telephone (08) 7221 8708 (Discipline of Optometry and Vision Science, Flinders University).

This study has been reviewed by the Southern Adelaide Clinical Human Research Ethics Committee. If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the executive officer on 8204 4507 or email research.ethics@health.sa.gov.au

SOUTHERN ADELAIDE HEALTH SERVICE / FLINDERS UNIVERSITY

CONSENT TO PARTICIPATION IN RESEARCH

I, ... request and give consent
(first name or given name) *(last name)*
to my involvement in the research project: **A system for measurement of vision-specific quality of life using item banking and computer adaptive testing (Eye-tem Bank) Phase II: Developing the Item bank**

I acknowledge the nature, purpose and contemplated effects of the research project, especially as far as they affect me, have been fully explained to my satisfaction by ..... and my consent is given voluntarily.

I acknowledge that the detail(s) of the following has/have been explained to me, including indications of risks; any discomfort involved; anticipation of length of time; and the frequency with which they will be performed:

I will be invloved in an interview which requires me to answer a set of questions about how my eye disease and its treatment are affecting me and my life (approx. 1hour duration)

I have understood and am satisfied with the explanations that I have been given.

I have been provided with a written information sheet.

I understand that my involvement in this research project may not be of any direct benefit to me and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the researchers in any respect.

I declare that I am over the age of 18 years.

I also cosent to have my clinical details (measurements of vision and diagnosis) exracted from my clinical file for this research *(please tick)* Yes ☐ No ☐

I acknowledge that I have been informed that should I receive an injury as a result of taking part in this study, I may need to start legal action to determine whether I should be paid.

Signature of Research Participant : ..... Date: .....

I, ... have described to .....
the research project and nature and effects of procedure(s) involved. In my opinion he/she understands the explanation and has freely given his/her consent.

Signature: ..... Date: .....

Status in Project: .....

COUNSELLING SERVICES INFORMATION SHEET

Dear participant,

Sometimes talking or answering questions about issues such as your health can evoke negative and unexpected feelings. If this occurs, it may be useful to talk to someone not connected with the research. A number of counselling services are available. Below are a list of numbers and organisations that you could contact in this situation.

Crisis Care Unit – Ph: 13 16 11 (Adelaide), 136 169 (Melbourne)

Provides counselling and practical help for individuals and families in any type of crisis. Available 4:00pm – 9:00am Monday to Friday and 24 hours on Saturday, Sunday and public holidays.

Lifeline - Ph: 13 11 14 (Adelaide & Melbourne)

Provides counselling for people with any type of crisis.

Living Hope – Ph: 8277 4033 (Adelaide)

Provides counselling for people with any type of crisis.

Social Work and Counselling Services

There are Social Work & Counselling Services available to patients and their families who are currently receiving treatment at Flinders Medical Centre, The Queen Elizabeth Hospital, the Royal Adelaide Hospital and the Royal Victorian Eye and Ear Hospital . Referral from medical (i.e. your Ophthalmologist), nursing or allied health staff is required.

General Practitioner

Your general practitioner can refer you to local community health centres.

Optometry and Vision Science

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Have you been diagnosed with Retinitis Pigmentosa?

Flinders University is conducting a study to explore the influence of retinitis pigmentosa on patient's overall **quality of life.** Therefore, volunteers are needed to **answer** a set of **simple questions** that ask about how your eye disease and its treatments are affecting you and your life.

What will be involved?

This study involves answering an **online survey** about how your eye disease and its treatment are affecting you and your life.

To participate or for further information please contact:

Mallika Prem Senthil
Optometry and Vision Science
Flinders University, Bedford Park, Adelaide, South Australia 5042
Ph: +61 8 7221 8708
prem0013@flinders.edu.au

Appendix 11: Travel grants and Awards

Mallika Prem Senthil

From: Lee-Ann Thomas
Sent: Friday, 21 April 2017 12:08 PM
To: Mallika Prem Senthil
Cc: Health Research; Konrad Pesudovs; Kay Govin
Subject: Mallika Prem Senthil - Outcome Notification - 2017 FMNHS RHD Student Publication Award Application

Dear Mallika,

On behalf of the Faculty of Medicine, Nursing and Health Sciences Research Committee I would like to congratulate you on your publication, titled:

Seeing through their eyes: lived experiences of people with retinitis pigmentosa.
M Prem Senthil, J Khadka and K Pesudovs.
Eye (2017), 1–8
DOI: 10.1038/eye.2016.315

The committee would like to award you with $500.00.

This amount will be credited to your bank account via Electronic Funds Transfer (EFT). Please allow a week or two for this payment to progress through the University's finance system.

We wish you all the best in completing your Higher Degree.

Kind Regards,
Lee-Ann

Mrs Lee-Ann Thomas
Research Administration and Finance Officer
Faculty of Medicine, Nursing and Health Sciences
Room 5.13, Health Sciences Building
Flinders University
GPO Box 2100, Adelaide SA 5001
P: + 61 8 8201 5892 | E: leeann.thomas@flinders.edu.au | W: http://www.flinders.edu.au

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From:	Mallika Prem Senthil
To:	Dr Prem Shanmugam
Subject:	FW: ARVO-Asia Travel Grant Notification
Date:	Thursday, 1 December 2016 10:38:37 AM

From: arvoasia@thinkbusinessevents.com.au [mailto:arvoasia@thinkbusinessevents.com.au]
Sent: Thursday, 1 December 2016 10:06 AM
To: prem0013@flinders.edu.au
Subject: ARVO-Asia Travel Grant Notification

Wednesday, 30-Nov-2016

Dear Dr. Mallika Prem Senthil,

Congratulations! Your application for a travel grant for the ARVO-Asia 2017 Conference was successful.

You will receive a full complementary registration. A registration confirmation receipt will be sent to you prior to the meeting.

Registration will be held at Brisbane Convention and Exhibition Centre. Please make sure to come to the registration desk to collect your name badge and other materials.

It is your responsibility to arrange your travel requirements.

If you have any questions please do not hesitate to contact
arvoasia@thinkbusinessevents.com.au

We look forward to seeing you in Brisbane, Australia in 2017.

Kind regards,
ARVO-Asia Program Committee

Mallika Prem Senthil

From: Health Research
Sent: Tuesday, 31 January 2017 2:38 PM
To: Mallika Prem Senthil
Cc: Konrad Pesudovs; Health Research; Kay Govin; Lee-Ann Thomas
Subject: Mallika Prem Senthil - Outcome Notification - 2016 RHD Student Publication Award Application

Dear Mallika,

On behalf of the Faculty of Medicine, Nursing and Health Sciences Research Committee I would like to congratulate you on your publication, titled:

Assessment of Patient-reported Outcomes in Retinal Diseases: A Systematic Review
Mallika Prem Senthil, Jyoti Khadka, Konrad Pesudovs
Survey of Ophthalmology
http://dx.doi.org/10.1016/j.survophthal.2016.12.011

The committee would like to award you with $500.00.

Would you please provide us with your banking details so we may arrange payment via Electronic Funds Transfer (EFT) directly into your bank account:

Name of Bank:
Account Name:
BSB:
Account #:

We wish you all the best in completing your Higher Degree.

With kind regards,
Elodie

Elodie Janvier MSc Eng(Res), MSc(Res), MSQM(Res)
Research Administration Manager
Faculty of Medicine, Nursing and Health Sciences

Phone +61 8 8201 **5624**
Flinders University| GPO Box 2100 | Adelaide | SA |5001
Health Sciences Building, Bedford Park - Room 5.15

Email: elodie.janvier@flinders.edu.au |Web: www.linkedin.com/pub/elodie-janvier/5b/7b/268

Student Finance Services

Student Administration
Flinders University
GPO Box 2100
Adelaide SA 5001
Telephone +61 8 82015511
scholarships@flinders.edu.au
www.flinders.edu.au/scholarships

Student ID: 2129143

6 May 2016

Dr Mallika Prem Senthil
Unit 1 8 Farne Tce
MARION SA 5043

Dear Dr Prem Senthil,

I am pleased to offer you my congratulations on securing the following scholarship:

SCHOLARSHIP:	**Research Student Conference Travel Grant**
Benefit(s):	Research Student Travel Conference Grant - $452
Special Conditions:	To assist with the cost of travel to the USA for the American Academy of Optometry Anaheim 2016. A brief report is required on your return as outlined in the rules.

To accept this offer, please log into the Flinders Student Information System and select;

- 'My Scholarships' tab; and
- Click on 'Scholarship Offer Summary'; and
- Click on 'ACCEPT'; and
- Enter 'Accepted Offer' from the drop down menu and click on 'Save'; and
- Click on 'Update Bank Details' to confirm or enter your bank details and click on 'Save'
- The status on the Scholarship Offer Summary page, will then show a status of 'Pending Bestowal'.

Your scholarship payments will be issued as per the individual scholarship rules at http://www.flinders.edu.au/scholarships-system/index.cfm/scholarships/search, and once any special conditions have been fulfilled; refer to any conditions specified above.

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Student Finance Services

Student Administration and Systems
Student Centre
Flinders University
GPO Box 2100
Adelaide SA 5001
Telephone +61 8 82013143
scholarships@flinders.edu.au
www.flinders.edu.au/scholarships

Student ID: 2129143

29 October 2013

Dr Mallika Premsenthil
"Unit 1, Block I, KTS Village, 222 Jalan Permata"
Kuching Sarawak 93200
MALAYSIA

Dear Dr Premsenthil,

I am pleased to offer you the following scholarship:

SCHOLARSHIP:	**International Postgraduate Research Scholarship**
Available from:	1 January 2014
Lastest start date:	31 March 2014
Course:	PHD/HSM Doctor of Philosophy
Tenure:	Expected tenure 3 EFTSL (up to a maximum of 4 EFTSL) Please note that if you have previously undertaken a research higher degree at the same level, or are already enrolled in the course to which this scholarship is linked, you may not be entitled to receive the scholarship for the maximum tenure period.
Benefit(s):	Tuition Fee Sponsorship - Amount as applicable Overseas Student Health Care Sponsorship - Amount as applicable
Special Conditions:	Your offer is conditional upon being admitted into the Phd/HSM
IP and/or Confidentiality Agreement:	Not required.
Research Contract:	Not required.
Relocation/Thesis Allowance	If you are entitled to a Relocation and/or Thesis Allowance this will be detailed in your conditions of award.

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Student ID: 2129143

29 October 2013

Dr Mallika Premsenthil
"Unit 1, Block I, KTS Village, 222 Jalan Permata"
Kuching Sarawak 93200
MALAYSIA

Dear Dr Premsenthil,

I am pleased to offer you the following scholarship:

SCHOLARSHIP:	**Australian Postgraduate Award**
Available from:	1 January 2014
Lastest start date:	31 March 2014
Course:	PHD/HSM Doctor of Philosophy
Tenure:	Expected tenure 3 EFTSL (up to a maximum of 4 EFTSL) Please note that if you have previously undertaken a research higher degree at the same level, or are already enrolled in the course to which this scholarship is linked, you may not be entitled to receive the scholarship for the maximum tenure period.
Benefit(s):	Australian Postgraduate Award (Full-time) rate - $25 392 per annum
Special Conditions:	Offer is conditional upon admittance to Phd.
IP and/or Confidentiality Agreement:	Not required.
Research Contract:	Not required.
Relocation/Thesis Allowance	If you are entitled to a Relocation and/or Thesis Allowance this will be detailed in your conditions of award.