Assessing health technology assessment (HTA) methodology and value frameworks to evaluate the cost-effectiveness of gene therapies (GTs) for rare diseases (RDs)

by Maria Farris

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Under the supervision of Professor Stephen Goodall and Professor Richard De Abreu Lourenco

Centre for Health Economics Research and Evaluation
Faculty of Health
University of Technology Sydney

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Certificate of Original Authorship

I, Maria Farris, declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Faculty of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

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Thesis format

This thesis is structured as a compilation of chapters and published/submitted manuscripts. The thesis begins with an introductory chapter to provide an overview of the research area and aims, followed by four original research chapters, each addressing one of four separate key objectives. The thesis ends with a final chapter discussing the central policy implications, main conclusions, limitations, and areas for further work. Where acronyms are used, they are applied throughout the whole thesis, and not reintroduced in each chapter.

Dissemination

The research presented in Chapter 2 is published*: **Farris M**, Goodall S, De Abreu Lourenco R. A systematic review of economic evaluations for RPE65-mediated inherited retinal disease including HTA assessment of broader value. Int J Technol Assess Health Care. 2023 Jun 14;39(1):e38. doi: 10.1017/S0266462323000326. PMID: 37313789; PMCID: PMC11570094.*

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Abbreviations list

AAV2	Adeno-associated virus serotype 2
ABS	Australian Bureau of Statistics
AIC	Akaike information criterion
AMA	American Medical Association
AMD	Age-related macular degeneration
AQoL-8D	Assessment of Quality of Life 8-Dimension
AUD	Australian dollars
BI	Budgetary impact
BIC	Bayesian information criterion
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDA-AMC	Canada's Drug Agency
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CI	Confidence interval
CUA	Cost utility analysis
DCE	Discrete choice experiments
DCEA	Distributional cost effectiveness analysis
DR	Diabetic retinopathy
EE	Economic evaluation
EQ5D	EuroQol-5D
EQVT	EuroQol Valuation Technology
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
FH	Full health
FST	Full-field light sensitivity
GDP	Gross domestic product
GP	General practitioners
GT	Gene therapy
GTs	Gene therapies
HEMA	Health Economics Methods Advisory
HILDA	Household, Income and Labour Dynamics in Australia
HRQoL	Health-related quality of life

HS	Health state
HST	Highly Specialised Technology
HSU	Health state utilities
HUI3	Health Utilities Index Mark 3
HTA	health technology assessment
ICER	Incremental cost-effectiveness ratio
I.C.E.R.	Institute for Clinical and Economic Review
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IDP	Industry Doctorate Program
IRD	Inherited Retinal Disease
LCA	Leber congenital amaurosis
LT-TTO	Lead-time TTO
LVAD	Left ventricular assist device
MAUI	Multi-attribute utility instruments
MCDA	Multi criteria decision analysis
MEA	Managed entry agreement
MLMT	Multiluminance mobility test
MSAC	Medical Services Advisory Committee
NCPE	National Centre for Pharmacoeconomics
ND	Not determined
NDIS	National Disability Insurance Scheme
NHS	National health service
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
OLS	Ordinary least squares
PBAC	Pharmaceutical Benefits Advisory Committee
PBM	Preference-based measures
PSD	Public Summary Document
QALY	Quality-adjusted life years
QC	Quality control
Qol	Quality of life
RCT	Randomised controlled trials
RD	Rare diseases
RP	Retinitis pigmentosa
RPE65 r	Retinal pigment epithelium 65 kDa protein
RR	Relative risk

RSA	Risk share arrangement
SD	Standard deviation
SG	Standard gamble
SMC	Scottish Medicines Consortium
TTO	Time Trade-Off
U.S. FDA	United States Food and Drug Administration
VA	Visual acuity
VAS	Visual analogue scale
VC	Videoconferencing
VF	Visual field
VN	Voretigene neparvovec
WTD	Worse-than-death
WTP	Willingness to pay
ZIN	Zorginstituut Nederland- National healthcare Institute, Netherlands

Abstract

Therapies for rare diseases (RDs) now represent over 35% of newly approved drugs, with a growing shift towards precision medicines like gene therapies (GT)(1-3). Regulatory bodies expedite GT approval based on early-phase clinical trials, given their significant potential benefits for patients with degenerative conditions lacking other treatments(4). Countries employing health technology assessment (HTA) for healthcare funding decisions struggle with GT for RD evaluation due to the poor quality of clinical evidence, leading to increased uncertainty in decision-making(5-7). Further, experts in health economics suggest that HTA should consider and value GT on broader value elements that has impact beyond patients and the healthcare system(8, 9).

Voretigene neparvovec (VN) is a GT for a RD, retinal pigment epithelium 65 kDa protein (RPE65) mutation-associated inherited retinal disease (IRD)(10-12). It offers possible societal benefits beyond the patient and the healthcare system. Using VN as a case study the research objectives were to 1) identify the challenges in the modelled economic evaluations (EEs) of VN and investigate whether broader elements of value were considered by reimbursement decision makers, 2) estimate the health-related quality of life (HRQoL) impact from vision impairment due to RPE65-mediated IRD, 3) detail the lifetime impact on caregivers of individuals with IRD and 4) explore the perspectives of Australian stakeholders regarding the consideration of broader elements of value in HTA in Australia.

This research comprehensively evaluates HTA appraisals, highlighting challenges in evaluating EE's and the importance of harmonising HTA guidelines globally to incorporate broader elements of value beyond mere cost-effectiveness. Combined, the research findings provide novel information for example the impact of IRD on patient HRQoL and caregiver burden. The research also concludes that reviewing the HTA decision-making criteria in Australia is necessary, as stakeholders support incorporating additional broad value elements into the HTA of all medicines (both rare and not rare) that extends beyond those outlined in current HTA guidelines.

The research emphasises the importance of accounting for the broader societal and caregiver impacts, which are often overlooked, to accurately assess the value of GTs. Addressing these challenges through informed public policy and refined HTA guidelines will be crucial for substantiating the value of GT, expediting access to these innovative treatments, and extending these evaluation principles to non-GT and beyond RDs.

Chapter 1 Introduction

i Overview

Gene therapy (GT) is an innovative approach that involves the introduction of therapeutic genetic material into a patient's cells to treat or prevent diseases(1, 13). GT offers a promising alternative for treating a wide range of currently incurable diseases by enabling long-lasting production of therapeutic proteins and addressing the root cause of the problem. At its core, this process requires the precise identification of malfunctioning genes, followed by cloning and loading a healthy version of these genes onto a vector, often a repurposed virus, which is used to transport and express the corrective gene in the target cells or tissues(14). There is potential in treating diseases caused by a single gene malfunction, including cardiovascular diseases, immunodeficiencies, cancer, and other conditions that drugs or antibodies cannot address effectively(1). GT is sometimes referred to as a highly specialised therapy (HST).

To date, registration of gene therapies (GTs) has been based on early phase, single arm clinical trials, where it has been unfeasible to conduct randomised controlled trials (RCTs) due to small patient numbers and the ethical dilemma of allocating patients to a control arm where, in the absence of an effective treatment, the disease leads to permanent disability and or premature mortality(8, 15). Faster regulatory approval timelines have been applied to GTs via priority pathways where regulators consider the potential benefit demonstrated in early phase trials supports expedited approval, outweighing the risk of waiting for additional data from larger and longer term trials (4). However, governments face even greater challenges when it comes to assessing the value for money in deciding to fund GTs as compared with registration, given the evidence is limited and the upfront costs per patient are very high (7, 9, 16). Using an economic evaluation (EE) to establish the cost-effective price for a potentially curative, one-time treatment, is associated with a high level of uncertainty, especially where the lifetime incremental benefit is derived from immature data (17, 18). Use of surrogate outcomes, lack of comparative evidence, small sample sizes and the need for long-term extrapolation of outcomes are some of the major hurdles identified by HTA agencies in assessing the value associated with existing GTs(9). As such some HTA agencies have

adapted their HTA assessment process to accommodate both the nature of innovative therapies such as GT and the limitations of the evidence that is able to be generated in rare diseases (RDs)(6). In addition, some researchers have proposed that HTA assessment of GT should extend beyond the traditional measure of health benefit within an EE which is the patient quality-adjusted life years (QALYs)(9). They suggest including broader elements of value such as the severity of the disease, caregiver burden, insurance value, scientific spillovers, and real option value to provide a more comprehensive assessment of GTs value. Researchers must investigate the extent to which broader value elements are considered by EEs and HTA decision-makers beyond traditional health metrics when assessing the value of GTs to inform future research.

ii Background

Rare diseases

Rare diseases (RDs) exhibit lower incidence and prevalence rates compared to other acute or chronic diseases. Globally, there is no universally recognised definition or consensus on the prevalence threshold for RDs. The European Union (EU) define RDs as serious, life-threatening, or chronically debilitating diseases that affect fewer than 50/100,000 individuals(19). The United States define a disease as rare when it affects fewer than 200,000 individuals (equivalent to a prevalence rate of 62/100,000 individuals), in Japan when it affects fewer than 50,000 individuals (equivalent to 39/100,000 individuals), and in Australia when it affects fewer than 2,000 individuals (equivalent to 9/100,000 individuals) (20-23). When considered individually, these diseases affect few people, however it is estimated that there are between 5,000 and 8,000 different RDs(2).

RDs include rare cancers of the blood, autoimmune diseases, genetic conditions, or toxic and infectious diseases(2). Experts on RDs generally agree that the majority of RDs, possibly 80% are genetic in origin, and the onset of the disease occurs in childhood for 50%-75% of RDs (24, 25). Rare genetic diseases demonstrate significant variability in terms of the age of patients at first clinical presentation, symptoms, morbidity, and life expectancy (26). While the disease are heterogenous they commonly share characteristics of chronicity and severity, frequently manifesting

as degenerative conditions and occasionally proving fatal(26). In addition, due to their low prevalence, the correct diagnosis is complex and subject to significant delay, and for most there is no effective treatment available (11, 27). There is limited evidence for the natural history of RDs, the cost burden of disease and differing clinical practices across countries(7, 28). These diseases are burdensome on both patients and their relatives and consequently impacting health related quality of life (HRQoL) (27). Patients with these diseases require management and multidisciplinary follow-up, including support for families (11, 29, 30).

From the economic point of view, there is evidence of the high impact on patients and relatives because of the inability to work or pursue a career of choice among the patients with an RD that presents early in life impacting the young and working, such as hereditary retinal diseases (30). In such diseases not being able to find employment has been reported to cause fear and anxiety, and a lack of mobility and inability to drive restricts job opportunities(30).

Gene therapy

The advent of gene therapies (GTs) has revolutionised the treatment of some very rare genetic diseases(1). Gene therapy (GT) is an innovative approach that involves the introduction of therapeutic genetic material into a patient's cells to treat or prevent diseases(31). At its core, this process requires the precise identification of malfunctioning genes, followed by cloning and loading a healthy version of these genes onto a vector, often a repurposed virus, which is used to transport and express the corrective gene in the target cells or tissues. The number of GTs in clinical trials almost doubled from 2007 to 2017, with many new GTs on the horizon(32).

GTs are biological entities that aim to achieve durable expression of a therapeutic gene to ameliorate disease symptoms caused by a mutation or deletion in the genome (31). Traditional therapies for chronic conditions require regular ongoing treatment, whereas GTs offer the possibility of lifelong benefits from a single administered dose. These one-time treatment options offer the

possibility of significantly changing clinical care from only being able to manage the symptoms from the chronic disease to targetting the underlying causes of diseases (1).

The substantial research and development costs combined with the limited market due to the small patient population, often leads to high prices for numerous therapies targeting RDs (20). GTs are no exception with prices likely further inflated to cover the long-term value offered by only requiring a single dose.

The benefits from these potentially curative new therapies, particularly where there are no alternative forms of therapy could be life changing for patients, and their families. The high unmet need in rare genetic diseases is one of the key reasons for public policy that has led to accelerated approval procedures by regulatory agencies to enable access for patients to such medicines(4). However, regulatory approval is only the first hurdle for access to such therapies, funding for GT by government or insurance payers is necessary for patients to gain access at an affordable price given the high cost of GT.

HTA to guide healthcare funding

The funding of healthcare is complex and involves the allocation of a finite resource (budget) to competing interventions such as pharmaceuticals, medical devices, public health programs and services. The national budget available for expenditure on healthcare takes up a significant proportion (9.9% of gross domestic product (GDP) in Australia) of overall government expenditure(33). In 2022, Australia ranked 15th amongst Organisation for Economic Co-operation and Development (OECD) in terms of expenditure on health as a proportion of GDP, indicating significant healthcare expenditure among OECD countries(33). As in most developed countries the demand for healthcare continues to increase and is accompanied by an increase in health spending which is largely attributed to advances in technology, an ageing population and consumers' awareness of and demand for new technologies, such as GTs. The continual increase in costs and

demands for new health technologies necessitates the prioritisation of spending on health interventions.

The funding and provision of health care in Australia and many other countries, relies greatly on government involvement. This dependency arises mainly from market failures, including the unpredictability of health, externalities and asymmetric information between health care professionals and society (34). Consequently, funding decisions for new interventions typically consider value for money or cost-effectiveness of the new intervention relative to current practice. Economic evaluation (EE) serves as a systematic approach, grounded in welfare economics, to identify the most cost effective intervention and offer recommendations regarding preferable outcomes (35). Cost-effectiveness and cost–utility analyses are two types of EE that both measure outcomes in health-related terms. Cost-effectiveness analysis (CEA) expresses value in terms of natural units, which are generally disease specific, for example the number of cancer cases detected, or life years gained. Cost–utility analysis (CUA) expresses value in terms of the quality-adjusted life years (QALY) which combines information on mortality and morbidity via HRQoL (or utility) and facilitates comparisons between healthcare interventions in different disease areas (17). Despite the label ‘quality of life’, to date QALY’s have narrowly focused on health status(36).

The quality aspect of the QALY is typically assessed using preference-based measures (PBM), which are developed through research on health measurement and quality of life (QoL)(17). PBMs consist of two components: the measurement element, which involves a description of a health state (HS, completed by patients), and the valuation element, which assigns scores (known as health state utilities, HSU’s) to these HSs based on population preferences. HSUs represent individual preferences for a given HS measured on a scale from zero (‘death’) to one (‘full health’), which, if combined with time spent in that state, generate QALYs that are then incorporated into CUA (37).

Health technology assessment (HTA) decision-making agencies assess the effectiveness, safety, value for money and budgetary impact of new health technologies. Specifically, the EE of health technologies is a widely recognised tool to inform decision-making in healthcare as part of HTA (38). It involves comparing the costs and outcomes of various interventions, providing decision makers with information about the relative value of different health technologies to determine their value for money (17). HTA systematically examines the comparative evidence of safety, clinical efficacy, cost-effectiveness via the incremental cost-effectiveness ratio (ICER), and budgetary impact to inform resource allocation decisions (39, 40).

An HTA process allow countries to assess the impact of new technologies in a manner that is specific to their jurisdiction. As a result, the evidence gathered is typically appropriate and pertinent to the population affected by the funding decision. Therefore, the findings of HTA analyses for a particular intervention in one jurisdiction are generally not transferable to others due to variations in healthcare systems and resource utilisation implications. During the HTA process, data utilised to evaluate an intervention for a disease include primary data, such as that from RCTs along with secondary data sources, such as health care costs associated with the disease. In addition, the adoption and application of HTA methodologies can vary significantly between sole-payer and multi-payer healthcare systems. For example, Australia, the United Kingdom, and Canada, operate under sole-payer systems and have integrated HTA into their decision-making processes (17). In countries such as the United States that have many payers in the form of insurance companies, the role of HTA is much more heterogenous.

The flow of funds for medical care within the Australian healthcare system is complex and includes multiple layers of public funding(41). The Australian Federal Government provides funds to the state and territory governments who, in turn, allocate these funds to health service providers such as public hospitals(41). The Australian Federal Government also funds the Pharmaceutical Benefits Scheme (PBS) for medicine reimbursement, and the Medicare Benefits Schedule (MBS) for new medical services(41). Funding for high cost, highly specialised therapies that are delivered in a

public hospital setting is a shared funding model between state and territory governments and Australian Federal Government managed under the National Health Reform Agreement (NHRA) (42).

The process for listing medicines on the PBS requires an independent HTA agency, the Pharmaceutical Benefits Advisory Committee (PBAC), consider clinical effectiveness, safety and cost-effectiveness relative to existing therapies using internationally recognised HTA methods. The Medical Services Advisory Committee (MSAC) is a HTA committee that provides advice to Government on whether a new medical service should be publicly funded on the MBS or under the NHRA. Both the PBAC and MSAC have flexibility in their decision-making and consider the ICER implicitly as part of a qualitative deliberation to arrive at a reimbursement decision. In contrast, some countries use an explicit ICER or willingness to pay (WTP) threshold in decision-making, although, in some cases the medicines may still be reimbursed even if the ICER is above the recommended threshold(43). Overall, HTA aims to optimise health outcomes given the available resources, while also evaluating broader implications such as the financial impact on the healthcare system, social and legal repercussions, and ethical considerations associated with the health technologies.

GTs are often associated with a higher price than conventional medicines, for example Zolgensma ® had a price in excess of US$2 million as the first GT for spinal muscular atrophy (SMA)(7). The high cost of GTs makes the assessment of value for money critical to payers but establishing the value of GTs for the treatment of RD is challenging(44-46). The clinical evidence for RDs is inherently based on small studies with poorly defined alternatives (e.g., the standard of care) against which the new treatment is compared (9, 47). There is also a reliance on short-term data, and, given the high unmet need, a desire for accelerated reimbursement.

Broader elements of value

Within the context of HTA, maximising health outcomes traditionally relies on producing the greatest number of patients QALYs for the given available resources (38, 45). Employing the QALY measure to evaluate the capacity of a health technology to increase the length of survival and HRQoL is a well-established 'standard' methodology for HTA assessments and practically it can be a very useful comparative measure for decision-making (48). However, some in the field of health economics propose that it does not fully capture "*additional elements of value*" a therapy may offer, both to individuals and to society(8). An ISPOR special taskforce report in 2018 identified and defined a series of additional elements of value in the "Value flower" presented in **Figure 1** below, for consideration in value assessments of medical technologies(45).

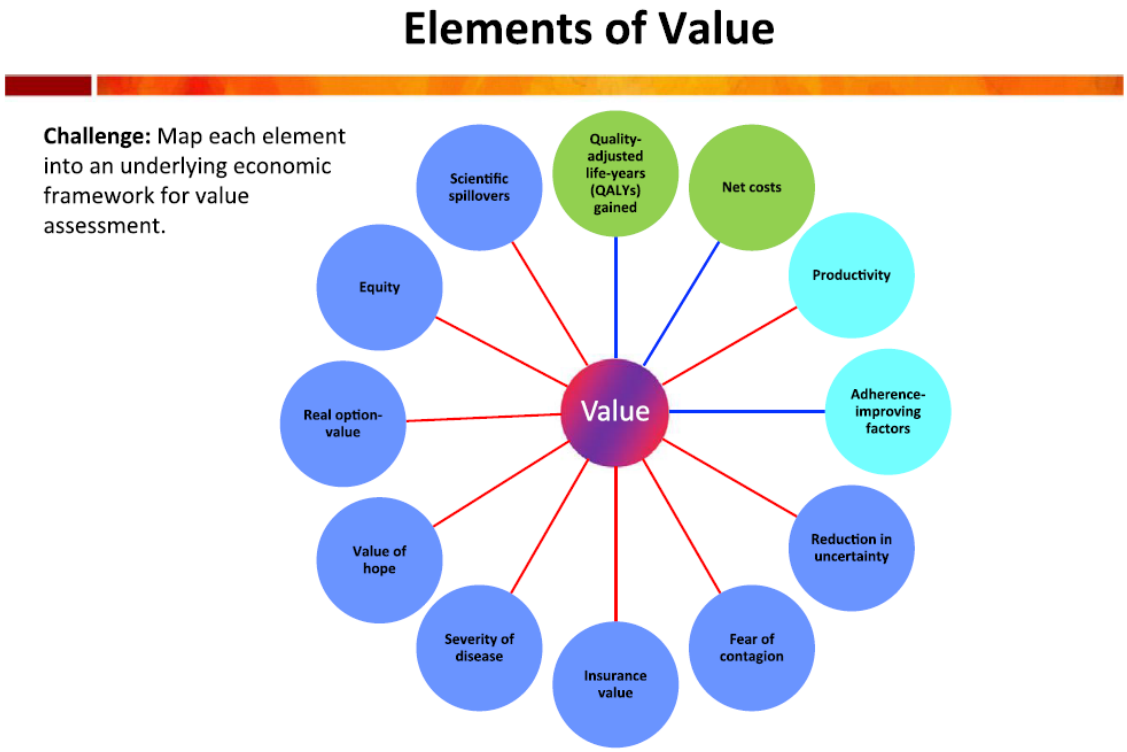


Figure 1 *Elements of value.*

Note. Green circles: core elements of value, blue circles : common but inconsistently used elements of value; dark blue circles: potential novel elements of value; blue line: value element included in traditional payer or health plan perspective; and red line: value element also included in societal perspective
Source(45)

Some researchers argue that the QALY (green circle at the top of the flower in **Figure 1**), the traditional and commonly used measure of health benefit within a CUA, captures only a subset of benefits that may be produced by a healthcare intervention. Furthermore, the QALY might not capture people's preferences to mitigate risk and uncertainty. For instance, individuals might favour a healthcare intervention with more consistent benefits, even if it does not enhance clinical outcomes on average, a preference that QALYs would not reflect (49). The green circles in **Figure 1** represent traditional and common elements of value, light blue traditional but less common and dark blue more novel elements of value.

A description of some of the more novel elements proposed are:

- “Real option value” - the value attributed to extending life and creating opportunities for the patient to benefit from other future advances in therapy,
- “Fear of contagion” - the reduction in fear associated with a treatment that stops the spread of a disease,
- “Scientific spillover” - the broad societal benefit from knowledge created from an innovative therapy and the public good used for the discovery of other agents,
- “Severity” -therapies that improve the health of individuals in severe states may be considered of higher value,
- “Insurance value”-benefit from knowing you are protected (physically having treatment) and financially.
- "Value of hope/caregiver value” - the value to caregivers (often valuing this informal care is referred to as family and caregiver health spillover(50)) in reducing the burden (emotional stress and time) in caring for patients with a severe disease receiving treatment.

Broader elements of value discussed in this thesis are those beyond the QALY, they are either traditional but less commonly applied in HTA such as productivity or novel such as real option value. These broader elements of value are sometimes referred to by other names in the literature

such as indirect non-health costs and benefits, additional elements of value or referred to as elements of value that have broader implications beyond the patients and the healthcare system.

GTs have the potential to deliver benefits that range from “potentially curative” treatments of rare, disabling, and/or life-threatening conditions often targeting young children to more moderate benefits for less severe conditions(31). None of these characteristics is exclusive to the RDs treated by GT; there are several therapies that treat severe, disabling, or life-threatening conditions. It is the combination of factors, high upfront costs associated with GT, the potential for a one-time cure, and the limited evidence available for restricted patient populations affected by RDs that leads to specific methodological challenges in valuing a GT (9).

Experts in the field thus suggest that HTA should consider and value GT on elements that go beyond the patient QALY, for example severity of disease (i.e., whether a GT that improves the health of individuals in severe states is given a higher value), insurance value, scientific spillovers, and real option value (9, 51). The experts emphasise that it is not feasible to capture all of the broader elements of value within an EE currently and although there is some research on how to capture broader elements of value in an EE, further research is needed to quantify how those broader elements of value might be incorporated into the QALY (51-54). Nevertheless, these broader elements of value could be considered qualitatively within the HTA that examines more than the clinical and cost-effectiveness of a health technology (51).

There is evidence to suggest that GTs are considered of greater value to society than non-GTs because of the rarity and severity of diseases they treat (32, 55, 56). Traditional medicines tend to be given on an ongoing basis to manage a chronic disease because the clinical benefit does not perpetuate without continuous dosing, GTs are typically administered in a single dose with potential lifelong benefits. GTs are administered as a single dose at a substantial cost which, coupled with their potential for long-term benefits, might be partially counterbalanced by long-term savings resulting from enhanced disease management that diminishes or replaces traditional therapies.

However, there is limited evidence to substantiate these assumptions for a GTs within an EE, thus adding to the 'uncertainty' in the estimated cost-effectiveness. Moreover, EE assessment of GTs faces a number of other challenges. Other limitations related to GT for RDs that contributes to a lack of confidence in the EE assessments include (1) the immaturity of evidence which makes reliable extrapolation of the long term benefit challenging, (2) the lack of definition of cure; (3) the absence of randomised controlled trials (RCTs); (4) a lack of or limitations of traditional HRQoL measures RDs ; (4) uncertain long-term value; and, (5) appropriate perspectives (healthcare or societal) of evaluation. The combination of these multiple uncertainties makes decision-making in HTA challenging which has raised the question of whether the existing HTA value assessment frameworks are appropriate or adequate for GT(7, 57). Consequently, some HTA agencies have developed supplementary processes for evaluating treatments for RDs, some of which are GTs(47). These supplemental processes differ from country to country and may encompass a range of features, including altered requirements for clinical and/or economic evidence, increased leniency regarding evidence quality, enhanced involvement of patient and clinical expert insights specific to the disease, additional considerations of value (including novel elements of value), acceptance of an ICER that is higher than standard WTP thresholds, or conditional reimbursement approval mechanisms such as a managed entry agreement (MEA) between government and the pharmaceutical industry that allows provisional earlier market access but requires CEA review once additional outcome data are available(6, 47).

It is within this context that this thesis focused on the HTA assessment of a recent GT for a RD for which EE have been conducted with a particular focus on whether broader consideration of other sources of value were considered by decision makers.

iii Case study

RPE65 mutation-associated retinal dystrophy is an RD, which is one of many different types of inherited retinal diseases (IRDs) (11). IRDs exhibit clinical heterogeneity and significant variation in

pathogenesis, progression, and patterns of genetic inheritance. They can arise from mutations in over 250 distinct genes (58).

Visual perception arises from the biological conversion of light energy into electrical signals by the retinal photoreceptors in the eye, specifically rods and cones(59-61). Although the chemical process supporting phototransduction is similar in both rods and cones, rods are responsible for vision in low-light conditions, whereas cones facilitate vision in bright-light conditions, colour vision, and spatial acuity. The loss of rod photoreceptor function is the primary cause of vision loss associated with biallelic mutations in the RPE65 gene, initially manifesting as a decreased ability to see in dim lighting (61). As the disease progresses, cone photoreceptors, which are crucial for functioning in bright light, typically undergo secondary degeneration.

This retinoid (visual) cycle is completed by regeneration of 11-cis-retinal, the vitamin A derivative that contributes to the visual pigment rhodopsin, via a two-step process that is catalysed in part by all-trans-retinyl isomerase (also known as the RPE65)(**Figure 2**)(11, 62). Proper functioning of this complete cycle is essential to maintain vision.

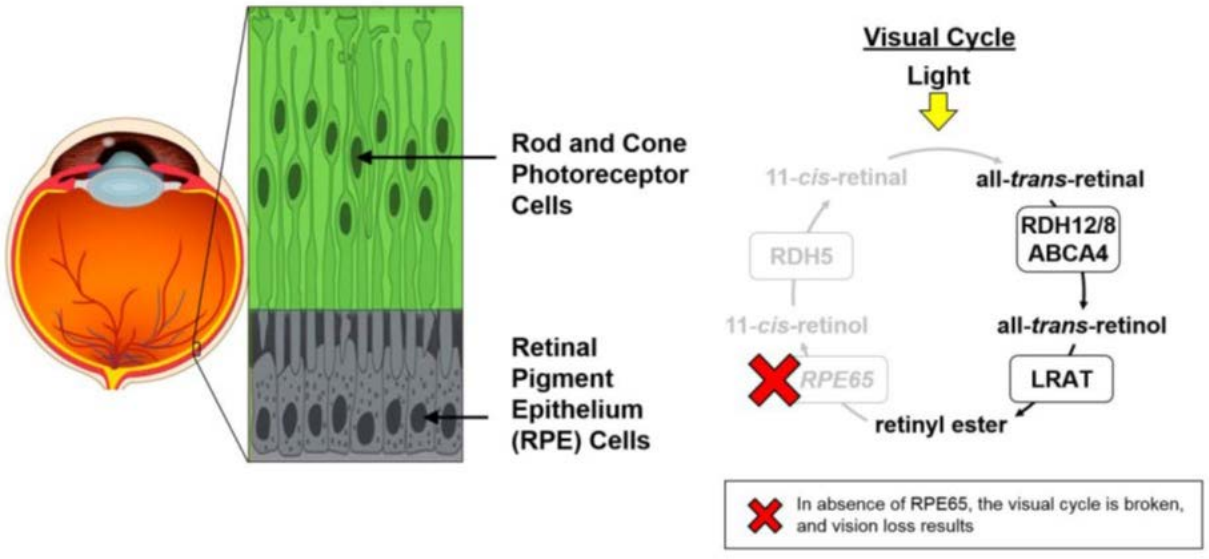


Figure 2 *The role of RPE65 in the visual cycle*
Source:(63)

For patients with RPE65 mutation-associated IRD, there are a variety of clinical diagnoses due to variable expressivity (different clinical manifestations despite the same mutation), incomplete penetrance (some individuals with the mutation don't show the same symptoms), and the influence of other genes and environmental factors. The common clinical diagnoses for RPE65 mutation-associated IRD include Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP)(11). Such patients suffer from severe and progressive retinal and visual deterioration. It can present from early childhood and progresses inexorably to complete blindness, usually by the time patients are 15 years of age (11).

Vision deteriorates over time, with the development of peripheral blind spots, which eventually merge to produce tunnel vision and blindness. Patients tend to lose around 50% of their visual field (VF) every 5 years (11, 64). Despite this reduction in VF, central visual acuity (VA) can be preserved until the advanced stages of the disease (i.e. they are in a state of tunnel vision until they go blind). Khorrami-Nejad et al., 2016 found that although VA is reserved in around 82% of the RP patients, deterioration in VF was noted in 80%; and this VF worsening was corroborated with visually impaired or blind children reporting significantly lower health related quality of life (HRQoL) scores (65).

Difficulty in performing daily tasks has been reported as the most prominent issue affecting the quality of life of patients with RP (30). Patients also express fear about going blind and uncertainties about their future. Patients with RP face emotional and psychological challenges to adapt to the stress and anxiety from the progressive vision loss that is perpetual. In addition to the impact on the patient with the condition, caregivers have been found to experience a greater degree of psychological and care-related burden when caring for those with more severe vision loss, including depression (66, 67).

Luxturna (voretigene neparvovec, VN), is a novel GT delivered intravitreally to the eye that reduces progression and offers positive impacts for patients as well as their families and society; it was first

registered by the U.S. FDA in 2017(63). Treatment with VN involves using a viral vector (adeno-associated virus serotype 2 [AAV2]) that infects RPE cells with a functioning copy of RPE65. Gene augmentation is the mechanism of action of VN, to express a normal, functional RPE65 protein in the RPE cells of the retina that restores the visual cycle (68).

The first EE of VN was a two state Markov transition moving patients from the first state (alive) to second state (dead), whereby the model tracked loss of VA and VF(69). The model, which reported an ICER of US$643,813/QALY from the healthcare system perspective, was appraised by the US Institute for Clinical and Economic Review (I.C.E.R.) in 2018 (69). Another EE for VN in the US setting was subsequently developed using a different model structure and HRQoL data in 2019 produced a different ICER (70). The model was a closed cohort health state transition model containing six health states reflecting the visual impairment (VI) associated with RPE65-mediated IRD and death; moderate VI (health state [HS]1; severe VI (HS2); profound VI (HS3); counting fingers (HS4); hand motion, light perception and no light perception (HS5); and death (HS6) and reported an ICER of US$79,618/QALY from the healthcare system perspective (70). In addition, VN has been appraised by national HTA agencies in England, Scotland, Ireland, the Netherlands, Australia and Canada (71). Patients with RPE65-mediated IRD experience severe vision loss from a young age, increasing the caregiver burden (11). The case of IRD, a rare disease (RD) that suffered the limitations associated with RDs such as a lack of evidence for the impact of the disease on HRQoL, or productivity, represents a compelling context for review (71). Various EEs appear to have addressed this challenge through a range of methodologies. (71). Furthermore, there exists a possibility that certain agencies considered broader value considerations, beyond the quality-adjusted life years (QALYs), in their assessments (69). Based on the apparent variability with which HTA agencies assessed value for VN as a GT for RD - particularly with respect to differences in what was considered of value and approaches to how those elements might be captured - it was therefore selected as the case study for the thesis.

The selection of VN as a case study for RPE65-mediated IRD was strategic to enable generalizability across GTs for RDs. VN exemplifies many characteristics common to GTs for RDs,

such as high upfront costs, limited clinical evidence due to small patient populations, limited understanding of broader disease burden such as societal impacts and potential for long-term benefits. These features align with broader challenges identified in the literature for GTs, such as uncertainty in long-term efficacy and the need for broader value considerations like caregiver burden and societal impacts (9). However, the specificity of VN to IRD—a condition with unique HRQoL impacts due to progressive vision loss—may limit its direct applicability to GTs for RDs with different clinical profiles (e.g., spinal muscular atrophy). Additionally, VN's focus on a paediatric and young adult population may not fully represent GTs targeting other age groups. Despite these limitations, the methodological challenges and broader value elements identified through VN (e.g., utility valuation gaps, caregiver impacts) are likely relevant to other GTs for RDs, as they reflect systemic issues in HTA for innovative therapies.

iv Research question

The primary aim of this research is to assess the challenges in evaluating the cost-effectiveness and whether broader value elements are considered in HTA decision-making of a GT for a RD. Specifically, the thesis seeks to: of a GT for a RD,

1. Detail the methodological challenges encountered in the EE's of VN (a GT for a RD, RPE65-mediated IRD) and investigate whether broader elements of value possibly associated with VN were considered by reimbursement decision makers.
2. Estimate Australian societal-based utility values for vision impairment due to RPE65-mediated IRD
3. Detail the lifetime impact on caregivers of patients with IRD
4. Understand the perspectives of stakeholders in HTA decision-making in Australia regarding the consideration of broader value aspects in EEs, transparency in HTA decision-making, and managing uncertainties associated with medicines for RDs

Figure 3 presents the approach used to address the aims of this thesis. Different sets of data and methods were used in this thesis. Each chapter addresses a study aim and is presented as a

unique study with objectives, methods, finding, discussions and conclusions. Primary data was collected to investigate aims two, three and four (Chapters 3, Chapter 4 and Chapter 5, respectively), with relevant human research ethics committee approval sought before the research commenced. Each approval covered all aspects of the data collection and details of the relevant institution providing ethics approval are provided in the relevant chapter.

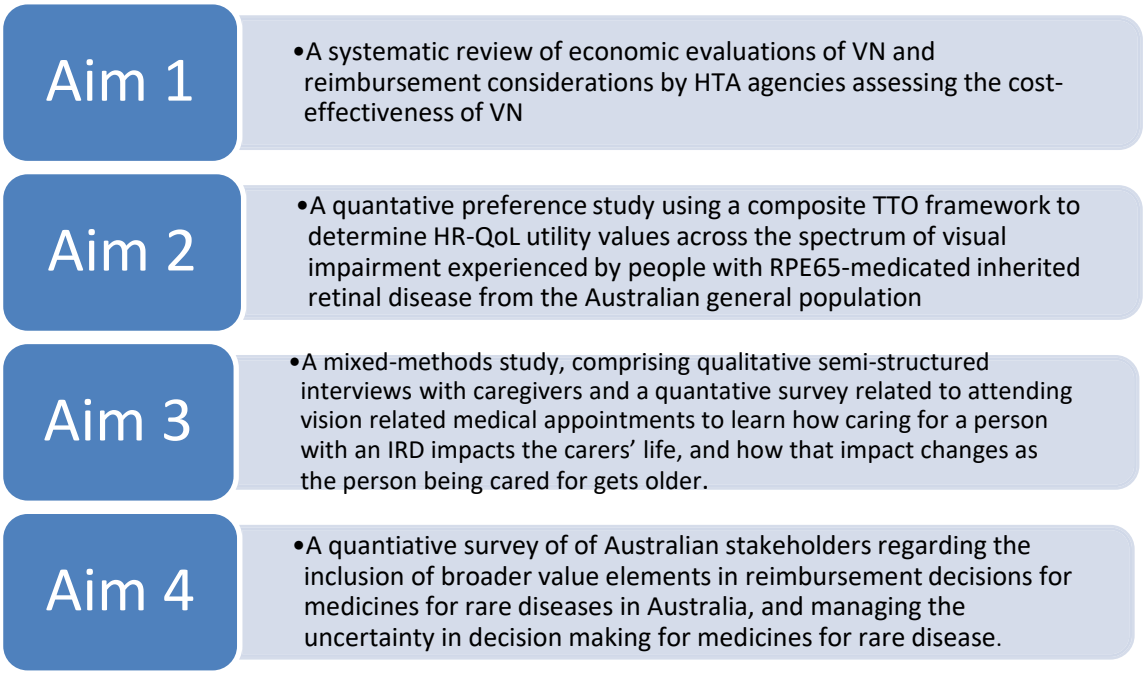


Figure 3 *Approach to thesis*

v Importance of the research

In the past few years, medicines for RDs have accounted for over 35% of the new drugs approved by the US Food and Drug Administration (FDA) (2). In addition, due to advances in science, there is an increasing trend towards the use of precision medicines such as GT. With an increasing number of GTs expected to progress to registration at a faster pace than conventional therapies, HTA agencies and governments are under increasing pressure to make potentially high-risk financial decisions due to the high, upfront cost associated with GTs, supported by limited evidence. It is crucial to understand the potential challenges in HTA appraisals to encourage discussions on suitable solutions that can be utilised to support EEs of GT in rare conditions developed in the

future. Equally, there is pressure on the pharmaceutical industry to demonstrate the value of therapies through EEs.

The primary research question of this thesis is to assess the challenges in evaluating the cost-effectiveness of gene therapies (GTs) for rare diseases (RDs) and to determine whether broader value elements are considered in HTA decision-making. The four specific aims outlined in Chapter 1 are directly aligned with this question, each addressing a distinct facet of the evaluation process. Aim 1 (systematic review of economic evaluations of VN) directly tackles methodological challenges and the incorporation of broader value elements by analysing existing evaluations and HTA decisions. Aim 2 (estimating Australian societal-based utility values) addresses the gap in HRQoL data specific to IRD, a critical input for CUA that impacts cost-effectiveness assessments. Aim 3 (detailing caregiver impacts) explores a key broader value element—caregiver burden—that is often overlooked in traditional evaluations, thus informing a more comprehensive value framework. Finally, Aim 4 (stakeholder perspectives on broader value elements) provides insights into the practical and policy implications of incorporating such elements into HTA in Australia, directly linking to decision-making processes. Collectively, the investigation of these aims provide a multi-dimensional approach to answering the research question by combining empirical data, qualitative insights, and stakeholder consensus, ensuring a robust assessment of both challenges and potential solutions in GT evaluation for RDs.

This thesis thus investigates the methodological challenges related to general value assessment and broader value elements considered within EEs of GTs and provides novel data for use in an EE of therapies for IRDs. In addition the thesis provides opinions of Australian stakeholders involved in HTA regarding the inclusion of broader value elements in reimbursement decisions for medicines for RDs in Australia that can help support the implementation of the recommendations from the recent Health Technology Assessment Policy and Methods Review (HTA review) in Australia (72, 73).

The aims of this thesis are situated within a growing body of literature that critiques traditional HTA methodologies for their limited scope in capturing the full value of innovative therapies like GTs for RDs (45). Aim 1 aligns with systematic reviews in the field that identify methodological challenges in GT evaluations, while extending this by focusing on a specific case study (VN) to provide granular insights (71). Aim 2 contributes to the literature on utility valuation for rare conditions, addressing a noted gap in IRD-specific HRQoL data (96). Aim 3 builds on studies of caregiver burden in chronic and rare diseases, offering novel data specific to IRD across life stages (66). Aim 4 resonates with policy-focused research which calls for stakeholder input to refine HTA frameworks, particularly in the Australian context post the HTA review (6). By integrating these aims, the thesis advances the broader discourse on adapting HTA to the unique challenges posed by GTs for RDs.

Furthermore, it is estimated that around 40 to 50 cell and GTs will be marketed by 2030, of which 13% are expected to be in ophthalmology to address conditions causing vision impairment (3) . Examples of such GTs in the research pipeline estimated to enter the pharmaceutical market in the near future are to treat choroideremia, an X-linked IRD that causes night blindness and a constricted visual field (1). Consequently, the research findings derived from this thesis are anticipated to contribute significant support to future EEs of GTs targeting RDs that may be developed subsequently.

Chapter 2 Research study 1 A systematic review of economic evaluations for RPE65-mediated inherited retinal disease including HTA assessment of broader value.

vi Chapter 2 summary

Chapter 2 reviews economic evaluations (EEs) of voretigene neparvovec (VN) and what was considered by health technology assessment (HTA) agencies (including the Medical Services Advisory Committee [MSAC] in Australia) in making their reimbursement recommendations.

The study is relevant to the key question of researching the methodological challenges encountered during these evaluations and to analyse the approaches of HTA agencies regarding these challenges. The research also investigates the extent to which HTA agencies incorporated broader value considerations into their assessments of the cost-effectiveness of VN.

The outcome of the review informed subsequent chapters in this thesis. The results included showing that there is a lack of health-related quality of life (HRQoL) or utility values and caregiver burden relevant to inherited retinal disease (IRD), which inspired two of the research studies conducted in Chapters 3 and 4 of this thesis. The lack of consideration of broader value in the VN reimbursement decision in Australia inspired the fourth research study of this thesis discussed in Chapter 5.

This review has been published: *Farris M, Goodall S, De Abreu Lourenco R. A systematic review of economic evaluations for RPE65-mediated inherited retinal disease including HTA assessment of broader value. Int J Technol Assess Health Care. 2023 Jun 14;39(1):e38. doi: 10.1017/S0266462323000326. PMID: 37313789; PMCID: PMC11570094.*(74).

vii Abstract

Objective

To summarise the key methodological challenges identified by HTA agencies assessing GT and consideration of broad elements of value.

Method

EEs of VN in RPE65-mediated IRD published in English were selected. HTA appraisals from Australia, Canada, Ireland, Scotland, England, and the United States were reviewed. An existing methodological framework was used to identify the challenges and considerations.

Results

Eight unique EEs were identified of which six were evaluated by HTA agencies. Incremental cost-effectiveness ratio (ICERs) ranged from $68,951 to $643,813 per quality-adjusted life years (QALY) gained (healthcare perspective) and *dominant* to $480,130 per QALY gained (societal perspective). The key challenges were the lack of validated surrogate outcome, utility values and indirect costs from IRD patients, and limited evidence of the long-term treatment effect. Two HTA agencies reviewed a range of novel broader elements of value and whether they were associated with VN while other agencies discussed some elements of broader value. Caregiver disutility was included in some, but not all, evaluations.

Conclusion

The methodological challenges were consistent with innovative interventions for rare diseases (RDs) and managed using standard methods. Broader value was important to decision-makers but inconsistently applied across agencies. Possible reasons are limitations in the evidence available of the broader benefits that VN offers and how to incorporate these within an EE. A need exists for greater guidance and consistency across jurisdictions regarding the consideration of broader value that considers latest best practice.

viii Introduction

Patients with RDs, their caregivers and families, are an important group in society that need more support due to significant disease burden and unmet clinical need (2, 56, 75, 76). Approximately eighty percent of RDs have a genetic origin, and seventy five percent affect children(1). Rare genetic conditions are lifelong, posing substantial challenges due to the complexity and ongoing nature of health service needs and lack of treatment options (77). Gene therapies (GTs) represent a breakthrough in therapy and offer the potential to address this unmet need.

While QALYs and costs often form the basis of value assessments in cost-effectiveness analyses (CEA), EEs of GT involve significant assumptions that cannot be validated, including around the durability of effect which will not be known for some time and the impact on future costs (45, 47). Furthermore, experts claim there are possible “other benefits” or “broader elements of value”, not captured by the QALY which are considered relevant to GT that could be considered in cost-effectiveness analysis (9).

Countries differ in their approach to appraising treatments for RD such as GT (47). Some have adapted their reimbursement processes to deal with common challenges, such as being accepting of lower levels of evidence, gaining greater disease specific insights from patient and clinical experts and consideration of other benefits offered by therapy in their decision-making(47).
The purpose of this review is two-fold to illustrate the methodological challenges encountered in the EEs of VN, a GT to treat RPE65-mediated IRD, a RD present from early childhood that progresses inexorably to complete blindness(11). Subsequently, the extent to which broader elements of value possibly created from the development of VN were considered by reimbursement decision makers will be explored.

While similar reviews have been conducted, this review includes EEs from three countries (Australia, Canada and Ireland) that have not previously been considered (71). This review also considers the general methodological challenges related to general value assessment and broader value elements specifically. More GTs will be forthcoming, so it is important to gain a deeper understanding of how the methodological challenges were managed and the extent to which broader value was considered by the reimbursement agencies.

ix Methods

Search strategy

A systematic search according to a prespecified search terms for published EEs and HTA agency reports for VN using the following databases: MEDLINE and EMBASE (via the Ovid platform) and EconLit (via the EBSCO platform) was conducted between April 2021 and August 2021 (**Supplementary Table 18** and **Table 19**, Appendix 1). The search strategy was not limited by language or year of publication (**Supplementary Table 20**, Appendix 1). A subsequent manual search was conducted of well-established HTA agencies to ensure all relevant EEs were captured. Reference lists of the included studies were reviewed for additional eligible studies.

Selection criteria and data extraction

The primary author (MF) reviewed reports against eligibility criteria and extracted data from each EE using the Consolidated Health Economic Evaluation Reporting Standards (CHEERs) checklist (**Supplementary Table 20**, Appendix 1). Reports not in English, conference abstracts, and systematic reviews were excluded, and only studies reporting the full EE were included.

Assessment of the decision-making process and broader value considered followed an existing methodological framework that included the interpretation of the evidence, “other considerations,” and stakeholder input (75). Information specific to HTA consideration was extracted from public summary documents as well as agency reports and reflects the base case analysis after any adjustments had been made during the review process (which may differ from the base case results put forward by the pharmaceutical industry sponsor)(75).

All cost data were adjusted to May 2021 prices and converted into USD using the relevant exchange rate (www.xe.com).

x Results

A total of nineteen records were identified, of which eleven met the inclusion criteria (**Figure 4**). Two reports represent a US evaluation conducted by Institute for Clinical and Economic Review

(I.C.E.R.) (69, 78), three reports were considered by National Institute for Health and Care Excellence (NICE) (79-82), and one report each of an Australian Medical Services Advisory Committee (MSAC) (83), Scottish Medicines Consortium (SMC) (84), Irish National Centre for Pharmacoeconomics (NCPE) (85), German (86), the United States (70), and Canadian Agency for Drugs and Technologies in Health (CADTH) (87). The eleven reports represent eight unique evaluations. Appraisal/reimbursement decisions were identified from six HTA agencies (CADTH, I.C.E.R., NICE, MSAC, NCPE, and SMC).

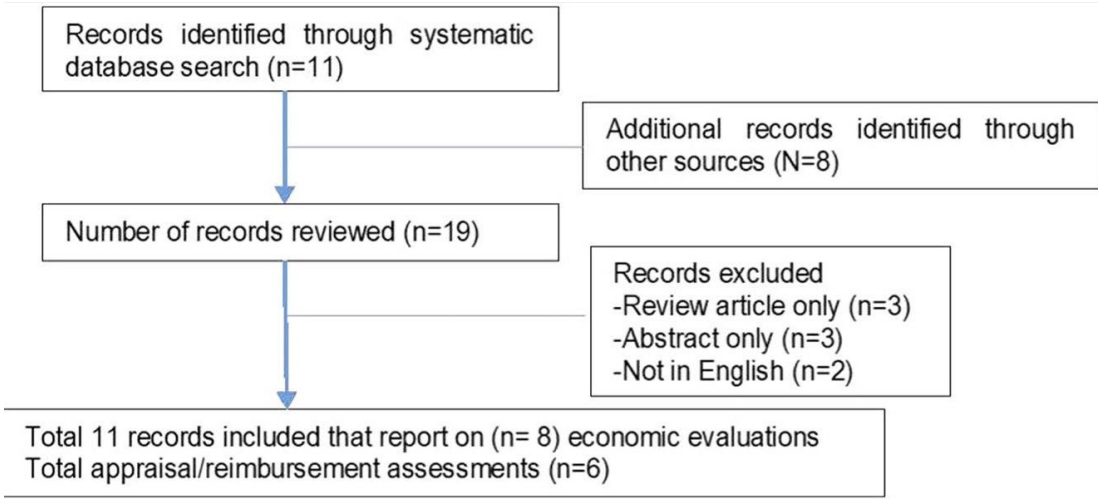


Figure 4 *PRISMA flowchart of the number of records included in this review*

Clinical evidence

All of the EEs relied on two clinical trials of VN: a phase I single arm safety and dose escalation study (Study 101/102, N = 12) and an open label phase III randomised controlled trial (RCT) (Study 301, N = 29) in which participants were randomised 2:1 to VN or best supportive care (BSC), with crossover allowed after 12 months (10, 68). Participants had a mean age of 15 years, confirmed biallelic RPE65 mutation, visual acuity (VA) equal to or worse than 20/60, or visual field (VF) less than 20 degrees (10). The phase III RCT was considered the main source of clinical effectiveness data.

Efficacy was assessed using functional vision (i.e., how a person functions in vision-related activities) and visual function (i.e., how the eyes perform, including VA, VF, and light sensitivity)

(63). A novel primary outcome, change in bilateral multiluminance mobility test (MLMT), was a novel outcome developed by the manufacturer (Spark Therapeutics, Inc. US) in collaboration with the US Food and Drug Administration (FDA) to support registration (63, 88). The MLMT is a composite of VA, VF, and light sensitivity and measures the performance of daily living activities that are vision dependent (10, 88). The change in bilateral MLMT score at 12 months was the primary outcome in the trial.

At 1 year, a clinically meaningful increase in mean bilateral MLMT change score was reported in Study 301 (1.8 in the intervention group and 0.2 in the control group, a difference of 1.6 ($p = 0.001$) (10). There were statistically significant improvements in full-field light sensitivity (FST) and VF (10).

Both trials supported a durable long-term improvement in functional vision, through to 7.5 years in Study 101 and 4 years in Study 301 (12, 82, 83).

All evaluations considered best supportive care (BSC) the appropriate comparator. BSC was informed by a retrospective chart review that described the long-term natural history of biallelic RPE65-mediated IRD (N = 70) (11).

Characteristics of economic evaluation analyses

The characteristics of the eight evaluations (reflecting base case evaluations put forward by the pharmaceutical industry sponsor) are provided in **Supplementary Table 21** in Appendix 1. Six EEs were conducted from a healthcare payer perspective and two from a societal perspective.

A two state Markov model was used by two evaluations (69, 86). In this model, patients transitioned from “alive with biallelic RPE65- mediated retinal disease” to “dead,” with the transition probability a function of age- and sex-specific mortality rate. Within the alive state, VA and VF were modelled using an exponential and linear form from the natural history study, respectively.

The remaining six evaluations were based on the same pharmaceutical industry sponsored model, adapted for each country. Consequently, these evaluations have the same structure but use different inputs (70, 81-85, 87). The model used a more complex parametric multistate survival model containing six health states (moderate visual impairment [VI] (health state [HS]1; severe VI (HS2); profound VI (HS3); counting fingers (HS4); hand motion, light perception and no light perception (HS5); and death (HS6)) representing deteriorating vision based on the course of VA and VF observed in the clinical trial (Study 301) and the natural history study and included mortality. Surrogate outcomes, VF and VA, defined the HSs due to a lack of natural history of progression, costs, or impact on HRQoL data on the MLMT. Data from Study 301 informed the transition probabilities in each of the BSC and VN arms in the initial phase during which individuals moved to either better or worse HSs. During the maintenance phase, the initial distributions across HSs was retained for a period followed by a long-term decline consistent with disease progression from less to more severe HSs and no regression to less visually impaired states.

The assumed duration of treatment effect varied from 10 years to a lifetime. All EEs were based on a lifetime horizon with a 1-year cycle length. Discounting of costs and benefits was at standard discount rates for each jurisdiction, varying from 1.5 percent (CADTH) to 5 percent (MSAC). NICE considered a scenario analysis applying a 1.5 percent rate (from the base case 3.5 percent) given the likelihood of long-term benefits.

The pharmaceutical industry-sponsored evaluations used a bespoke utility study to indirectly elicit utility values for each HS (82-84, 87, 89). In this study, vignettes describing the HSs were valued by six clinical IRD experts using the EuroQol-5D (EQ-5D) and Health Utilities Index Mark 3 (HUI3). Justification for this approach was that there was a lack of IRD-specific utility values available, and that utility values available in the literature for comparable disorders of vision loss primarily assessed VI only through VA and focused on older patients with age-related macular degeneration (AMD), diabetic retinopathy (DR), or glaucoma (90-93). Those available studies excluded patients with no light perception (NLP) suggesting that the resulting utility data may be of limited relevance

in the younger population with RPE65-mediated IRD (94). Utility values based on the HUI-3 were used in most of the pharmaceutical industry -sponsored models because, unlike the EQ-5D, the HUI-3 contains a visual domain (81-85). Because normal vision was included in the moderate visual impairment health state (i.e., HS1) the model submitted to MSAC in Australia increased the utility value in line with utility values reported for normal vision (83, 90). The two independent evaluations relied on health state utility (HSU) values from a community-based sample that used the standard gamble (SG) to value HSs based on declining VA in people with DR (69, 86).

In recognition of caregiver and broader family burden associated with IRD, a caregiver disutility was applied in the four worst HSs (HS 2–HS 5) in the base case in three evaluations (NICE, SMC, MSAC) and included in a scenario analysis from a societal perspective by CADTH (81, 83, 84, 87). Caregiver disutilities incorporated in the EE submitted to NICE were sourced from a publication reporting health spillover disutility of illness on family members or caregivers and used disutility estimates from parents of children with activity limitations (50).

Results of economic evaluations

The EE results are summarised in **Table 1.** ICERs are presented from a healthcare and societal perspective separately. All ICERs reflect the published price of VN submitted for evaluation by the pharmaceutical industry sponsor and do not take into account any confidential price discounts.

Table 1 *Results of voretigene neparvovec economic evaluations*

Source (country)	**Costs, $**			**QALYs**			**Incremental cost-effectiveness ratio, $**
	VN	BSC	Incremental	VN	BSC	Incremental	
Healthcare perspective							
I.C.E.R. (US)(69)	*$1,039,019*	*$213,399*	*$825,621*	*17.3*	*16.0*	*1.3*	*$643,813*
Uhrmann (Germany)(86)	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Johnson (US)(70)	$1,156,329	$406,404	$749,925	18.1	8.6	9.4	$79,618
CADTH (Canada)(87)**	$996,782	$244,227	$752,555	27.6	18.4	9.2	$81,491
MSAC (Australia)(83)*	NR	NR	$475,399-$547,979	11.2	3.70	7.5	$68,951-$83,467
NICE (England/Wales)(81)	$891,919	$62,948	$828,972	10.7	3.6	7.1	$117,347
SMC (Scotland)(84)	$892,542	$46,012	$846,530	10.6	3.6	7.0	$121,730
NCPE (Ireland)(85)	NR	NR	$797,234	NR	NR	4.6	$172,169
Societal perspective							
I.C.E.R. (US)(69)	*$2,515,320*	*$1,899,605*	*$615,715*	*17.3*	*16.0*	*1.3*	*$480,130*
Uhrmann (Germany)(86)	*NR*	*NR*	*$876,154*	*NR*	*NR*	*4.8*	*$181,887*
Johnson (US)(70)	$2,220,069	$2,780,106	-$560,038	18.1	8.6	9.4	-$59,458
CADTH (Canada)(87)*	NR	NR	$290,682	NR	NR	10.9	$26,540
MSAC (Australia)(83)**	NR	NR	NR	NR	NR	NR	NR
NICE (England/Wales)(81)	NR	NR	$618,944	NR	NR	7.1	$87,616
SMC (Scotland)(84)	NR	NR	NR	NR	NR	NR	$91,800
NCPE (Ireland)(85)	NR	NR	NR	NR	NR	NR	NR

Note: The cost-effectiveness results from the two state Markov model (as opposed to the six-state Markov model) are presented in *italics*. All prices have been converted into USD using the relevant exchange rate in May 2021 (www.xe.com).
Abbreviations: BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technologies in Health; I.C.E.R., Institute for Clinical and Economic Review; MSAC, Medical Services Advisory Committee; NICE, National Institute for Health and Care Excellence; NCPE, National Centre for Pharmacoeconomics; NR, not reported; QALY, quality-adjusted life-year; SMC, Scottish Medicines Consortium; VN, voretigene neparvovec.
*.The final ICER was not reported in the MSAC Public Summary Document (PSD); however, data were sourced from Novartis Pharmaceuticals Australia and included as a range, reflecting the approach to reporting of ICERs in Pharmaceutical Benefits Advisory Committee (PBAC) PSDs.
**.The sponsor submitted scenario analyses, able 12 of the CADTH pharmacoeconomic report, includes societal perspective which is represented here

From a healthcare perspective, apart from MSAC, the incremental costs were fairly consistent across evaluations, ranging from $749,925 to $846,530. The lower incremental costs ($475,399 to $547,979) reported in the MSAC evaluation may reflect the broader healthcare costs (incl. pensions and government subsidies) attributed to the BSC arm (83, 95).

Except for I.C.E.R., QALY gains ranged from 4.6 to 9.4, reflecting the differences in duration of treatment effect, discount rates, and caregiver disutility applied in three evaluations (MSAC, NICE, and SMC). I.C.E.R. reported a 1.3 QALY gain, which is derived from a utility function whereby vision-related disability is linearly proportional to VA or VF. Clinical experts criticised the approach for failing to adequately reflect the substantial utility reduction associated with IRD at the point of severe vision loss with experts quoting a utility of 0.26 associated with the blind state (no light perception) (96). Acknowledging the limitation of the extrapolation, a scenario analysis applying a non-linear utility function adjusted the QALY gain to 5.2 which is similar to the other EEs.

There was much wider variability in the incremental costs from a societal perspective, ranging from cost saving (−$59,458) to $876,154 (69, 70, 84, 86, 87). The variability was attributed to subjective estimates of the resource use, variation in indirect costs between different countries, and extrapolation methods. **Table 2** presents a summary of the indirect and direct costs included in the EEs. While the source for indirect caregiver and patient productivity loss was based on IRD in the model published by Johnson (70), the indirect costs used by I.C.E.R. were sourced from AMD (69). Despite both reflecting the US context, the indirect costs attributed to blind patients were double in the model by Johnson compared with I.C.E.R., which illustrates the range of costs from different sources (**Supplementary Table 23** in Appendix 1).

Table 2 *Summary of Healthcare and Societal costs incorporated in VN economic models*

	I.C.E.R. (US), 2018	Uhrmann (Germany), 2020	Johnson (US) 2019	CADTH (Canada) 2020	NICE (England/Wales), 2019	SMC (Scotland), 2020	MSAC (Australia), 2020	NCPE (Ireland), 2020
Treatment cost	H	S	H	H	H	H	H	H
Treatment side effect costs	H			H	H	H	H	H
Treatment associated cost (eligibility, surgery)	H	S	H	H	H	H	H	H
Medical cost (trauma from fall, depression, related to vision)	H	S	H	H	H	H		
Transportation cost	S	S						
Home modifications		S						
Caregiver productivity loss	S	S	S	S	S			
Education	S			S	S	S		
Patient productivity loss	S	S	S	S	S	S		
Pension			S	S	S		H	
Nursing home	S			H	H	H		
Rehabilitation/aids				H	H	H		
Carer allowance					S			
Non health care resources				S				

Note: "H" reflects costs included in healthcare perspective, "S" reflects costs included in the societal perspective.

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; ICER, Institute for Clinical and Economic Review; MSAC, Medical Services Advisory Committee; NICE, National Institute for Health and Care Excellence; NCPE, National Centre for Pharmacoeconomics; SMC, Scottish Medicines Consortium.

While all evaluations considered societal costs, only evaluations by NICE, CADTH, and SMC included a societal benefit in terms of a caregiver disutility avoided. The incremental QALY gains reported from a societal perspective had a similar range to that reported from the healthcare perspective.

The resulting ICERs from a healthcare perspective ranged from $68,951 per QALY gained reported by MSAC driven by the comparatively low incremental cost to $643,813 per QALY gained reported by I.C.E.R. driven by the comparatively low incremental benefit. In comparison, when applying a societal perspective, the ICERs ranged from dominant to $480,130 reflecting the broader benefits considered (indirect costs of treatment rather than HRQoL impact).

HTA decisions

Six evaluations were appraised by HTA agencies, five by government reimbursement agencies (CADTH, MSAC, NICE, SMC, NCPE), and one by an independent research institute (I.C.E.R.). The methodological challenges and consideration by HTA agencies, including considerations of broader value, are presented in **Table 3.**

Table 3 *Summary of VN economic modelling challenges and management by reimbursement agency*

Methodological challenges	Consideration by agencies
Clinical evidence based on small sample size	All agencies accepted the clinical evidence based on a small sample size in the context of a rare disease. NICE and CADTH required cross over data from BSC arm of Study 301 be included in transition probabilities to increase sample size.
Use of surrogate outcomes in the economic model	All agencies accepted the model based on surrogate outcomes in the context of a rare disease.
Clinical evidence with limited follow up data	Various long term effect assumptions were accepted by agencies. NICE, MSAC and SMC accepted a 40-year treatment effect after seeking expert advice that supported the duration was biologically plausible whereas CADTH reduced it to 10 years after advice from clinical experts that the proposed duration (40 years) was likely an overestimate. NICE removed the 10-year treatment waning and the 25% residual treatment effect on the basis that they were not based on any biological rationale.
Incorporating appropriate cost and offsets when data are lacking	All agencies were broadly in agreement with the costs included. MSAC noted the ancillary costs of treatment were unknown and required, as part of the funding arrangements, that ancillary cost data be collected over 3 years to inform future cost-effectiveness analyses.
Utilities based on proxy utility assessment	All of the agencies conducted sensitivity analyses using alternative utility values. CADTH applied revised utility values derived from clinical experts who completed the bespoke utility elicitation exercise. MSAC did not accept that use of VN could result in a utility value associated with normal to moderate vision impairment, and capped utility at moderate vision only.

Other considerations	Consideration by agencies
Impact on QOL	With the exception of NCPE, qualitative and quantitative reports to each agency presented the impact of the condition on the patient and caregiver. Fear of having a degenerating condition, the negative impact on future employment, relationships and family were reported by patients. Guilt from passing on the gene, emotional distress in watching a patient's vision degenerate, and the need to provide ongoing physical and emotional support to the affected patient were reported by parents and caregivers.
Nature of condition	The agency reports reflected an understanding that the disease commences in early childhood and is progressive. Also that treatment with VN could be in adults as well as children but primarily children were treated in the clinical trial.
Rarity, severity, unmet need	The disease was acknowledged in most reports as severe and progressive without any pharmacological treatment options available. CADTH reported that incident cases treated might present younger with less severe disease at baseline.
Innovative nature and impact on specialised services	Only I.C.E.R. and NICE discussed the innovative nature of therapy. NICE acknowledged VN was a "step change" in patients' treatment. Out of the 12 I.C.E.R. committee members 5 voted that VN would positively impact beyond the treatment on the infrastructure of care through improved understanding of the condition and improved care for patients
Modelling/consideration of broader elements of value	The healthcare perspective formed the base case evaluation for all agencies except for I.C.E.R. Based on being a rare condition where indirect and nonmedical costs are substantial, I.C.E.R. presented a modified societal perspective (considering the societal costs but not societal benefits) as well as a healthcare system perspective. Broader value was considered systematically in the I.C.E.R. review via a 12 member independent panel who voted on the likelihood that VN offered "other benefits" such as reducing the complexity of care, novel mechanism of action compared to existing treatments, improving sensitisation of clinicians and understanding of the condition that may revolutionise care and the importance of these against the uncertainty in long term benefit. There was no quantitative measure for other benefits and disadvantages. Broader value was considered systematically in the NICE review. Multistakeholder input was sought via a questionnaire to understand the broader impact from VN, namely on specialised service organisation and provision, resource allocation and equity, societal and ethical issues, plus impact on patients or caregivers. NICE noted there were considerable unmeasured benefits related to sustaining vision in children, and these had been considered qualitatively in its decision making. NICE accepted the inclusion of caregiver disutility, proposing alternate values to those of the sponsor and excluding disutility values for caregivers of adults but including disutility for caregivers of children in all heath states as appropriate for decision making(97). The SMC accepted the caregiver disutility as applied in the base case by the applicant, and explicitly requested further data collection as part of the 3-year provisional approval to include the patient and caregiver lived experience. Caregiver disutility was only applied as part of the societal perspective assessment by CADTH and not in the base case health care system perspective as submitted by the sponsor. Caregiver disutility was not accepted by MSAC.

Abbreviations: BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technologies in Health; I.C.E.R., Institute for Clinical and Economic Review; IRD, inherited retinal disease; MSAC, Medical Services Advisory Committee; NICE, National Institute for Health and Care Excellence; NCPE, National Centre for Pharmacoeconomics; QOL, quality of life; SMC, Scottish Medicines Consortium; VN, voretigene neparvovec

The agencies accepted the shortcomings in the evidence presented and modelling assumptions, noting the absence of evidence often associated with RDs, particularly genetic diseases that are

heterogenous in presentation. All agencies thus relied heavily on expert opinion to validate model assumptions.

Two different methods to elicit stakeholder feedback, an in-depth questionnaire (using a systematic approach on a range of specific considerations) or routinely gathered generic insights (as part of a standard process), were used to support the broader considerations associated with VN in all evaluations except for NCPE. Common broad elements of value such as patient productivity and caregiver costs, as well as transport costs and blindness pension, were considered through a societal perspective scenario analysis by all decision-makers except for MSAC and NCPE. I.C.E.R. considered a modified societal and healthcare perspective in their decision-making, although they only included societal cost, not benefit. CADTH's scenario analysis of the societal perspective considered both cost and caregiver disutility. The caregiver disutility was considered in the healthcare perspective analysis considered by NICE and SMC but not the costs to the caregiver. A number of novel considerations of value beyond clinical and cost-effectiveness, such as an impact on the "infrastructure" of care through increased disease screening and awareness that may revolutionize care or "improved specialised service provision," were taken into account explicitly by NICE and I.C.E.R. (69, 81).

The timing of the appraisal, ICER range, and decisions are presented in **Table 4.**

Table 4 *Details of reimbursement decisions for VN*

Source (country), year	ICER range (USD) considered	Decision	Basis of decision
I.C.E.R. (US),2018(69)	$135,333/QALY - $643,813/QALY	Acceptable cost-effectiveness	A modified societal perspective and health care perspective informed decision making. A higher ICER threshold was accepted for ultra-rare orphan diseases. Special weighting was given to other benefits and contextual considerations despite the high price, and thus higher cost-effectiveness ratios, than may be applied to decisions about other treatments.
NICE (England/Wales),2019(81)	$156,720/QALY - $212,334/QALY	Approved	VN was considered eligible for HST process for ultra-rare disease which increases the WTP threshold and allowed the application of a QALY weighting that reduced the ICER below the threshold considered value for money

			$135,450(£100,000)/QALY. NICE concluded that VN can be considered an appropriate use of NHS resources. A commercial offer or discount was offered by the sponsor company.
CADTH (Canada),2020(87)	$159,408 /QALY	Conditional approval	CADTH required adjustments to the model that substantially increased the ICER to $159,408($CAN200,477)/QALY and noted to achieve an ICER of $39,760($CAN50,000)/QALY a 74% price reduction would be required. VN was approved subject to initiation and prescribing criteria and price reduction.
MSAC (Australia),2020(83)	$68,662/QALY to $165,111/QALY	Conditional approval	VN was approved subject to a price reduction to address uncertainties and a pay-for-performance arrangement for 3 years during which time local and broader evidence on its effectiveness is required to be generated. A cost-effectiveness review including the new data is required after 3 years.
SMC (Scotland),2020(84)	$92,394/QALY to $269,886/QALY	Conditional approval	VN was eligible for an ultra-orphan pathway. After initial review a 3-year approval was granted despite uncertainties but was subject to price reduction required to increase cost-effectiveness. The sponsor is required to provide a data collection plan and a full appraisal will be conducted using data collected over the 3-year period.
NCPE (Ireland),2020(85)	$214,915/QALY	Rejected	NCPE performed a threshold analysis and stated the probability of cost-effectiveness at both $51,157(€45,000)/QALY and $22,736(€20,000)/QALY using the NCPE adjusted base case was 0%.VN was not considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments

Abbreviations: BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technologies in Health; HST, highly specialised therapy; I.C.E.R., Institute for Clinical and Economic Review; IRD, inherited retinal disease; MSAC, Medical Services Advisory Committee; NICE, National Institute for Health and Care Excellence; NCPE, National Centre for Pharmacoeconomics; NHS, national health service; QALY, quality-adjusted life years ; SMC, Scottish Medicines Consortium; VN, voretigene neparvovec; WTP, willingness to pay.

The range of ICERs accepted by agencies was broad ($68,662/QALY to $643,813/QALY). The rationale for accepting what would otherwise be considered above standard thresholds appeared to be the nature and rarity of the condition, although it was difficult to judge from most HTA reports which considerations impacted the decision the most. The report by I.C.E.R. however refers to raising the willingness-to-pay (WTP) threshold in response to "*special weighting… given to other benefits*" as part of an appraisal framework established for ultra-rare disease treatments, and the report by NICE states, "*there were considerable uncaptured benefits related to sustaining vision in children, and that these had been considered qualitatively in its decision making*" (69, 81).

Despite these concessions, a price reduction was uniformly suggested or requested by agencies to improve cost-effectiveness. Conditional approval, via ongoing data collection to inform re-evaluation and pay-for-performance agreements, was also implemented to address uncertainty by MSAC and SMC (83, 84). These agencies required collection of clinical and patient outcomes (plus caregiver experience and ancillary costs of treatment) as a means of addressing uncertain clinical benefit, patient and caregiver benefit, and costs.

xi Discussion

A range of economic modelling challenges were identified across the evaluations of VN. Such economic challenges are common to other innovative interventions for RDs and managed using standard methods, such as expert opinion to validate assumptions and scenario analyses testing different assumptions (57, 71). The distinguishing feature, common to GTs for RD, is the concentration and magnitude of these challenges and the lack of a biological analogue on which to assess the plausibility of model assumptions (9). Broader elements of value were considered by all reimbursement decision-makers and the review revealed challenges in modelling these broader elements of value that are considered relevant to assessing GT but are not typically captured in standard QALY estimates.

Various novel elements of value such as insurance value, severity of disease, value to caregivers, lack of alternatives, substantial improvement in life expectancy, and scientific spillovers are proposed as being particularly relevant to GT (9, 45). While most agencies discussed severity of disease, value to caregivers, and lack of alternatives, only NICE and I.C.E.R. systematically considered a wider range of "*other benefits*" possibly offered by VN (9, 69, 81). Of particular relevance to a novel GT such as VN, the improvement in disease management through advancing infrastructure and knowledge, and "*scientific spillover*" through advancement in the broader field of GT were considered (69, 81). Whether such broader elements of value factored into the final approval across the other agencies is unclear. Three agencies however accepted the inclusion of

caregiver disutility in the QALY (reducing the ICER by 9 percent), albeit subject to different approaches (81, 84, 87). Evaluations considered by NICE and SMC included caregiver disutility within a healthcare perspective for which a recommendation was made without considering broader societal costs (in terms of productivity loss). NICE challenged the disutility value including how many caregivers per patient it should apply to and whether to apply it to caregivers of adult IRD patients (the final decision was to remove the caregivers disutility value for adult IRD patients) (82). In contrast, CADTH included the costs and disutility to the caregiver within the societal perspective only, but these were not an explicit consideration in their decision-making. While the ICER, the conventional measure of "value for money" was reflected in the decision-making by all agencies, the wide range of ICERs approved ($68,662/QALY to $643,813/QALY) for this novel therapy was striking and implies that perhaps the broader benefits beyond the QALY were considered in the decision-making. Alternatively this variance indicates that agencies exercise pragmatism in their decision-making that does not rely solely on estimates of cost-effectiveness (46). Consequently, this emphasises the need for improved transparency in HTA decision-making processes.

Two EEs included in the review did not have a pharmaceutical industry sponsor, the US I.C.E.R. and academic institute from Germany (86) and as such provide unique insights into the broader elements of value that might be considered in an EE of a GT given they are less likely to follow HTA guidelines and not be as influenced by commercial incentives to demonstrate value compared with pharmaceutical industry sponsored CEAs (98). Decision-makers are constrained by their own HTA guidelines reflecting their values, preferences, and constraints, for example, the healthcare perspective guiding NICE included the carer disutility whereas the healthcare perspective evaluated by MSAC did not (99, 100). It is important to note that HTA guidelines are a "guide" and it is the responsibility of pharmaceutical industry sponsor companies to argue for the inclusion of broader elements of value in their application. The complexities in considering such value in EEs may be one reason that pharmaceutical industry sponsor companies have not included broader elements. For instance, there is limited evidence to support the informal care for patients with IRD and there are ongoing challenges in incorporating them into an EE (101). There is an ongoing need for

reimbursement agencies to review the latest best practice. The Australian government for example is currently undertaking a Health Technology Assessment Policy and Methods Review (HTA review) to keep pace with rapid advances in health technology (72).

A common method of considering broader value via a societal perspective that includes non-related healthcare costs and consequences on caregivers and social services, and economic productivity can profoundly affect whether a therapy is deemed cost-effective (9, 45). A comparison of the ICER ranges reported from a healthcare perspective ($68,951 to $643,813, **Table 2**) with a societal perspective (dominant to $480,130) illustrates this point. While the final recommendation by I.C.E.R. was explicitly based on a side-by-side analysis of the healthcare perspective and “modified societal perspective” (including the societal cost but no benefit), it is not clear whether the societal perspective influenced the reimbursement decisions across the other agencies (7, 46). A review of the societal perspective was evident in most evaluation reports so despite the study perspective being specified by the relevant decision-maker, conducting the CEA from both a societal and a healthcare perspective is one way of demonstrating the broader consequences of a GT that pharmaceutical industry sponsor companies should consider.

The extrapolation assumptions applied to ongoing treatment effects and costs had a significant impact on the ICER for VN in all evaluations and were challenged by all agencies. Expert advice from clinicians was sought by all agencies, and despite the same clinical evidence being considered by all agencies, a different interpretation resulted from seeking opinions from different experts. For example, experts consulted by CADTH thought a 40-year treatment effect were optimistic and thus the base case was updated to reflect a shorter, 10-year treatment effect (87). This change resulted in a 200 percent increase in the ICER estimate (87). Other agencies however accepted the proposed 40-year treatment effect. Similarly, experts consulted by NICE objected to the assumed treatment waning period as not being supported by any biological rationale, but this was not a concern for other agencies such as MSAC. Immature evidence and lack of treatment analogue to support the long-term treatment effect for a once in a lifetime therapy will be an ongoing challenge

for any GT, like VN (8, 71). The novel nature of the treatment means there will inevitably be variation in international opinion regarding the durability of effect. Each jurisdiction differs in their approach to validating such uncertainty for their respective HTA agency and is limited by financial constraints such that the proposal by Huygens et al. to conduct a formal expert elicitation study to generate plausible treatment effect duration assumptions may not always be possible (71). Alternative approaches to collecting expert input, such as clinical advisory meetings or surveys, might be considered albeit recognising the potential limitations arising from the number of respondents and their representativeness (99, 102).

The lack of IRD-specific utility values was a substantial modelling challenge that is not uncommon in RDs. The benefit estimated in the model is driven by HRQoL; thus, the results are sensitive to the choice of utility values. Utility values related to vision loss available in the literature focused on older patients with vision loss from conditions of limited relevance in the younger population with RPE65-mediated IRD. Hence, the pharmaceutical industry-sponsored models incorporated utilities based on proxy assessments (94). All agencies were critical of the proxy utility estimates and undertook HRQoL sensitivity using utility data evaluated in different sight disorders that substantially impacted the ICER (+38 percent to +308 percent) (69, 82, 89). Furthermore, research has shown that ophthalmologists who take care of patients with AMD underestimated the HRQoL (utility) loss associated with AMD by 95% to 750% compared to actual AMD patients with the same level of vision loss indicating that the proxy utility values may not represent the impact of the disease on IRD patient HRQoL (103). While agencies prefer measurement of health by patients, indirect elicitation of utility values is considered acceptable for RDs (99, 102). Rather than sourcing proxy utility estimates, the use of direct elicitation methods such as the SG, time trade-off (TTO), or discrete choice experiments (DCE) from the general population might be a better alternative for utility values for IRD (97, 99, 102).

Limitations

Only EEs available in English were included. Most evaluations were funded by the pharmaceutical industry therefore reflecting the same underlying clinical data and methods; variations in HTA agencies' considerations of those evaluations may thus reflect differences in parameter inputs and in underlying decision-making frameworks. A wider understanding of how broader aspects of value feature in decision-making could be gained from looking at the EEs from more countries. This analysis was based on public information available in HTA reports, and as such it was subject to the varying transparency with which HTA agencies report their decision-making processes.

Conclusions

This review provides a deeper understanding of the assumptions accepted and the consideration of other benefits in HTA in GT that may assist in developing EEs in this setting. The analysis highlights that evaluations from a societal perspective do not always reflect both cost and benefit, and that societal benefits in terms of caregiver value are considered acceptable by some agencies in the healthcare perspective. Of specific relevance to the challenge in modelling GT are the extrapolation assumptions and broader elements of value considered acceptable by reimbursement agencies. This (study) illustrates the importance of quantifying the broader aspects of value to include in EEs of GT and underscores the need for greater guidance (and consistency) across jurisdictions in relation to consideration of broader element of value, and the need for reimbursement agencies to constantly review their guidelines and processes against the latest best practice. Thus, there is a need to expand on the understanding of the broader benefits that VN offers to patients with IRD and how to deal with those benefits within an EE given that VN, and other GTs with similar benefit profiles, will be the subject of future cost-effectiveness analyses.

Chapter 3 Research study 2 Estimating Australian Population Utilities for Inherited Retinal Disease Using Time Trade-Off.

xii Chapter 3 summary

One of the methodological challenges identified in the review that formed research Study 1 (Chapter 2) was the lack of inherited retinal disease (IRD) specific utility values for IRD due to the rare nature of the condition. This prompted the second part of this research to determine preference-based health related quality of life (HRQoL) utility values across the spectrum of visual impairment experienced by people with RPE65-mediated IRD from the Australian general population.

A time trade off (TTO) study to generate utility values for health states (HSs) with varying levels of functional vision in patients with an IRD, among the general public in the United Kingdom (UK) had been conducted since the appraisals of the EE of VN reviewed in Chapter 2, however the study did not include the worse than death (WTD) state (104). This omission is significant, considering the increased suicide rates associated with severe vision impairment (105).

The aim of Chapter 3 is to estimate Australian societal-based HRQoL data using a TTO protocol adapted from the UK study. The research in Chapter 3 utilised the composite TTO (cTTO) methodology that incorporates the WTD state. The derived health state utilities (HSU) can be utilised in a cost-utility-analysis (CUA), a form of cost-effectiveness analysis (CEA) that quantifies value in terms of the quality-adjusted life years s (QALYs).

The research provides an example of how to estimate the HRQoL impact from an RD using population preferences to value health states.

This research study has been published: *Farris M, Goodall S, De Abreu Lourenco R, Mulhern B, Manipis K, Meshcheriakova E, Lewandowska M. Estimating Australian Population Utilities for Inherited Retinal Disease Using Time Trade-Off. Pharmacoecon Open. 2024 Nov;8(6):911-922. doi: 10.1007/s41669-024-00515-5. Epub 2024 Aug 5. PMID: 39102180; PMCID: PMC11499549*. (106)

i Abstract

Purpose

IRD causes progressive loss of visual function degenerating towards complete blindness. Economic Evaluation (EE) of gene therapies (GTs) for rare forms of genetic IRDs have had to rely on HRQoL estimates from other diseases because there are limited data available for such a rare condition. This study aimed to estimate Australian societal-based utility values for IRD health states that can be used in a cost-utility-analysis (CUA) using a time trade-off (TTO) protocol adapted from a UK study.

Methods

The EuroQol Valuation Technology (EQVT) protocol composite TTO (cTTO) framework was followed which includes worse-than-death (WTD) states and quality control (QC) measures. Preferences were collected from a general population sample of 110 Australian adult participants. Five health state vignettes from the UK study which had been validated with patients and clinicians were presented randomly to participants during videoconferencing (VC) interviews with one of four interviewers. Technical and protocol feasibility were assessed in a pilot of 10 interviews. QC measures were used to monitor interviewers' performance during the study.

Results

One participant withdrew consent. The final analysis was conducted on 109 respondents (including 4 non-traders). The average time to complete the interview was 44.2 minutes (SD 8.7). Participants reported mean visual analogue scale (VAS) scores between 63.15 for "moderate impairment" and 17.98 for "hand motion" to "no light perception". Mean HSU's varied between 0.76 (SD 0.26) in "moderate impairment", and 0.20 (SD 0.58) in "hand motion" to "no light perception". Of all HSU evaluations 14% were considered WTD which most commonly occurred in the most severe visually impaired health state.

Conclusion

This study provides valuable information on HSU's across a range of IRD health states from the Australian general population perspective. The utilities obtained in this study can be used as inputs into CUA of IRD therapies.

ii Introduction

HTA agencies accept HR-QoL data collected in clinical studies or HR-QoL valuation by the general public, with some HTA agencies favouring country-specific preferences (102). However, for many conditions, such as RD's, capturing HR-QoL directly from patients may not be feasible for a number of reasons. Disease-specific measures often do not exist, generic multi-attribute utility instruments (MAUIs) may be too broad and insensitive to detect the change in symptoms that impact a patients' QoL, and statistical validation is limited due to small sample sizes with RD (37).

This has led to alternative methods of estimating HR-QoL or HSUs such as: the use of proxy-reported MAUIs (i.e., an assessment of the health state experienced by someone else) or direct elicitation from unaffected populations asked to make hypothetical judgements using vignettes to value health state description (94, 107, 108). Another method is using HSU's from a separate sample of patients with characteristics similar to those enrolled in the clinical trials (90).

IRDs are rare heterogenous conditions that result in either progressive or stationary retinal dysfunction causing loss of visual function, including loss of visual acuity and peripheral vision, and night blindness (68, 109, 110). There are over 250 disease-causing genetic variants identified, with mutations in the RPE65 gene leading to an assortment of clinical diagnoses, that present from early childhood and infancy to adolescence, degenerating towards complete blindness thus having a detrimental impact on patients' HRQoL (11).

Gene replacement therapy, VN, is now available in many countries for the RPE65 mediated IRD, and other genetic therapies for other IRDs, including choroidoremia and x-linked retinitis pigmentosa, are being evaluated in clinical trials (108). The advent of GTs for rare forms of genetic blindness is positive for patients, however prohibitively high treatment costs typically associated

with GT means that public subsidisation is required to ensure that these treatments are available as part of usual care.

EE of interventions which affect HRQoL commonly employs -CUA which typically expresses the cost-effectiveness of interventions as the cost per QALY. The reliability of such analyses is partially dependent on accurately capturing the HRQoL impacts associated with the treatments. However, there are limited data on HRQoL data and utility values in patients with IRD, with no trials providing primary data for patient-reported health utilities (89, 109). Thus, in an HTA appraisal of VN by the National Institute for Health and Care Excellence (NICE) the HRQoL estimates were based on two sources (89). The first source was generic preference MAUI values (EQ5D and Health Utility Index [HUI]) collected from people with visual impairment due to diabetic retinopathy. The second source was from 6 retinal specialists based on proxy vignettes of IRD health states (81). The use of retinal specialists was criticised because it was suggested that they would focus on issues related to vision rather than the impact on all areas of the patients' life, and the lower HSU's were thought to lack face validity (89). The use of assumptions and reliance on data related to other diseases meant the reported cost-effectiveness for the treatment of RPE65 IRD using VN are contradictory (69, 80). This highlights the importance of using HSU's from IRD because conditions such as diabetic retinopathy visual impairment commences at different stages of life, deteriorates at a different rate compared with IRD's and importantly may result in limited vision rather than no vision whatsoever (that is no light perception) which can have vastly different impacts on HRQoL(91).

Another criticism in the evaluation of VN by NICE was that the method to elicit the HRQoL or utility values did not align with the methodology required by the HTA agencies (83, 90, 91, 94, 96, 100). A study in the UK was therefore conducted recently to generate utility values for health states of varying levels of functional vision related to IRD via direct elicitation from the general public using a TTO method in accordance with UK NICE HTA guidelines (104).

Vignettes for five health states that represent the functional impairment to daily living associated with declining sight because of IRD, from the low range of vision present at birth to no vision at all, were developed for the recent utility study in the UK (104). The five health states were considered to be adequate, as they were developed based on testimonials from patients with IRD and aligned with those accepted in the economic model by HTA agencies such as NICE in the UK, Medical Services Advisory Committee (MSAC) in Australia and Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada. Although the HSU's from the study may therefore be applicable to the Australian context, HTA guidelines require country specific preference based HRQoL utility values. Implementing the existing UK TTO protocol in Australia was a pragmatic way to estimate HSU's that meet the requirements of HTA agencies and allows comparison with the values obtained for the UK (102). There was however a limitation from the UK TTO study which was that valuation of worse-than-death (WTD) states were excluded (104). Existing data support the considerable stress among individuals with one of the IRDs RP with documented links to suicidality, which is an outcome that should be considered in the valuation of these health states (30, 105).

The purpose of the current study is to estimate Australian societal-based utility values that can be used in CUA using a TTO protocol adapted from the UK study. This will produce values that are in line with the requirements of key Australian HTA agencies, including the Australian MSAC and PBAC(99, 102, 111).

iii Methods

The protocol for this study was based on the TTO study from the UK. Changes from the UK TTO study were made to follow the existing best practice protocol for composite TTO framework which includes methods for valuing WTD health states and QC measures (104, 107, 112, 113). Five health states from the UK TTO study which had been validated with 5 patients with RP and 2 ophthalmologists in the UK were used. The health states were defined according to American Medical Association (AMA) guidelines on visual disability that encompassed VA changes reflecting

the clarity of vision, i.e. ability of the eye to distinguish details of objects at a given distance and VF changes, reflecting peripheral vision or the ability to see above, below and to the side of something observed (89, 104). The scales of visual disability defining each HS vignette align with the range of visual standards in international guidelines that are applicable to Australia (114).

Each of the five health states were a written description of the functional experience of patients living with progressively worse visual impairment. Impairment was described in terms of independence, social life, family life, tangible limitations, and employment, both during the daytime and nighttime.

- Health State 1 vignette defined as VA better than 20/200 or VF radius of greater than 10° described as “Moderate visual impairment”(115),
- Health State 2 vignette defined as VA from 20/200 to 20/500 or VF radius of 6° to 10° described as “Severe visual impairment”(115),
- Health State 3 vignette defined as VA from 20/500 to 20/1,250 or VF radius of 2° to 6° described as “Profound visual impairment”(115),
- Health State 4 vignette defined as VA from 20/1,250 to 20/20,000 or VF radius of less than 2° described as "Counting fingers"(115),
- Health State 5 vignette defined as VA worse than 20/20,000 described as "Hand motion" to “no light perception”(115),

These health states were reviewed for logic and applicability to the Australian population. The description of the symptoms were grouped under thematic headings such as “physical, social, independence, work” to make the lengthy written descriptions easier to read and comprehend (**Supplementary Figure 5-Figure 10**, Appendix 2). Emotional statements associated with a symptom within each vignette such as, “*You may feel sad or frustrated that you have slightly reduced independence now*“ were altered to avoid directing the respondent on how they should feel about a particular symptom. Instead, the emotional state was presented as ”*You feel sad or frustrated about your condition and its impact*.”

The target sample was 110 participants which aligns with other TTO studies eliciting values for vision disorders (Lloyd et al. 2008 N=122, Brown et al. 2001 N=65) (91, 96). Quotas were applied for age, sex, education and geographical distribution to be consistent with the Australian adult population with respect to those characteristics (116-120). The interview protocol was piloted on the first 10 participants recruited to assess comprehension.

Members of the Australian general population who were not employed in healthcare or market research and with access to web-based tools (MS Teams) were identified using a panel of individuals who had previously indicated a willingness to participate in research studies. The study excluded any participants diagnosed with a visual disability (e.g., RP) or pre-existing eye conditions (e.g., glaucoma). Participants who required reading glasses were not excluded. Recruitment and interviews were scheduled by a market research agency (IPSOS Australia, North Sydney). Upon providing informed consent an interview was scheduled between the participant and the interviewer, and the participant was provided a copy of the health states to review prior to the interview.

Interviews were conducted between October 2022 and November 2022. Videoconferencing (VC) interviews were conducted one-to-one with audio and video connection via MS Teams with one of 4 interviewers. The one-to-one setting allowed interviewers to provide detailed instruction and feedback to the participant where appropriate. Participants were able to withdraw consent and/or ‘change their mind’ on the answers provided at any point by informing the interviewer. Participants were paid $AUD60 by IPSOS for attending the interview.

This study was approved for conduct under the Centre for Health Economic Research and Evaluation program ethics approval from the University of Technology Sydney Ethics Committee on September 8, 2022 (UTS HREC REF NO. ETH21-6090).

Health state utility elicitation (quantitative)

The interview was structured in four parts: 1) background information provided to participant about condition including revision on health states; 2) two visual analogue scale (VAS) 'warm-up' exercises; 3) five TTO exercises; and 4) respondent feedback about questions asked.

To avoid biasing participants' responses, health state descriptions were not labelled in any manner that suggested differences in severity or importance and were presented to respondents in a random order. The interviewer shared their computer screen containing visual aids (VAS feeling thermometer and TTO board) with participants to improve respondents' comprehension of the valuation tasks, as is standard in TTO protocols (113). The participants responded verbally, and the HSU scores were recorded on a score sheet developed for the study that was based on the TTO valuation of MAUIs (113, 121).

Prior to cTTO valuation, a VAS scoring of the same health state descriptions was used as a "warm-up" exercise. The cTTO method was then used to elicit HSU's by asking the participant first of all to select between 10 years in the health state (followed by death), and 10 years in full health (FH) (followed by death), and then a variable shorter period of life in FH if FH was selected. The process then followed a 'ping-pong' approach with the time in FH reduced by half (to 5 years) and then traded back and forth between higher and lower values that were iteratively narrowed until the participant was indifferent between the two life choices (**Supplementary Figure 11A**, Appendix 2) (113). A lead-time TTO (LT-TTO) method was used to elicit preferences for health states considered WTD (**Supplementary Figure 11 b and c**, Appendix 2). In the lead-time TTO (LT-TTO) 10 years in FH is added to the two life options such that participants choose between (1) 10 years of FH (lead-time) followed by 10 years in the health state followed by death, or (2) to live 20 − x years in FH (10 years lead-time followed by up to another 10 years of FH), followed by death, or (3) to indicate that the two options were equally desirable (indifferent between the two life choices). The

possible utility value ranges from -1 to 1, with 0 value “equivalent to being dead”, 1 (“perfect health”) and negative values indicating a state worse than being dead.

The TTO included debriefing questions for respondents that were not willing to trade any lifetime in the iteration with the longest time with FH (i.e., 10 years in FH). The purpose was to elicit the reasons behind non-trading (e.g., fatigue, lack of understanding, lack of interest) and to offer respondents an opportunity to trade lifetime in terms of weeks instead of years.

To ensure consistency among the four interviewers training was conducted which included: an introduction of related HRQoL concepts, explanation of the TTO protocol, interviewer instructions, and practice in groups. After five interviews, compliance was assessed using the three QC measures proposed by the EuroQol Group (time taken to complete all five TTO tasks, negative values and non-traders); QC assessment continued in a staged approach after every 20 interviews (122, 123). The first QC measure was based on interview time because explaining the cTTO task takes time (expected 25 minutes) and thus short task duration may indicate poor engagement. The second QC measure of the proportion of negative values reflects that the WTD task is more difficult to understand than BTD so respondents may be reluctant to value a health state as WTD if the task is not adequately explained (and thus lower proportion moving to WTD and fewer negative values). Finally non-trading, where a participant assigns a value of 1 to all five HS’s, could signal that the participant is trying to shorten the task by expressing their indifference in the first step to the iterative procedure, or it could signal that the task has been misunderstood or not wanting to trade life could be for religious reasons. If there are many non-traders per interviewer, even when the time for the interview looks appropriate, it could indicate poor task explanation. Similar procedures have been already employed for the collection of EQ5D data and have shown to improve data quality(124).

Following the pilot interviews (n=10), there were slight changes to the TTO interview script. The changes included the interviewer confirming the amount of time the participant is willing to trade to

avoid the health state after the point of indifference is reached, and also providing a summary of the health states for interviewers to read if that participant asked for a brief review of the health state after having read the complete health states previously. No changes were made to the health state descriptions following the pilot interviews; data from the pilot were thus included in the final calculation of HSU's (therefore giving a total sample size of n=110).

Data analysis

All score sheet responses were transcribed into an Excel spreadsheet for analysis by the primary investigator with a 10% sample of transcriptions checked against the source score sheet by EM. Any incorrect transcription would be corrected, leading to a further 10% review until no further transcription errors were identified.

Quantitative results (including demographic characteristics, TTO HSUs, and VAS scores) were tabulated and analysed descriptively using Microsoft Excel and are presented as means, medians, standard deviations, and 95% confidence intervals (where appropriate). Demographic data were consistent with the characteristics of the 2021 Australian Census (ABS 2021/2022).

Utility values were calculated from TTO results using the EQ-VT protocol. Statistical analysis was conducted using RStudio 2022.02.3(125). The distribution of individual TTO HSU's was examined by Shapiro-Wilk test and differences between scenarios tested using nonparametric Wilcoxon signed-rank test. A p value below 0.05 was considered statistically significant. To analyse the association between HSU, demographic characteristics (education, employment, age, gender and marital status) and interviewers, an ordinary least squares (OLS) regression model was employed using the R package lme4. Analysis residuals were reviewed after each regression, and the following goodness of fit statistics were presented for each model: adjusted R-squared, F-statistic p-value, Akaike information criterion (AIC), and Bayesian information criterion (BIC).

iv Results

The demographic characteristics of the sample are presented in **Table 5**. Compared with the population statistics for Australia (ABS 2021/2022) the sample had a slightly higher proportion of participants in their third decade (22% vs 15%), a higher proportion who were married (60% vs 47%) and a higher proportion of degree-level or higher education qualifications (47% vs 31%).

Of the 110 planned interviews, 1 participant withdrew consent after completing the VAS, thus the final analysis was conducted on 109 respondents (including 4 non-traders).

Table 5 *TTO participant demographic characteristics*

Study Sample	**n**	**%**	**Australian public demographics**	**%**
Age			**Age**	
18 to 24	8	7%	15 to 19	6%
25 to 34	17	15%	20 to 29	13%
35 to 44	24	22%	30 to 39	15%
45 to 54	17	15%	40 to 49	13%
55 to 64	21	19%	50 to 59	12%
65 and over	23	21%	60 and over	23%
Sex			**Sex**	
Female	60	55%	Female	51%
Male	50	45%	Male	49%
Marital status			**Marital status**	
Married/De facto	66	60%	Married or civil partnered	47%
Separated/Divorced/widowed	21	19%	Divorced/widowed	14%
Education level			**Education level**	
Degree-level education	52	47%	Degree-level education	31%
Employment Status			**Employment Status**	
Employed	74	67%	Employed	78%
Geographic distribution			**Geographic distribution**	
New South Wales	35	32%	New South Wales	32%
Victoria	30	27%	Victoria	26%
Queensland	23	21%	Queensland	20%
South Australia	8	7%	South Australia	7%
Western Australia	8	7%	Western Australia	10%
Tasmania	3	3%	Tasmania	2%
Australian Capital Territory	2	2%	Australian Capital Territory	2%
Northern Territory	1	1%	Northern Territory	1%

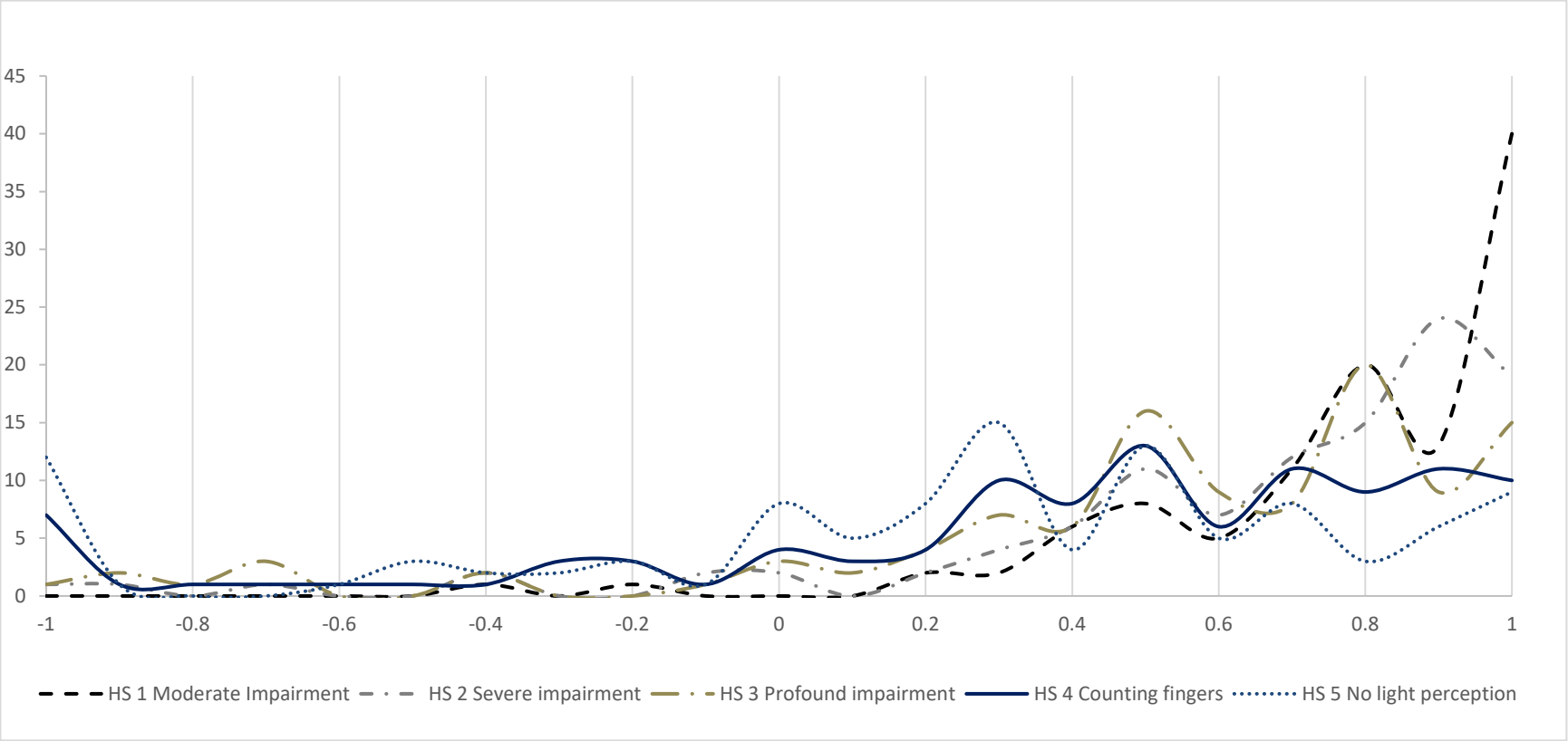
The average time to complete the interview was 44.2 minutes (SD 8.7). Twenty interviews were completed by interviewer 1, 25 by interviewer 2, 4 by interviewer 3 and 60 by interviewer 4. The quality assessment of the initial and ongoing interviews did not identify any issues of data quality.

Utility and VAS values by TTO for each health state are presented in **Table 6,** the frequency of HSU distributions in **Figure 5** and boxplots in **Supplementary Figure 12**, Appendix 2. Mean HSU and VAS values followed the logical and expected order, with increasing visual impairment leading to decreased utility in each case. Participants had a high mean VAS (77.39) indicating good overall health on average. Mean HSU's varied between 0.76 (SD 0.26) in "moderate impairment", and 0.20 (SD 0.58) in "hand motion" to "no light perception".

Table 6 *Mean VAS score and health state utility values*

Health State	n	VAS score				Utility			
		Mean	SD	Median	Range (min., max.)	Mean	SD	Median	Range (min., max.)
"own health "	109	77.39	13.80	80	(30,100)	-	-	-	-
"Moderate impairment"	109	63.15	16.52	65	(15,95)	0.76	0.26	0.80	(-0.4,1.0)
"Severe impairment"	109	52.16	15.13	50	(15,85)	0.63	0.39	0.75	(-1.0, 1.0)
"Profound impairment"	109	40.43	14.27	40	(15,70)	0.50	0.46	0.60	(-1.0, 1.0)
"Counting fingers"	109	27.48	14.76	25	(5,65)	0.35	0.55	0.48	(-1.0, 1.0)
"Hand motion" to "no light perception"	109	17.98	15.29	10	(0,60)	0.20	0.58	0.30	(-1.0, 1.0)

Figure 5 *Frequency of utility values across IRD health states*



Nonparametric testing results of the Shapiro-Wilk test indicated that the distribution of utility values for all health states was skewed (**Supplementary Figure 13,** Appendix 2). The Kruskal-Wallis test showed a significant difference in HSU's ($p<0.05$), and a pairwise Wilcoxon test was conducted to determine significant differences between individual states. All pairs of health states showed significant differences in utility values ($p<0.05$).

Of the total 545 (109*5) HSU evaluations across all respondents there were 75 (14%) instances that were considered WTD which most commonly occurred in the most severe visually impaired health state ("Hand motion" to "no light perception",41%, 31/75) (**Table 7**).

Table 7 *Distribution of worse-than-death trades across health states*

Health State	n	WTD
"Moderate impairment"	109	2 /75 (3%)
"Severe impairment"	109	9 /75 (12%)
"Profound impairment"	109	12 /75 (16%)
"Counting fingers"	109	21 /75 (28%)
"Hand motion" to "no light perception"	109	31 /75 (41%)

Regression analysis revealed that not being married was significantly associated with lower HSU's for the four worst visual impairment health state valuations (severe impairment to no light perception), and not being employed was significantly associated with a lower value for the least visually impaired health state (Moderate visual impairment)**(Table 8**). One interviewer was also found to be associated with higher HSU's across all health state valuations. An alternative specification of the model tested age as a squared variable but it was not significant, and it did not improve the model fit so modelling age as a linear variable was retained. Random and normal distribution of residuals were evident in residual plots and the goodness of fit statistics support the robustness of each of the models.

Table 8 *Results of regression analyses (n=109, Standard Error in brackets)*

Subgroup	"Moderate Impairment" (N=109)	"Severe impairment" (N=109)	"Profound impairment" (N=109)	"Counting Fingers" (N=109)	"No light perception" (N=109)
Intercept	0.609 (0.102)	0.361 (0.152)	0.388(0.177)	0.147 (0.220)	-0.064 (0.226)
Age	0.003 (0.002)	0.004 (0.003)	0.000 (0.003)	0.004 (0.004)	0.002 (0.004)
Gender[a]	0.000 (0.051)	-0.020(0.076)	-0.015 (0.088)	-0.00 (0.111)	0.111 (0.113)
Marital status[b]	-0.042 (0.050)	-0.161 (0.074)*	-0.209 (0.086)*	-0.247 (0.108)*	-0.333 (0.110)**
Education[c]	-0.017 (0.056)	0.015 (0.083)	0.079 (0.097)	0.044 (0.121)	0.142 (0.124)
Employment[d]	-0.176 (0.065)**	-0.164 (0.097)	-0.179 (0.113)	-0.192 (0.141)	-0.179 (0.144)
Interviewer 2[e]	-0.004 (0.077)	0.043 (0.002)	-0.013 (0.133)	-0.076 (0.166)	0.083 (0.170)
Interviewer 3[e]	-0.043 (0.135)	-0.106 (0.202)	-0.171 (0.236)	-0.045 (0.294)	0.099 (0.301)
Interviewer 4[e]	0.160 (0.064)*	0.299 (0.095)**	0.336 (0.111)**	0.282 (0.138)*	0.386 (0.141) **
Adjusted R^2	0.1069*	0.1335**	0.1511**	0.07792*	0.1256**
F-statistic	2.62*	3.08**	3.40**	2.14*	2.94**
AIC	14.16	100.84	134.05	182.01	187.48
BIC	41.07	127.75	160.96	208.92	214.40

* Significant at p<0.05, ** Significant at p<0.01, *** Significant at p<0.001

Note: All variables other than age were entered as categorical variables

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

a.Reference category: Female

b.Reference category: Married

c.Reference category:Degree educated (bachelor or post graduate degree)

d.Reference category: Employed (full time or part time)

e.Reference category:Interviewer 1

v Discussion

This study elicited societal utility values for five health states for IRD using the TTO methodology with members of the Australian general public. The health states describe visual disability from “moderate impairment” to the most visually disabled “no light perception” and align with prior research in the disease area (89, 104). The utility values, which varied between 0.76 for “moderate impairment”, and 0.20 for “hand motion” to “no light perception”, were similar to the average health-related utility of 0.58 reported from 70 Australian patients with various forms of IRD, but are substantially lower than the average utility value reported by the wider Australian population for their own health (for whom a normative utility value of 0.81 was measured by Assessment of Quality of Life 8-Dimension (AQoL-8D) rather than direct TTO)(109, 126).

This study was replicating prior research and thus utilised the TTO methods of eliciting societal utility values. Caution may therefore be warranted when comparing utilities derived through other methods such as discrete choice experiments (DCE), since different valuation methods may elicit different utility values. In the context of TTO-based research, notwithstanding the utility value associated with the most severe HS (hand motion” to “no light perception”), the values from the present study are within the range of other published utility values established using TTO methodology in patients with impaired vision which have been identified through a systematic literature review (0.78–0.26, **Table 9**) (90, 91, 104).

Table 9 *Comparison of health state utility values from the current study and existing literature*

Vision health state	Current TTO study	Brown et al. 1999(90) TTO (N=325)[a]	Brown et al. 2001(91) TTO (N=75)[b]	O'Brien et al. 2023(104) TTO UK study (N=110)
Moderate vision impairment	0.76 (SD 0.26)	0.67 (SD 0.21)	0.65 (SD 0.21)[e]	0.78 (SD 0.20)
Severe vision impairment	0.63 (SD 0.39)	0.63 (SD 0.16)		0.65 (SD 0.25)
Profound vision impairment	0.50 (SD 0.46)	0.54 (SD 0.17)		0.50 (SD 0.27)
Counting Fingers	0.35 (SD 0.55)	0.52 (SD 0.29)	0.47 (SD 0.29)[f]	0.43 (SD 0.28)
Hand Motion- Light Perception	0.20 (SD 0.58)[c]	0.35 (SD 0.29)[d]		0.33 (SD 0.26)[g]
No Light Perception			0.26 (SD 0.08)	

Abbreviations: SD, standard deviation

a .Patients included in the study primarily suffered from age related macular degeneration or diabetic retinopathy

b. Patients included in the study suffered from age related macular degeneration, diabetic retinopathy, retinal detachment, cataract , glaucoma, endophthalmitis, and central retinal vein obstruction.

c. The utility value 0.20 (SD0.58) is for the combined "hand motion-light perception" and "no light perception" health states.

d. The utility value 0.35 (SD 0.29) is for the combined "hand motion-light perception" and "no light perception" health states.

e. The utility value 0.65 (SD 0.21 is for the combined "moderate vision impairment", "severe vision impairment" and "profound vision impairment" health states.

f. The utility value 0.47 (SD0.29) is for the combined "counting fingers" and "hand motion-light perception" health states.

g. The utility value 0.33 (SD0.26) is for the combined "hand motion-light perception" and "no light perception" health states.

In this study married participants reported higher HSU values for the most severe health states (severe visual impairment to no light perception). Marital status has been shown in other TTO studies to influence the number of years traded-off (127). This consistent finding across health states may infer that being married improves a persons' outlook on life when faced with a trading exercise. Alternatively, it may ascribe to the notion that married participants, especially those with children, consider the broader impact of their choices and focus on longevity rather than HRQoL due to their desire to live long enough with their spouse and for their children (128).

Prior research has focused on the range of utility values in the most severe states of visual impairment because vision loss-related disability is not linearly proportional to deteriorating visual acuity or field. Indeed "legal blindness" (defined as VA ≤20/200) captures a wide range of impairment from "severe vision loss" to "near-blindness" which encompasses the ability to count fingers [CF] or detect light [light perception, LP] and finally complete blindness (no light perception [NLP])(114). A TTO conducted in patients that were "legally blind" by Brown et al. (2001) aimed to discriminate utility values across a range of vision these patients. The study showed a mean utility of 0.26 for patients with NLP and 0.47 for those with CF-LP which demonstrates that utility value

decreases dramatically with the total loss of light perception in each eye (**Table 9**). This granularity of HRQoL impairment has had a substantial impact on the economic modelling of IRD (reducing the utility value for the worst HS to reflect NLP in the EE of VN produced by Institute for Clinical and Economic Review in the US increasing the QALY gain from 1.3 to 5.2) thus highlighting the importance of elucidating utility values across the full spectrum of visual impairment (69).

The HSU reported in this study for the most severe health state “hand motion” to “no light perception” health state (0.20) aligns with the HSU’s elicited by Brown et al. (2001) but is lower than the HSU for the same health state from the UK TTO study (0.33). This is likely a consequence of allowing health states to be rated as WTD in the current study which meant that respondents used it, while in the UK study they were unaware of WTD and thus bounded at 0. A WTD state was selected in 14% of scenarios, most commonly for the most severe visually impaired health state (“Hand motion” to “no light perception”), reducing the HSU value. This finding aligns with the increased suicide rates associated with severe vision impairment reported in the literature thus highlighting the importance of including methods for valuing WTD health states (105).

HSU values are used to inform the estimation of QALY’s in CUAs required for HTA. HTA agencies prefer estimates of HRQoL or utility from the within-trial evidence from patients (using generic or disease-specific utility instruments), however in the absence of such data or where there are particular health state impacts for a condition that are not well captured by existing generic instruments, direct elicitation of utility weights by the general public, via TTO methods for example, are acceptable (111). Direct elicitation based on the general population in their own country is requested because resources allocated for health technology in countries such as Australia and the United Kingdom come from the public such that preferences should reflect their own society (102, 129). However, there is a resource burden, in terms of time and money, associated with conducting TTO studies and notwithstanding the differences in the HSU for the most severe visually impaired health state (“Hand motion” to “no light perception”), a similar study using the same health state vignettes conducted in the UK produced HSU’s similar to those in the present study. This study

therefore supports the consideration of the HSU's from this study in CUA conducted in other countries with similar cultures and HTA processes as in Australia.

One of the criticisms of the vignette approach is that it may not accurately reflect the extent to which patients learn to cope with and adjust to their disease (130). For instance, elements of adaptation might be expected among patients with IRD considering that they live their whole lives with the deteriorating condition and do not know of anything else. Vignettes may also lead people to focus specifically on certain aspects of the description and could place undue weight on a specific descriptor (99). There are however criticisms with other HRQoL instruments such as generic instruments lacking sensitivity to vision loss (EQ5D), and that the use of vision-specific instruments (National Eye Institute Visual Function Questionnaire, NEI VFQ) focus on physical rather than social or personal aspects of HRQoL (87, 131, 132). There is also the problem of collecting HRQoL data from other diseases that may not accurately reflect that circumstances of patients with IRD may have a different impact upon HRQoL. For example, generic instruments showed a greater impact of glaucoma (a disease the impacts peripheral vision) on mental rather than physical aspects of QoL, and vice-versa for age-related macular degeneration (a disease diagnosed later in life that affects central vision and thus the ability to conduct tasks day to day). This was attributed to patients with early stages of glaucoma (in whom there is minimal functional impairment), worrying about blindness that affects their mental QoL, while physical aspects of QoL remain relatively unaffected (131, 132). Patients with RPE65-mediated IRD are impacted from birth and suffer loss of central vision and peripheral vision as well as night blindness therefore vignettes that adequately represent changes in this RD that has limited HRQoL and utility data were important. The health state development for this study was based on patient and carer testimonials, supported by qualitative findings from previous research to comprehensively represent the spectrum of disease and its daily impact on patients with IRD (30, 104). For example, the health states in the current study provide the context to living with impaired vision due to IRD that included limitations to everyday activities such as commuting and socialising in the day and the nighttime and the increasing worry experienced from impending loss of vision due to the degenerative nature of the condition.

The adaptations made to the health state vignettes have some strengths and limitations that should be considered when interpreting the study results. Best practice guidance on the development of health state vignettes suggests that uncertain statement such as “you may feel” should be avoided because respondent interpretation of such statements may vary (107). However, by rewording such statements and presenting such emotional impacts as certainties, as occurred in this study, means the vignettes may no longer be a reasonable representation of the typical experience of an IRD patient, It is important to note that although the updated health state descriptors were not revalidated with patients or clinicians, the similarity of the resulting HSU’s with those from the UK study indicates that the changes to the HS’s didn’t impact on the respondent interpretation.

Despite the development of vignettes that reflect real life experience of patients, the utility values from this study do not represent all IRDs. IRDs are a large group of clinically heterogeneous conditions such that visual acuity, visual field and night vision may not deteriorate in parallel as they are presented in the vignettes, but rather at different trajectories than is reflected in the health states. Furthermore, some IRD’s do not affect VA, VF and night vision for example, cone dystrophies typically present with progressive loss of visual acuity, photophobia and colour vision disturbance (133). The potential difference in utilities between different IRD’s could be explored in future research.

IRD is detected in early childhood with vision deteriorating over the patient's life (11). The average age of patients receiving VN for RPE 65 mediated IRD in clinical trials was 15 years and the product is available to children over the age of 3 years (10). The current study was however restricted to adults and this can be an issue for the comparability of these values and their use in EEs, and it raises the question of whose values should be sought when valuing children’s health (102). While there is the argument that the adult general public as taxpayers and potential beneficiaries from publicly funded healthcare should be the source of valuations, it can be argued that children are also beneficiaries of healthcare services and older children may contribute financially through tax

system. However, research indicates that TTO tasks are unreliable in young, adolescent, populations because they have difficulty in understanding and interpreting the TTO tasks (134). In addition, adolescents have been found to underestimate the effects of mild, moderate, and severe vision loss upon HRQoL compared with patients with actual vision loss, and thus are not good patient surrogates for utilities used in cost-utility analysis (135).

The feasibility of conducting valuation studies online via VC interviews has been challenged for two reasons (136). The first being that the iterative procedure in the TTO task is complex, which is why face-to-face interviews have traditionally been used, and thus VC interviews may result in poor quality data. Second, despite the advantage of greater geographical reach and more rapid data collection, requirement for VC interviews can pose a barrier preventing older people, less educated people, diseased populations and less technically skilled from being sampled. Indeed, the sample enrolled in this study shared demographic characteristics consistent with the Australian population generally but there was a higher proportion of participants with degree-level or higher education qualifications compared with the general population (47% vs 31%, **Table 5**) in the study. However no significant differences in HSU by education were observed in the regression analyses **(Table 8**). Moreover recent research demonstrates that VC administered interviews provides equivalent data quality to face:to:face interviews and that VC as a mode of administration does not impact on TTO interview task duration, number of moves or proportion of specific responses (123, 136).

There are some limitations to discuss. The study had a sample size of 109 which is in line with the UK TTO study but may be considered a limitation due to it being smaller than other TTO utility studies (90, 136). This study intended to replicate a prior TTO study conducted in the UK as closely as possible. Consequently, images representing visual impairment in each health state were not presented to participants; only text descriptions of each health state were provided, which could be a further limitation of this study. In addition, because the health states describe impairment associated with either VA or VF changes, the HSU's will need to be applied to specific IRDs with caution because the health states cannot necessarily be attributed to various levels of VA and VF

impairment. Finally despite developing an interviewer script and training the interviewers, interviewer effects were detected in regression analyses with a single interviewer, who had conducted over half of the interviews, positively impacting the HSU's across the health states **(Table 8**).This reinforces the need for continuous data monitoring and checks during data collection as recommended in TTO protocols (112). Protocol compliance by interviewers is also a possible limitation that can lead to poor comprehension of the valuation task by the respondent. The HSU order in a small proportion of the sample (10%, 11/109) was not logical, that is at least two of the five HS's were not clearly ordered in terms of severity and the difference in HSU was greater than 0.05, which may signal poor comprehension and task misunderstanding. However, the average interview duration (44.2 minutes) is greater than what is expected for 5 HS's as according to standard QC measures respondents generally take 5 minutes to complete each TTO task. This indicates that interviewers spent sufficient time explaining the task to participants and participants had time to ask questions (122, 124). Furthermore, only four respondents (4%) were classic "non-traders", which was a QC measure of task comprehension used in the study. Otherwise non-trading occurred in 28 (26%) interviews, similar to other TTO studies, most commonly for 1 HS only (12%) and generally in the mildest HS, moderate vision impairment, on the basis that it did not impact much on HRQoL (**Supplementary Table 24 and Table 25**, Appendix 2)(137).The percentage of non-trading, as a measure of possible interviewer effects, indicates respondents had a reasonable understanding of the task.

Conclusion

This study provides valuable information on HSU's across a range of IRD health states from the Australian general population perspective. Overall, our findings provide important insight into the perception of vision loss with health state utility values. These utility values were elicited using a method and sample that may allow the resulting values to be incorporated into EEs for HTA purposes in Australia and other countries, with similar cultures and HTA processes, in assessing the value to society of new technologies for IRD.

Chapter 4 Research study 3 Caregiving for patients with IRD.

vi Chapter 4 summary

In recognition of the caregiver and broader family burden associated with inherited retinal disease (IRD), a caregiver disutility was applied in the four worst health states (HSs) in three economic evaluations (EEs) reviewed in research Study 1 (Chapter 2). While National Institute for Health and Care Excellence (NICE), the health technology assessment (HTA) agency in the UK, accepted the inclusion of caregiver disutility in the quality-adjusted life years (QALY) calculation included in the EE of VN they challenged the disutility value applied including how many caregivers per patient it should apply to and whether to apply it to caregivers of adult IRD patients(81, 82). This inspired the third part of this research which explored qualitatively, through focus group interviews, the impact from caring for patients with IRD over their lifetime.

The aim of Chapter 4 is to investigate how caring for a person with an IRD impacts the caregivers life, and how that impact changes as the person being cared for gets older.

The findings from the study provides evidence to support applying caregiver burden over time which challenges the deliberation by NICE to reduce or remove the caregiver disutility value after the patient with IRD turns 18 in the EE of a gene therapy (GT) in IRD(81, 82).

The research presented in Chapter 4 was submitted for publication to the Quality of Life Research journal in August 2025 and is currently under review.

vii Abstract

Purpose

Rare genetic conditions, mainly affecting children, pose significant challenges for caregivers due to their complex and continual healthcare requirements. Considering unrelated healthcare costs and the emotional strain experienced by caregivers is essential for assessing the cost-effectiveness of treatments for these diseases. This research explores the implications of caring for an individual with an IRD on the caregiver's life and how this impact evolves as the patient ages.

Method

Semi-structured interviews were conducted face to face or virtually with seven caregivers using a guided script. Audio recordings were transcribed verbatim. Employing a mixture of inductive and

deductive analytic approaches a thematic analysis was conducted. A medical resource burden survey captured the time commitment of caregivers attending healthcare appointments for patients with IRD.

Results:

The results highlighted the multifaceted nature of their support roles across various life stages. Caregivers provided critical assistance with daily activities while also adapting to the changing needs of patients with IRD. They reported emotional challenges, alongside a strong sense of duty and obligation in fulfilling their caregiving responsibilities. Many caregivers struggled to relinquish control, regarding it as both a necessity and a responsibility because of the limits on the individuals they care for. The need for social support emerged. Furthermore, their caregiving duties often led to significant personal and employment-related sacrifices, emphasising the critical need for more structured support and resources for caregivers. Overall, the findings reveal the layered emotional and practical challenges experienced by caregivers of patients with IRDs, underscoring the importance of acknowledging and addressing their well-being.

Conclusion:

This study underscores the significant emotional, social, and economic challenges faced by caregivers, advocating for tailored support systems and increased recognition of caregiver burden in research, policy, and practice. Additionally, it emphasises the integration of caregiver burden into HTAs to provide a comprehensive assessment of the social value of new technologies for IRDs.

viii Introduction

Taking care of an ill or disabled individual imposes a well-documented burden on the caregiver (138-142). The caregiving burden encompasses the emotional, physical, and financial strains experienced by those providing care to patients, which can significantly impact their quality of life (QoL). It is suggested that health intervention reimbursement decisions should be viewed in the context of the entire family and that integrating caregiver burden into HTA's can capture a more comprehensive picture of the costs and benefits associated with a health intervention(143, 144).

Rare genetic conditions are predominantly diagnosed in children and pose substantial challenges to caregivers due to the complexity and ongoing nature of health service needs (1, 77). The possibility of lifelong caring, limited capacity for independent living and lack of treatment options means paediatric rare genetic conditions have a large impact on families and caregivers (77, 145, 146).

IRDs constitute a group of clinically and genetically heterogeneous degenerative conditions in which gene mutations cause a progressive loss of photoreceptor cells and an impairment for visual function. Individual IRDs are rare and gradually lead to an irreversible visual decline including potentially to blindness (58, 62, 147, 148). As the disease progresses and visual function becomes increasingly impaired, patients with IRD adapt however support is still needed and is largely provided by unpaid community-dwelling caregivers, usually friends or family members (30).

Capturing the impact on the caregiver in an EE is critical for therapies that may offer long term benefits allowing patients with a rare disease (RD) to live a relatively normal life and potentially alleviate caregiver burden (9). Inclusion of nonrelated healthcare costs and consequences of IRDs, such as alleviating the emotional stress of seeing a close relative or friend suffering from a serious condition and time spent in providing informal care, have been shown to have profound effects on whether a therapy is deemed cost-effective (74, 149).

The aim of the research is to investigate how caring for a person with an IRD impacts the carers' life, and how that impact changes as the person being cared for gets older.

ix Methods

This is a mixed-methods study, comprising semi-structured interviews with caregivers and a survey related to attending vision related medical appointments with those who are being cared for (**Supplementary Table 26 and Table 27**, Appendix 4). The theoretical framework used to explore

the humanistic burden of IRD on caregivers is phenomenology. Phenomenology is concerned with in-depth understanding of the participants' lived experiences and the meanings the participants perceive of those experience (150).

To assess the time commitment of caregivers attending healthcare appointments for patients with IRD, participants were required to complete and return a medical resource burden survey before the interview, (**Supplementary Table 27,** Appendix 4).

Sample size, recruitment and ethical consideration

Determining if a sample size is adequate in qualitative research is relative, since the events and experiences are the focus of the research rather than the individuals (151). The intent of the recruitment process in this study was to reach theme saturation in the qualitative interviews with respect to identifying the factors that impact caregivers of patients with IRD and how these factors change as the patients with IRD grow older. Prior to study start ethics approval was obtained (UTS HREC ETH23-8979).

Evidence suggests the majority of themes from a focus group discussion are identified after 3 focus groups (of 5-6 participants each), and among individual interviews little new information is gained beyond the first five to six interviews (152). As such we originally planned to recruit 20 participants to enable 3-4 focus groups. A minimum of 3 caregivers was required to host a focus group, otherwise interviews were planned to be held individually.

Caregivers residing in Australia were invited to participate if they were an unpaid caregiver and the person being cared for (for example child, husband, wife, parent, family member) had received a diagnosis of IRD before 18 years of age (regardless of the IRD subtype), are English speaking, and had or currently have an active role in IRD care. Caregivers were required to attend an online virtual interview, or a face to face focus group. Because of the low prevalence of individual IRD's the study recruited a convenient sample that relied on carer voluntary participation (147).

The study was advertised to carers via vision related patient organisations (Retina Australia, Vision Australia, Cure Blindness Australia). Due to the slow recruitment of volunteers through patient organisations a new recruitment strategy was implemented after obtaining ethics approval. Suitable caregivers were identified from a panel of individuals who had previously indicated a willingness to participate in research studies by market research agency (Ekas marketing research Australia). Written informed consent was obtained from the participants and they were asked to complete a medical resource utilisation form. Participants were compensated $100 and up to $50 for travel or parking costs (if they attended face to face focus group). The sampling of panels of individuals who had volunteered to conduct research using the inclusion criteria presented above continued and interviews conducted until the emerging theoretical themes were saturated.

At the beginning of each focus group/ interview, participants were informed that the session would be recorded. The interviewees were made aware they could stop the interview at any time they needed. During the interviews supports were planned in case the researcher perceived discomfort or distress of the interviewee. These supports included: discontinuation of the interview or referral for support; neither were required by those participating in the study.

Interviews and data analysis

A semi-structured interview guide based on open-ended questions captured the participants' experiences of caregiving how it has changed over time across all aspects of life (physical, mental, financial and social) (**Supplementary Table 26,** Appendix 4). The interview questions were formed based on literature describing carer burden (142, 153). Prior to initiation of caregiver interviews, the appropriateness and order of the interview questions were discussed within the research team. In-depth semi-structured interviews with open-ended questions grouped as general impact, medical management, family life, worry, social, physical/emotional and financial were undertaken by two researchers (RDL, MF). An open and naïve approach was used in the interviews to explore the participants' responses by asking probing questions, e.g. by using mirroring and paraphrasing (154, 155). The interviews were conducted by the first two authors (RDL and MF), who had no former

relationships with the participants prior to study commencement. All interviews were audio recorded and transcribed verbatim by MF using otter.ai. To ensure accuracy, MF reviewed each transcript by replaying the audio recording and checking the text word for word, manually correcting any errors.

A qualitative thematic analysis was used to identify and analyse themes in the interview transcripts (156, 157). Data analysis was performed iteratively using three methodological principles: maintaining an openness to the phenomenon of interest, identifying and exploring preconceptions, and maintaining an ongoing reflective attitude guided the phenomenological approach to data analysis.

Researchers read and re-read the quotations line-by-line to familiarise themselves with the data prior to coding. Coding of the first transcript was conducted following review of the transcript line-by-line by two researchers (MF and RDL) and coding the data together, discussing and reconciling, and refining the coding throughout the process to generate a codebook. The three remaining transcripts were coded by a single researcher (MF) with any new codes added to the code book. No new codes were generated after the third transcript. Upon completion of coding the transcripts, 42 codes were generated. Coded data were reviewed in relation to each other and sorted into preliminary themes. Themes were identified systematically by the researchers using a combined deductive and inductive approach which allows the exploration of a-priori themes **(Table 10**), but also leaves space to discover other unexpected aspects of the participants' experience (142, 158, 159). The interpretation of themes was discussed and agreed by the research team. Because of the low sample size, it was agreed among the researchers that codes generated from at least 2 individual responses would constitute a theme. In the final stage a narrative description with extracts for each theme was compiled by one researcher (MF), this was discussed and agreed for each theme by all researchers. NVivo 12 software was used for data storage, coding and mapping.

Responses to the medical resource questionnaire were summarised using descriptive statistics. The survey data are presented for two categories of caregiver, those who care for persons less than

18 years and those who care for those ≥18 years with the intention of identifying whether there are obvious differences in the frequency of visit and types of health care required by children and adolescents compared with adults to better understand the time commitment required from caregivers across the life span of the patient with IRD

Table 10 *A-priori themes and subthemes used for deductive analysis*

Major theme	Positive subtheme/code	Negative impacts subtheme/code
Coping	Social support Normalisation Appreciating child's resilience	Avoiding glaucoma related thoughts Emotional detachment Blaming health professionals
Emotional well-being	Managing fleeting anxiety Feeling hopeful or grateful Feeling proud of child	Feeling anxious or scared Feeling shocked, guilty or regretful Feeling low or helpless
Medical and social support	Medical care becomes routine Positive reinforcement with child Community establishment	Perceived that treatment is hurting child Overprotective of child Fear of schoolyard bullying
Social well being	Relationship teamwork Connecting with other carers Sharing experience	Relationship conflict Trouble caring for other children Social isolation
Clinical and familial control	Acceptance of disease outcomes Trusting the child to be autonomous Confidence in managing disease	Wanting a cure Attending appointments with adult child Worried about others caring for child
Family planning	Gaining knowledge of future risk Confident in detecting condition Planning ophthalmic follow ups	Worried about future children or grandchildren Not wanting more children Self blame for genetics

Source: Knight LSW, Ridge B, Staffieri SE, Craig JE, Prem Senthil M, Souzeau E. The Caregiver Experience in Childhood Glaucoma: An Interview Study. Ophthalmol Glaucoma. 2022;5(5):531-43(142).(142)

Medical resource survey and data analysis

The medical resource burden questionnaire asked caregivers to report, "*Approximately how often they attend appointments with healthcare practitioners specifically for or related to IRD with the person care(d) for*"? Caregivers selected one of seven options for frequency of visits from never to weekly across ten categories of health care. Formal statistical comparisons of the medical resource burden between the two groups, those who care for persons less than 18 years and those who care for those ≥18 years, was not conducted due to the small sample of caregivers in the study, However, comparing the number of caregivers attending medical visits and the frequency provides some indication of the time commitment borne by caregivers.

Data Quality (Trustworthiness, Dependability, Transferability)

Quality in qualitative research can be evaluated from the aspects of clarification and justification, procedural rigour, sample representativeness, interpretative rigour, reflexive and evaluative rigour and transferability (160). In terms of rigour, the main concept of this study was well defined, and the design, sampling and choice of data collection method of this project were in line with the desired outcome of the study. The interview questions were formulated in a way that addressed the research concepts and questions. To achieve consistent content, the same researcher asked the same questions during interviews.

Confidentiality

Participants were assured their data were de-identified (anonymised) and their experiences were used only for the research purposes of this project. Participant responses were recorded using an anonymised identification number. Electronic data were stored in the primary analysts (MF) folder on the secure University of Technology OneDrive. Data will be retained for a minimum of five years and then deleted.

x Results

Participant characteristics

Six caregivers were identified through the market research agency and two responded to an advertisement in a Retina Australia newsletter. One participant withdrew consent while organising the focus group such that a total of seven eligible caregivers were interviewed between May and December 2024. A face-to-face interview was conducted with a group of three caregivers, a videoconference with a group of two caregivers and two videoconference meetings with single participants. The interview times ranged from 35 mins to 100 mins. Four caregivers reflected on caregiving of children and adolescents (n=4) aged 5-17 years, and three reflected on caregiving of adults (n=4) aged 35 to 86 years (noting one parental caregiver had two adult children with an IRD, **Table 11**). The persons cared for were diagnosed with kerataconus, retinitis pigmentosa, cone/rod dystrophy and rod dystrophy. The age range of the caregivers was 40 – 71 years, and most

caregivers were parents with children affected with IRD (n=5) while one was a daughter caring for her father and the other had been a friend who had been volunteering to assist a patient with IRD for over 10 years.

Table 11 *Caregiver focus group participant demographics*

Sociodemographic characteristics of the caregivers, n=7	
Gender,	
Female	5
Male	2
Age group of persons cared for,	
0-18 years	4
19-37 years	1
38-55 years	1
55-73 years	0
>74 years	1
Caregiver relationship	
Parent	5
Child	1
Friend	1

Seven overarching themes were generated, five themes established based on the deductive coding and two themes were established using an inductive process. The themes, codes and concept for each code are presented in **Table 12**.

Table 12 *Major themes identified for caregivers in the study*

Major theme (coding type)	**Codes**	**Concept**
Coping (deductive theme)	• appreciate persons resilience • adapting or accepting situation • normalisation or learning to cope	Caregiver coping i.e. adapting to the caregiving situation
Emotional well-being (deductive theme)	• fear of hereditary impact on oneself • feeling anxious or scared • feeling exhausted • feeling fearful • feeling hopeful or grateful • feeling low, despondent, discouraged or sad • managing emotional side • feeling shocked guilty or regretful • self-blame for IRD • feeling unprepared or ill equipped • worry about the future • frustration • positive reinforcement of person cared for • reward from caring • impact on own health	Caregiver emotional well being (positive and negative feelings associated with being a caregiver)

Medical and social support (deductive theme)	• worry about lack of autonomy • advocating for self or IRD person • attending appointments • community or family support network • getting medical appointments or care for IRD person	Caregiver getting medical and social support for IRD person
Social well being (deductive theme)	• relationship conflict • resolve conflicts or disagreements caused by or involving IRD person impact on family • competing needs	Caregiver social well being (impact on immediate and extended familial and extrafamilial relationships)
Relinquishing control (deductive theme)	• acceptance of disease outcomes • change living habitat or arrangement • lack of trust in others caring • looking for a cure or treatment • trusting IRD person to be autonomous	Learning to accept the IRD persons condition and their actions and helping the RD person adapt
Need for support (inductive theme)	• desire for help or support for caregiver. • feeling forgotten • feeling taken for granted • lack of support • impact on life • impact on work • financial impact	Caregivers expressed a need for help for themselves and did not feel they were receiving support.
Duty (inductive theme)	• protective or avoidance • responsibility or dependence • unrelenting constant demands • preparing for independence	Most caregivers felt obliged to assume their caregiving roles, viewing it as a necessity rather than a choice. Caregivers expressed felling they have no alternative but to fulfill the caregiver role.

- Theme 1 – caregiver coping

Caregivers (2/7) highlighted the resilience of the individuals they care for, emphasising their ability to normalize their condition which is a positive coping mechanism. They recognise and commend the person's resilience in managing life despite challenges presented from vision loss. For instance, a caregiver spoke proudly of their teenage son acknowledging that despite having to forego playing a sport and even missing out on sporting scholarship, the son showed strength in handling his disease outcomes "*(father) So he had to give all that up and watch his class mates continue. So that was just part of it. That was explained to him. But I think he's taken it all in his stride quite well*". Similarly, another caregiver described the friend they were caring for who was in their third decade of life, as having adapted to her conditions, noting she had continually adjusted to her condition since birth. The caregiver celebrated the strength and resilience of the person cared for, reflecting she was living an outgoing life, recognising she was thriving in the face of adversity "(*friend) she's*

just had to become adjusted to…She's very outgoing…maybe because it has been since birth. She doesn't know any different"

All (7/7) caregivers expressed a positive focused coping strategy of accepting of the IRD condition in the person they cared for. Accepting the condition was consistent among caregivers but it was evident that they are constantly adapting to the changing needs of the patient with IRD and dealing with the consequences of deteriorating vision. Caregivers of younger children find hope in their ability to adapt to the condition and witness their resilience, illustrated by a caregiver settling in and taking their child's condition as normal. "(*father) We…settled…..in and take it as normal and take a look how he goes now*". Caregivers of middle-aged patients with IRD acknowledge the limitations of deteriorated vision and recognised the individuals' efforts to help themselves but they expressed there was an ongoing need to step in and provide guidance and support. "(*mother) mum, you know there's nobody and I've got to pick my daughter up at three o'clock from school …so can you come*". Caregivers of elderly individuals noted an increase in the assistance they were providing over time and the requirement to take a more directive role because of the diminished capabilities in the aged person, "(*daughter) he was going himself to the public hospital but he fell on public transport … now he's got a private appointment because the delay (in public) was too long for a period of time…. I go with hi*m".

Caregivers often found themselves managing the frustrations of the person they care for, particularly as age and deteriorating vision present new challenges, such as instances where the individual may resist assistance and inadvertently face difficulties due to their limited vision " (*mother) he wouldn't let me hold his arm, and he would run into people…And I'd be saying, he can't see you, trying to apologize to people and smooth it over*" and "(*daughter) this level of frustration because…his independence has gone….I seem to get the blame for a lot of things*". These examples illustrate the complex emotions and adaptive strategies employed by caregivers as they support patients with IRD through various stages of life (161).

- Theme 2 - Emotional well-being of the caregiver

There was a mix of positive and negative feelings experienced by the caregiver. Almost all caregivers (6/7) conveyed a sense of anxiety regarding a variety of challenges associated with the disease including the initial diagnosis, uncertainty about the progression of the disease, concerns about the patients with IRD being unable to travel from one place to another or potentially harming themselves due to vision loss, or the responsibility of ensuring the patient with IRD can attend appointments.

"(*father) The worry that worry is always on the back of your mind. The worry is not something like you're going to show 24/7 Yeah, but in the back of my mind, I'm always concerned, ….maybe he's going to fall, maybe he's going to miss his steps. … let's say something is very simple, two minute, instant, noodles, .. need a hot water.. whether it's a water in the cup and put it in the microwave or use a kettle into the container, as a normal person, this is a very simple task. But for him We are always worried that .... maybe misjudge with the hot water and its going to burn him*"

While a couple of caregivers (2/7) expressed feeling optimistic and hopeful for younger patients with IRD "(*father) we just have to stay positive and show him the positive side to life….hopefully there will be some sort of solution for our sons future….as long as you have a healthy outlook…without good eyesight I think he can still have an enjoyable life*", a caregiver of patients with IRD who were middle aged described an emotional journey that had been dynamic from to very despondent times to positive and hopeful times *"(mother) he really straightened out…first time in his life…would have been about 30 or so…I saw the potential*"

Overall, however, most (5/7) caregivers expressed a sense of sadness and feeling regretful at opportunities lost as they witness the impact of vision deterioration on the lives of patients with IRD. They mourn the lost opportunities and dreams that the patient with IRD may experience. For example, a caregiver of a young teenager expressed sadness at the thought of their child not experiencing certain aspects of a typical teenage life, "(*father) can't drive a car, it limits a lot of options for him… your freedoms are.. limited … there's a lot of things you won't be able to*

experience". As the age of patients with IRD increases and vision loss deteriorates further, so does the weight of the sadness felt by caregivers, as exemplified by a mother's profound sorrow and feeling helplessness in the face of her child challenges "(*mother) just so tragic, and you know, as a mother, it's just heartbreaking, and there's nothing that I can do to make that any better*". Even in the late stages of life, caregivers continue to express deep empathy and sadness for the person they care for, acknowledging the cumulative impacts of the gradual loss of abilities "(*daughter)he's going through all these changes, and they're stacking up… its tough because everything is slowly being taken away…I feel sorry for him*".

- Theme 3- Medical and social support by the caregiver

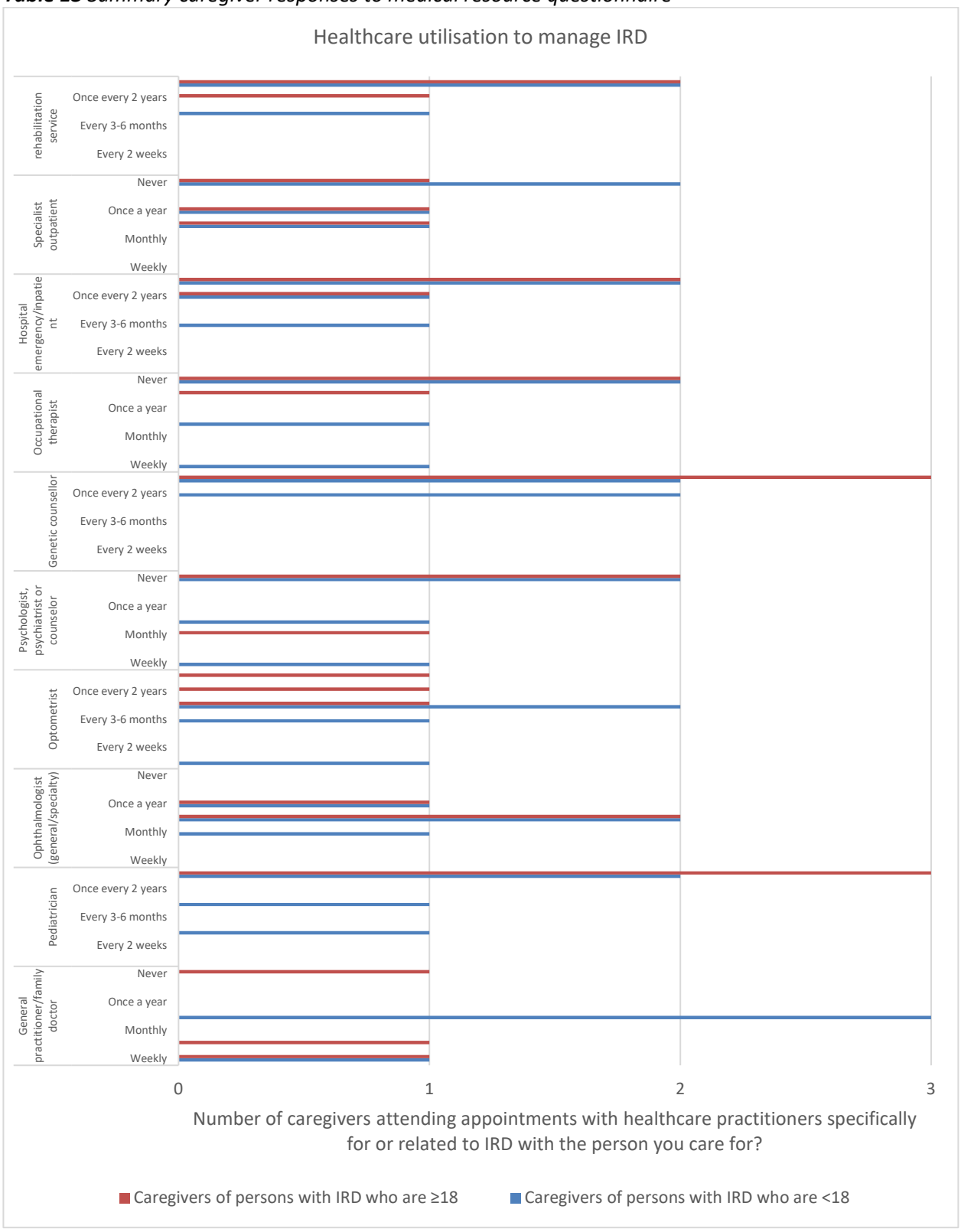
The four caregivers (4/7) of younger patients with IRD volunteered the overwhelming experience of the diagnostic process, actively seeking treatment, and attending multiple medical appointments with different doctors within the same specialty seeking a variety of opinions " (*mother) we went from 2 therapies a week to 6 …then he had the next drop in vision, and life has really changed since that drop in vision. You didn't have to worry about him because he could see enough to know. But now there's a lot of safety concerns. There's a lot of trips to hospital because he has misjudged something*". This contrasted with the experiences of caregivers of middle age to older patients with IRD who either did not mention the diagnostic journey (3/7) or reflected on it briefly and factually without conveying a sense of having been overwhelmed "(*mother) was the first one diagnosed, we were all, everyone in the family was checked and we had no sign of it. We had no family history of it. And when, two years later, when (second son) turned 10, I recognised the early symptoms of night blindness, and knew that he must have it. So now I have these two sons with retinitis pigmentosa*"

All caregivers were focused on providing support for the medical needs of the patients with IRD, recognising that these needs extend beyond the IRD itself, as some individuals also required medical support for other co-existing health conditions. For instance, multiple (5/7) caregivers expressed concerns about the emotional well-being of the patient with IRD, indicating the need for

psychological and psychiatric support in addition to medical care "(*mother) he is in denial. He doesn't .. want to become highly visible…. he internalises. So that's why we're seeing a psychologist, and we're going to have to see a psychiatrist, and he's becoming a loner*". Caregivers also emphasised the challenges and time-consuming nature of medical appointments and treatments, reflecting the significant commitment involved in supporting the patient with IRD "(*friend) You know, seeing the ophthalmologist you've got a certain time and then of course the appointment never runs on time. So you know you've got that wait and then depending on what assessments they do, that can take time you know, waiting for dilating drops, etc, etc. split lamps so that can take I allow myself a good day*". Additionally, they describe the practical measures taken to assist with medication management, such as organising and labelling medication to ensure safety and minimise errors due to the individual's visual impairment "(*daughter) I have to double check everything. I've got to read all the prescriptions to make sure … ticked every box*".

A summary of the response to the medical resource burden associated with IRD questionnaire are presented in **Table 13**. One caregiver of a child or adolescent did not respond to the question about attending rehabilitation services with the person who has an IRD such that there were only three responses for this cohort and this category. The most frequently attended medical appointment for IRD by caregivers was to the GP (6/7 caregivers attending every week to every 3-6 months) and ophthalmologist (7/7 caregivers attending visits monthly to annually). Overall, respondents expressed a similar burden attending medical appointments with children and adolescents as for adults specifically for or related to IRD thus inferring a similar time commitment for medical support from caregivers irrespective of the age of the patient with IRD.

Table 13 *Summary caregiver responses to medical resource questionnaire*



All caregivers were also actively involved in providing diverse support to help those with IRD navigate daily life. For example caregivers described the need to provide transportation to and from school, facilitating educational support in younger and middle aged patients with IRD or assisting middle aged patients with IRD with shopping task or general mobility due to in some cases the reluctance to use a cane due to pride " (*mother) I still do basically everything I used to do when he was a toddler*." For instance, the caregiver of a school aged person sought educational support outside of school through a tutor due to the illness affecting the child's confidence and relationships at school.

Caregivers of older patients with IRD expressed the need to learn new skills themselves to assist in navigating computer systems for example to assist the patient with IRD due to the lack of timely or co-ordinated support from universities. They also commented that providing housing support on and off over many years as one of the largest impacts they faced. These instances underscore the ongoing assistance provided by caregivers for older patients with IRD in ensuring access to education opportunities and housing as well as the additional effort required of caregivers to address the shortfall of existing support.

"(*mother) mate used to help…getting transport from A to B, help with technology…technology is a huge issue…he uses an iPhone which is probably best for blind people, and he uses it well, but these things never work the way they should…there's always difficulties*" and "(*mother)requires so much support with just getting food in, getting to places…, and all of the technology related things that you have to do these days*."

The NDIS is a system that aims to provide support for people with a disability and allows people to stay at home and receive care. Few caregivers (3/7) stated they had to get involved in the person they cared for seeking support from the Australian National Disability Insurance Scheme (NDIS; https://www.ndis.gov.au/). Those seeking support from the NDIS on behalf of the patient with IRD felt like victims of a system that claims to assist but often complicates matters, requiring them to navigate progressively challenging obstacles. Reflecting on the struggle to maintain NDIS care for a

middle-aged son with IRD and comorbid health issues requiring 9-10 hours of support, one caregiver described the smooth process of allied health organising the NDIS package that became very stressful for her to then renew, "(*mother) So after being in hospital with all the allied health people. He got a fabulous NDIS package at the end of that, because it was all coordinated through them. That was very good. But a year later, they chopped it when it was due to be redone …a battle that went on for seven or eight months…very stressful*". Another caregiver was annoyed that vision support only started when vision had substantially declined and that it took over 12 months to assess a claim, "(*mother) They said that they don't support low vision. So even though at the time everybody knew that (son) would eventually go legally blind. NDIS will not step in until you hit that 6/60 marker. That's kind of like the tick on the box*". One caregiver who was balancing the care of her father with IRD and young daughter described feeling as though she was "(*daughter) drowning in things*" stated they didn't have time to explore NDIS for her father or caregiving respite.

- Theme 4- Social well-being of the caregiver

Two caregivers with children affected by IRD stated they had received or currently receive help from their own parents and were grateful for family support to share the caregiving responsibilities "(mother) when my mother was around, she was able to do a lot" "(*mother)She…did a lot of the heavy lifting in regards the boys…help that I needed when I was working*"

All caregivers who provided care for a family member (6/7) expressed that their caring responsibilities have negatively impacted on their own immediate family in some way. Of the five caregivers who had children, three expressed the challenges associated with parenting or providing attention to their other children. For example, one caregiver of a teenager reflected on her daughters increased household contributions, …"(*mother) my daughter is making up for a lot. She is picking up my pieces where I am unable to cope…..she gets frustrated*", while another caregiver reflected on the impact on her unaffected son, "(*mother) my son, who is unaffected by RP… he has felt…overlooked quite a lot*". A daughter caring for her elderly father noted that her husband had taken on a significant portion of their daughter's education which affected their families' dynamics,

"(*daughter) My husband does a lot of our daughter's education stuff…there's a lot of stuff that we have to do… he attends most of those things, but he works full time. So, there's a lot of juggling*". One of the caregivers was a single parent so was particularly conscious of devoting attention to all of his children "(*father) he is one of five. So, I can't afford to spend too much time with just one…I've got to have broader vision to see that everybody else is happy to and traveling. They all have their own problems but not necessarily health problems. But as a father, you've got to make sure that they're all traveling well*"

Most caregivers (4/7) expressed a desire for interaction with a social network of individuals facing similar circumstances "(*daughter) where people that are going through the same thing we can connect with you know, even if you don't want to connect with them personally, you can see group hopes, and you know, maybe this has gone on all you know, have you noticed, someone is experiencing this*". They emphasised the need for support and assistance, with one caregiver of a school aged child expressing they needed help noting they are part of the "*sandwich generation*" who also needed to care for their aging parents thus acknowledging that the situation may become more challenging with time. Most of the caregivers (4/7) were unaware of a support group for families of individuals with similar eye conditions and expressed a desire for a network or group they could connect with to share experiences with other facing similar challenges. "(*father) I just don't I already know if there are any support groups out there, you know, for family of from people who have this type of eye conditions, if there's some sort of a network, or if there is some sort of a group*"

- Theme 5- Relinquishing control

Parental caregivers (5/7) found it challenging to relinquish their role and trust patients with IRD to become autonomous. For example, one caregiver of an adolescent was encouraging their son to self-administer eye drops but felt compelled to remind his son to administer the drops for fear of the disease progressing. Another caregiver of an adolescent stated explicitly that it was their responsibility to provide care "(*father) But it's our children? I personally think, it's, it's, it's our responsibility as a parent to give our son support*". This might imply a reluctance to encourage

independence or may relate to the act of being a parent. One caregiver of a middle-aged patient with IRD reflected on their realisation, "(*mother) It took a long time for each of them to accept that they really needed, needed to acknowledge that they were blind …I spent years trying to make them do what I thought they should be doing to improve things. And of course you can't, we can't control what anyone else does, and that was a very hard lesson for me*." Letting go of control seemed to depend on how well the person being cared for managed their vision loss and how strongly the caregiver felt responsible for their care.

All carers understood the clinical progression of the condition would limit the abilities of the person being cared for or expressed that it had already imposed limitations on the patient with IRD such as giving up contact sports, loss of driver license, reduced interactions and connection with peers, unable to go food shopping unassisted and loss of job. Helping the person they cared for adapt mentally to the limitation was mentioned by all caregivers, all stated that the person they cared for had or was receiving professional psychological support, in some cases at the bequest of the caregiver. A couple of caregivers (2/7) were particularly proud of how the person they cared for had adapted to the vision disorder and its implications stating they were "(*father)taking it in their stride quite well*" and were "(*friend)very outgoing….despite having these issues*". Although all carers were accepting of the condition, some (5/7) expressed feelings of regret due to the impact of the chronic deteriorating condition on the events that would otherwise be routine without the inherited retinal condition such as driving, or playing sports or games with their peers, or having a job. While all caregivers accepted the disease course was incurable and some expressed pride in the patient with IRD managing, one caregiver expressed being hopeful for a cure *"(father)we were looking for a cure or maybe some type of treatment… hopefully, there will be some sort of a solution for our sons future*".

- Theme 6 "Duty" theme

Most caregivers (5/7) felt compelled to take on their caregiving responsibilities, perceiving it as a necessity rather than a choice; some stating that they are the best qualified to provide care. There

is a common subtheme of “Duty” or “obligation”, as they express a sense of having no alternative but to fulfill the role of caregiver. One caregiver of a teenager implied she had a duty to protect them because they had expressed fear of potential relocation to a nursing home or supported accommodation. An elderly mother of a middle aged patient with IRD described her duty in having to find alternative care arrangements for her son because she needed to plan for her own retirement highlighting *“(mother)it’s a big burden for him to try and get somebody else to take him on*”. A caregiver of their parent expressed the sense of duty as a family member, which was unfairly borne solely by them, noting that the responsibility is disproportionately placed due to her male siblings being too busy and less emotionally capable of understanding their parent’s needs, ”(*daughter) I feel like I'm a lone ranger,… two brothers, but they seem to be always busy. And it's always dumped on me*”

- Theme 7 Caregiver need for support

Parental caregivers (5/7) didn’t see themselves as caregivers, they see themselves as a parent or a child with a duty to support their family. Furthermore, some caregivers (4/7) expressed feeling overwhelmed by the immense responsibility placed upon them and that they felt forgotten and under supported. They highlighted their lack of formal training and qualifications, relying instead on their lived experiences to navigate daily challenges “(*daughter) all this stuff just fallen on our shoulders. And there's just not that … understanding or not even I might say acknowledgement, I don't want to be acknowledged but just something to say, is there anything you need as a caregiver .. there is the service or there is this group that you can chat to or something about it? That would be* good”.

Most caregivers (5/7) volunteered they needed for support for themselves. When government caregiver assistance was discussed one caregiver who lamented the difficult bureaucracy in getting NDIS support for her son found the process to gain caregiver assistance for herself cumbersome and stated, “(*mother)My path is already difficult. I don't need anyone injecting more difficulty, please. I want someone on my side*”. A couple of caregivers expressed feeling that they were

forgotten by their other family members who “always seem to be busy” and by health care professionals, with one suggesting, “(*daughter) I think it would be good that you know that medical professionals actually ask the carers, how are you going, you know, how's things at home its good that they focus on the patient? That's really good. Obviously, that's what they need to also think about, you know, is there any other outstanding circumstances that could affect you know, your dad, or your son, or your friends, you know, yeah, I just think that we sort of a bit forgotten*”

All of the caregivers (7/7) expressed they had changed their employment conditions to be able to undertake their caregiving role. Most caregivers (5/7) combined their employment and caregiving roles however two caregivers had ceased employment to maintain a caregiving role. Changes in employment conditions included being unable to return to work after the IRD diagnosis due to the frequency of medical appointments “(*mother) we still don't know if I actually will be able to return to work…has a therapist for everything… because they've realised they don't quite understand the trajectory we have to get as much in as possible to his vision memory now…. so that he will still recall it, even if he can't remember, it's really important*”, or having to reduce full time work to part time work, requesting to maintain hybrid working conditions, “(*mother) I've pushed for hybrid .. so that I can be here .. supervising*”, so that they can spend more time observing how their teenage son with IRD is coping and be there to assist, or one caregiver who increased their hours of work because his wife can only work casually because she is the primary caregiver “(*father) I work full time…. we just need to…take care of our children. My partner …she stays at home during the time…she can contribute more than myself, because, you know I work quite long hours*”.

xi Discussion

This thematic analysis of interviews with caregivers of patients with IRD revealed several themes that highlight the multifaceted challenges and emotional experiences associated with caregiving in Australia, and their need for support. The themes revealed in the study corroborates prior research that has shown that caregiving of individuals with an IRD leading to visual impairment from a young

age poses a substantial threat to a caregivers psychosocial well-being and continually does so as the patient with IRD ages and faces new challenges (142, 162). Our study is unique in that it included both working age and retired caregivers in Australia, and captured the experience of caring for children, adolescents, adults and elderly patients with IRD.

The emotional well-being of caregivers has been frequently highlighted in studies examining the impact of caregiving for individuals with visual impairment (VI) (66, 142, 163, 164). In this study, caregiver emotional well-being emerged as a dynamic construct, oscillating between positive emotions such as optimism and hope, and negative emotions including sadness and anxiety. Notably, anxiety was a dominant pervasive emotion reported by all caregivers. Anxiety among caregivers was largely attributed to the progression of vision loss in patients with IRDs and the accompanying responsibility of assisting with their evolving needs. This finding reflects what is known from the broader caregiver literature; the act of caring for an individual with VI has been well-document to negatively impact various domains of HRQoL, including physical (e.g. fatigues, sleep deprivation), psychological (suffering, anxiety, depression) and social (economic challenges, workplace disruptions, strained relationships) (66, 163, 165). This impact is cumulative, with HRQoL deteriorating as the duration of caregiving increases. For example, a recent study reported a negative association between caregiving duration and caregiver HRQoL, indicating that the burden of caregiving intensifies over time (166). Similarly, Braich et al. (2016) demonstrated a significant decline in caregiver HRQoL as the severity of VI in the care recipient increased, further underscoring the time -dependent burden (66).

Although this study did not specifically assess HRQoL, as noted above high levels of anxiety were observed among both parental and non-parental caregivers, spanning a wide age range of individuals care for (5 to 86 years, **Table 11**). This highlights that the emotional toll of caregiving does not necessarily diminish as patients with IRDs transition to adulthood and adapt to vision loss. This also challenges perceptions that caregiving burden may lessen over time, an assumption that may have influenced HTA agencies to apply non-uniform caregiver disutility values-used to quantify

the reduction in HRQoL-across caregivers of children, adults, and those of retirement age in the EE of a GT for IRDs (82). These findings underscore the need for a more nuanced consideration of caregiver burden in EEs, particularly given the persistent emotional impact reported by caregivers across diverse contexts.

Informal caregiver time costs have been estimated to constitute 16% and 14% of the total socioeconomic burden of IRDs in the United Kingdom and the Republic of Ireland, respectively (167). The time caregivers dedicate to supporting the medical needs of patients with IRDs encompasses a broad spectrum of activities, including attending medical appointments not only with ophthalmologists and optometrists but also with psychological services, occupational therapists, general practitioners (GPs), and visits to the hospital. The finding is consistent with prior research highlighting high rates of health care service utilisation (168-170). This caregiving responsibility extends across the entire lifespan of patients with IRDs. In this study, data from the medical resource use questionnaire revealed a comparable caregiving burden for children and adolescents as for adults, suggesting that the time commitment required for medical support does not substantially decrease as patients with IRDs transition into adulthood. This finding underscores that the time-related component of caregiver burden, which is often incorporated into EEs, remains significant regardless of the age of the person affected by IRD. The lifelong nature of IRDs implies that caregiving responsibilities may shift between different individuals over time, such as from parents to partners or children. This dynamic was reflected in the current study, where caregivers included not only parents but also adult children. These findings raise important questions for EEs of IRD interventions, particularly regarding the appropriate number of caregivers to be considered and whether disutility values assigned in EEs to account for caregiver burden should differ over the life of the patients. Further research is needed to address these questions and to ensure that the full scope of caregiver burden is adequately captured in EEs.

Caregivers in this study highlighted the burden of supporting activities such as education, housing, as well as applying for social services. A particular challenge reported by some caregivers was

navigating the National Disability Insurance Scheme (NDIS) in Australia. The NDIS aims to provide individualised funding for people with permanent and significant disabilities that affect their capacity to participate in daily activities. Caregivers expressed frustration with the narrow eligibility criterion for individuals with VI to be considered eligible for NDIS support. The eligibility for the NDIS requires a diagnosis of severe VI, defined as corrected VA of ≤6/60 (20/200) on the Snellen Scale in both eyes or VF of 10 degrees or less in the better eye, as assessed by an ophthalmologist (114, 171, 172). Caregivers expressed that patients with IRD experience significant challenges in daily living well before meeting the NDIS eligibility threshold for “Severe vision impairment”, a finding supported by published evidence (106). This criterion ignores that effective management of IRDs requires collaboration with experts knowledgeable about IRDs, including ophthalmology, neuropsychiatry, psychology, neurology, orthoptics, developmental therapy, occupational therapy, and/ orientation and mobility specialties early before patients experience severe VI because visual disorders in children can disrupt essential functions like bonding, cognition, motor skills and spatial awareness (173). Firstly, the restrictive NDIS eligibility criterion risks neglecting the broader spectrum of visual function deficits and the necessary therapies to prepare for severe VI. Secondly, caregivers pay out of pocket costs for IRD specialists up until the point that the NDIS eligibility threshold for “Severe vision impairment” is met placing a large financial burden on caregivers. Reducing bureaucratic barriers and ensuring timely delivery of support would help caregivers manage their responsibilities more effectively.

Moreover, caregivers felt there was an inadequate understanding of VI among NDIS staff, which required them to repeatedly explain the impacts of vision loss on the person they were caring for to justify requests for support services. For example there are various types and levels of VI that impact daily living differently, loss of VA where the eye does not see objects as clearly as usual is different to loss of visual field, where the eye cannot see as wide an area as usual without moving the eyes or turning the head; in addition most people who are "blind" have some usable vision that can help them move around in their environment and do things in their daily lives but is still significantly limiting (174). Two people may have the same visual acuity, but one may be able to

use his or her vision better to do everyday tasks. This challenge to understand the complexity of vision is understandable because IRDs represent a diverse group of clinically heterogeneous conditions that impact the functional performance among individuals with VI differently (133). Public understanding of VI is limited, and recent research suggests that the effectiveness and fairness of the NDIS in providing vision rehabilitation services suffer due to complicated procedures and inadequate training for staff and local area coordinators (171, 175, 176). There is a need for improved resources that articulate the various types and stages of VI. Such resources could aid caregivers in explaining and securing essential services for individuals they care for. Family experts have highlighted that access to information is a critical coping mechanism for caregivers to manage stress (164). Addressing these gaps in understanding and resource availability may alleviate some caregiver burden associated with IRD's. In addition, policymakers should invest in specialised training for NDIS staff and local area co-ordinators to improve their understanding of VI, including the diverse clinical presentation of IRD's.

Two themes induced in the analysis: the sense of duty experienced by caregivers and their need for support, are consistent with the results of previous research about caregivers for patients with IRD conducted in Spain (162). Caregivers in this study highlighted accessing financial assistance and respite support through government programs was burdensome reflecting broader systematic inadequacies (https://www.carergateway.gov.au/). In addition, the interviews revealed that the informal caregivers have or are balancing paid employment with their caregiving responsibilities. This finding is supported by research from the Household, Income and Labour Dynamics in Australia (HILDA) survey which shows informal caregiving reduces carers' workforce participation, with carers more likely to decrease working hours or leave employment altogether resulting in lower average earnings compared with non-carers (177, 178). Overall, this underscores the significant economic trade off associated with informal caregiving. While the NDIS aims to provide as much care as possible privately, through encouraging self-care, there is a substantial burden imposed on caregivers that needs to be acknowledged. Support for carers-such as financial assistance and access to short notice caregiving help-may influence the ability of working carers to effectively

balance their work and caregiving responsibilities. Raising awareness about the critical role of informal caregivers and the challenges they face could encourage greater governmental support.

This study relied on the participation of caregivers who volunteered their time, which may introduce potential biases. It is possible that some participants, having experienced caregiving as a traumatic process, engaged in this study as a form of therapeutic outlet. Given the small sample size, this could have influenced the findings. Conversely, individuals who experienced significant trauma as a result of caring for someone with an IRD may have chosen not to participate, potentially due to the discomfort associated with revisiting distressing events. These factors may limit the generalisability of the findings to the broader population of caregivers of patients with IRD. Nevertheless, the study cohort was diverse, encompassing caregivers of young children, adolescents, adults, parents and friends, as well as a wide range of IRD conditions and varying time since diagnosis (**Table 11**). This diversity provides a rich representation of the lived experience of caregivers across different relationship types, disease profiles and timelines.

While the sample size for this study is relatively small (n=7), this is consistent with established guidelines and evidence in qualitative research that emphasize the importance of information richness over quantity of participants(179). Two studies provide strong methodological support for the adequacy of small sample sizes in qualitative studies when participants are carefully selected for their relevance to the research question and their ability to provide rich meaningful data (179, 180). Boddy (2016) argues that the determination of sample size in qualitative research is contextual and depends on the study's focus and methodological paradigm (180). For research grounded in constructivist approaches such as the current thematic analysis, small sample sizes are justified due to the depth and richness they provide. Similarly, Malterud (2015) emphasises that small, focused samples are particularly appropriate when the study employs a rigorous and detailed analysis plan (179). The rigorous design, clear focus, and diverse participant characteristics in this study ensures that the sample provides rich and meaningful data, making it an ideal foundation for thematic analysis.

Conclusion

Thematic analysis offers a robust qualitative approach for exploring complex, nuanced experiences of caregivers, particularly in the context of rare heterogeneous conditions such as IRDs. This study highlights the enduring emotional, social, and economic toll of caregiving for patients with IRDs, emphasising the importance of tailored support systems and the need for greater recognition of caregiver burden in research, policy, and practice. It further advocates for the inclusion of caregiver burden over the patient's lifetime in EEs conducted for HTAs, ensuring a more comprehensive assessment of a social value of new technologies for IRDs.

Chapter 5 Research study 4 Stakeholder survey about broad elements of value in health technology assessment in Australia: industry and academia more similar than different.

xii Chapter 5 summary

As discussed in Chapter 1 experts in the field suggest that health technology assessment (HTA) should consider and value a technology using elements that go beyond the patient quality-adjusted life years (QALY). In chapter 4, the broader impact of inherited retinal disease (IRD) on caregivers was explored; this chapter explores the opinions of Australian stakeholders involved in HTA and their views on what broad elements of value should be considered by HTA decision makers in Australia.

The aim of Chapter 5 is to explore Australian stakeholders' views on the significance of broader value elements in EEs, the transparency of reimbursement decision-making in Australia, and strategies to handle uncertainty related to medicine for rare disease (RD).

The research study supports the recommendation from Australia's recent HTA policies and methods review (HTA review) advising that a value framework should be developed, that incorporates, in a transparent manner, broader value elements into decision-making to improve consistency of decisions. This research proposes a mechanism, an explicit checklist on broader elements of value considered beyond the QALY, that may help meet this need.

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xiii Abstract

Objective

Researchers propose wider individual and societal benefits (or broad elements of value) be included in economic evaluations (EEs) of health technologies. This study investigates opinions of Australian stakeholders regarding the inclusion of broader value elements in reimbursement decisions for health technologies for rare diseases (RDs) in Australia.

Method

Stakeholders were invited via email to complete an online survey about their views on broader elements of value in HTA. Responses were summarised using descriptive statistics and compared using chi-square statistics.

Results

Forty-four respondents (academia (n=11), private sector (n=33)) completed the survey between October 2023 and May 2024. Only 27% of stakeholders agree the current information about the sources of value considered in reimbursement decisions is sufficient. Stakeholders consistently agree labour productivity (>50%), adherence (>80%), reducing uncertainty due to a new diagnostic (>70%), disease severity (>71%), value to caregivers (>70%), and equity (>70%) should be considered in HTA. The majority (>70%) agreed managed entry agreements (MEA), risk share arrangements (RSA), and multi criteria decision analysis (MCDA) be used in reimbursement decision-making for medicines for RDs. Significantly fewer academic stakeholders (40%) versus private sector (77%), believe an increased willingness to pay (WTP) threshold be applied to medicines for RD.

Conclusions

Academic and private sector stakeholders hold similar views when considering medicines for non-rare and rare diseases. Stakeholders favour considering more value elements in HTA than referred to in the Pharmaceutical Benefits Advisory Committee (PBAC) and Medical Services Advisory Committee (MSAC) HTA guidelines. This study highlights further advice is needed on the factors considered in reimbursement decisions and how that would influence guidelines.

xiv Introduction

EE is widely used in HTA to inform reimbursement decisions in healthcare (17, 46). As part of HTA, an EE assesses the incremental cost-effectiveness of a new therapy and the incremental cost-effectiveness ratio (ICER) is judged against an implicit or explicit “cost-effectiveness or willingness to pay (WTP) threshold,” to help judge the efficient allocation of healthcare resources (16).

EEs can only include benefits for which adequate data are generated (181). Typically, only direct patient health benefits via health related quality of life (HRQoL) and survival (used to calculate QALYs) are considered in an EE (49). They can however adopt a wider, societal perspective and incorporate broader elements of value such as indirect non health benefits, like productivity gains, offered by a health technology (97, 144, 182). The perspective taken by decision makers is often outlined by HTA guidelines reflecting their country values and preferences, and they may be required to consider a government perspective only rather than the societal perspective (17, 49). Several studies suggest wider benefits to individuals and society should be included in EEs (45, 57, 183). An International Society for Pharmacoeconomics and Outcomes Research (ISPOR) special task force on value assessment recommend a series of broader value elements in HTA assessments (45). If HTA does not include the broader value of a therapy then treatments with wide ranging impacts may be undervalued and receive inappropriately high incremental cost-effectiveness ratios (ICERs) (182, 184). Some of the broad value elements suggested range from conventional concepts, such as adherence improving factors or disease severity, to novel elements of value such as scientific spillover (45).

RDs are a group of diverse diseases, characterised by low prevalence and often have severely debilitating symptoms that substantially affect the HRQoL of patients and their families (6, 77). EEs of medicines for RDs often produce high and uncertain ICERs, in part due to their high cost and difficulty generating robust evidence supporting clinical efficacy due to small sample sizes, single arm studies, shorter duration of patient follow up and reliance on immature clinical evidence to inform modelling (6, 16). Different reimbursement agencies provide varying recommendations based on EEs of the same medicine for RD, partly because factors like disease severity and broader elements of value were considered, leading to greater acceptance of higher and uncertain ICERs (5, 7, 74). Additionally, some RD medicines have gained expedited access in cases of high unmet need through payment mechanisms like outcome-based managed entry agreements (MEA’s) to address the financial risks associated with uncertain clinical evidence (7).

To improve the quality of EEs experts recommend an impact inventory to explicitly and transparently consider the broader health and nonhealthy impacts of a medicine (144). It is however noted that methods to include broad value elements into value assessment are unclear such that HTA agencies use different approaches (9, 185, 186). Two mechanisms to formally include broader elements of value into an EE are a multi criteria decision analysis (MCDA), or the deliberative process (187). The latter is used by reimbursement agencies such as the National Institute for Health and Care Excellence (NICE) in England and Wales and the PBAC and MSAC in Australia. However, deliberative processes have their shortcomings as the relative importance of various criteria varies between stakeholders, which elements of value contributed to the decision is not always clear and how the decision was reached is not always transparent (6, 39, 102, 187-189).

This study investigates the opinions of Australian stakeholders in the HTA process about the importance of various broader elements of value in EEs, transparency in reimbursement decision-making in Australia, and opinions on mechanisms to manage uncertainty associated with medicines of RDs.

xv Methods

A quantitative survey was conducted of stakeholders involved in HTA in Australia, representing academia, specialist consultants and the pharmaceutical industry. An invitation was emailed to potential participants (including government agencies and representatives of patient organisations) via local professional societies and invitees were encouraged to forward the survey to other relevant colleagues. No responses from government agencies and patient representatives were received.

The survey was developed using the Qualtrics Survey platform and was completed between 02 October 2023 and 14 May 2024. Questions were based on the broader elements of value proposed by ISPOR and mechanisms suggested, and adopted, to manage uncertainty in value assessment

(45, 188-190). The questions were discussed with an expert health economists experienced in HTA prior to implementation. Prior to initiation of the survey, the appropriateness and order of the questions were discussed within the research team. Pilot testing of the survey was conducted with internal and external members of the research team to assess comprehension. The survey comprised 32 questions across six sections (**Supplementary Figure 14**, Appendix 3) and was intended to take approximately 10 minutes to complete.

Because value elements are sometimes referred to by other names in the literature or the names may not represent the essence of what is considered, a brief description of each 'value element' was included in the survey (**Supplementary Figure 14**, Appendix 3).

Most questions sought agreement to statements on a 5-point Likert scale: 1=strongly disagree, 2=somewhat disagree, 3=neither disagree nor agree, 4=somewhat agree, 5=strongly agree (respondents could choose a sixth category 'Don't know'). Depending on the resulting number of respondents, and to ensure >5 minimum responses per category (for statistical testing), the categories ‘strongly agree’ and ‘somewhat agree’ were collapsed into one group ('Agree'), and the categories ‘strongly disagree’ and ‘somewhat disagree’ into another group ('Disagree'). The category ‘neither disagree nor agree’ or “don’t know” is henceforth referred to as ‘neither’ within the text. The remaining questions asked participants whether they agreed with statements with response options 'yes', 'no' or 'not sure', and to nominate methods (via a free text field) to incorporate added value not currently utilised in EEs. Provided a response was not 'yes' the participant was reported to 'Agree'. A response “No” or “Not Sure” reflected that the participant did Not Agree with the statement

Five major categories of stakeholders were defined for respondents to self-allocate 1) pharmaceutical industry, 2) specialist consultants, 3) academia, 4) government agency and 5) representative of patient organisation. Responses to each question were summarised using descriptive statistics and reported for the cohort overall and by respondent categories separately.

Test for difference between respondent categories were performed using chi-square statistics (5% significance level). The relative risk (RR) (academic group versus Private sector groups) and 95% confidence interval (CI) are estimated for each response.

Where no background demographics were reported for a participant who consented, their data were removed from the sample. If demographic data were reported but only partial survey response data was provided, participant responses were only included in those questions to which they contributed (thus the sample size varies per question). All analyses were performed using Excel on a MS Windows platform. This study received ethics approval in September 2023 (HREC REF NO. ETH21-6090).

xvi Results

Forty-four respondents completed the survey from academia (n=11) and the private sector (n=33). The respondent categories were aggregated into 'academia' and the 'private sector' (pharmaceutical industry and specialist consultants). The sample was adjusted by excluding three respondents without demographic data. The majority of respondents in both groups had a post graduate degree (Masters 27/44, 61% or Doctoral 14/44, 32%) and the top three primary qualifications were in health economics (28/44, 64%), pharmacy (11/44, 25%) and science (10/44, 23%). Mean (standard deviation, SD) years of experience was 7.3 years in academia and 14.3 years in the private sector (**Table 14**). Most (67%) in private sector held managerial roles compared with only 18% (2/11) of the academic group.

Table 14 *Background information for all stakeholders and by subgroup*

	Australian stakeholders (N=44)	***Australian stakeholder subgroups***	
		Academia (N=11)	***Private (consultants = 10, pharmaceutical industry=23)***
Years involved in HTA in Australia, mean	12.1 years	*7.3 years*	*14.3 years*
Position Managerial, n/N (%)	22/44 (50%)	*2/11 (18%)*	*20/33 (61%)*
Academic qualification, n/N (%)	14/44 (32%) Doctoral degree 27/44 (61%) Masters degree 3/44 (7%) Undergraduate degree	*8/11 (72%) Doctoral degree* *3/11 (27%) Masters degree*	*6/33 (18%) Doctoral degree* *24/33 (72%) Masters degree* *3/33 (10%) Undergraduate degree*
Area of academic qualification[a], n/N (%)	28/44 (64%) health economics 11/44 (25%) pharmacy 6/44 (14%) statistics 10/44 (23%) science 6/44 (14%) public health 7/44 (16%) business/economics/MBA	*9/11 (82%) health economics* *2/11 (18%) statistics* *1/11 (9%) science* *1/11 (9%) pharmacy* *1/11 (9%) public health*	*19/33 (58%) heath economics* *10/33 (30%) pharmacy* *9/33 (27%) science* *7/33 (21%) business/economics/MBA* *4/33 (12%) statistics* *1/33 (<1%) medicine* *5/33 (15%) public heath*

a. multiple disciplines reported per individual in some cases

Few (<30%) Australian stakeholders agree that the current HTA methods applied in Australia are adequate to appropriately assess the CE of all medicines or medicines for RD (**Table 15**). Despite the absence of a significant difference in responses between stakeholders, it is noteworthy that academic respondents were four times more likely (RR 4.36) to agree that the HTA methods used in Australia are adequate for all medicines, compared to their private sector counterparts. However, the substantial uncertainty surrounding this estimate is reflected in the wide confidence interval (range 0.84 to 22.79). The majority of stakeholders disagreed with the statement that the public information on reimbursement decisions in Australia provides sufficient information about which sources of value are considered and how they contributed to decision-making (73%; academia=55% versus private sector=80%, p=0.1031) (**Table 15**). It is important to emphasise the variation in response rates, despite the lack of statistical significance. Notably, academics were twice as likely (RR 2.27) to concur that the publicly available information on reimbursement decisions is adequate compared with the private sector. Of the 24 respondents from the private sector who disagreed, 83% felt that while they knew which sources of value were considered, they did not know how they contribute to decision-making. Equal proportions of respondents from academia thought that either the sources of value considered were not known (33%) or did not

know how they contributed to decision-making (33%).

The majority of stakeholders (70%; academic=50% versus private sector=77%, p=0.1110) agreed that having an explicit checklist on broader value considered beyond the QALY by decision makers would be more informative than what is currently published in Australia (**Table 15**). There is an imbalance in responses however, a RR of 0.65 suggests that the academic group were 35% less likely to agree than private sector stakeholders that a checklist may be more informative. Importantly, the 95% CI range (0.34 to 1.25) indicates uncertain precision of this effect.

Stakeholders were invited to explore mechanisms to facilitate expedited access to treatments for RDs, while effectively managing the uncertainties associated with cost-effectiveness analysis (CEA) and budgetary impacts (BI). This consideration is driven by the significant unmet need and the demand for accelerated access to such medicines. A description of the mechanisms were as follows: MEA, outcome based managed entry agreement that allows earlier market access but requires CEA review once additional outcome data are available. For example: clinical data from pre-specified study protocol for all patients subsidised or from existing planned or progressing studies [26]); MCDA, multicriteria decision analysis which involves a deliberative process where decision makers and stakeholders come together to define the problem and determine the criteria, weighting and evidence requirements for decision [24, 28]); RSA, financial risk share arrangement that financially subsidises based on medicine or patient performance. For example: a percentage rebate is paid if the number of treatments per patient or accepted duration of treatment is exceeded. Subsidy ceases if patients do not meet agreed clinical measures [26]); WTP, willingness to pay is an increase in the ICER considered acceptable for treatments of RDs.

Most Australian stakeholders (>68%) agreed the four mechanisms (MEA's, financial risk share arrangements [RSA's], MCDA's and increased ICER's considered acceptable for treatments of RDs denoted as WTP), should be used in making reimbursement decisions about medicines for RD (**Table 2**). Over seventy percent (>70%) of academia and private sector respondents agreed that MEA's RSA's and MCDA should be used in making reimbursement decisions for medicines for RD

in Australia **(Table 15**). Significantly fewer academic respondents (40%) compared with the majority of private sector respondents (77%) (p=0.0320) agreed that an increase in the ICER considered acceptable for medicines for RDs in Australia, should be used in decision-making.

Table 15 *Comparison between adequacy of HTA methods, sufficiency of public information and mechanisms for decision making*

Q: Do you think the current HTA methods applied in Australia are adequate to appropriately assess the cost effectiveness of all medicines? n/N (%) agree			
Total cohort	5/43 (12%)		
Academia	*3/11 (27%)*	*RR: 4.36 (95%CI 0.84, 22.79) p=0.06*	
Private sector	*2/32 (6%)*		
Q: Do you think the current HTA methods applied in Australia are adequate to appropriately assess the cost effectiveness of medicines for rare diseases? n/N (%) agree			
Total cohort	8/44 (18%)		
Academia	*2/11 (18%)*	*RR:1.0 (95%CI 0.24, 4.25) p=1.0*	
Private sector	*6/33 (18%)*		
Q: Do you agree that the current public information regarding reimbursement decisions in Australia provides sufficient information about which sources of value are considered and how they contributed to decision-making, n/N (%)			
Total cohort	11/41 (27%) agree	*Reasons for disagreement* 6/30 (20%) state we don't know which sources of value are considered 22/30 (73%) state while we know which sources of value are considered, we don't know how they contribute to decision-making 2/30 (6.7%) did not select a re	
Academia	*5/11(45%) agree*	*RR:2.27 (95%CI 0.87, 5.97) p=0.10*	*Reasons for disagreement* *-2/6 (33%) state we don't know which sources of value are considered* *-2/6 (33%) state while we know which sources of value are considered, we don't know how they contribute to decision-making* *-2/6 (33%) not sure*
Private sector	*6/30 (20%) agree*		*Reasons for disagreement* *- 4/24 (17%) state we don't know which sources of value are considered* *-20/24 (83%) state while we know which sources of value are considered, we don't know how they contribute to decision-making*
Q: Do you agree that an explicit checklist of sources of value beyond the patient QALY and whether they were considered by decision maker would be more informative than what is currently published in Australia? n/N (%) agree			
Total cohort	28/40 (70%)		
Academia	*5/10 (50%)*	*RR:0.65 (95%CI, 0.34, 1.25) p=0.11*	
Private sector	*23/30 (77%)*		
Q: Do you agree the following mechanism, MEA should be used in Australia in making decisions about reimbursement of medicines for rare disease, n/N (%) agree			
Total cohort	*32/40 (80%)*		
Academia	*9/10 (90%)*	*RR: 1.17 (95%CI 0.88, 1.56) p=0.36*	
Private sector	*23/30 (77%)*		
Q: Do you agree the following mechanism, RSA should be used in Australia in making decisions about reimbursement of medicines for rare disease, n/N (%)			

Total cohort	*33/40 (83%)*	
Academia	*9/10 (90%)*	*RR: 1.13 (95%CI 0.86, 1.48) p= 0.47*
Private sector	*24/30 (80%)*	
Q: Do you agree the following mechanism, MCDA should be used in Australia in making decisions about reimbursement of medicines for rare disease, n/N (%)		
Total cohort	*29/40 (73%)*	
Academia	*7/10 (70%)*	*RR: 0.96 (95%CI 0.60, 1.51) p=0.84*
Private sector	*22/30 (73%)*	
Q: Do you agree the following mechanism, WTP should be used in Australia in making decisions about reimbursement of medicines for rare disease, n/N (%)		
Total cohort	*27/40 (68%)*	
Academia	*4/10 (40%)*	*RR: 0.52 (95%CI 0.24, 1.14) p=0.03*
Private sector	*23/30 (77%)*	

Abbreviations: CI, confidence interval; MEA, outcome based managed entry agreement (defined as allows earlier market access but requires CEA review once additional outcome data are available. For example: clinical data from pre-specified study protocol for all patients subsidised or from existing planned or progressing studies [26]); MCDA, multicriteria decision analysis (defined as involves a deliberative process where decision makers and stakeholders come together to define the problem and determine the criteria, weighting and evidence requirements for decision [24, 28]); RR, relative risk; RSA, financial risk share arrangement (defined as with subsidy based on medicine or patient performance. For example: Percentage rebate if the number of treatments per patient or accepted duration of treatment is exceeded. Subsidy ceases if patients do not meet agreed clinical measures [26]); WTP, willing ness to pay (defined as increase the ICER considered acceptable for treatments of rare diseases).

The majority of all Australian stakeholders (>65%) believed that six of the eleven broader value elements recommended by ISPOR: labour productivity, adherence, reducing uncertainty due to a new diagnostic, severity of disease, value to caregivers, and equity should be considered in HTA of all medicines and medicines for RD (**Table 16**). Whereas few stakeholders agreed that the value of hope, real option value, scientific spillover, fear of contagion or insurance value should be considered **(Table 16**).

The degree of consensus between the stakeholder groups is demonstrated by a RR close to 1.0 accompanied by a narrow confidence interval. This indicates consensus between academia and private sector respondents on the majority of broader value elements agreed should be considered in HTA of all medicines and medicines for RD in Australia, namely adherence, reducing uncertainty due to a new diagnostic, severity of disease, and equity. Furthermore, the analysis revealed no statistically significant differences in responses when analysed by sector (Table 16). Interestingly the likelihood of agreeing to include “Labour Productivity” in HTA of all medicines and medicines for RD in Australia is approximately 30% less in the academic respondents compared with private sector respondents. Also, the likelihood of the academic group agreeing to include “Value to caregivers” in HTA of medicines for RD in Australia (RR0.75) is 25% less likely than the private

sector, yet the degree of concordance was greater when considering HTA of all medicines (RR0.86). In addition, the majority of both stakeholder groups did not agree that the Value of Hope should be considered in HTA of all medicines and medicines for RD in Australia (<43%), the likelihood of agreeing that it should be included was 50% lower in the academic respondents compared with private sector respondents (RR 0.46 and RR0.38, respectively). Each group was aware of methods to capture impacts on costs and outcomes for the broad sources of value, such as HRQoL measures, subgroup analysis and distributional cost-effectiveness analysis (DCEA) (**Table 1**7).

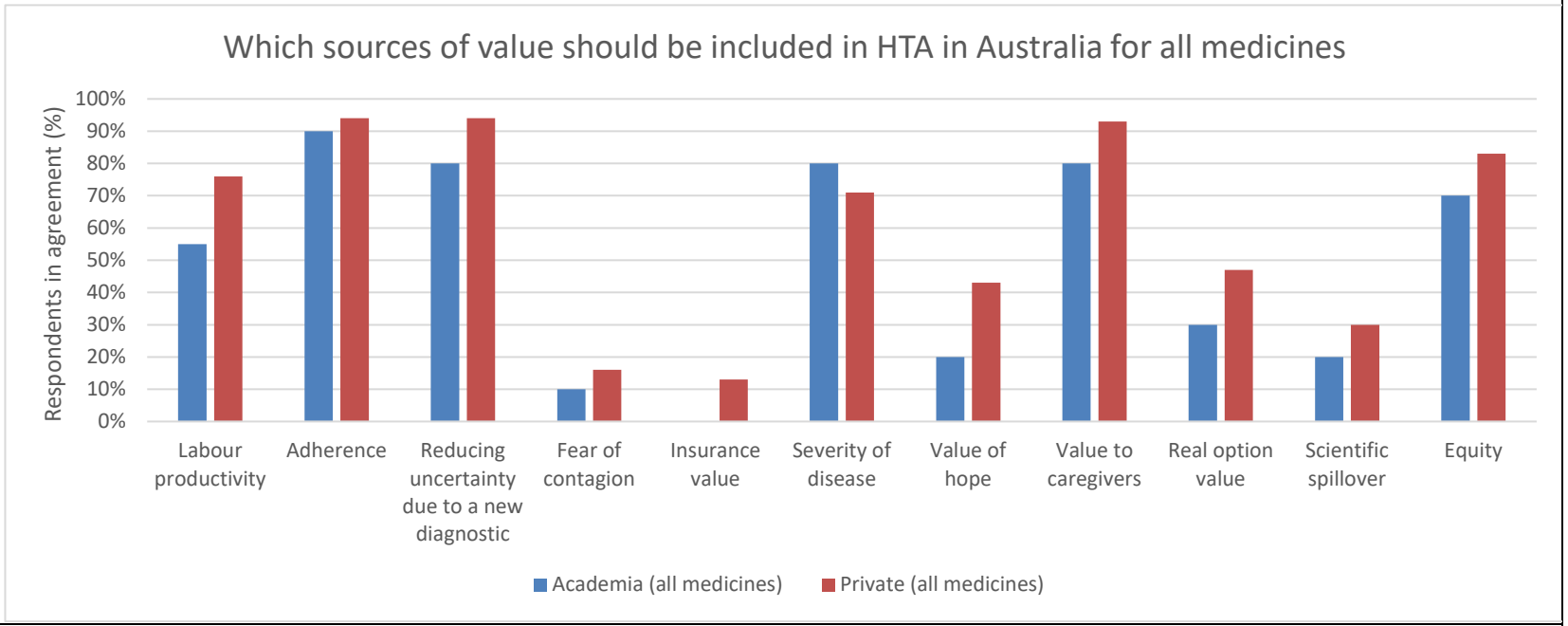
Table 16 *Comparison between sources of value that should be considered in HTA for all medicines and medicines for rare disease*

Broad elements of value	All medicines, n/N (%) agree				Medicines for rare disease, n/N (%) agree			
	Total cohort	*Stakeholder sectors*			Total cohort	*Stakeholder sectors*		
		Academia	*Private sector*	*RR (95%CI), p-value*		*Academia*	*Private sector*	*RR (95%CI), p-value*
Labour productivity	31/43 (72%)	*6/11 (55%)*	*25/32 (78%)*	*0.70 (0.40, 1.23), 0.1326*	26/40 (65%)	*5/10 (50%)*	*21/30 (70%)*	*0.71 (0.37, 1.39), 0.2508*
Adherence	39/42 (93%)	*9/10 (90%)*	*30/32 (94%)*	*0.96 (0.77, 1.20), 0.6877*	34/40 (85%)	*8/10 (80%)*	*26/30 (87%)*	*0.92 (0.66, 1.30), 0.6091*
Reducing uncertainty due to a new diagnostic	37/41 (90%)	*8/10 (80%)*	*29/31 (94%)*	*0.86 (0.62, 1.18), 0.2093*	34/40 (85%)	*7/10 (70%)*	*27/30 (90%)*	*0.78 (0.51, 1.19), 0.1250*
Fear of contagion	6/41 (15%)	*1/10 (10%)*	*5/31 (16%)*	*0.62 (0.08, 4.70), 0.6335*	4/40 (10%)	*1/10 (10%)*	*3/30 (10%)*	*1.0 (0.12,8.56), 1.00*
Insurance value	4/41 (10%)	*0*	*4/31 (13%)*	*ND*	6/40 (15%)	*1/10 (10%)*	*5/30 (17%)*	*0.60 (0.08, 4.54), 0.6091*
Severity of disease	30/41 (73%)	*8/10 (80%)*	*22/31 (71%)*	*1.13 (0.77, 1.65), 0.5751*	31/40 (78%)	*8/10 (80%)*	*23/30 (77%)*	*1.04 (0.73, 1.51), 0.8270*
Value of Hope	15/40 (38%)	*2/10 (20%)*	*13/30 (43%)*	*0.46 (0.13, 1.70), 0.1869*	9/40 (22%)	*1/10 (10%)*	*8/30 (27%)*	*0.38 (0.05, 2.64), 0.2744*
Value to caregivers	36/40 (90%)	*8/10 (80%)*	*28/30 (93%)*	*0.86 (0.62, 1.19), 0.2235*	35/40 (88%)	*7/10 (70%)*	*28/30 (93%)*	*0.75 (0.50, 1.14), 0.0533*
Real option value	17/40 (43%)	*3/10 (30%)*	*14/30 (47%)*	*0.64 (0.23, 1.78), 0.3558*	11/40 (28%)	*0*	*11/30 (37%)*	*ND*
Scientific spillover	11/40 (28%)	*2/10 (20%)*	*9/30 (30%)*	*0.67 (0.17, 2.58), 0.5397*	10/40 (25%)	*1/10 (10%)*	*9/30 (30%)*	*0.33 (0.05, 2.32), 0.2059*
Equity	32/40 (80%)	*7/10 (70%)*	*25/30 (83%)*	*0.84 (0.54, 1.30), 0.3613*	34/40 (85%)	*8/10 (80%)*	*26/30 (87%)*	*0.92 (0.66, 1.30), 0.6091*

Abbreviations: CI, confidence interval; ND, not determined; RR, relative risk

Note: The questions posed to participants were, "Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia", and then participants nominated if they were aware of methods to include each source of value in a cost-effectiveness analysis (presented in Table 5); a table of 11 value elements was then presented to participants and they were asked "Do you agree that the following sources of value should be considered in cost effectiveness analysis of a medicine for rare disease in Australia?" for each value..

Table 17 *Comparison between stakeholder groups regarding sources of value that should be considered in HTA for all medicines and suggested methods to include them into EEs*



Suggested methods related to assessment of costs or outcomes:						
Productivity: human capital approach, friction cost, willingness to pay study, patient preference, G method(191)	**Adherence:** persistence, discontinuations, observed utilisation within trial and post listing surveillance	**Reducing uncertainty**: decision tree/ Bayes revision node to capture test accuracy before modelling costs & outcomes in responders and non-responders,	**Severity:** utility study, ICER threshold, QALY weighting, scenario analysis (using results from complementary subgroups), specific funding pools	**Value of hope**: Utility studies (Time trade off, standard gamble and other preference based measures).	**Value to caregivers**: Productivity, indirect carer costs, CareQoL and other measures of utility	**Equity:** Threshold increase, equity weightings, funding for specific populations, subgroup analysis, distributional cost-effectiveness analysis

xvii Discussion

This study examined views from academic and private sector stakeholders involved in HTA on which broad elements of value should be considered by decision makers in Australia, and mechanisms to mitigate uncertain cost effectiveness (CE) and budget impact associated with medicines for RDs.

The majority of respondents agreed that current public information regarding reimbursement decisions in Australia provides insufficient information about the consideration of sources of value in decision-making. Furthermore, the majority of respondents agreed that current HTA methods applied in Australia are inadequate to appropriately assess the CE of all medicines and medicines for RD. Australian reimbursement recommendations are made transparent to the public by publishing them online as public summary documents (PSDs) (69). They provide contextual information pertaining to each recommendation and although they are limited in terms of the amount of information published, they provide insight into the factors and trade-offs noted through the deliberative process in arriving at reimbursement recommendations (82). Transparency on which inputs are accepted (and under what conditions) by HTA decision makers is necessary because it enables stakeholders to collect relevant data to inform decision-making (72). This study highlights transparency on what was considered in PBAC and MSAC decision-making in the PSD needs further improvement. Of interest the participants in the Australia's recent HTA policies and methods review (referred to as the "HTA review") expressed concern that PSDs fail to adequately convey how certain evidence types impact health technology funding decisions (192). The HTA review findings are consistent with those from this survey.

More private sector stakeholders (77%) than academic stakeholders (50%) thought an explicit checklist of sources of value beyond the QALY and whether they were considered by decision maker, would be more informative than what is currently published in Australia. Private sector stakeholders, particularly those in the pharmaceutical industry, may have more interest in PBAC and MSAC decision-making than academics, as they depend on these decisions for medication

funding (**Table 14**). Nonetheless, experts suggest a checklist for reimbursement decision-making as a useful framework to standardise the consideration of sources of value, minimise bias and improve transparency (9, 45, 144, 193). The HTA review recommends that the Australian Government develop and support an explicit qualitative values framework to ensure HTA decisions consider broader value, enhancing transparency and consistency in funding health technologies (192). Importantly the recommendation states the framework should allow enough flexibility for the deliberation process itself to add value that is not pre-weighted and scored. Examples of explicit qualitative value frameworks and transparent reporting by HTA committees include the I.C.E.R. in the US that refers to "*Potential other benefits and contextual considerations*" such as health disparities, caregiver burden, or impact the entire "*infrastructure*" of care that committee members individually rate during deliberation (69). The I.C.E.R value framework is systematic regarding the factors incorporated into decision-making and explicitly reported (69, 194). NICE includes non-quantified additional health benefits such as to the health system (e.g. equity), and innovation (82, 102). The NICE final outcome describes how such "other factors" impacted decision-making (82).

Less than 20% of Australian stakeholders agree that fear of contagion and insurance value should be considered in HTA of all medicines or medicines for RD in Australia. Six broad value elements that most Australian stakeholder felt should be considered in HTA of medicines in Australia (labour productivity, adherence, reducing uncertainty due to a new diagnostic, severity of disease, value to caregivers, and equity) are recommended in several HTA guidelines whereas only two (severity of disease and equity) overlap with the 'less -readily quantifiable' factors quoted to "*influence*" PBAC decision-making in Australia (49, 195). Only one of the six broad value elements (equity) overlap with less -readily quantifiable' factors quoted to "*influence*" MSAC decision-making in Australia(99). The PBAC HTA guidelines highlight several factors considered during PBAC deliberations, such as the overall confidence in the evidence and assumptions presented, equity, severity, the capacity to target therapy, the existence of effective therapeutic alternatives, public health considerations, and any other pertinent factor influencing a medicine's suitability for listing on the PBS. The MSAC HTA guidelines highlight the following are considered during MSAC deliberation, equity, value of

knowing, presence of effective alternatives, and other relevant factors (including the impact on organisations, or the way in which organisational issues may create barriers or facilitators to the uptake of the new technology or efficiency of health care delivery, ethical concerns, and social aspects)(99). These qualitative assessments, along with CE and BI, may obscure the weight of each factor in reimbursement decisions. Additionally, while the guidelines assert that "*Supplementary analyses may be appropriate where the proposed intervention has important societal implications*"—thereby permitting the inclusion of broader values in supplementary CEA—the relegation of non-health benefits to supplementary analyses might result in them being overlooked in the decision-making process and omitted from the PSD.

A recent review of 53 HTA guidelines representing 52 countries revealed an average of 5.9 of a possible twenty-one societal and novel value elements were mentioned although the authors acknowledge simply recommending novel elements of value in HTA guidelines may not lead to them being incorporated into decision-making (49). Australian HTA guidelines outline a preferred approach for PBAC and MSAC submissions but allow alternative approaches if justified with data. Stakeholders can include alternative value elements in submissions, but decision-makers must transparently evaluate these. Transparency is crucial for pharmaceutical industry sponsors, as developing evidence is resource-intensive and can guide future evidence generation. Including well-supported broader value elements in decision-making acknowledges therapy benefits and aids patient access to medicines (5, 74, 185).

There are challenges quantifying some broad value elements, and a lack of consistent methodology for their inclusion in EEs as well as expertise in assessing the methodologic approaches (45, 49, 182). Both stakeholder groups were generally aware of methods to incorporate agreed-upon value elements into HTA of medicines. However, some elements like fear of contagion and insurance value lacked acknowledged methods. Suggested methods, within the CE framework, included preference-based methods, scenario analysis, and DCEA. Academics had higher method knowledge, indicating varying skill sets among stakeholders. This underscores the need for PBAC

and MSAC HTA guidelines to provide guidance on data and methods to support broader value elements, alongside improving transparency in decision-making. For example the Medical Services Advisory Committee (MSAC) in Australia includes the 'value of knowing' as a less quantifiable factor influencing decisions and offers technical guidance on evidence to support this element whereas the PBAC does not provide specific guidance on how to address less quantifiable factor influencing decisions (99).

The inquiry into proposed decision-making mechanisms for reimbursing medicines for RD in Australia was framed by the context that medicines for RD are generally expensive with limited evidence of clinical effectiveness, attributed to small, non-comparative clinical studies and lack of epidemiological data. RSA's and outcome based MEA's are existing mechanisms employed in Australia to subsidise medicines despite the lack of confidence in the evidence for a medicine (190). Most stakeholders agreed RSA's and MEA's should be used in making reimbursement decisions about medicines for RDs. RSA's described in this study are a practical financial arrangement that continues to subsidise a medicine only when treated patients meet specific clinical criteria, it also provides certainty around financial expenditure to the government despite patient population size uncertainty. Outcome based MEA's are challenging to implement in Australia due to the absence of infrastructure linking medicine utilisation and clinical outcomes, and thus most MEA's implemented in Australia to date are limited to reviewing the recommendation to reimburse a medicine once additional outcome data become available from a clinical trial that is underway (190, 196, 197). If MEA's are to be used to expedite access to medicines for RDs in Australia despite uncertain clinical evidence, handling challenges such as establishing infrastructure to support comprehensive data collection as well as price adjustments based on outcomes arrangements or product delisting due to suboptimal performance are some of the significant tasks for both payers and the pharmaceutical industry (190, 198).

The MCDA method referred to in this survey was a quantitative MCDA whereby stakeholder preferences are used to specify a value for each criterion, the values are weighted, and an overall

score generated for each intervention (187). The use of quantitative MCDA in HTA is not widespread but most Australian stakeholders responding to the survey believe it should be used to make reimbursement decisions about medicines for RDs in Australia (199). The formal structure of MCDA, avoids some of the issues in less structured deliberative processes, explicitly elicits decision makers preferences and allows for the inclusion of broader value elements important to stakeholders but not easily accommodated in standard CEA's (187, 189, 200). Two systematic reviews of quantitative MCDA found it useful for focusing discussion and reporting decisions transparently but found no evidence of improved decision-making quality or timeliness (193, 195). Importantly, weighting of the relative importance of various value elements would likely differ between stakeholders such as patients and payers (187). Consequently, the HTA review recommendation to develop a "qualitative value framework" that is neither pre-weighted nor pre-scored.

There was significant disagreement between the stakeholder groups regarding increasing WTP thresholds in making reimbursement decisions about medicines for RD. Among the many countries that use CEs to inform funding decisions (such as England and Wales, Australia, New Zealand, Canada, Sweden, the Netherlands, and others), only England and Wales, and the Netherlands use an explicit WTP threshold to make funding recommendations (43). The PBAC do not explicitly report a fixed WTP value to judge the acceptability of a medicine as CE, but revealed and stated preference studies of PBAC decision-making shows a preference for smaller ICERs to recommend a medicine (40, 201). The view from academic stakeholders aligns with surveys of the Australian general public which shows there is no WTP a premium for rarity although there is a case for paying more for drugs that treat severe conditions, or where there is no alternative treatment available (56, 202, 203). Nonetheless the PBAC have stated their willingness to accept a higher ICER in the face of significant uncertainty in the CE of a medicine for a RD (196).

A limitation of our study is the small sample size in this survey, and the unequal group sizes (academia, N=11; private sector, N=33). The timing of the survey, conducted during the recent HTA

review in Australia, may have influenced participation, as stakeholders could have experienced fatigue due to the extensive feedback collection during the review. Discrepancies in sample sizes may account for the lack of significant differences observed, as smaller samples increase variability and standard error, reducing estimate reliability and sensitivity to detect differences. Additionally, recruitment through email and professional societies may introduce selection bias, as it depends on self-selection by more engaged stakeholders. Nevertheless, the participants had considerable expertise, averaging between 7-14 years of HTA experience, predominantly with health economic qualifications (**Table 14**), making their opinions likely a reliable reflection of other health economists in Australia. The absence of data from critical groups, such as government policymakers and patient representatives, limits the generalisability of our findings. Further research to include insights from these groups and expand the sample size would be beneficial. There may be other value elements that stakeholders think should be considered in HTA of medicines in Australia beyond what was considered in this survey. Nevertheless, the broad value elements in the survey covers a wide range of value from societal elements (health impacts beyond the treated individual and costs beyond the healthcare sector such as productivity and scientific spillover), to novel elements (e.g., insurance value, fear of contagion and value of hope). Regardless, the list of broad elements of value are not intended to be final preferences of stakeholders.

xviii Conclusion

The perspectives of Australian stakeholders in both the academic and private sectors were largely congruent, showing no significant differences between general medicines and those for RDs. Stakeholders from both sectors involved in HTA in Australia expressed concerns that current methods are inadequate for assessing medicines and that public statements lack transparency regarding which value sources influenced reimbursement decisions. There was consensus among both groups favouring the inclusion of more value elements in HTA decision-making than currently recognised in the PBAC and MSAC HTA guidelines, specifically advocating for the integration of six out of the eleven values from the ISPOR value framework.

The survey's findings offer valuable insights relevant to the Australian HTA review's recommendations, suggesting an explicit qualitative framework be developed, informed by public consultation and existing research. Additional research to gather perspectives from patients and decision-makers and to increase the sample size would be advantageous. This study underscores the necessity for enhanced guidance in reimbursement guidelines and for greater transparency in the publication of decisions related to the values influencing decision-making.

Chapter 6 Discussion and conclusion

The assessment of gene therapies (GTs) via health technology assessment (HTA) for reimbursement decision-making faces a number of challenges, including a high upfront cost and evidence limitations such as immaturity of evidence and the absence of rigorous randomised controlled trials (RCTs)(7, 8, 15). Given these limitations it is challenging to demonstrate the cost-effectiveness of gene therapy (GT)(9, 16). It has been argued that the traditional measure of health benefit within an EE captures only a subset of benefits that may be produced by a healthcare intervention and other broader elements of value beyond the patient should be considered when estimating value for money(45). Overall, it is argued that GT offers broader elements of value that should be factored into assessments of value for money(9). This thesis focuses on exploring the extent to which HTA agencies appear to have adopted this viewpoint, and the implications for conducting economic evaluations (EEs) of GT for rare disease (RD). In conducting a review of EE and HTA decision-making for reimbursement of voretigene neparvovec (VN), a GT to treat an RD, RPE65-mediated inherited retinal disease (IRD), this research identified key issues in demonstrating the cost-effectiveness and considerations by HTA agencies in making their funding decisions.

In this chapter the key findings and issues raised by the work conducted in this thesis are discussed. The findings related to the systematic review of HTA appraisals of VN, each subsequent research study undertaken, and their implications are discussed. Key questions raised by the research are then considered. Subsequently, we discuss the study's limitations and outline potential avenues for future research, which acknowledges among other things that the specific focus on RPE65-mediated IRD may restrict the transferability of these insights to alternative therapeutic interventions and other diseasesFinally, the chapter concludes with reference to the overall research question posed at the beginning of the thesis.

xix Key findings

The systematic literature review (SLR) in Chapter 2 of the technical evaluation of the EE and HTA final reimbursement decisions for VN identified limitations in the EEs modelling structure and the cost and utility data assumptions that informed the model. These limitations were partly

due to the rarity of the disease but also to the characteristics of GT as a single administration treatment lacking long-term evidence or medicinal analogues. It is partly due to such challenges that HTA agencies have adapted their HTA assessment process to accommodate the novel nature of innovative therapies such as GT and the limitations of the evidence that is able to be generated in RD(6, 204).

The differences in VN EE modelling methods, health-related quality of life (HRQoL) and indirect cost data between models noted in Chapter 2 emphasise the necessity for condition-specific data for an RD to accurately capture the disease's true impacts. In one case, a change from a linear to a non-linear utility function, which better reflects the utility reduction in severe vision loss associated with RPE65-mediated IRD, adjusted the quality-adjusted life year (QALY) gain from 1.3 to 5.2(69). Similarly, the use of indirect caregiver and patient productivity loss data that did not reflect RPE65-mediated IRD resulted in indirect costs of the blind HS that were half those calculated when IRD-specific sources for productivity loss were sourced (**Supplementary Table 23** in Appendix 1). Finally, the sensitivity analysis on HRQoL utility data from sight disorders that don't reflect RPE65-mediated IRD substantially impacted the incremental cost-effectiveness ratio (ICER) (74). This led to the question of what other methods could be used to determine HRQoL for an RD such as RPE65-mediated IRD; this was investigated in the study in Chapter 3.

Researchers have been working to improve identification and estimation of broad value elements for years, and progress continues to be made. However, it is impractical to account for all addition value elements within an EE currently due to methodological constraints(45). The SLR in Chapter 2 revealed however that HTA decision-makers do consider various broad value elements beyond the patient QALY, generally not within the framework of the EE, but as a consideration within their deliberative decision-making. Except for the Institute for Clinical and Economic Review (I.C.E.R.) in the United States (US) and the National Institute for Health and Care Excellence (NICE) in England, the HTA considerations for VN in REP65-mediated IRD were generally limited to the nature of the condition (being rare and severe) and impact on the caregiver. How these factors impacted on final reimbursement decisions were not always

transparent, but the severity of the condition was considered qualitatively by most HTA committees and the caregiver impact considered quantitatively via application of a caregiver disutility in calculating QALY gains, albeit only attributed to children less than 18 years in the NICE evaluation. The range of ICERs accepted by agencies was broad ($68,662/QALY to $643,813/QALY) and above standard known willingness to pay (WTP) thresholds, implying that broader benefits beyond the QALY were considered in the decision-making. Conditional approvals were granted in some cases contingent upon a managed entry agreements (MEA) to address uncertainties in clinical benefit that were presented in the limited evidence for the RD, as well as patient and caregiver benefit and associated costs. The lack of evidence to support the caregiver burden associated with caring for adult patients with IRD inspired the research in Chapter 4.

The findings presented in Chapter 3 offer utility values for HSs with varying levels of functional vision (0.76 for moderate visual impairment to 0.20 for patients that recognise hand motion only to not having any light perception) from 110 members of the Australian general population (**Table 8**). The study builds on utility data that had been elicited from a time trade off (TTO) study conducted in the UK and confirms the findings of other TTO studies in visual impairment (90, 91, 104). The utility values across four health states (HSs) (0.76 for a patient with moderate vision impairment to 0.35 for patients whose vision impairment allows them to only count fingers) are similar to those elicited in the United Kingdom (UK) TTO study (0.78 to 0.43, respectively). Further the results from Chapter 3 are similar to other published utility values established using TTO methodology in patients with impaired vision due to a range of diseases such as age related macular degeneration, diabetic retinopathy, retinal detachment, cataract , glaucoma, endophthalmitis, and central retinal vein obstruction (0.67 when suffering moderate visual impairment to 0.26 when a patient has no light perception) (**Table 9**). However, the utility value for the most severe vision impairment state, ranging from ‘hand motion’ to ‘no light perception’ (0.20), is lower than the UK TTO study's utility value (0.33). This discrepancy likely due to the TTO method applied in the UK which did not incorporate a worse-than-death (WTD) trading option.

The findings of the analyses conducted in Chapter 3 raise a few important considerations linked to the measurement of HRQoL for use in an EE. First, the research in Chapter 3 underscores the importance of considering WTD valuations in TTO studies. The research presented in Chapter 3 employed the composite time-trade-off (cTTO) methodology, in which a given HS is evaluated as BTD or WTD. Although there are concerns regarding the use of 'dead' as a baseline in valuation methods like TTO, the cTTO method effectively incorporates the lead-time TTO (LT-TTO) approach to elicit preferences for HSs considered WTD, offering a pragmatic solution to this methodological challenge.(112, 113, 205). The research highlights that allowing WTD as a trading option is important because it can have a significant impact on the resulting utility scores, which can ultimately influence the conclusions of a cost-utility analysis (CUA).

Second, since the utility values derived in Chapter 2 closely align with the utility values established in the UK TTO study, it may be pragmatic for countries that share cultural attributes and HTA similarities to Australia to consider using the direct utility weights obtained from this study. HTA agencies accept direct utility weight elicitation from the general public, such as through TTO methods when existing HRQoL instruments do not adequately capture specific health state impacts. Some HTA guidelines however require direct elicitation from the general population that represent the type of patients being treated in the health care system where the CUA will be used (102, 129). For example, if the utility values are being collected for an economic model for NICE, then it is most appropriate to include participants from England and Wales(102). However, conducting TTO studies poses a significant time and cost burden. Despite differences in utility value for the most severe visual impairment, which is attributed to including the WTD trading option, the utility values from the Australian and UK study are virtually identical.

Moreover, the findings from the vignette study can serve as an example for future HRQoL research concerning RD, particularly those with limited patient populations where it is difficult to procure robust data. The study in Chapter 3 included HS vignettes developed in consultation with 5 patients with a rare IRD and validated with 2 clinicians which demonstrates that a vignette study can effectively remedy the lack of utility data in patients with RD.

In addition, the research in Chapter 3 provides a valuable example of a vignette study that may be particularly useful for collecting utility data for RDs affecting young children. Written descriptions or vignettes of HSs, derived from qualitative interviews with children with RD's and their caregivers, that explore the functional impairments experienced by patients in areas like social life, family life, education, and employment, can then be utilised in a cTTO study. Many GTs under development are designed for RDs affecting young children (1, 3). As such, many patients targeted by GTs are too young to communicate their own HRQoL or they may be incapable of describing their own HRQoL if they have cognitive damage. Further, the diseases that GT treat are generally rare meaning the sample size of clinical studies is small, in the case of VN the sample size in the pivotal RCT was 32 patients (12). Consequently, proxy reports of HRQoL, typically provided by parents or caregivers in the case of young children, are likely to be conducted and while such reports are reliable for observable attributes they are less so for aspects requiring interpretation, like social and emotional well-being(206). Additionally, evaluating proxies' own HRQoL is crucial to understand their impact on perceived burdens. Alternative methods that are widely used to capture HRQoL or utility data alongside clinical trials are the pre-scored generic multi-attribute utility instruments (MAUI) measures, such as the EuroQol-5D (EQ-5D) or 36-item Short Form survey (SF-36) (207). However, they may not be suitable for assessing young children's health states, and they may be insensitive to the symptoms expressed due to the disease as is the case for the EQ-5D and vision (131, 206, 208). The cTTO with the Australian general population in Chapter 3 exemplifies how such limitations can be addressed.

Taken together with the above, the utility data generated in Chapter 3 are a valuable resource for use in conducting EEs of IRD. Also, because the utility values reflect varying levels of visual impairment, it may also be applicable to other vision-impairing conditions. However, its broader use in other conditions that affect vision would require further research to validate other diseases impact patients similarly to IRD.

The research in Chapter 4 presents the caregiver burden from seven working age and retired informal caregivers (who were predominantly family members) and the experience of caring for children, adolescents, adults and elderly people with a range of IRD's. IRDs are lifelong conditions, and the research in Chapter 4 shows caregiving duties transition from parents to other family members, such as partners or children.

The results from the study build on and confirm the findings from other work that have explored the emotional well-being of caregiving for individuals with visual impairment which adds to the robustness of the findings (142, 163, 164). The research in this thesis found caregiver emotional well-being is dynamic, oscillating between positive emotions and negative emotions, however anxiety in the caregiver was the dominant emotion. An important finding from the study was that anxiety was largely attributed to the progression of vision loss in patients with IRDs and the accompanying responsibility of assisting with their evolving needs.

Ongoing time commitment by the caregivers for patients with IRD from supporting activities such as medical care, education, housing, and applying for support services via the Australian National Disability Insurance Scheme (NDIS) remained significant as patients with IRD age(172). Another key finding from the study was the significant economic trade off associated with informal caregiving. The study consistently found that informal caregivers balance their caregiving duties with paid employment responsibilities. Further, while the NDIS aims to provide as much care as possible privately for the patient with IRD, through encouraging self-care, there is a substantial burden imposed on caregivers to support the patients to prove their eligibility to the NDIS and to advocate for support from the NDIS(172).

The study results highlight several issues related to the integration of caregiver burden into EEs. First, the ongoing caregiving responsibilities due to the lifelong nature of IRDs challenges the approach of excluding disutility values for carers of adults but including disutility for caregiving of children with IRD in the VN EE (an approach that was deemed appropriate and used for decision-making by NICE)(82).

Second, the economic trade off associated with informal caregiving for patients with IRD supports incorporating caregiver productivity costs into EEs for IRD. The findings from this study support the need for future research to quantify the caregiver burden in terms of productivity loss and HRQoL impact for caregivers of patients with IRD. The work from this thesis adds to the literature by informing that the caregiver burden be measured across the patient's lifespan and not just prior to becoming an adult.

Further research to understand whether caregiving burden differs when caring for specific types of IRD through researching a large sample of caregivers could help to understand whether the findings are applicable to caregivers of any IRD. In addition, further work is needed to establish the HRQoL of caregivers for patients with IRD and corresponding disutility values for inclusion in EEs. Although the NICE committee agreed to include disutility values for carers (referred to as spillovers) in its appraisal of VN, the EE utilised caregiver disutility values from a wide range of conditions. The disutility data were from caregiving of children with disorders (e.g., spina bifida,) elderly affected by diseases (e.g., Alzheimer's disease and dementia); to caregiving patients with physically disabling conditions (e.g., arthritis, multiple sclerosis), and medical conditions (e.g. cancer and stroke); none of which are specifically representative of IRDs(50, 97). There are some complexities in measuring caregiver disutility(52). While generic MAUI's such as the EQ-5D have been used to measure caregiver utility, these instruments were not specifically designed for this purpose and may therefore be inadequate. For example, the risk of double counting health impacts arises when using generic HRQoL instruments to derive utilities from caregivers due to unintended inclusion of health spillover effects. This occurs when patients consider family impacts or caregivers mix their health changes with the patients and consider the financial effects from caregiving while valuing health states (209, 210). Finally although HRQoL instruments are available for carers (e.g., Care-related Quality of Life [CarerQol] instrument) these include non-health domains in addition to health, and as such may be incompatible with CUA's (211). Direct measurement, that is asking carers to value their current HRQoL using a preference-based method such as TTO or standard gamble (SG) is however a possible solution(52).

The finding from Chapter 2, along with findings from Chapter 4 highlighted that broad value elements beyond the patient QALY, namely caregiver impact, should be and are considered for treatment related to IRD by international HTA decision-makers. This led to the research in Chapter 5 - surveying the opinions of 44 Australian stakeholders involved in HTA on whether and how broad elements of value are considered by HTA decision makers in Australia. Stakeholders expressed a perception of insufficient information regarding which value sources are factored into HTA decision making in Australia. The research identified a consensus on the lack of clear documentation about the value elements influencing decision-making, especially concerning how various value sources affect these decisions. Stakeholders agreed that an inventory checklist of what was considered for reimbursement decision-making could standardise the evaluation of value sources, thereby reducing bias and enhancing transparency. Most stakeholders surveyed advocated for the consideration of additional broad value elements in the HTA of medicines beyond what is reported in HTA guidelines to *influence* decisions by the PBAC and MSAC in Australia, namely severity of disease, labour productivity, adherence, reducing uncertainty due to a new diagnostic, and value to caregivers. The consideration of additional broad value elements in HTA applied to both medicines for RD and medicines for non-RDs.

Stakeholders surveyed on research study 4 were asked to nominate mechanisms to expedite access to treatments for RDs while managing the uncertainties in CEA and budget impact. This was on the basis that such approaches address the significant unmet need and demand for rapid access to medicines for RD. This assertion is supported by an analysis across 10 medicines for RD that were commonly appraised across four HTA agencies :NICE in England, the Scottish Medicines Consortium(SMC) in Scotland, the Dental and Pharmaceutical Benefits Board (TLV) in Sweden and the Haute Autorite´ de Sante´ (HAS) in France(5). The risk and value preferences likely impacted the appraisal process and contributed to differences in approving the medicines across the different countries. In addition to the “decision modulators” such as acceptance of higher WTP and uncertain ICERs, and agency “specific modulators” such as elicited and non-elicited societal preferences like consideration of disease severity, there were a number of “process specific modulators” such as lower discount rates accepted,

imposing a restriction on use, imposing MEA with re-assessment requirements that contributed to explaining different reimbursement decisions across the countries.

The research in chapter 5 supports the use of two mechanisms to manage uncertainty in HTA decision-making for medicines for RD. The two methods to manage the uncertainty in decision-making for medicines for RD are RSAs and outcome-based MEAs(190). RSAs provide financial stability by linking subsidies to specific clinical criteria, whereas outcome-based MEAs face implementation difficulties in Australia due to inadequate infrastructure for tracking medicine use and outcomes. The results of this thesis broadly support the use of these agreements, and while RSA's are commonly implemented for high cost therapies for diseases that have limited evidence, MEA's are not commonly used because there is a need in Australia for infrastructure enhancements for data collection and strategies for pricing adjustments or product delisting if necessary.

Stakeholders also supported the implementation of a quantitative MCDA in the decision-making process in Australia. There were differing perspectives among stakeholders regarding the potential increase of WTP thresholds when making reimbursement determinations for RD medications. Academic stakeholders (n=11) did not agree that an increased WTP (defined as an increased in ICER considered acceptable for treatments of RD) should be used as a mechanism in Australia in making decisions about reimbursement of medicines for RD. In practical terms however the PBAC have shown their willingness to accept a higher ICER in the face of significant uncertainty in the CE of a medicine for a RD(196).

Overall, the systematic review in Chapter 2 identified significant methodological challenges in evaluating therapies like VN for RDs, including the lack of condition-specific utility evidence and inconsistent consideration of broader value elements in reimbursement decisions. These issues highlight the difficulty in demonstrating cost-effectiveness of gene therapies (GTs) and the need for comprehensive value assessment frameworks. Building on these insights, the findings from Chapters 3-5 address these gaps and advance methodologies for assessing GT value.

Specifically, Chapter 3's utility valuation study provided Australian-specific HRQoL data for IRD, using techniques like the cTTO method to refine quality-adjusted life year (QALY) estimates, tackling evidence immaturity noted in Chapter 2. In Chapter 4, the caregiver burden findings underscored the need to quantify family spillover effects through innovative methods like longitudinal surveys for economic evaluations (EEs), aligning with calls for broader value considerations. Additionally, Chapter 5 revealed Australian stakeholder consensus on value elements such as caregiver value and disease severity should be captured within Australian HTA, proposing standardized value inventories to ensure comprehensive and transparent assessments, directly addressing the methodological innovation suggested in the systematic review for adapting HTA processes to the unique challenges of GTs and RDs

xx Recommended application of this research to HTA

The research in this thesis identified important methodological challenges in evaluating a GT for an RD and provides data sources to alleviate some of those challenges, and methods to manage substantial variability in how HTA agencies account for broad elements of value and manage uncertainties associated with medicines for RDs. The results of this thesis have implications for the development of EEs for GT in a RD. They also have implications for the future development of a value framework for use by HTA decision makers in Australia and inform a number of questions of importance for the research area and wider policy issues. These questions are posed and possible answers discussed below.

1.What do the results mean for developing EEs for GT in RD, and decision making by HTA agencies?

The findings in Chapter 2 reveal challenges in EEs for RD therapies, particularly the lack of disease-specific utility data. Chapter 3 illustrates that using a cTTO methodology with the Australian general population is an effective and straightforward way of providing reliable utility estimates while reducing dependence on potentially inaccurate patient data or clinician-derived estimates. Chapter 4 highlights the lifelong caregiving needs associated with IRDs, recommending caregiver disutility should apply for patients with IRD after they turn 18 in EEs

developed for the disease, and supports accounting for the economic impacts of informal caregiving in these evaluations.

The research raises a key question about the appropriate methodology to integrate caregiver burden into EEs for IRD. Across international decision-making jurisdictions, different HTA guidelines regarding the inclusion of caregiver impact exist (49). HTA guidelines on the conduct of EEs published by the NICE in the UK, and the Zorginstituut Nederland (ZIN) in the Netherlands advocate for family health spillover incorporation into EEs on the basis that healthcare interventions which enhance patient well-being may also provide broader advantages to their family members or caregivers who are supporting the patient affected by illness. Despite advocating for their inclusion, evidence indicates that including the spillover effects of health conditions and healthcare interventions into EEs is not common. For instance, a recent review of NICE appraisals found that less than 5% of technology appraisals incorporated caregiver HRQoL into EEs(212). In addition to its infrequent incorporation there are high levels of methodological variation in the evaluations incorporating caregiver burden. This was evident in the VN EEs; I.C.E.R. approved an EE based on the modified societal perspective that accounted for the caregiver productivity costs but not the caregiver HRQoL impact whereas NICE approved the EE accounting for the caregiver HRQoL impact but not the caregiver costs(69, 81).

The findings of this thesis indicate that caregivers of patients with IRDs at various ages experience both an adverse effect on their emotional wellbeing and a reduction in income resulting from their informal caregiving duties. Incorporating these benefits into EEs has been demonstrated to substantially improved cost-effectiveness and influence funding recommendations (77, 182). However despite some HTA agencies supporting the inclusion of caregiver spillovers in EE's there is concerns about possible distribution effect on equity consideration when spillover impacts are considered and different opinions on methods to include spillover effects(97, 102, 212, 213). Consequently 'consensus guidelines' have been established to promote best practice in accounting for health spillovers to caregivers and family in EEs(52). The guidelines recommend that spillover health (dis)utility estimates can be

determined using either direct or indirect measurement (214, 215). It is also important to estimate whether caregiver burden relates to a number of specific caregivers and other family members, *or* the closest member in the affected person's network of family and caregiver This process should be informed by relevant data, HTA guidelines, and the context of the health condition or intervention. In addition, QALY gains and losses should be reported separately for patients and caregivers and then spillover effects should be aggregated with patient effects through additive summation of the reported QALY gains and losses. Finally, the caregiver spillover should be measured over a time horizon sufficient to encompass all relevant impacts of the health condition, including the comprehensive effects of caregiving responsibilities.

The research in Chapter 4 demonstrates the caregiver burden was present for patients with IRD whether they be children, adults or elderly. The result of this thesis suggest that such burden should be captured over the patient and caregiver lifetime, supporting the use of lifetime time horizons in EE. To achieve a comprehensive understanding of the caregiving burden from IRD, further research is essential to estimate health (dis)utility values from caregivers of IRD patients and to identify circumstances when the family and caregiver burden should be excluded from an EE.

Although the data presented in Chapter 4 are specific to IRD, the findings regarding caregiver burden may be relevant to other conditions with similar care needs. For example, it could be hypothesised that the research findings from this thesis are applicable to other conditions akin to IRD, which manifest from a young age, progressively worsen over time, and do not reduce life expectancy, such as spinal muscular atrophy (SMA) Type 3 (216). As such any caregiver spillover associated with non-IRD diseases that have a similar disease deterioration and impact should be measured and considered in EEs over a lifetime horizon.

The result of this thesis underscores the need for international collaboration among HTA agencies. The research in Chapter 3 highlighted the disparity in how caregiver spillover was implemented in EE and considered by HTA agencies. By establishing international standards and sharing best practices, they can harmonise HTA processes which would promote more

consistent and equitable access to medicines, particularly for RDs. A standardised approach to considering broader value elements, such as caregiver burden, would be beneficial for patients and industry because they would have a clear understanding of what research data are meaningful and necessary to satisfy HTA requirements. The research findings in Chapter 5 emphasised the necessity for clear guidance, as Australian stakeholders expressed a desire to understand which value elements are considered in HTA decision-making and how these elements influence decisions. While the research focused on Australian HTA stakeholders, its implications likely extend to other jurisdictions.

The benefit of harmonised HTA processes is that it might expedite access as inconsistencies in drug reimbursement can lead to uneven global health outcomes. Patients with earlier access to innovative therapies with proven therapeutic benefit typically experience better outcomes, and for RDs with small patient cohorts, generating adequate evidence to meet varied reimbursement standards is challenging. This policy change would mitigate these disparities, ensuring equitable access to necessary treatments for all patients. Notably, this year (2025) saw the announcement of the Health Economics Methods Advisory (HEMA) initiative, bringing together representatives from the USA-based ICER, England's NICE, and Canada's Drug Agency (CDA-AMC) (https://icer.org/health-economics-methods-advisory-hema/). The HEMA aims to critically and independently investigate pressing topics in global health economics and HTA methods, aligning with the proposal outlined in this thesis.

Importantly, HTA agencies that take cost-effectiveness into account will maintain specific local consideration of costs and WTP thresholds that are relevant to their jurisdiction even if there are standardised guidelines for incorporating broader elements of value in EEs. This alignment on broader value considerations and accounting methods will not compromise the decision-making autonomy of HTA agencies. Nonetheless, merely recommending in guidelines that HTA agencies consider broader elements of value may not ensure their integration into cost-effectiveness analysis (CEA) or influence final decision-making. For example, HTA coverage recommendations currently for identical drugs across countries differs which reflects independence in funding recommendations, despite HTA's role in guiding resource allocation

decisions (75, 217). These variations may be attributed to contextual differences, such as the perspective adopted (health care or societal) and different WTP thresholds.

2.If broader elements of value to individuals and society associated with GT for a RD are adopted universally by HTA agencies, what guidance and further research is needed?

This research underscores the importance of harmonising HTA guidelines to incorporate broader elements of value beyond mere cost-effectiveness. Such harmonisation may facilitate more consistent and equitable access to medications, especially for RDs. Additionally, less established HTA organisations may lack the expertise and resources necessary to evaluate broader value elements and would benefit from collaboration with more prominent HTA organisations.

As GTs have emerged, HTA agencies have been assessing whether their current processes need modification to adapt to these innovative treatments for RD. HTA agencies have identified a number of issues when making complex reimbursement decisions, which are also present for therapies to treat more prevalent diseases, but more challenging when reviewing therapies for RD (5). Some HTA agencies have developed new HTA programmes to handle the challenges in appraising therapies for RD such as the Highly Specialised Technology (HST) programme at NICE(6). Additionally, in 2019, the I.C.E.R. in the United States conducted a review of its evaluation methods for potential one-time cures, drawing from its experience with GTs(218). This assessment led to updates in their value assessment framework, incorporating broad elements of value specifically pertinent to GTs, such as the value of hope, insurance value, scientific spillovers, and real option value.

Should HTA agencies globally integrate the broader value of a therapy in reimbursement decision-making, it becomes imperative to provide guidance on best practices and undertake further research to guarantee effective and consistent implementation. While some broader elements of value have the evidence to support their inclusion into an EE, such as caregiver

spillover, others such as equity have ill-defined concepts of value (i.e. focus on equity in overall wellbeing or specifically equity in health) and are often considered qualitatively within HTA decision-making (45). By setting international standards and exchanging best practices, these agencies can harmonise HTA processes. European efforts to harmonise HTA commenced over a decade ago with the establishment of the European Network for Health Technology Assessment (EUnetHTA), serving as a model for creating a standardised HTA process that enhances consistency across EU member states(219).

There are debates about how expansive to make value assessments. A recent review of 53 HTA guidelines representing 52 countries by Breslau et al. revealed an average of 5.9 of a possible 21 societal and novel broader value elements differentiated as being “societal” or “novel” value elements were mentioned(49). Although the review indicated that definitions of societal elements vary somewhat across jurisdictions and guidelines, 'societal elements' generally encompass aspects of the informal healthcare sector (such as patient-time costs, unpaid caregiver-time costs, and transportation costs) as well as non-healthcare sectors, including productivity, consumption, social services, legal or criminal justice, education, housing, and the environment, “novel” elements are those not typically included in conventional cost-effectiveness analysis (equity, fear of contagion, insurance value, value of hope etc.). Determining which broader elements of value to include in guidance is essential to the harmonisation process, which must also define those elements and their applicability; examples are provided below.

- Value of hope: Reflects, “the extent to which the chance for a cure is valued (e.g., some patients may be willing to trade some survival (e.g. undertake a risky procedure) for a chance of a “cure” even if only for a small probability of cure/improved survival” (45). Many patients, for example, might opt for a risky but potentially transformative cancer treatment.
- Fear of contagion: Reflects, “reducing the anxiety associated with the risk of future illness, even if the expected number of cases prevented is low” (45). This may be applied when evaluating vaccines.

- Real option value: Reflects, “value generated when a health technology that extends life creates opportunities for the patient to benefit from other future advances in medicine” (45). Studies have estimated the real option value of a cancer drug that allowed patients to survive until the introduction of a new treatment, with estimates varying from 0.4 to 57 percent(220, 221).
- Scientific spillovers: Reflects, “Broad societal benefit from knowledge created from a treatment with a new mechanism of action. It is considered a public good used for the discovery of other agents” (45).

While many broad elements of value have been proposed, there is a suggestion that some may be particularly relevant for novel therapies in RD(7-9). Although unmet need and disease severity are frequently stated as arguments in favour of special appraisal for GTs targeting RDs, it is important to emphasise that these characteristics are not exclusively associated with GTs. A one off treatment is not novel to GT; other existing health technologies that are delivered once with lifelong consequences have been managed via HTA, such as the use of direct-acting antivirals for hepatitis C virus that removes the virus after a brief course, and has lifelong effects, or vaccines that impose lasting immunity (204). Another example is the left ventricular assist device (LVAD) which is a durable mechanical pump that replaces the role of the damaged ventricles in the heart and restore normal blood flow for patients with heart failure (222). Further, some novel elements of value are more relevant for some therapies more than others. For example, insurance value from having antibiotic treatment available in case of sudden, or major increase in incidence of infections has been included in a framework in England for the value assessment of new antimicrobials evaluated by NICE (223). For instance, the real option value of a cancer-curing therapy pertains to the indirect health benefits that may arise when patients, whose lives are extended due to the treatment, subsequently gain access to utilise new technologies (considered as 'options') that they would not have otherwise had the opportunity to use (224). The result of this thesis supports that HTA decision-making for medicines should consider an additional four broad value elements beyond what is currently reported in HTA guidelines to *influence* decision-making, namely labour productivity, adherence,

reducing uncertainty due to a new diagnostic, and value to caregivers; and these should apply for both RD and non-RD.

Following on, the broader impact of some therapies, such as impact on caregivers, is considered applicable for other conditions that are not necessarily rare such as childhood disorders (e.g., spina bifida, congenital malformations), diseases of the elderly (e.g., Alzheimer's disease and dementia), physically disabling conditions (e.g., arthritis, multiple sclerosis), and medical conditions such as cancer and stroke(50).

There are also inherent equity concerns regarding the inclusion of value dimensions that solely increase the assessed value of certain treatments that would support their higher price without establishing a mechanism to balance this increase with the resultant opportunity costs and associated health losses due to other treatments foregone (218)..

The review's findings suggest that harmonised guidelines for accurately capturing broader value elements in EEs and HTA decisions should include diverse diseases and therapies. These guidelines should be based on systematically assessed, reliable sources, requiring reviews of published methodologies and input from various stakeholders, including bioethicists and social scientists (225). This approach ensures that incorporating comprehensive value elements into HTA is consistent and robust

The integration of broader value elements into HTA decision-making is a subject of ongoing debate. Research in Chapters 2 and 5 supports the current view that the evaluation of value beyond the QALY frequently relies on "deliberative decision-making," which often lacks a defined framework and transparency(9). This raises concerns about the potential risk of double-counting broader value elements, both in the QALY and in other qualitatively assessed value components (8). Several methodologies have been proposed to formally incorporate these broad value elements into an EE. These include extended CEA, augmented CEA, MCDA, and synthesising multiple value elements into a singular measure using the QALY(187). Guidance is needed on whether to incorporate broader elements of value in EE or HTA deliberations

qualitatively or quantitatively. This thesis provides qualitative evidence supporting the application of caregiver disutility over patients' lifetimes with IRD in economic models when such data exists. For instance, the VN EE presented to NICE included caregiver disutility values from various conditions. With caregiver spillover data already quantified, the thesis's qualitative data helps validate its application across a patient's lifetime in VN appraisal, illustrating how qualitative evidence supports quantitative data validation. While qualitative methods offer flexibility, quantitative approaches provide transparency but require robust preference determination. Consequently, policymakers and stakeholders should consider additional funding to develop methods for better quantifying novel value elements and incorporating broader value elements into decision-making.

Finally, due to the variability in HTA decision-makers' acceptance of broader value elements in assessing GTs for RDs, the pharmaceutical industry should prioritise investing in appropriate methods to assess these broader elements of value, beyond the patient, presented by therapies in their research and development pipeline. For example, investing in vignette studies, as demonstrated in Chapter 3 of this thesis, can directly elicit utility values from the general population to address the scarcity of utility data in RD patients. This investment is crucial for supporting and enhancing patient access to innovative medicines by aligning with diverse assessment criteria and demonstrating comprehensive value.

3.Should broader elements of value to individuals and society be considered by the PBAC and MSAC?

The results this thesis suggest that the PBAC and MSAC should include a wide range of value elements in reimbursement decision-making of all medicines (not just those for RDs) beyond the traditional CEA metrics. Specifically, the research in chapter 5 supports the following broader value elements labour productivity, adherence, severity of disease, value to caregivers, and equity should be transparently integrated into the decision-making process. This approach would result in a more informed process of resource allocation across various therapies and broader population groups. The research from this thesis supports Recommendation 26 from the recent Australian HTA review “Developing an explicit qualitative values framework” on the

basis that a value framework that incorporates broader value elements into decision-making will improve consistency of decisions (226). The HTA review advise that the development of a value framework should occur in consultation with stakeholders as this approach offers the potential benefit of encouraging stakeholders—including applicants, HTA agencies, patient groups, and committee members—to consider relevant value domains in each technology assessment. By establishing an explicit value framework, applicants will address value considerations consistently, which could also serve as a useful tool for patient or public submissions to HTA decision makers. This would enable these groups to effectively highlight and target areas of value that might otherwise be inadequately understood by the committees.

There were mixed views noted in the preamble to Recommendation 26 from the HTA review on the range of elements that should be represented in the qualitative framework(226). Some stakeholders explored the inclusion of a much broader range of elements: societal benefits such as productivity benefits, reduced carer burden, treatment choice and real option value (e.g. life-extending treatments that may increase treatment options in the future). All stakeholders consistently emphasised the importance of equity and prioritising populations like First Nations people (226). The recommendation from the HTA review is for the Australian Government to support the development of an explicit qualitative values framework for HTA advisory committees. The results from Chapter 5 of this thesis from two stakeholder groups in Australia (academia and the pharmaceutical industry plus specialist consultants) concur with the development of such a framework, and advocate for the consideration of additional broad value elements to *influence* decisions by the PBAC and MSAC. Further, this thesis shows that an online stakeholder survey is an effective method for capturing diverse perspectives beyond academia and industry in Australian HTA, to capture a comprehensive view of broader value elements to be included in HTA decision-making.

Recommendation 26 specifies that the framework should publish explicit guidance about how the decision-making committee will consider each value element and their impact on decision-making. A possible approach for the development and implementation of value framework in Australia is that undertaken by I.C.E.R. in the US. The I.C.E.R. approach to value assessment

is similar to that of PBAC and MSAC in Australia, in that it explicitly considers comparative clinical effectiveness, ICER and budget impact, as well as other relevant factors. However, the updated US I.C.E.R. value framework includes a wide range of other benefits or disadvantages and contextual considerations, and is more systematic regarding how the factors are incorporated into decision-making (**Supplementary Table 28 and Table 29**, Appendix 5). The value framework used by the US I.C.E.R. was established in 2020 when the committee undertook an assessment of the challenges associated with EE of GTs (218). Like the PBAC and MSAC, the US I.C.E.R. does not report a single ICER threshold for establishing the cost-effectiveness of a technology. Instead, the US I.C.E.R. proposes a price range, called the health-benefit price benchmark, which is the price of a health technology that results in an ICER of USD100,000 – USD150,000. The committee then applies the impacts of those contextual considerations or benefits/disadvantages to influence whether the maximum price of a technology should be toward the top or toward the bottom of the range (or possibly beyond the range). They do this by considering whether the other benefits or disadvantages and contextual considerations point toward a relatively lower or higher longer-term value for money. The approach of using other relevant factors to adjust the cost-effectiveness range as applied by the US I.C.E.R. is similar in some ways to the approach taken by NICE. However, while the impact of broad value elements on the cost-effectiveness range is not explicitly quantified by the US I.C.E.R., NICE use a combination of non-quantified modifiers (called structured decision-making) and quantified modifiers (or decision rules) to adjust the ICER. Quantified decision modifiers or rules include applying greater QALY weights to populations with severe disease, measured as a QALY shortfall, and QALY weights to populations receiving highly specialised technologies (HST), such as GT, that experience large incremental QALY gains. Thus, other HTA committees have adjusted their approach to HTA decision-making to transparently account for the broader value offered by therapies. In the case of VN, as described in Chapter 2, the value assessment described above used by NICE and I.C.E.R. lead to the two agencies advising the therapy was cost effective while three other HTA agencies provided conditional approvals subject to a range of requirements(74).

The HTA review Recommendation 26 “Developing an explicit qualitative values framework” highlights that flexibility in the deliberative process is necessary to add value to decisions and avoid rigid pre-weighted scoring systems (226). The recommendation requested consideration of value elements be explicit at all stages of technology assessment and clearly communicated in public summary documents (PSDs) including how the elements are considered during committee deliberations. Australian reimbursement recommendations are made transparent to the public by publishing them online as PSDs (69). They provide contextual information pertaining to each recommendation and although they are limited in terms of the amount of information published, they provide insight into the factors and trade-offs noted through the deliberative process in arriving at reimbursement recommendations (82). Although as noted in Chapter 5 stakeholders disagreed that the public information on reimbursement decisions in PSDs in Australia provides sufficient information about which sources of value are considered and how they contributed to decision-making. The results of this thesis suggest that a checklist for reimbursement decision-making may be an effective way to standardise the HTA appraisal of value sources. The research in Chapter 5 supports that a checklist function as an “Impact Inventory,” which includes a comprehensive list and corresponding checkboxes for all health and non-health effects considered in a HTA (see example in **Supplementary Table 30** in Appendix 5). This inventory should encompass effects attributable to the healthcare sector, informal healthcare sector, and non-health sectors, while also documenting the type of evidence supporting each effect. Such a checklist could be a routine feature in PSD’s to make each evaluation more explicit and transparent and improve the quality of HTA appraisals(144). An explicit list of considerations to inform what is ultimately human judgement sensitive to context is particularly important given a “weighted criteria with some sort of formulaic approach to decision-making” (quantitative MCDA) is not recommended in HTA recommendation (226).

In the recommendation for an explicit value framework, it is stated that the framework should explain how sponsors (pharmaceutical industry) could provide data to respond to broad value elements and explain how patients and citizens could provide submissions to respond to the proposed broader value offered by a therapy (226). National HTA agencies have established guidelines tailored for evaluations conducted in their jurisdiction to ensure consistency and high-

quality in EEs. While PBAC and MSAC HTA guidelines states the committee allows value inputs from various sources if justified, Chapter 5 reveals that most respondents find current public information inadequate regarding value consideration in reimbursement decisions. Thus, PBAC and MSAC HTA guidelines should explicitly define value elements, state when they will be considered, and clarify the circumstances of their usage.

However, since the original PBAC HTA guidelines were published in 1995 they have been updated five times (https://pbac.pbs.gov.au/). Australian stakeholders have indicated that updating guidelines is their least favoured means of achieving methodological advancement (227). Thus, while revising HTA guidelines in Australia would assist in meeting the requirements of Recommendation 26, organising conferences and short courses for pharmaceutical industry sponsors, patient groups, and citizen groups may also prove beneficial.

4. What mechanisms should the PBAC and MSAC use to manage uncertainties that exist in making HTA decisions for medicines in RD?

Chapter 5 research endorses two mechanisms to support uncertainty in HTA decision-making for RD medicines: RSAs and outcome-based MEAs. RSAs provide financial stability by linking subsidies to clinical criteria, while MEAs face implementation challenges due to inadequate infrastructure for tracking medicine use and outcomes. The thesis supports these agreements, noting that RSAs are common for high-cost therapies with limited evidence, whereas MEAs require improved data collection infrastructure and pricing strategies in Australia.

Recommendation 19 from the Australian HTA review, “Managed entry agreements” cited the need for changes in the process in Australia to enable the successful implementation of MEA’s (226). Namely that the Government should undertake a revision of the policy and guidance framework for MEAs after consulting with stakeholders. The recommendation for the government to revise the MEA framework highlights the necessity for clear guidance on processes and pricing negotiation policies to establish MEA terms. This research contributes to the literature advocating MEAs as a mechanism to manage uncertainty in HTA decisions for RD medicines in Australia. The research also adds to the HTA review recommendation by

advocating the need for infrastructure enhancements in data collection in Australia to facilitate wider MEA adoption.

xxi Limitations of this thesis and suggestions for further research

The research conducted in this thesis has a number of limitations that lead to opportunities for further research.

The methodological challenges identified in the EE modelling in Chapter 2 may be specific to RPE65 mediated IRD and may not be applicable to other GTs for an RD. In addition, how broader aspects of value feature in decision-making discussed in Chapter 2 represent six HTA final reimbursement decisions for VN that were published in English and may not represent how the agencies consider all GTs in RD. This criticism could be answered by reviewing EE modelling challenges and HTA decisions for other GTs in other RD's, and from looking at the evaluations of VN from more countries and agencies.

The HRQoL data from Chapter 3 may only be applicable to RPE65-mediated IRD affecting visual impairment. While the HS vignettes in the TTO study captured patient experiences associated with RPE65-mediated IRD. IRDs include a diverse array of conditions where visual acuity, visual field, and night vision may deteriorate along different paths than depicted in the vignettes. Future research could explore utility differences among various IRDs to understand whether the HSUs from the cTTO may be applicable in other diseases which impact patients similarly to IRD.

For the thematic analysis conducted in Chapter 4, the population was recruited to represent caregivers of patients with IRD. Even though the study cohort was diverse, encompassing caregivers of young children, adolescents, adults, parents and friends, as well as a wide range of IRD conditions and varying time since diagnosis, the sample size for this study is relatively small (n=7) which may limit the generalisability of the findings to the broader population of caregivers of patients with IRD. It would be beneficial to interview more caregivers to understand the robustness of the data, and to see if views differ by IRD type.

The small sample size in the survey presented in Chapter 5, the unequal group sizes (academia, N=11; private sector, N=33) and the absence of data from critical groups, such as government policymakers and patient representatives, limits the generalisability of our findings. Further research to include insights from these groups and expand the sample size would be beneficial to understand the consistency and of what is important to stakeholders in Australia. There may also be other value elements that stakeholders think should be considered in HTA of medicines in Australia beyond those proposed by ISPOR that were captured in the survey. As such future research should explore consumer and decision-maker perspectives on incorporating broad value elements into decision-making processes, methods for accounting for these values, and enhancing transparency in decision-making.

xxii Concluding remark

If EE and HTA does not recognise the full value of a therapy, including the wide-ranging impacts, it may be undervalued. This research provides a comprehensive evaluation of the current EEs and HTA appraisals, highlighting crucial areas for improvement, particularly in the context of innovative therapies like GTs for RDs, exemplified by RPE65-mediated IRD. The findings accentuate the necessity for condition-specific data to accurately capture broader elements of value, including the HRQoL impacts on both patients and caregivers. Chapter 3 illustrates the effectiveness of employing the cTTO method with a general population to overcome limitations in utility data, offering a pragmatic approach to capturing HRQoL impact in a RD. Additionally, the research highlights the importance of caregiver impacts in RD, strengthening the case for such effects to be considered in HTA decision-making by integrating caregiver disutility values. A survey of Australian stakeholders involved in HTA pointed to the need for greater transparency in HTA decision criteria and suggested that standardising appraisals with a checklist framework could capture broader value elements like labour productivity, adherence, and diagnostic certainty. Collectively, these insights contribute to developing more comprehensive and inclusive HTA practices that accommodate the nuanced value propositions of contemporary therapies.

Appendix 1

Table 18 and Table 19 display the search terms and agency websites explored to identify published EEs and HTA agency reports for VN in Research study 1. **Table 20** presents the eligibility criteria for the selection of reports, **Table 21** presents extracted data from each EE using the Consolidated Health Economic Evaluation Reporting Standards checklist and **Table 22** presents the characteristics of the eight EEs reviewed in Research study 1 (SLR). **Table 23** presents a comparison of indirect visual health state costs attributed in two EEs from the US.

Table 18 *Systematic literature review search strategy- MEDLINE and EMBASE (via the Ovid platform) and EconLit (via the EBSCO platform)*

Topic	Search	Keywords
Inherited retinal disease and Voretigene neparvovec	S1	#1 leber congenital amaurosis'/exp #2 retina dystrophy'/exp #3 vitelliform macular degeneration'/exp OR 'vitelliform macular dystrophy'/exp #4 inherited retinal disease'/exp OR 'inherited retina disease' OR 'inherited retinal dystrophy'/exp OR 'inherited retina dystrophy' #5 retinitis pigmentosa'/exp #6 early onset severe retinal dystrophy' OR eosrd #7 early childhood retinitis pigmentosa' OR ecrp #8: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #9 rpe65 mutation' #10 rpe65-mediated' #11 biallelic rpe65' #12 rpe65' OR 'rpe 65' OR 'rpe65 gene' OR 'rpe65 protein' OR 'rpe65 protein'/exp OR 'rpe65 gene'/exp #13 rpe65 AND gene #14 #9 OR #10 OR #11 OR #12 OR #13 #15 #8 AND #14 #16 aav2-hrpe65v2'/exp OR 'aav2-hrpe65v2':ti,ab OR 'aav2' #17 voretigene neparvovec'/exp OR 'voretigene neparvovec':ti,ab #18 #16 OR #17 #19 #15 AND #18
Economic evaluations	S2	#1 economic evaluation #2 cost-effectiveness #3 cost-utility #4 #1 OR #2 OR #3
Combined searches	S3	S1 AND S2
Limits	Exclude not in English, conference abstracts and systematic reviews.	
Result	11 citations	

Table 19 *Search terms in manual review of HTA websites*

Terms: Inherited retinal disease Retinal dystrophy Leber congenital amaurosis Retinitis pigmentosa Voretigene neparvovec Luxturna Databases/websites: CEA Registry, Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Clinical and Economic Review (I.C.E.R.), National Centre for Pharmacoeconomics Ireland (NCPE), National Institute for Health and Care Excellence (NICE), Swedish Dental and Pharmaceutical Benefits Agency (TLV), Norwegian medicines agency (NoMA), Netherlands National healthcare institute (ZIN), Scottish Medicines Consortium (SMC), and Australian Medical Services Advisory Committee (MSAC)

Table 20 *Inclusion and exclusion criteria*

Included	Full economic evaluation reported
Excluded	Reports not in English, conference abstracts and systematic reviews

Table 21 *Generic data extracted for systematic review*

• Title
• Abstract
• background and objectives
• target population
• setting and location
• study perspective
• comparators
• time horizon
• discount rate
• choice of health outcomes
• measurement of effectiveness
• measurement and valuation of preference based outcomes
• estimating resources and costs
• currency, price, date and conversion
• choice of model
• assumptions
• analytical methods
• study parameters
• incremental costs and outcomes
• characterising uncertainty
• characterising heterogeneity
• Discussion- study findings, limitations, generalisability and current knowledge
• Source of funding
• Conflicts of interest

Table 22 *Data extracted from VN evaluation reports*

Source (country), year	Base case Perspective	Source of efficacy data	CE model structure	Measure of VN benefit and extrapolation	BSC extrapolation	Discounting	Mortality
I.C.E.R. (US), 201816	Healthcare system	Study 301 2-year data available	2 state Markov model	Treatment effect is maintained for 10 years followed by a 10-year waning period. During the waning period, visual outcomes changed at a progressively increasing proportion of the BSC rate of change, according to how much of the waning period had passed. For example, in year 1 of the waning period, the change in visual outcome was 1/10 the SoC rate, and in year 2 it was 2/10 and so on. After the waning period ends vision change is at the same rate as BSC.	A function for VA was created by age based on the natural history of disease assuming an exponential functional form. An equivalent method was used to create a function for VF using a linear functional form	3% costs and benefits	No mortality risk attributed due to vision loss.
Uhrmann (Germany), 202024	Societal	Study 301 4-year data available	2 state Markov model	Treatment effect is maintained over a lifetime.	A function for VA was created by age based on the natural history of disease assuming an exponential functional form. An equivalent method was used to create a function for VF using a linear functional form	3% costs and benefits	No mortality risk attributed due to vision loss.
CADTH (Canada) 202026	Healthcare system	Study 301 3-year data available	6 state Markov followed by parametric MSM	Markov transitions from VN arm of study 301 in first year. Parametric MSM based on natural history data after year 1 (Weibull). VN full treatment effect maintenance for 40 years	Parametric MSM based on natural history data after year 1 (Weibull).	1.5% costs and benefits	Excess mortality risk associated with visual impairment33.

				(100% RRR) followed by a linear waning of effect (down to 25% RRR) over a 10-year period and a residual treatment effect (25% RRR)			
NICE(England/Wales), 2019	Healthcare system	Study 301 3-year data available	6 state Markov followed by parametric MSM	Markov transitions from VN arm of study 301 in first year. Parametric MSM based on natural history data after year 1 (Weibull). VN full treatment effect maintenance for 40 years (100% RRR) followed by a linear waning of effect (down to 25% RRR) over a 10-year period and a residual treatment effect (25% RRR)	Parametric MSM based on natural history data after year 1 (Weibull).	3.5% costs and benefits	Excess mortality risk associated with visual impairment33.
SMC (Scotland), 202022	Healthcare system	Study 301 3-year data available	6 state Markov followed by parametric MSM	Markov transitions from VN arm of study 301 in first year. Parametric MSM based on natural history data after year 1 (Weibull). VN full treatment effect maintenance for 40 years (100% RRR) followed by a linear waning of effect (down to 25% RRR) over a 10-year period and a residual treatment effect (25% RRR)	Parametric MSM based on natural history data after year 1 (Weibull).	NR	Excess mortality risk associated with visual impairment 33
MSAC (Australia), 2020	Healthcare system	Study 301 3-year data available	6 state Markov followed by parametric MSM	Markov transitions from VN arm of Study 301 in first 3 years. Parametric MSM based on natural history data after year 1 (Weibull). VN full treatment effect maintenance for 40 years (100% RRR) followed by a linear waning of effect (down	Parametric MSM based on natural history data after year 1 (Weibull).	5% costs and benefits	Excess mortality risk associated with visual impairment 33

				to 25% RRR) over a 10-year period and a residual treatment effect (25% RRR)			
NCPE (Ireland), 2020	Healthcare system	Study 301 3-year data available	6 state Markov followed by parametric MSM	NR	NR	4% costs and benefits	Excess mortality risk associated with visual impairment 33

Abbreviations: BSC, best supportive care; CADTH , Canadian Agency for Drugs and Technologies in Health; I.C.E.R., Institute for Clinical and Economic Review; MSAC, Medical Services Advisory Committee; MSM, multistate model; NCPE, National Centre for Pharmacoeconomics Ireland; NICE, National Institute for Health and Care Excellence; NR, not reported; RRR, relative risk reduction; SMC, Scottish Medicines Consortium; SOC, standard of care; VA, visual acuity; VF, visual field; VN, voretigene neparvovec.

Table 23 *Comparison of indirect visual health state costs attributed in two EEs from the US in USD*

<table>
<tr><th colspan="2">Johnson et al.(51) nonmedical/indirect resource costs</th><th>Health state in EE</th><th colspan="2">I.C.E.R.(69) nonmedical/indirect resource costs</th></tr>
<tr><td rowspan="2">Caregiver productivity loss

Child patient (<18) $8,969
Adult patient $5,733</td><td rowspan="2">Indirect patient productivity

70% who finished high school: $15,076

30% who finish college: $22,662

Government program costs
Age 0-19 $996
Age 20-64 $1,900
Age 65+ $996</td><td>Mild vision impairment</td><td rowspan="3">education support
Age 0-17 $11,984

patient productivity
Age 18-39 $9,930
Age 40-64 $21,074
Age 65+ $7,316

Nursing home
Age 65+ $7,988</td><td>Transport
$2,764-$6,118

Caregiver costs
$4,860-$11,972</td></tr>
<tr><td>Moderate vision impairment</td><td rowspan="2">Transport
$8,287

Caregiver costs
$25,468</td></tr>
<tr><td rowspan="2">Caregiver productivity loss

Child patient (<18) $54,597
Adult patient $34,744</td><td rowspan="3">Blind health state

Indirect patient productivity

80% who finished high school: $15,614

19% who finish college: $52,877

Government program costs
Age 0-19 $2,286
Age 20-64 $3,697
Age 65+ $1,879</td><td>Severe vision impairment</td></tr>
<tr><td>Profound vision impairment</td><td rowspan="2">Transport
$10,563

Caregiver costs
$32,652</td></tr>
<tr><td>Caregiver productivity loss

Child patient (<18) $72,590
Adult patient $69,702</td><td>Counting fingers</td><td>Blind health state

education support
Age 0-18 $11,984

patient productivity
Age 18-39 $18,068</td></tr>
</table>

Source: Jensen, I., et al. Estimating the life-time indirect costs of vision impairment (VI) in inherited retinal degeneration (IRD): economic impact on education, government benefit programs, productivity and tax loss for patients and caregiver burden Presented at: American Academy of Ophthalmology October 28, 2018(228)	Source: Jensen, I., et al. Estimating the life-time indirect costs of vision impairment (VI) in inherited retinal degeneration (IRD): economic impact on education, government benefit programs, productivity and tax loss for patients and caregiver burden Presented at: American Academy of Ophthalmology October 28, 2018(228)	Hand motion, light perception, no light perception	Age 40-64 $27,221 Age 65+ $7,315 <u>Nursing home</u> Age 65+ $7,988 Source: Wittenborn J, Rein D. Cost of Vision Problems: The Economic Burden of Vision Loss and Eye Disorders in the United States. Presented to: Prevent Blindness America: NORC at the University of Chicago;2013.(230)	Source: Brown MM, Brown GC, Lieske HB, Tran I, Turpcu A, Colman S. Societal Costs Associated with Neovascular Age-Related Macular Degeneration in the United States. Retina. 2016;36(2):285-298(229)

Appendix 2

Supplementary Figure 5 to Figure 9 presents the descriptions for the five Health States included in the TTO study that formed Research study 2. **Supplementary Figure 10** presents the images of visual impairment shown to participants to illustrate the tunnel vision and night vision impact patients experience. **Supplementary Figure 11** presents the cTTO task presented to study participants and the TTO iteration scheme. **Supplementary Figure 12** presents a boxplot and **Supplementary Figure 13** presents the histogram for the HSU data elicited in Research study 2. **Supplementary Table 24** presents the proportion of nontrading across Health States and **Supplementary Table 2**5 presents the distribution of non-trading across Health States in Research study 2.

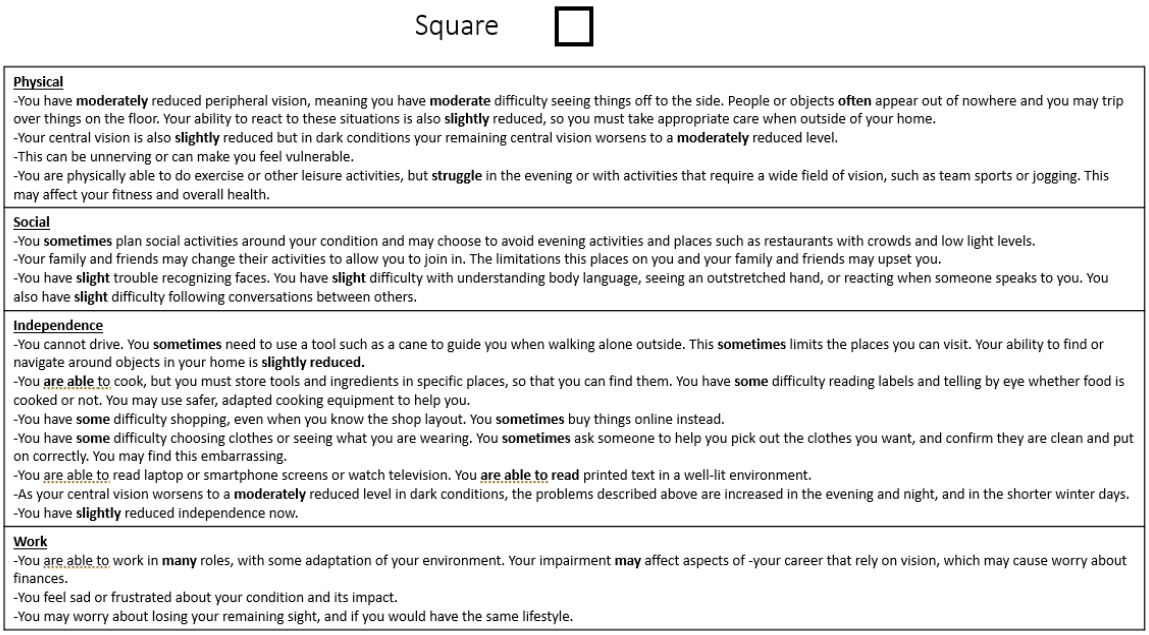


Figure 6 *Moderate visual impairment health state description*

Triangle △

Physical
-You have **greatly** reduced peripheral vision, meaning you have a lot of difficulty seeing things off to the side. People or objects very often appear out of nowhere and you may trip over things on the floor. Your ability to react to these situations is also **moderately** reduced, so you must take appropriate care when outside of your home.
-Your central vision is also **moderately** reduced and in dark conditions, your remaining central vision worsens to a **greatly** reduced level. -This can be unnerving or can make you feel vulnerable
-You are physically able to do exercise or other leisure activities in the daylight, but **cannot** do these in the evening. You also **cannot** do activities that require a wide field of vision, such as team sports or jogging. This may affect your fitness and overall health.

Social
-You **frequently** plan social activities around your condition and may choose to avoid evening activities and places such as restaurants with crowds and low light levels.
-Your family and friends may change their activities to allow you to join in, but **you do also miss out** on some activities. The limitations this places on you and your family and friends may upset you.
-You have **moderate** trouble recognizing faces. You have **moderate** difficulty with understanding body language, seeing an outstretched hand, or reacting when someone speaks to you. You also have **moderate** difficulty following conversations between others.

Independence
-You cannot drive. You **often** need to use a tool such as a cane to guide you when walking alone outside which limits the places you can visit. Your ability to find or navigate around objects in your home is **moderately** reduced.
-You **are able** to cook, but you must store tools and ingredients in specific places, so that you can find them. You have **a lot of** difficulty reading labels and telling by eye whether food is cooked or not. You may use safer, adapted cooking equipment to help you.
-You have **a lot** of difficulty shopping, even when you know the shop layout. You often buy things online instead.
-You have **moderate** difficulty choosing clothes, or seeing what you are wearing, due to your reduced central vision. You **often** ask someone to help you pick out the clothes you want, and confirm they are clean and put on correctly. You may find this embarrassing.
-You have **some difficulty** watching the television and this **may be** uncomfortable for you.
-You are able to read laptop or smartphone screens if these are **adapted** to display **larger** text. This **may limit** your ability to complete daily activities using these devices.
-As your central vision worsens to a **greatly** reduced level in dark conditions, the problems described above are increased in the evening and night, and in the shorter winter days
-You have **moderately** reduced independence now and may not be able to fulfil what you had planned for your life.

Work
-You are only able to work in **some** roles as you have **some** difficulty reading computer screens and printed text. Your impairment is **likely** to affect aspects of your career that rely on vision, which may cause worry about finances.
-You feel sad or frustrated about your condition and its impact.
-You may worry about losing your remaining sight, and that you may have to stop working in the future

Figure 7 *Severe visual impairment health state description*

Circle ○

Physical
-You have **extremely** reduced peripheral vision, meaning you have **extreme** difficulty seeing things off to the side. People or objects **constantly** appear out of nowhere and you may trip over things on the floor. Your ability to react to these situations is also **greatly** reduced, so you must take appropriate care when outside of your home.
-Your central vision is also **greatly** reduced, and you struggle to see details of any object or person. In dark conditions, your remaining central vision worsens to an **extremely** reduced level.
-You **often** rely on hearing and touch to navigate. This can be unnerving or can make you feel vulnerable.
-You are physically able to do exercise or other leisure activities in the daylight, but **cannot** do any hobby that relies on vision. You **may not** feel comfortable exercising in groups, or in new locations. This may affect your fitness and overall health.

Social
-You mainly plan social activities around your condition and may choose to avoid evening activities and places such as restaurants with crowds and low light levels.
-Your family and friends may change their activities to allow you to join in, **but you do also miss out** on some activities. The limitations this places on you and your family and friends may upset you.
-You have **a lot of difficulty** recognizing faces. You have a **lot of difficulty** with understanding body language, seeing an outstretched hand, or reacting when someone speaks to you. You also have **a lot of difficulty** following conversations between others.

Independence
-You cannot drive. You **very often** need to use a tool such as a cane to guide you when walking alone outside which limits the places you can visit.
-Your ability to find or navigate around objects in your home is **greatly** reduced.
-You **are able** to cook **slowly and with difficulty**, but only recipes you are familiar with. You must store tools and ingredients in specific places, so that you can find them. You cannot read labels or tell by eye whether food is cooked or not. You may use "talking" cooking equipment to help you.
-You have **extreme** difficulty shopping so you **very often** buy things online instead.
-You have **a lot of** difficulty choosing clothes, or seeing what you are wearing, due to your reduced central vision. You **very often** ask someone to help you pick out the clothes you want, and confirm they are clean and put on correctly. You may find this embarrassing.
-You have a lot of difficulty watching the television, and this **is likely** uncomfortable for you.
-You are able to read laptop or smartphone screens if these are **specially adapted** to display **much larger** text. This limits your ability to complete daily activities using these devices.
-As your central vision worsens to an extremely reduced level in dark conditions, the problems described above are increased in the evening and night, and in the shorter winter days.
-You have **greatly** reduced independence now, and may not be able to fulfil what you had planned for your life.

Work
-You are only able to work in **a few** roles as you have **a lot of** difficulty reading computer screens and printed text. Your impairment is **very likely** to affect aspects of your career that rely on vision, which may cause worry about finances.
-You feel sad or frustrated about your condition and its impact.
-You may worry about losing your remaining sight, and what this may mean for your career or family life.

Figure 8 *Profound visual impairment health state description*

Rectangle 

Physical
-Your peripheral vision is **almost totally** reduced to a level that makes it impossible for you to see things off to the side. People or objects **constantly** appear out of nowhere and you may trip over things on the floor. Your ability to react to these situations is also **extremely** reduced, so you must take appropriate care when outside of your home.
-Your central vision is also **extremely** reduced, and you struggle to see details of any object or person. In dark conditions, you **cannot see** even general details of any object or person, whether in your central or peripheral vision. -You **very often** rely on hearing and touch to navigate.
-This can be unnerving or can make you feel vulnerable.
-You are physically able to do exercise or other leisure activities in the daylight but **cannot** do any hobby that relies on vision.
-You **do not** feel comfortable exercising in groups, or in new locations.
-This may affect your fitness and overall health.

Social
-You **always** plan social activities around your condition and avoid evening activities and places such as restaurants with crowds and low light levels.
-Your family and friends change their activities to allow you to join in, but you do also miss out on some activities. The limitations this places on you and your family and friends may upset you.
-You have **extreme** difficulty recognizing faces. You have **extreme** difficulty with understanding body language, seeing an outstretched hand, or reacting when someone speaks to you. You also have **extreme** difficulty following conversations between others.

Independence
-You cannot drive. You **constantly** need to use a tool such as a cane to guide you when walking alone outside which limits the places you can visit.
-Your ability to find or navigate around objects in your home is **extremely** reduced.
-You **are able** to cook **slowly and with difficulty**, but only recipes you are familiar with. You must store tools and ingredients in specific places, so that you can find them. You **cannot** read labels or tell by eye whether food is cooked or not. You may use "talking" cooking equipment to help you.
-You **cannot** read any item at the shops, and **struggle** to perceive which section you are in. This means you **almost always** rely on others to shop for you, or buy things online instead.
-You have **extreme** difficulty choosing clothes, or seeing what you are wearing, due to your reduced central vision. You **constantly** rely on others to give you advice about clothing, as well as the rest of your appearance, like your face and hair.-You may find this embarrassing.
-You **cannot** read laptop or smartphone screens and rely on special adaptations to read any electronic text **aloud** to you. This **limits** your ability to complete daily activities using these devices.
-As you **cannot see** even general details of any object or person in dark conditions, the problems described above are increased in the evening and night, and in the shorter winter days.

Work
-You **cannot** work in any role that requires the use of sight. Aspects of your career that rely on vision are **almost certainly** affected by your impairment, and this is **likely to be** worrying in terms of finances.
-You have **extremely** reduced independence now, and do not feel secure in your life.
-You may feel depressed or frustrated about your condition and its impact.

Figure 9 *Counting fingers visual impairment health state description*

Pentagon 

Physical
-You can only perceive levels of light and dark in your surroundings or see moving objects that are directly in front of your eyes. You **cannot see** even general details of any object or person, whether in your central or peripheral vision.
-Due to your loss of peripheral and central vision, you are **completely unable** to see people or objects around you.
-You have **no ability** to react to events using vision. You must rely on hearing or touch to avoid any hazards when alone.
-You are physically able to do exercise or other leisure activities in the daylight but **cannot** do any hobby that relies on vision. You **do not** feel comfortable exercising in groups, or in new locations.
-This may affect your fitness and overall health.

Social
-You are **uncomfortable with many social activities** so choose not to attend.
-The limitations this places on you and your family and friends may upset you.
-You **rely entirely on a person's voice** to recognize them. You **cannot** perceive anyone's body language and **rely entirely on people's voices** to try to understand where they are and who they are speaking to.

Independence
-You cannot drive. You **completely rely on a tool** such as a cane to guide you when walking alone outside. You may sometimes struggle to identify your own front door.
-You may find this embarrassing.
-You must **rely on hearing or touch** to navigate your home or find any object.
-You **cannot** cook, due to the risk of accident. Therefore, you must rely on others to do this for you.
-You **cannot** see or read any item at the shops, or perceive which section you are in. This means you **almost always** rely on others to shop for you or buy things online instead.
-You are **unable** to choose clothes or perceive any detail of your appearance or the clothes you are wearing. You **constantly** rely on others to give you advice about clothing, as well as the rest of your appearance, like your face and hair. You may find this embarrassing.
-You **cannot** read laptop or smartphone screens and rely on special adaptations to read any electronic text **aloud** to you. This **limits** your ability to complete daily activities using these devices.

Work
-You **cannot** work in any role that requires the use of sight and you may be dependent on benefit payments.
-Aspects of your career that rely on vision are **almost certainly** affected by your impairment, and this is **likely to be** worrying in terms of finances.
-You have **extremely** reduced independence now.
-You may feel depressed or frustrated about your condition and its impact.
-You sometimes feel as though you are just surviving rather than living an enjoyable life.

Figure 10*"Hand motion" to "no light perception" visual impairment health state description*

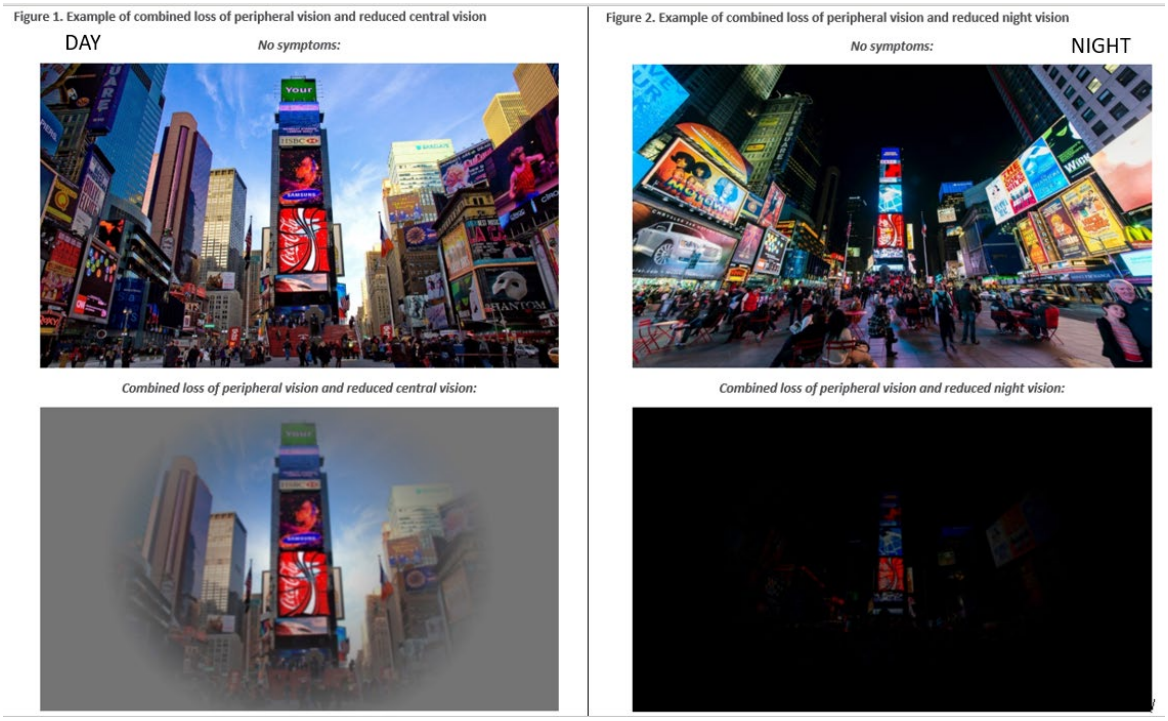


Figure 11 *Images of visual impairment in the day and night*

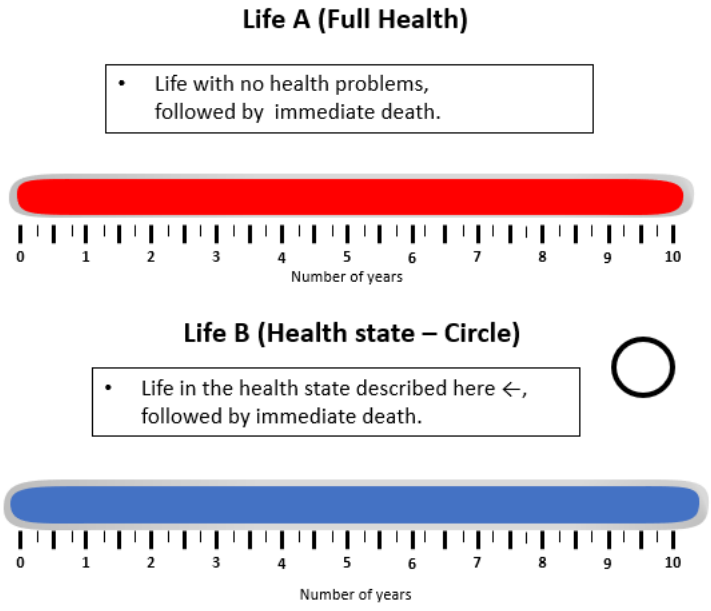
a.

Do you:

•prefer to live for 10 years in full health, and then die **(Life A)**

•prefer to live for 10 years in the (square, triangle, rectangle, circle, pentagon) health state, and then die **(Life B)**

•consider these to be the same or (**cannot decide)**



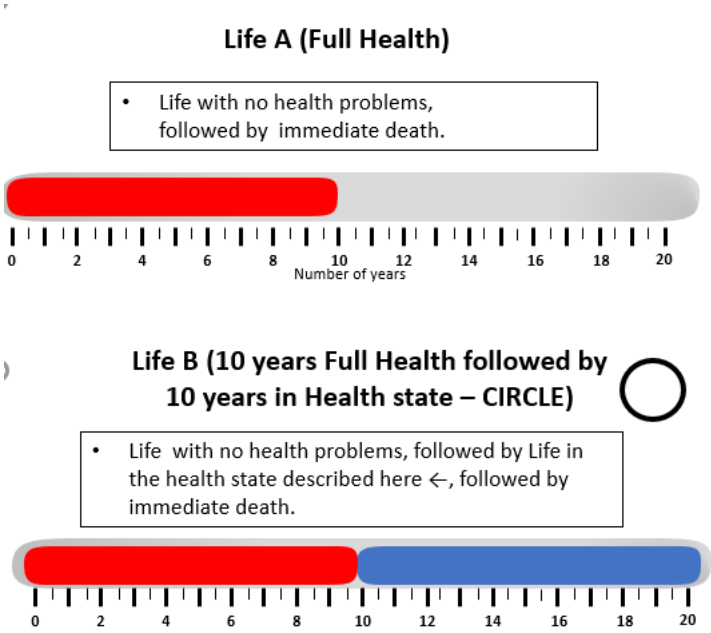
b.

Do you:

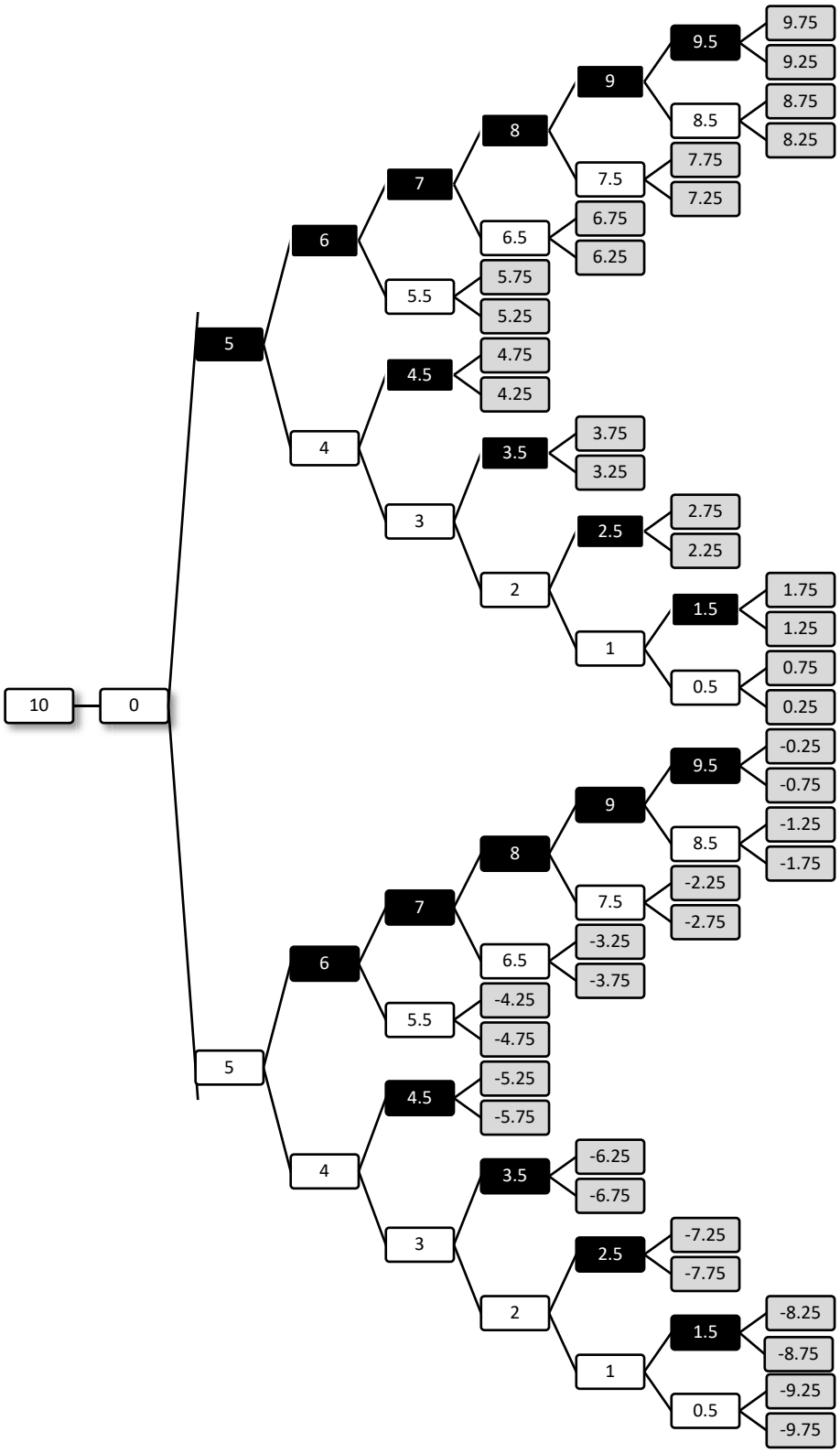
•prefer to live for 5 years in full health, and then die **(Life A)**

•prefer to live for 20 years in Life B – 10 years in the red health state followed by 10 years in the (square, triangle, rectangle, circle, pentagon) health state, and then die **(Life B)**

•consider these to be the same or **(cannot decide)**



cTTO task example. a. better than dead scenario b. worse than dead scenario c iteration procedure. The iteration procedure used to vary t is described elsewhere [24], but briefly, it uses a ping-pong approach starting with t in 10 years (t = 10 years in full health = 'Life A' and 10 years in the impaired health state = 'Life B') and moving to t = 0 if a respondent chooses A. If the respondent then chooses B, t is increased to t = 5 (a) followed by 1-year increments/decrements or 6-month increments/decrements depending on respondent's choices. If at t = 0 the respondent chooses A, the worse-than-dead side of the task is shown (b), where t = 10. If the respondent chooses A again, t is decreased to t = 5 followed by 1-year increments/decrements or 6-month increments/decrements depending on the respondent's choices. Utilities shown in Fig. 1c for the impaired health states are calculated using t of the point of indifference: U = t/10 for states considered better-than-dead, and U = (t-10)/10 for states considered worse-than-dead.
Abbreviation: cTTO; composite time trade-off



c.

Iteration scheme for the TTO scenarios. Numbers in boxes = lifetime in full health (Life A), shadowed white boxes = starting point, black

box = prefer visual impairment for 10 years (Life B), white box = prefer full-health-option (Life A), grey box = interpreted interval of indifference.

Figure 12 *cTTO task example and TTO iteration scheme*

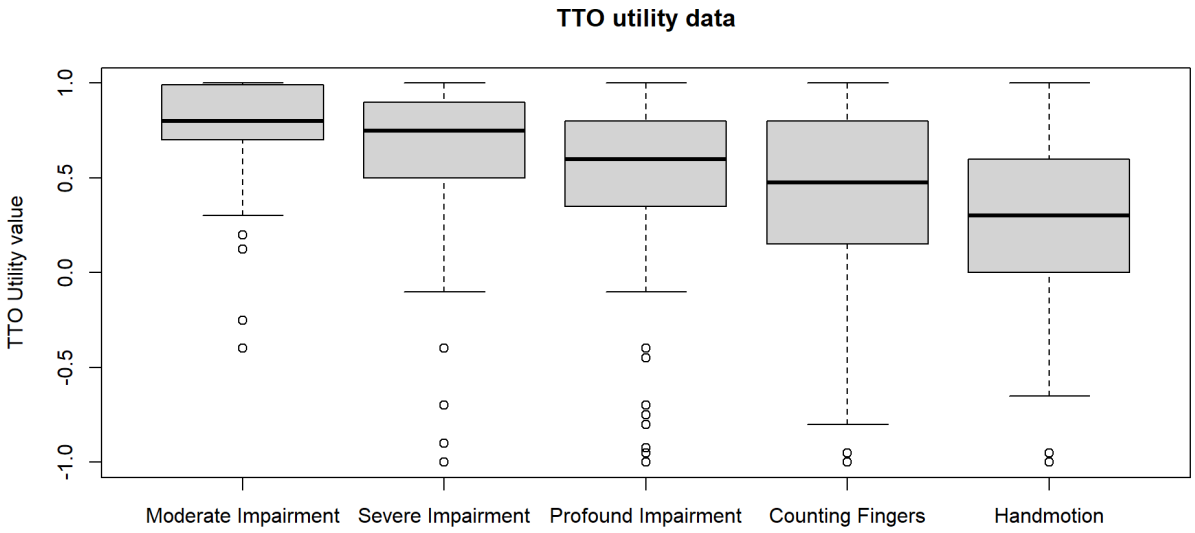
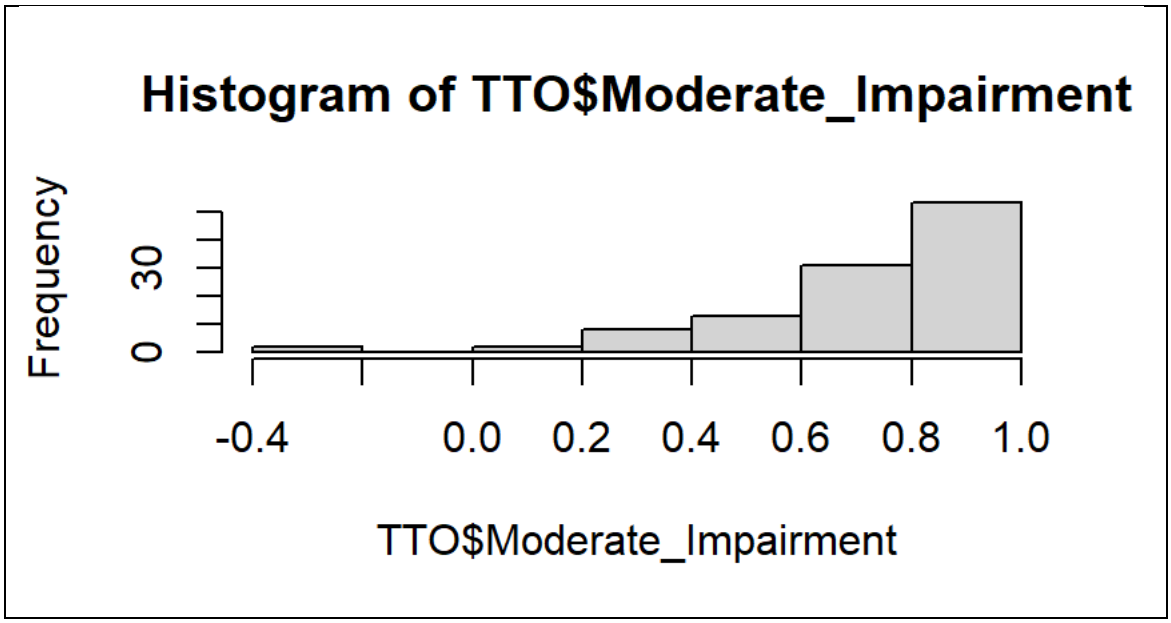
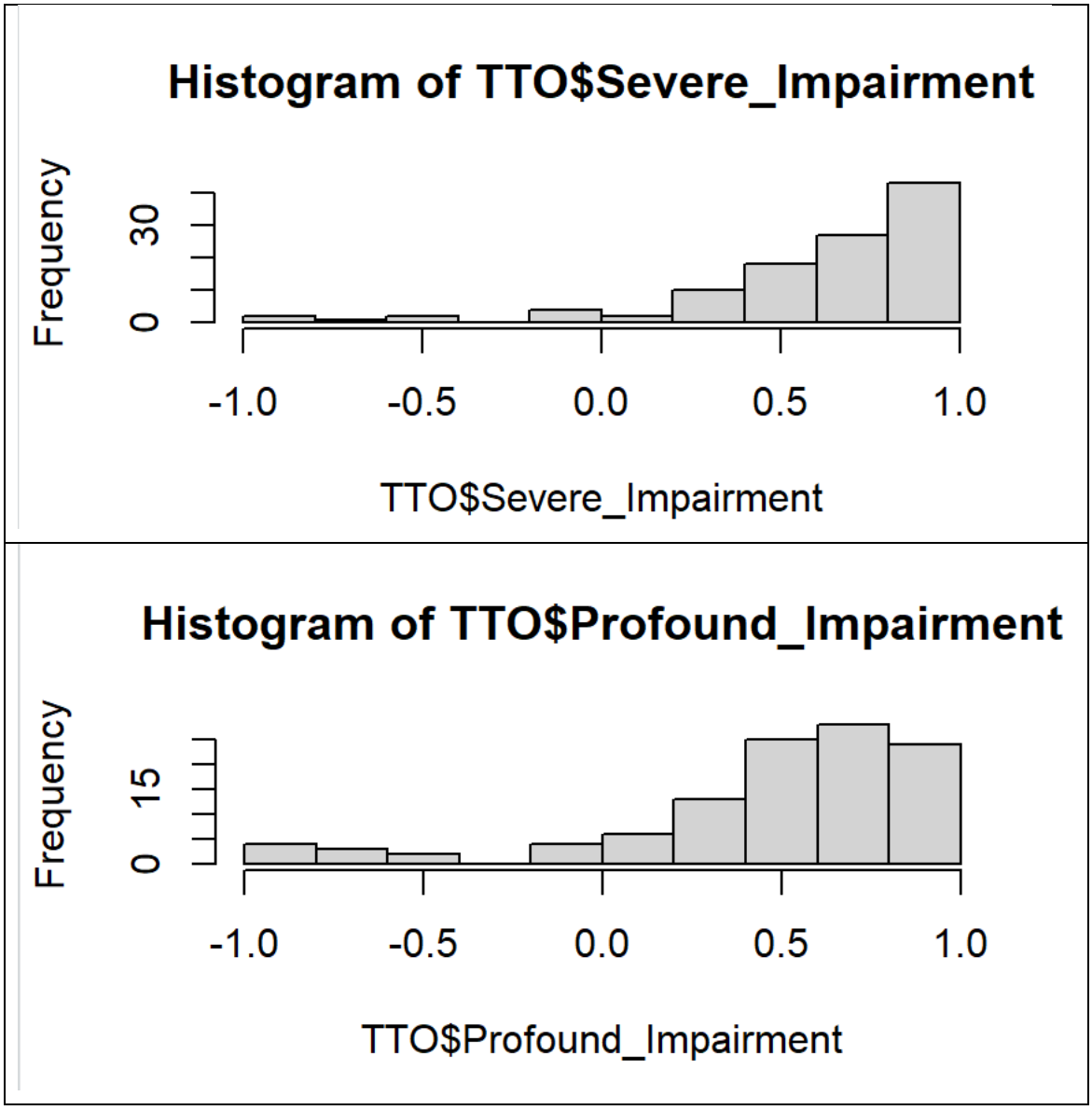


Figure 13 *Boxplot of utility values per health state*




Histogram of TTO$Severe_Impairment
Frequency
0
30
-1.0
-0.5
0.0
0.5
1.0
TTO$Severe_Impairment
Histogram of TTO$Profound_Impairment
Frequency
0
15
-1.0
-0.5
0.0
0.5
1.0
TTO$Profound_Impairment

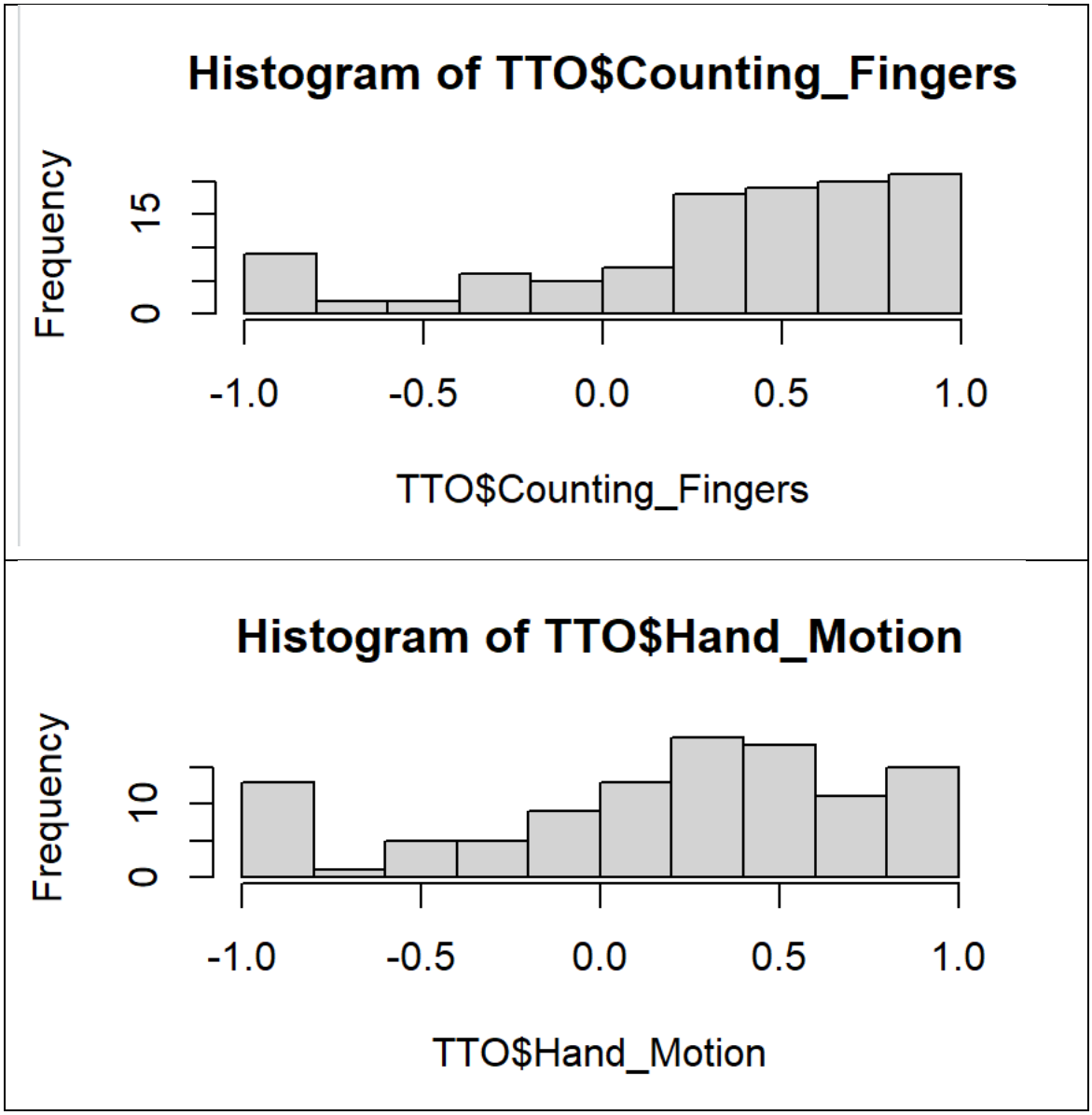


Figure 14 *Histogram of utility values per health state*

Table 24 *Proportion of health states not traded*

Number of Health States not traded	Frequency
5	4/109 (4%)
4	1/109 (1%)
3	2/109 (2%)
2	8/109 (7%)
1	13/109 (12%)

Table 25 *Distribution of non trading across health states and reasons*

Reason for non trading	**"Moderate impairment"**	**"Severe impairment"**	**"Profound impairment"**	**"Counting fingers"**	**"Hand motion" to "no light perception"**	**Total**
A.Want to **live as long** as possible irrespective of health state	3	4	2	3	3	15/59 (25%)
B. RP Health state does not have much impact on my **quality of life**	21	8	5	1	1	36/59 (61%)
A and B	2	1	1	2	2	8/59 (14%)
Total	26/59 (44%)	13/59 (22%)	8/59 (14%)	6/59 (10%)	6/59 (10%)	

Appendix 3

Supplementary Table 26 presents the caregiver interview guide used in Research study 3.

Supplementary Table 27 presents the medical resource burden questionnaire completed by caregivers in Research study 3.

Table 26 *IRD caregiver interview guide*

IRD caregiver focus group run sheet

Duration of the focus group: 2 hours
Number of participants per focus group: minimum 3
Note: Focus group will be audio-recorded for transcription

Interview guide

I. Interviewer thanks participant for agreeing to participate in this project.

II. Interviewer confirms participant information sheet has been reviewed and the informed consent form has been received.

III. Interviewer introduces the research topic, explaining the aim of the overall thesis project and the interviews. Sample script for introduction is provided below:

'*The aim of this thesis project is to investigate how has caring for a person with IRD impacted on your life? Has the impact changed over time?* "…..

- This interview will be recorded and is confidential. Reminded that they can stop the meeting if they need a break, or if they wish to cease participation. This is completely ok and there are no consequences from doing so.
- Are you happy to proceed?
- Start Otter AI meeting recording AND Zoom meeting recording

IV. The following general open-ended questions to be asked

Q. By way of introduction, can you share with us your experience as being a carer for someone with an inherited retinal disease?

Q. How has caring for a person with IRD impacted on your life?

Q. Has the impact changed over time?

The focus group discussion should cover the following topics

General

- What sort of assistance does your child or the person you care for require of you? (e.g. physical such as planning outings, assistance attending outings, assistance cooking at home or emotional)

- How many carers help care for your child or the person you care for? Are they part of your family (e.g. spouse and or paid care)
- Has the number of people helping to care for your child or the person you care for changed as your child or the person you care for gets older?

Medical management

- Do you attend appointments with healthcare practitioners with your child or the person you care for specifically for or related to IRD?
- How do you feel when you have to take your child or the person you care for to their eye appointment? Has this changed over time?
- How much of your day is taken up with an appointment?

Family life

- How has your family life been impacted by the experience of being a caregiver for someone with IRD?
- Do you feel that your family has good support"?
- How did/does caring with a person with IRD affect your relationship with: the child's other parent? Your (other) children? Your partner/husband/wife…? How has this changed over time?

Worry

- What worries or concerns do you have regarding the future for your child or the person you care for (e.g. social life, education, employment, living independently)?
- Has the worry for your child or the person you are caring for changed as your child/person gets older?

Social

- How has having a child with IRD or caring for someone with IRD affected your social life?

Physical/Emotional

- This question may or may not apply to all caregivers but…thinking back to when the child/person was first diagnosed and the months after that, how did your role as caregiver affect you physically? Do you feel different now?
- This question may or may not apply to all caregivers but …thinking back again to those first few months, how did your role as caregiver affect you emotionally? Do you feel different now?
- What helps you cope with your child's or the person you are caring for current state of health?

Financial

- How does being a carer impact on your employment?
- How does/did having a child or a person you care for with IRD and its management affect you financially?

Table 27 *IRD caregiver medical resource burden questionnaire*

ETH23-8979 - "Assessing the Caregiver experience for patients with inherited retinal disease (IRD) diagnosed in childhood"

UTS UNIVERSITY OF TECHNOLOGY SYDNEY

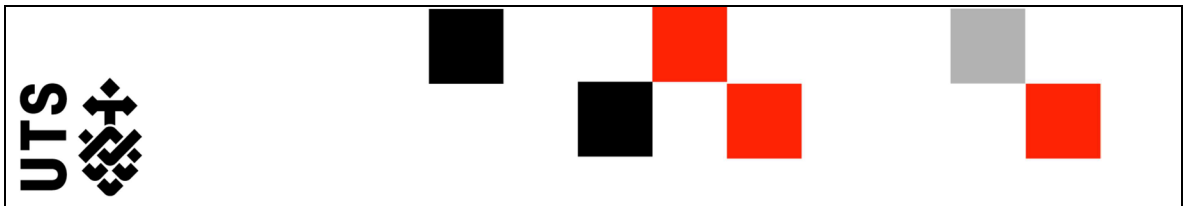
Medical Resource Questionnaire

Approximately how often do you/did you attend appointments with healthcare practitioners specifically for or related to IRD with the person you care(d) for?

		Weekly	Every 2 weeks	Monthly	Every 3 to 6 months	Once a year	Once every 2 years	Never
a.	General practitioner/ family doctor							
b.	Paediatrician							
c.	Ophthalmologist (General)							
d.	Ophthalmologist (specialized)							
e.	Optometrist							
f.	Psychologist, psychiatrist or counsellor							
g.	Genetic counsellor							
h.	Occupational therapist							
i.	Hospital emergency department							
j.	Hospital inpatient							
k.	Specialist outpatient or clinic							
l.	Rehabilitation service							
m.	Other							

Appendix 4

Supplementary Figure 14 presents the stakeholder survey completed by participants in Research study 4.



[UTS HREC REF NO. ETH21-6090] - On-line stakeholder survey: Consideration of broader value in health technology assessment (HTA) in Australia-PARTICIPANT INFORMATION SHEET

WHO IS CONDUCTING THIS RESEARCH?

My name is Maria (preferred name Mish) Farris (Maria.H.Kokoszk@alumni.uts.edu.au) and I am a research student at the Centre for Health Economics Research and Evaluation (CHERE), part of the Faculty of Health at the University of Technology Sydney (UTS). I am conducting the research under an Industry Doctorate Program with UTS as an employee of AstraZeneca. My supervisors are Professor Stephen Goodall and Associate Professor Richard De Abreu Lourenco and they can be contacted at Stephen.Goodall@uts.edu.au and Richard.DeAbreuLourenco@uts.edu.au.

Your participation in this research is totally voluntary, and information is provided below to help you to decide if you wish to participate. Contact details are also provided, for any questions you may have.

WHAT IS THE RESEARCH ABOUT?

Health technology assessment (HTA) systematically examines the comparative evidence of safety, clinical efficacy and cost-effectiveness of medicines to support reimbursement (funding allocation). This research is to understand the views held by stakeholders involved in HTA in Australia on the consideration of sources of value beyond the QALY in economic evaluations of medicines, particularly for rare diseases.

To participate in this research, you don't need to have a prior understanding of sources of value beyond the QALY; a description of other potential sources of value is provided in the survey.

The information you provide will be used to understand views from different stakeholders such as the private sector (pharmaceutical industry, specialist consultants and executive members of patient organisations), as well as public sector stakeholders (academia and government) about

the role for different sources of value in HTA. The survey is anonymous and we would like you to be completely open with your views which will be treated in total confidence.

WHY HAVE I BEEN INVITED?

You are being asked to participate because you are a stakeholder involved in HTA in Australia.

Before you decide to participate in this research study, please confirm that the following apply to you:

- Are an adult (age 18} resident of Australia, and willing to give explicit informed consent to participate and for answers to be recorded.
- Are involved in HTA in Australia as a member of the pharmaceutical industry, specialist consultants, executive members of patient organisations, HTA evaluators, academic, reimbursement committee or Government.
- Able to complete the survey via a web-based tool (Qua/tries).

FUNDING

There is no remuneration for completing the survey. MF has received funding support for this project from AstraZeneca Australia, Pty Ltd.

WHAT DOES MY PARTICIPATION INVOLVE?

If you decide to participate, you will be presented with 24 questions with a selection of responses to choose from. You will be asked to answer some background questions such as type of organisation, position in the organisation, length of time involved in HTA and academic qualifications. You will be asked to nominate whether you agree or disagree with various statements and you will also be asked to rate how much you agree with statements that are presented to you.

The survey is presented on-line via the Qualtrics platform. The survey is expected to take 10-20 minutes to complete.

ARE THERE ANY RISKS/INCONVENIENCE?

We do not anticipate any health risks to you from participating in this study. The survey is anonymous meaning we will not collect personal details such as your name or any identifying characteristics.

We do not anticipate that any of the questions included in the survey will cause discomfort to you. There will be no direct health benefit to you from participating in this study.

DO I HAVE TO TAKE PART IN THIS RESEARCH PROJECT?

Your participation in this research is totally voluntary and choosing to participate or declining to participate will not impact your relationship with researchers or the University of Technology Sydney. You can decline to participate for any reason, and do not need to justify your decision. You are fully able to decline to participate, or decline to continue to participate, now or at any other time. If you decline to participate, we will not capture any more information from you.

WHAT IF I WITHDRAW FROM THIS RESEARCH PROJECT?

If you wish to withdraw from the survey once it has started, you can do so at any time without having to give a reason. If you do decide to withdraw from the study while completing the survey, it may not be possible to withdraw your data from the study results. This is because your responses are recorded as you progress through the survey. If you are interrupted during the survey and are unable to finish you will have 1 week to come back to the survey to complete the survey, otherwise your partial response is recorded as complete.

WHAT WILL HAPPEN TO INFORMATION ABOUT ME?

By providing your consent, you agree to the research team collecting and using background information about you for the research project and your survey responses. All this information will be anonymous because your data will not be linked to any personal identifiers. The Qualtrics database will not collect your IP address, location data or contact information.

Your background information will only be used for the purpose of this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

The results of this research may also be shared through open access (public) scientific databases, including internet databases. This will enable other researchers to use the data to investigate other important research questions.

WHAT IF I HAVE ANY QUERIES OR CONCERNS?

If you have queries or concerns about the research that you think I or my supervisor can help you with, please feel free to contact us via one of the following email addresses Maria.H.Kokoszk@alumni.uts.edu.au, Stephen.Goodall@uts.edu.au or Richard.DeAbreuLourenco@uts.edu.au. Alternatively you can contact me on ph: +61 2 9514 4720

NOTE:

This study has been approved in line with the University of Technology Sydney Human Research Ethics Committee [UTS HREC] guidelines. If you have any concerns or complaints about any aspect of the conduct of this research that you wish to raise independently of the research team, please contact the Ethics Secretariat on ph.: +61 2 9514 2478 or email: Research.Ethics@uts.edu.au], and quote the UTS HREC reference number. Any matter raised will be treated confidentially, investigated and you will be informed of the outcome

[UTS HREC REF NO. ETH21-6090] - On-line stakeholder survey: Consideration of broader value in health technology assessment (HTA) in Australia-CONSENT FORM

I agree to participate in the research project being conducted by Maria (Mish) Farris [Maria.H.Kokoszk@alumni.uts.edu.au or ph:+61 2 9514 4720].

I have read the Participant Information Sheet or someone has read it to me in language that I understand.

I understand the purposes, procedures and risks of the research as described in the Participant Information Sheet. I freely agree to participate in this research project as described and understand that I am free to withdraw at any time without affecting my relationship with the researchers.

I am aware that I can contact Maria Farris, Professor Stephen Goodall, Associate Professor Richard De Abreu Lourenco or the Ethics Secretariat if I have any concerns about the research.

Please check the following box to indicate your consent

☐I give consent

☐ I do not give consent

Please select which applies to you

Pharmaceutical Industry

Consultants

Academia

Government Agency

Representative of patient organisation

Other _____

How many years have you been involved in Health Technology Assessment (HT A) in Australia for?_____

Please nominate your position in your organization

Managerial role

Non-managerial role

Academic qualification Doctoral degree Masters degree Undergraduate degree No degree
Area of academic qualification Science Pharmacy Health economics Statistics Medicine Other: _____ None
Do you think the current HT A methods applied in Australia are adequate to appropriately assess the cost effectiveness of all medicines? Yes No Not sure
Do you think the current HT A methods applied in Australia are adequate to appropriately assess the cost effectiveness of medicines for rare diseases? Yes No Not sure
In some HT A markets, sources of value beyond the patient QALY are taken into account in a reimbursement decision. An ISPOR task force defined 11 possible additional elements of value to consider. Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia.

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
1.Labour Productivity: Relates to costs associated with production loss and replacement costs due to illness, disability and death of productive persons, both paid and unpaid.	○	○	○	○	○

If agree are you aware of methods to include Labour Productivity in a cost effectiveness analysis?

Yes

No

Not sure

Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia.

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
2.Adherence: Patient adherence and health outcomes relating to advantageous simpler dosing schedules, alternate routes of administration, or combination treatments over existing alternatives.	○	○	○	○	○

If agree are you aware of methods to include Adherence in a cost effectiveness analysis?

Yes

No

Not sure

If yes please nominate whether these methods relate to costs and/ or outcomes below by ticking all that apply? Please name the method in the free text field if you are able to:.

Outcomes

Costs

Name the method:_____

Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia.

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
3.Reducing uncertainty due to a new diagnostic: A companion diagnostic test that could differentiate "good responders" and "poor responders" may provide the ability to avoid an ineffective treatment in poor responders as well as costs and consequences of treatment-related adverse events.	○	○	○	○	○

If agree are you aware of methods to include Reducing uncertainty due to a companion new diagnostic in a cost effectiveness analysis?

Yes

No

Not sure

If yes please nominate whether these methods relate to costs and/ or outcomes below by ticking all that apply? Please name the method in the free text field if you are able to:.

Outcomes

Costs

Name the method:_____

Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia.

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
4. Fear of contagion: Reducing the anxiety associated with the risk of future illness, even if the expected number of cases prevented is low.	○	○	○	○	○

If agree are you aware of methods to include Fear of Contagion in a cost effectiveness analysis?

Yes

No

Not sure

If yes please nominate whether these methods relate to costs and/ or outcomes below by ticking all that apply? Please name the method in the free text field if you are able to:.

Outcomes

Costs

Name the method:_____

Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia.

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
5.Insurance value: reflects the value from an effective treatment for a disease reducing fear among all consumers of getting the disease.	○	○	○	○	○

If agree are you aware of methods to include Insurance Value in a cost effectiveness analysis?

Yes

No

Not sure

If yes please nominate whether these methods relate to costs and/ or outcomes below by ticking all that apply? Please name the method in the free text field if you are able to:.

Outcomes

Costs

Name the method:_____

Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia.

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
6.Severity of disease: A gain in health may be more valuable to patients with a poor baseline prognosis (i.e., more severe disease).	○	○	○	○	○

If agree are you aware of methods to include Severity of Disease in a cost effectiveness analysis?

Yes

No

Not sure

If yes please nominate whether these methods relate to costs and/ or outcomes below by ticking all that apply? Please name the method in the free text field if you are able to:.

Outcomes

Costs

Name the method:_____

Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia.

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
7.Value of hope: Reflects the extent to which the chance for a cure is valued. For example, some patients may be willing to trade some survival (e.g. undertake a risky procedure) for a chance of a "cure" even if only for a small probability of cure/improved survival.	○	○	○	○	○

If agree are you aware of methods to include Value of Hope in a cost effectiveness analysis?

Yes

No

Not sure

If yes please nominate whether these methods relate to costs and/ or outcomes below by ticking all that apply? Please name the method in the free text field if you are able to:.

Outcomes

Costs

Name the method:_____

Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia.

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
8.Value to caregiver: Extent to which health care can benefit family carers by reducing their caring responsibilities.	○	○	○	○	○

If agree are you aware of methods to include Value to Caregiver in a cost effectiveness analysis?

Yes

No

Not sure

If yes please nominate whether these methods relate to costs and/ or outcomes below by ticking all that apply? Please name the method in the free text field if you are able to:.

Outcomes

Costs

Name the method:_____

Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia.

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
9.Real option value: Value generated when a health technology that extends life creates opportunities for the patient to benefit from other future advances in medicine.	○	○	○	○	○

If agree are you aware of methods to include Real Option Value in a cost effectiveness analysis?

Yes

No

Not sure

If yes please nominate whether these methods relate to costs and/ or outcomes below by ticking all that apply? Please name the method in the free text field if you are able to:.

Outcomes

Costs

Name the method:_____

Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia.

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
10.Scientific spillovers: Broad societal benefit from knowledge created from a treatment with a new mechanism of action. It is considered a public good used for the discovery of other agents.	○	○	○	○	○

If agree are you aware of methods to include Scientific Spillover in a cost effectiveness analysis?

Yes

No

Not sure

If yes please nominate whether these methods relate to costs and/ or outcomes below by ticking all that apply? Please name the method in the free text field if you are able to:.

Outcomes

Costs

Name the method:_____

Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia.

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
11.Equity: Fairness in the distribution of health and health care within society, across rich and poor, young and old, marginalized and not, employed or unemployed for example.	○	○	○	○	○

If agree are you aware of methods to include Equity in a cost effectiveness analysis?

Yes

No

Not sure

If yes please nominate whether these methods relate to costs and/ or outcomes below by ticking all that apply? Please name the method in the free text field if you are able to:.

Outcomes

Costs

Name the method:_____

Do you agree that the following sources of value should be considered in a cost effectiveness analysis of a medicine for rare diseases in Australia?

	Yes	No	Not sure
Labour productivity	○	○	○
Adherence	○	○	○
Reducing uncertainty due to a new diagnostic	○	○	○
Fear of contagion	○	○	○
Insurance value	○	○	○
Severity of disease	○	○	○
Value of hope	○	○	○
Value to caregiver	○	○	○
Real option value	○	○	○
Scientific spillover	○	○	○
Equity	○	○	○

Do you agree that the current public information regarding reimbursement decisions in Australia provides sufficient information about which sources of value are considered and how they contributed to decision-making?

Yes

No

Not sure

Please specify which of the following apply:

we don't know which sources of value are considered

while we know which sources of value are considered, we don't know how they contribute to decision-making

Do you agree that an explicit checklist of sources of value beyond the patient QALY and whether they were considered by decision maker would be more informative than what is currently published in Australia? Yes No Not sure
Generally medicines for rare disease are expensive, the clinical evidence is from short term small single arm studies and the estimated market size and expected utilisation is not known. This leads to greater uncertainty in cost-effectiveness analysis and budget impact which delays reimbursement decisions. However, the high unmet need means there is a desire for accelerated reimbursement and delayed access could result in significantly higher costs and health losses. Thus, some countries have implemented a range of mechanisms to enable faster access.
Rate the extent to which you agree or disagree that the following mechanisms should be used in Australia in making decisions about the reimbursement of medicines for rare disease?

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
Multiple Criteria Decision Analysis (MCDA) a deliberative process where decision makers and stakeholders define the problem and determine the criteria, weighting and evidence requirements for a reimbursement decision.	○	○	○	○	○

	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
Willingness to pay (WTP) Increase the ICER considered acceptable for treatments of rare diseases.	○	○	○	○	○

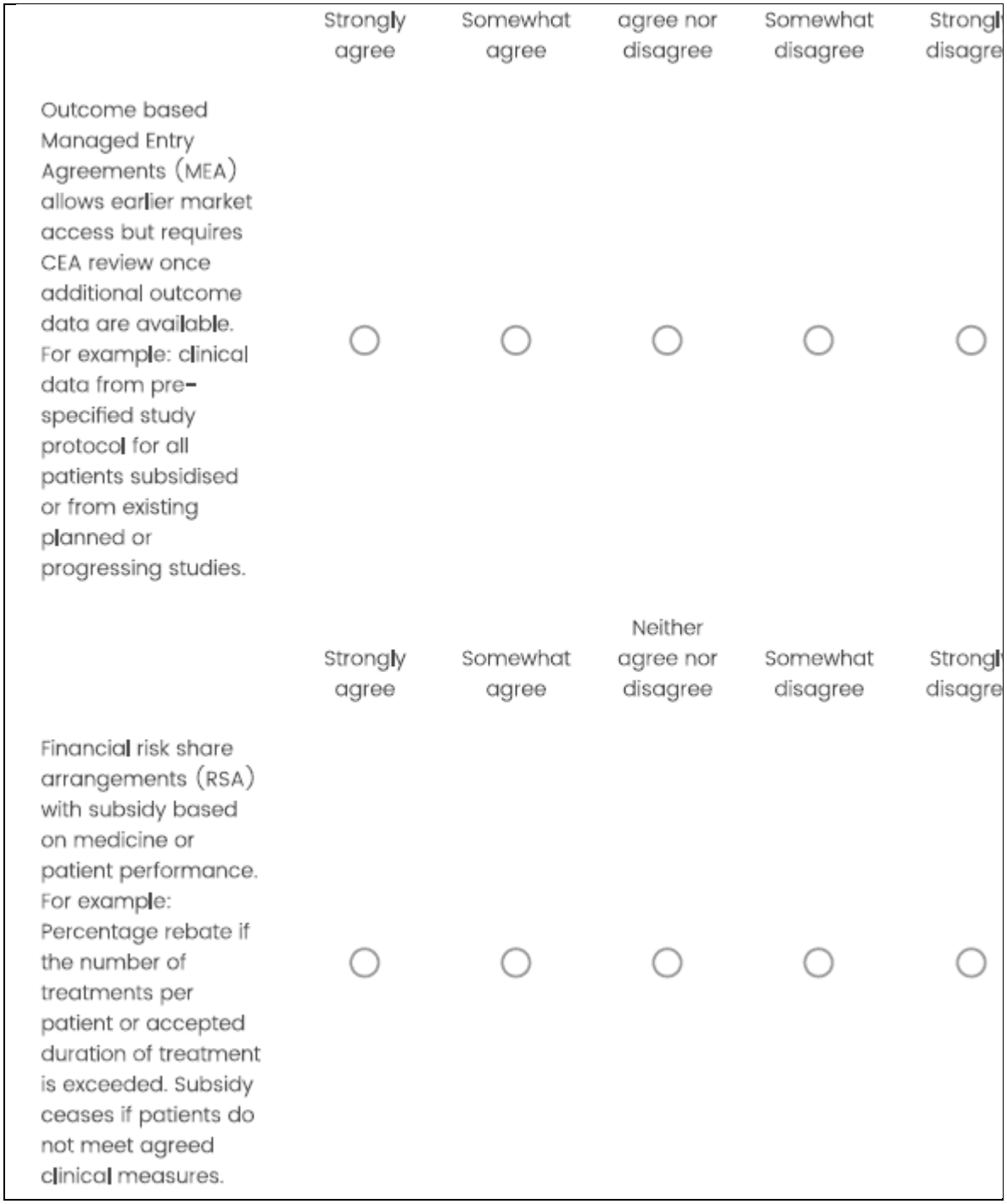


Figure 15 *Stakeholder survey*

Appendix 5

Supplementary Table 28 presents the context considerations and **Supplementary Table 29** presents the potential other benefits considered by US I.C.E.R. during HTA appraisal..

Supplementary Table 30 presents an example of a CEA impact inventory checklist.

Table 28 *Context considerations used by I.C.E.R. during HTA appraisal*

When making judgments of overall long-term value for money, what is the relative priority that should be given to any effective treatment for [CONDITION], on the basis of the following contextual considerations:					
Contextual Consideration	Very Low Priority=1	Low priority=2	Average priority=3	High priority=4	Very high priority=5
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability					
Magnitude of the lifetime impact on individual patients of the condition being treated					
Other (as relevant)					

Source:(194)

Table 29 *Potential other benefits or disadvantages used by I.C.E.R. during HTA appraisal*

What are the relative effects of [TREATMENT] versus [COMPARATOR] on the following outcomes that inform judgment of the overall long-term value for money of [TREATMENT]?					
Potential Other Benefit or Disadvantage	Major Negative Effect=1	Minor Negative Effect=2	No Difference=3	Minor Positive Effect=4	Major Positive Effect=5
Patients' ability to achieve major life goals related to education, work, or family life					
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life					
Patients' ability to manage and sustain treatment given the complexity of regimen					
Society's goal of reducing health inequities					
Other (as relevant)					

Source:(194)

Table 30 *Cost effectiveness analysis Impact Inventory Template*

Sector	Type of Impact (list category within each sector with unit of measure if relevant)[a]	Included in This Reference Case Analysis From...Perspective?		Notes on Sources of Evidence
		Health Care Sector	Societal	
Formal Health Care Sector				
Health	Health outcomes (effects)			
	Longevity effects	☐	☐	
	Health-related quality-of-life effects	☐	☐	
	Other health effects (eg, adverse events and secondary transmissions of infections)	☐	☐	
	Medical costs			
	Paid for by third-party payers	☐	☐	
	Paid for by patients out-of-pocket	☐	☐	
	Future related medical costs (payers and patients)	☐	☐	
	Future unrelated medical costs (payers and patients)	☐	☐	
Informal Health Care Sector				
Health	Patient-time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non–Health Care Sectors (with examples of possible items)				
Productivity	Labor market earnings lost	NA	☐	
	Cost of unpaid lost productivity due to illness	NA	☐	
	Cost of uncompensated household production[b]	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal or Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of intervention on home improvements (eg, removing lead paint)	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other (specify)	Other impacts	NA	☐	

Source:(144)

Appendix 6 reviewer updates to Chapter 3 Research study 2

Estimating Australian Population Utilities for Inherited Retinal Disease Using Time Trade-Off.

Abstract

Purpose

IRD causes progressive loss of visual function degenerating towards complete blindness. Economic Evaluation (EE) of gene therapies (GTs) for rare forms of genetic IRDs have had to rely on HRQoL estimates from other diseases because there are limited data available for such a rare condition. This study aimed to estimate Australian societal-based utility values for IRD health states that can be used in a cost-utility-analysis (CUA) using a time trade-off (TTO) protocol adapted from a UK study.

Methods

The EuroQol Valuation Technology (EQVT) protocol composite TTO (cTTO) framework was followed which includes worse-than-death (WTD) states and quality control (QC) measures. Preferences were collected from a general population sample of 110 Australian adult participants. Five health state vignettes from the UK study which had been validated with patients and clinicians were presented randomly to participants during videoconferencing (VC) interviews with one of four interviewers. Technical and protocol feasibility were assessed in a pilot of 10 interviews. QC measures were used to monitor interviewers' performance during the study.

Results

One participant withdrew consent. The final analysis was conducted on 109 respondents (including 4 non-traders). The average time to complete the interview was 44.2 minutes (SD 8.7). Participants reported mean visual analogue scale (VAS) scores between 63.15 for "moderate impairment" and 17.98 for "hand motion" to "no light perception". Mean HSU's varied between 0.76 (SD 0.26) in "moderate impairment", and 0.20 (SD 0.58) in "hand motion" to "no light perception". Of all HSU

evaluations 14% were considered WTD which most commonly occurred in the most severe visually impaired health state.

Conclusion

This study provides valuable information on HSU's across a range of IRD health states from the Australian general population perspective. The utilities obtained in this study can be used as inputs into CUA of IRD therapies.

Introduction

HTA agencies accept HR-QoL data collected in clinical studies or HR-QoL valuation by the general public, with some HTA agencies favouring country-specific preferences (102). However, for many conditions, such as RD's, capturing HR-QoL directly from patients may not be feasible for a number of reasons. Disease-specific measures often do not exist, generic multi-attribute utility instruments (MAUIs) may be too broad and insensitive to detect the change in symptoms that impact a patients' QoL, and statistical validation is limited due to small sample sizes with RD (37).

This has led to alternative methods of estimating HR-QoL or HSUs such as: the use of proxy-reported MAUIs (i.e., an assessment of the health state experienced by someone else) or direct elicitation from unaffected populations asked to make hypothetical judgements using vignettes to value health state description (94, 107, 108). Another method is using HSU's from a separate sample of patients with characteristics similar to those enrolled in the clinical trials (90).

IRDs are rare heterogenous conditions that result in either progressive or stationary retinal dysfunction causing loss of visual function, including loss of visual acuity and peripheral vision, and night blindness (68, 109, 110). There are over 250 disease-causing genetic variants identified, with mutations in the RPE65 gene leading to an assortment of clinical diagnoses, that present from early childhood and infancy to adolescence, degenerating towards complete blindness thus having a detrimental impact on patients' HRQoL (11).

Gene replacement therapy, VN, is now available in many countries for the RPE65 mediated IRD, and other genetic therapies for other IRDs, including choroidoremia and x-linked retinitis pigmentosa, are being evaluated in clinical trials (108). The advent of GTs for rare forms of genetic blindness is positive for patients, however prohibitively high treatment costs typically associated with GT means that public subsidisation is required to ensure that these treatments are available as part of usual care.

EE of interventions which affect HRQoL commonly employs -CUA which typically expresses the cost-effectiveness of interventions as the cost per QALY. The reliability of such analyses is partially dependent on accurately capturing the HRQoL impacts associated with the treatments. However, there are limited data on HRQoL data and utility values in patients with IRD, with no trials providing primary data for patient-reported health utilities (89, 109). Thus, in an HTA appraisal of VN by the National Institute for Health and Care Excellence (NICE) the HRQoL estimates were based on two sources (89). The first source was generic preference MAUI values (EQ5D and Health Utility Index [HUI]) collected from people with visual impairment due to diabetic retinopathy. The second source was from 6 retinal specialists based on proxy vignettes of IRD health states (81). The use of retinal specialists was criticised because it was suggested that they would focus on issues related to vision rather than the impact on all areas of the patients' life, and the lower HSU's were thought to lack face validity (89). The use of assumptions and reliance on data related to other diseases meant the reported cost-effectiveness for the treatment of RPE65 IRD using VN are contradictory (69, 80). This highlights the importance of using HSU's from IRD because conditions such as diabetic retinopathy visual impairment commences at different stages of life, deteriorates at a different rate compared with IRD's and importantly may result in limited vision rather than no vision whatsoever (that is no light perception) which can have vastly different impacts on HRQoL(91).

Another criticism in the evaluation of VN by NICE was that the method to elicit the HRQoL or utility values did not align with the methodology required by the HTA agencies (83, 90, 91, 94, 96, 100). A study in the UK was therefore conducted recently to generate utility values for health states of

varying levels of functional vision related to IRD via direct elicitation from the general public using a TTO method in accordance with UK NICE HTA guidelines (104).

Vignettes for five health states that represent the functional impairment to daily living associated with declining sight because of IRD, from the low range of vision present at birth to no vision at all, were developed for the recent utility study in the UK (104). The five health states were considered to be adequate, as they were developed based on testimonials from patients with IRD and aligned with those accepted in the economic model by HTA agencies such as NICE in the UK, Medical Services Advisory Committee (MSAC) in Australia and Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada. Although the HSU's from the study may therefore be applicable to the Australian context, HTA guidelines require country specific preference based HRQoL utility values. Implementing the existing UK TTO protocol in Australia was a pragmatic way to estimate HSU's that meet the requirements of HTA agencies and allows comparison with the values obtained for the UK (102). There was however a limitation from the UK TTO study which was that valuation of worse-than-death (WTD) states were excluded (104). Existing data support the considerable stress among individuals with one of the IRDs RP with documented links to suicidality, which is an outcome that should be considered in the valuation of these health states (30, 105).

The purpose of the current study is to estimate Australian societal-based utility values that can be used in CUA using a TTO protocol adapted from the UK study. This will produce values that are in line with the requirements of key Australian HTA agencies, including the Australian MSAC and PBAC(99, 102, 111).

Methods

The protocol for this study was based on the TTO study from the UK. Changes from the UK TTO study were made to follow the existing best practice protocol for composite TTO framework which includes methods for valuing WTD health states and QC measures (104, 107, 112, 113). Five health states from the UK TTO study which had been validated with 5 patients with RP and 2

ophthalmologists in the UK were used. The health states were defined according to American Medical Association (AMA) guidelines on visual disability that encompassed VA changes reflecting the clarity of vision, i.e. ability of the eye to distinguish details of objects at a given distance and VF changes, reflecting peripheral vision or the ability to see above, below and to the side of something observed (89, 104). The scales of visual disability defining each HS vignette align with the range of visual standards in international guidelines that are applicable to Australia (114).

Each of the five health states were a written description of the functional experience of patients living with progressively worse visual impairment. Impairment was described in terms of independence, social life, family life, tangible limitations, and employment, both during the daytime and nighttime.

- Health State 1 vignette defined as VA better than 20/200 or VF radius of greater than 10° described as “Moderate visual impairment”(115),
- Health State 2 vignette defined as VA from 20/200 to 20/500 or VF radius of 6° to 10° described as “Severe visual impairment”(115),
- Health State 3 vignette defined as VA from 20/500 to 20/1,250 or VF radius of 2° to 6° described as “Profound visual impairment”(115),
- Health State 4 vignette defined as VA from 20/1,250 to 20/20,000 or VF radius of less than 2° described as "Counting fingers"(115),
- Health State 5 vignette defined as VA worse than 20/20,000 described as "Hand motion" to “no light perception”(115),

These health states were reviewed for logic and applicability to the Australian population. The description of the symptoms were grouped under thematic headings such as “physical, social, independence, work” to make the lengthy written descriptions easier to read and comprehend (**Supplementary Figure 5-Figure 10**, Appendix 2). Emotional statements associated with a symptom within each vignette such as, “*You may feel sad or frustrated that you have slightly reduced independence now*“ were altered to avoid directing the respondent on how they should feel

about a particular symptom. Instead, the emotional state was presented as "*You feel sad or frustrated about your condition and its impact*."

The target sample was 110 participants which aligns with other TTO studies eliciting values for vision disorders (Lloyd et al. 2008 N=122, Brown et al. 2001 N=65) (91, 96). Quotas were applied for age, sex, education and geographical distribution to be consistent with the Australian adult population with respect to those characteristics (116-120). The interview protocol was piloted on the first 10 participants recruited to assess comprehension.

Members of the Australian general population who were not employed in healthcare or market research and with access to web-based tools (MS Teams) were identified using a panel of individuals who had previously indicated a willingness to participate in research studies. The study excluded any participants diagnosed with a visual disability (e.g., RP) or pre-existing eye conditions (e.g., glaucoma). Participants who required reading glasses were not excluded. Recruitment and interviews were scheduled by a market research agency (IPSOS Australia, North Sydney). Upon providing informed consent an interview was scheduled between the participant and the interviewer, and the participant was provided a copy of the health states to review prior to the interview.

Interviews were conducted between October 2022 and November 2022. Videoconferencing (VC) interviews were conducted one-to-one with audio and video connection via MS Teams with one of 4 interviewers. The one-to-one setting allowed interviewers to provide detailed instruction and feedback to the participant where appropriate. Participants were able to withdraw consent and/or 'change their mind' on the answers provided at any point by informing the interviewer. Participants were paid $AUD60 by IPSOS for attending the interview.

This study was approved for conduct under the Centre for Health Economic Research and Evaluation program ethics approval from the University of Technology Sydney Ethics Committee on September 8, 2022 (UTS HREC REF NO. ETH21-6090).

Health state utility elicitation (quantitative)

The interview was structured in four parts: 1) background information provided to participant about condition including revision on health states; 2) two visual analogue scale (VAS) 'warm-up' exercises; 3) five TTO exercises; and 4) respondent feedback about questions asked.

To avoid biasing participants' responses, health state descriptions were not labelled in any manner that suggested differences in severity or importance and were presented to respondents in a random order. The interviewer shared their computer screen containing visual aids (VAS feeling thermometer and TTO board) with participants to improve respondents' comprehension of the valuation tasks, as is standard in TTO protocols (113). The participants responded verbally, and the HSU scores were recorded on a score sheet developed for the study that was based on the TTO valuation of MAUIs (113, 121).

Prior to cTTO valuation, a VAS scoring of the same health state descriptions was used as a "warm-up" exercise. The cTTO method was then used to elicit HSU's by asking the participant first of all to select between 10 years in the health state (followed by death), and 10 years in full health (FH) (followed by death), and then a variable shorter period of life in FH if FH was selected. The process then followed a 'ping-pong' approach with the time in FH reduced by half (to 5 years) and then traded back and forth between higher and lower values that were iteratively narrowed until the participant was indifferent between the two life choices (**Supplementary Figure 11A**, Appendix 2) (113). A lead-time TTO (LT-TTO) method was used to elicit preferences for health states considered WTD (**Supplementary Figure 11 b and c**, Appendix 2). In the lead-time TTO (LT-TTO) 10 years in FH is added to the two life options such that participants choose between (1) 10 years of FH (lead-time) followed by 10 years in the health state followed by death, or (2) to live 20 − x years in FH (10 years lead-time followed by up to another 10 years of FH), followed by death, or (3)

to indicate that the two options were equally desirable (indifferent between the two life choices). The possible utility value ranges from -1 to 1, with 0 value “equivalent to being dead”, 1 (“perfect health”) and negative values indicating a state worse than being dead.

The TTO included debriefing questions for respondents that were not willing to trade any lifetime in the iteration with the longest time with FH (i.e., 10 years in FH). The purpose was to elicit the reasons behind non-trading (e.g., fatigue, lack of understanding, lack of interest) and to offer respondents an opportunity to trade lifetime in terms of weeks instead of years.

To ensure consistency among the four interviewers training was conducted which included: an introduction of related HRQoL concepts, explanation of the TTO protocol, interviewer instructions, and practice in groups. After five interviews, compliance was assessed using the three QC measures proposed by the EuroQol Group (time taken to complete all five TTO tasks, negative values and non-traders); QC assessment continued in a staged approach after every 20 interviews (122, 123). The first QC measure was based on interview time because explaining the cTTO task takes time (expected 25 minutes) and thus short task duration may indicate poor engagement. The second QC measure of the proportion of negative values reflects that the WTD task is more difficult to understand than BTD so respondents may be reluctant to value a health state as WTD if the task is not adequately explained (and thus lower proportion moving to WTD and fewer negative values). Finally non-trading, where a participant assigns a value of 1 to all five HS’s, could signal that the participant is trying to shorten the task by expressing their indifference in the first step to the iterative procedure, or it could signal that the task has been misunderstood or not wanting to trade life could be for religious reasons. If there are many non-traders per interviewer, even when the time for the interview looks appropriate, it could indicate poor task explanation. Similar procedures have been already employed for the collection of EQ5D data and have shown to improve data quality(124).

Following the pilot interviews (n=10), there were slight changes to the TTO interview script. The changes included the interviewer confirming the amount of time the participant is willing to trade to avoid the health state after the point of indifference is reached, and also providing a summary of the health states for interviewers to read if that participant asked for a brief review of the health state after having read the complete health states previously. No changes were made to the health state descriptions following the pilot interviews; data from the pilot were thus included in the final calculation of HSU's (therefore giving a total sample size of n=110).

Data analysis

All score sheet responses were transcribed into an Excel spreadsheet for analysis by the primary investigator with a 10% sample of transcriptions checked against the source score sheet by EM. Any incorrect transcription would be corrected, leading to a further 10% review until no further transcription errors were identified.

Quantitative results (including demographic characteristics, TTO HSUs, and VAS scores) were tabulated and analysed descriptively using Microsoft Excel and are presented as means, medians, standard deviations, and 95% confidence intervals (where appropriate). Demographic data were consistent with the characteristics of the 2021 Australian Census (ABS 2021/2022).

Utility values were calculated from TTO results using the EQ-VT protocol. Statistical analysis was conducted using RStudio 2022.02.3(125). The distribution of individual TTO HSU's was examined by Shapiro-Wilk test and differences between scenarios tested using nonparametric Wilcoxon signed-rank test. A p value below 0.05 was considered statistically significant. To analyse the association between HSU, demographic characteristics (education, employment, age, gender and marital status) and interviewers, an ordinary least squares (OLS) regression model was employed using the R package lme4. Analysis residuals were reviewed after each regression, and the following goodness of fit statistics were presented for each model: adjusted R-squared, F-statistic p-value, Akaike information criterion (AIC), and Bayesian information criterion (BIC).

Results

The demographic characteristics of the sample are presented in **Table 5**. Compared with the population statistics for Australia (ABS 2021/2022) the sample had a slightly higher proportion of participants in their third decade (22% vs 15%), a higher proportion who were married (60% vs 47%) and a higher proportion of degree-level or higher education qualifications (47% vs 31%).

Of the 110 planned interviews, 1 participant withdrew consent after completing the VAS, thus the final analysis was conducted on 109 respondents (including 4 non-traders).

Table 31 *TTO participant demographic characteristics*

Study Sample	**n**	**%**	**Australian public demographics**	**%**
Age			**Age**	
18 to 24	8	7%	15 to 19	6%
25 to 34	17	15%	20 to 29	13%
35 to 44	24	22%	30 to 39	15%
45 to 54	17	15%	40 to 49	13%
55 to 64	21	19%	50 to 59	12%
65 and over	23	21%	60 and over	23%
Sex			**Sex**	
Female	60	55%	Female	51%
Male	50	45%	Male	49%
Marital status			**Marital status**	
Married/De facto	66	60%	Married or civil partnered	47%
Separated/Divorced/widowed	21	19%	Divorced/widowed	14%
Education level			**Education level**	
Degree-level education	52	47%	Degree-level education	31%
Employment Status			**Employment Status**	
Employed	74	67%	Employed	78%
Geographic distribution			**Geographic distribution**	
New South Wales	35	32%	New South Wales	32%
Victoria	30	27%	Victoria	26%
Queensland	23	21%	Queensland	20%
South Australia	8	7%	South Australia	7%
Western Australia	8	7%	Western Australia	10%
Tasmania	3	3%	Tasmania	2%
Australian Capital Territory	2	2%	Australian Capital Territory	2%
Northern Territory	1	1%	Northern Territory	1%

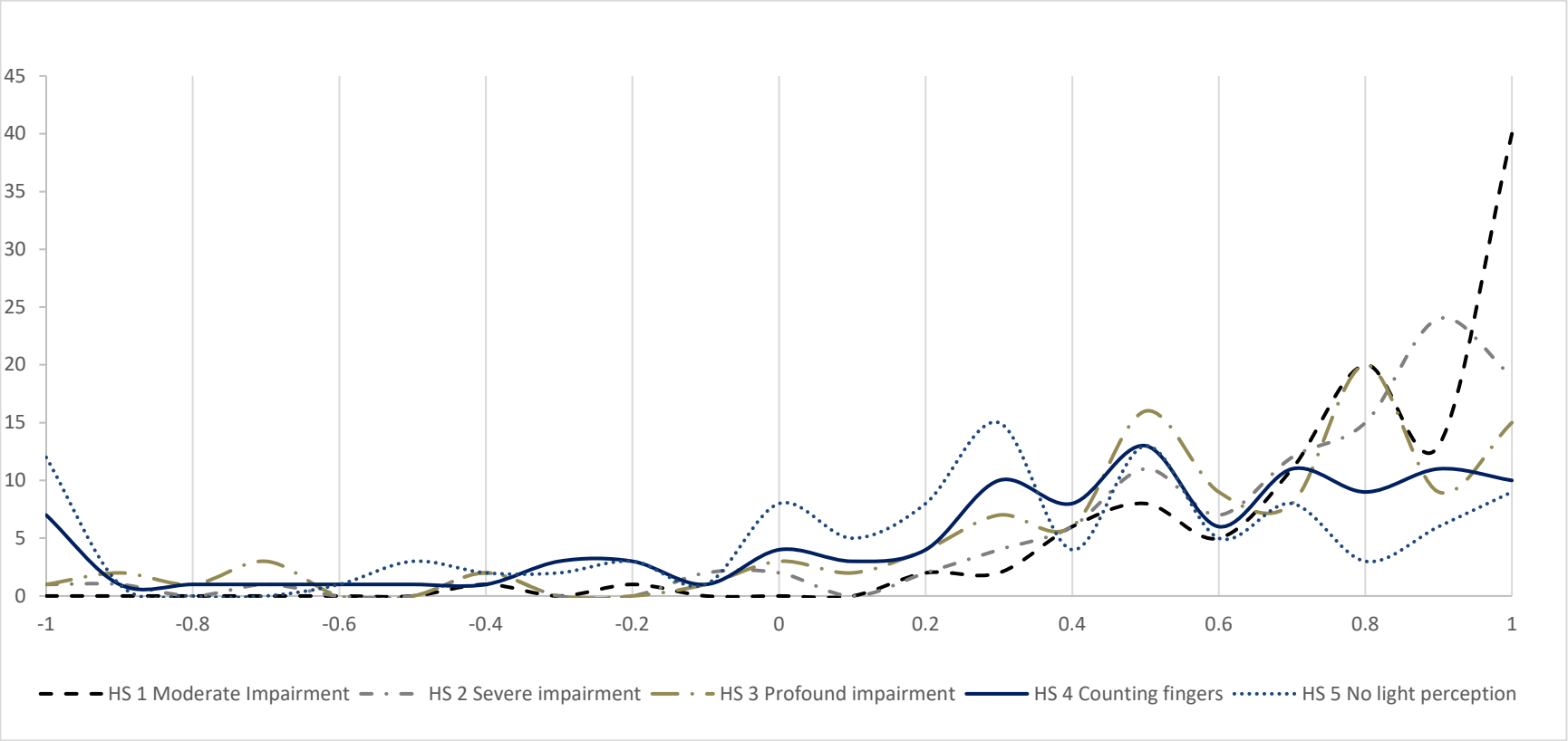
The average time to complete the interview was 44.2 minutes (SD 8.7). Twenty interviews were completed by interviewer 1, 25 by interviewer 2, 4 by interviewer 3 and 60 by interviewer 4. The quality assessment of the initial and ongoing interviews did not identify any issues of data quality.

Utility and VAS values by TTO for each health state are presented in **Table 6,** the frequency of HSU distributions in **Figure 5** and boxplots in **Supplementary Figure 12**, Appendix 2. Mean HSU and VAS values followed the logical and expected order, with increasing visual impairment leading to decreased utility in each case. Participants had a high mean VAS (77.39) indicating good overall health on average. Mean HSU's varied between 0.76 (SD 0.26) in "moderate impairment", and 0.20 (SD 0.58) in "hand motion" to "no light perception".

Table 32 *Mean VAS score and health state utility values*

Health State	n	VAS score				Utility			
		Mean	SD	Median	Range (min., max.)	Mean	SD	Median	Range (min., max.)
"own health "	109	77.39	13.80	80	(30,100)	-	-	-	-
"Moderate impairment"	109	63.15	16.52	65	(15,95)	0.76	0.26	0.80	(-0.4,1.0)
"Severe impairment"	109	52.16	15.13	50	(15,85)	0.63	0.39	0.75	(-1.0, 1.0)
"Profound impairment"	109	40.43	14.27	40	(15,70)	0.50	0.46	0.60	(-1.0, 1.0)
"Counting fingers"	109	27.48	14.76	25	(5,65)	0.35	0.55	0.48	(-1.0, 1.0)
"Hand motion" to "no light perception"	109	17.98	15.29	10	(0,60)	0.20	0.58	0.30	(-1.0, 1.0)

Figure 16 *Frequency of utility values across IRD health states*



Nonparametric testing results of the Shapiro-Wilk test indicated that the distribution of utility values for all health states was skewed (**Supplementary Figure 13,** Appendix 2). The Kruskal-Wallis test showed a significant difference in HSU's ($p<0.05$), and a pairwise Wilcoxon test was conducted to determine significant differences between individual states. All pairs of health states showed significant differences in utility values ($p<0.05$).

Of the total 545 (109*5) HSU evaluations across all respondents there were 75 (14%) instances that were considered WTD which most commonly occurred in the most severe visually impaired health state ("Hand motion" to "no light perception",41%, 31/75) (**Table 7**).

Table 33 *Distribution of worse-than-death trades across health states*

Health State	n	WTD
"Moderate impairment"	109	2 /75 (3%)
"Severe impairment"	109	9 /75 (12%)
"Profound impairment"	109	12 /75 (16%)
"Counting fingers"	109	21 /75 (28%)
"Hand motion" to "no light perception"	109	31 /75 (41%)

Regression analysis revealed that not being married was significantly associated with lower HSU's for the four worst visual impairment health state valuations (severe impairment to no light perception), and not being employed was significantly associated with a lower value for the least visually impaired health state (Moderate visual impairment)**(Table 8**). One interviewer was also found to be associated with higher HSU's across all health state valuations. An alternative specification of the model tested age as a squared variable but it was not significant, and it did not improve the model fit so modelling age as a linear variable was retained. Random and normal distribution of residuals were evident in residual plots and the goodness of fit statistics support the robustness of each of the models.

Table 34 *Results of regression analyses (n=109, Standard Error in brackets)*

Subgroup	"Moderate Impairment" (N=109)	"Severe impairment" (N=109)	"Profound impairment" (N=109)	"Counting Fingers" (N=109)	"No light perception" (N=109)
Intercept	0.609 (0.102)	0.361 (0.152)	0.388(0.177)	0.147 (0.220)	-0.064 (0.226)
Age	0.003 (0.002)	0.004 (0.003)	0.000 (0.003)	0.004 (0.004)	0.002 (0.004)
Gender[a]	0.000 (0.051)	-0.020(0.076)	-0.015 (0.088)	-0.00 (0.111)	0.111 (0.113)
Marital status[b]	-0.042 (0.050)	-0.161 (0.074)*	-0.209 (0.086)*	-0.247 (0.108)*	-0.333 (0.110)**
Education[c]	-0.017 (0.056)	0.015 (0.083)	0.079 (0.097)	0.044 (0.121)	0.142 (0.124)
Employment[d]	-0.176 (0.065)**	-0.164 (0.097)	-0.179 (0.113)	-0.192 (0.141)	-0.179 (0.144)
Interviewer 2[e]	-0.004 (0.077)	0.043 (0.002)	-0.013 (0.133)	-0.076 (0.166)	0.083 (0.170)
Interviewer 3[e]	-0.043 (0.135)	-0.106 (0.202)	-0.171 (0.236)	-0.045 (0.294)	0.099 (0.301)
Interviewer 4[e]	0.160 (0.064)*	0.299 (0.095)**	0.336 (0.111)**	0.282 (0.138)*	0.386 (0.141) **
Adjusted R^2	0.1069*	0.1335**	0.1511**	0.07792*	0.1256**
F-statistic	2.62*	3.08**	3.40**	2.14*	2.94**
AIC	14.16	100.84	134.05	182.01	187.48
BIC	41.07	127.75	160.96	208.92	214.40

* Significant at p<0.05, ** Significant at p<0.01, *** Significant at p<0.001

Note: All variables other than age were entered as categorical variables

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

a.Reference category: Female

b.Reference category: Married

c.Reference category:Degree educated (bachelor or post graduate degree)

d.Reference category: Employed (full time or part time)

e.Reference category:Interviewer 1

Discussion

This study elicited societal utility values for five health states for IRD using the TTO methodology with members of the Australian general public. The health states describe visual disability from "moderate impairment" to the most visually disabled "no light perception" and align with prior research in the disease area (89, 104). The utility values, which varied between 0.76 for "moderate impairment", and 0.20 for "hand motion" to "no light perception", were similar to the average health-related utility of 0.58 reported from 70 Australian patients with various forms of IRD, but are substantially lower than the average utility value reported by the wider Australian population for their own health (for whom a normative utility value of 0.81 was measured by Assessment of Quality of Life 8-Dimension (AQoL-8D) rather than direct TTO)(109, 126).

This study was replicating prior research and thus utilised the TTO methods of eliciting societal utility values. Caution may therefore be warranted when comparing utilities derived through other methods such as discrete choice experiments (DCE), since different valuation methods may elicit different utility values. In the context of TTO-based research, notwithstanding the utility value associated with the most severe HS (hand motion" to "no light perception"), the values from the present study are within the range of other published utility values established using TTO methodology in patients with impaired vision which have been identified through a systematic literature review (0.78–0.26, **Table 9**) (90, 91, 104).

Table 35 *Comparison of health state utility values from the current study and existing literature*

Vision health state	Current TTO study	Brown et al. 1999(90) TTO (N=325)[a]	Brown et al. 2001(91) TTO (N=75)[b]	O'Brien et al. 2023(104) TTO UK study (N=110)
Moderate vision impairment	0.76 (SD 0.26)	0.67 (SD 0.21)	0.65 (SD 0.21)[e]	0.78 (SD 0.20)
Severe vision impairment	0.63 (SD 0.39)	0.63 (SD 0.16)		0.65 (SD 0.25)
Profound vision impairment	0.50 (SD 0.46)	0.54 (SD 0.17)		0.50 (SD 0.27)
Counting Fingers	0.35 (SD 0.55)	0.52 (SD 0.29)	0.47 (SD 0.29)[f]	0.43 (SD 0.28)
Hand Motion- Light Perception	0.20 (SD 0.58)[c]	0.35 (SD 0.29)[d]		0.33 (SD 0.26)[g]
No Light Perception			0.26 (SD 0.08)	

Abbreviations: SD, standard deviation

a .Patients included in the study primarily suffered from age related macular degeneration or diabetic retinopathy

b. Patients included in the study suffered from age related macular degeneration, diabetic retinopathy, retinal detachment, cataract , glaucoma, endophthalmitis, and central retinal vein obstruction.

c. The utility value 0.20 (SD0.58) is for the combined "hand motion-light perception" and "no light perception" health states.

d. The utility value 0.35 (SD 0.29) is for the combined “hand motion-light perception” and “no light perception” health states.
e. The utility value 0.65 (SD 0.21 is for the combined “moderate vision impairment”, “severe vision impairment” and “profound vision impairment” health states.
f. The utility value 0.47 (SD0.29) is for the combined “counting fingers” and “hand motion-light perception” health states.
g. The utility value 0.33 (SD0.26) is for the combined “hand motion-light perception” and “no light perception” health states.

In this study married participants reported higher HSU values for the most severe health states (severe visual impairment to no light perception). Marital status has been shown in other TTO studies to influence the number of years traded-off (127). This consistent finding across health states may infer that being married improves a persons’ outlook on life when faced with a trading exercise. Alternatively, it may ascribe to the notion that married participants, especially those with children, consider the broader impact of their choices and focus on longevity rather than HRQoL due to their desire to live long enough with their spouse and for their children (128).

Prior research has focused on the range of utility values in the most severe states of visual impairment because vision loss-related disability is not linearly proportional to deteriorating visual acuity or field. Indeed “legal blindness” (defined as VA ≤20/200) captures a wide range of impairment from “severe vision loss” to “near-blindness” which encompasses the ability to count fingers [CF] or detect light [light perception, LP] and finally complete blindness (no light perception [NLP])(114). A TTO conducted in patients that were “legally blind“ by Brown et al. (2001) aimed to discriminate utility values across a range of vision these patients. The study showed a mean utility of 0.26 for patients with NLP and 0.47 for those with CF-LP which demonstrates that utility value decreases dramatically with the total loss of light perception in each eye (**Table 9**). This granularity of HRQoL impairment has had a substantial impact on the economic modelling of IRD (reducing the utility value for the worst HS to reflect NLP in the EE of VN produced by Institute for Clinical and Economic Review in the US increasing the QALY gain from 1.3 to 5.2) thus highlighting the importance of elucidating utility values across the full spectrum of visual impairment (69).

The HSU reported in this study for the most severe health state “hand motion” to “no light perception” health state (0.20) aligns with the HSU’s elicited by Brown et al. (2001) but is lower than the HSU for the same health state from the UK TTO study (0.33). This is likely a consequence of

allowing health states to be rated as WTD in the current study which meant that respondents used it, while in the UK study they were unaware of WTD and thus bounded at 0. A WTD state was selected in 14% of scenarios, most commonly for the most severe visually impaired health state (“Hand motion” to “no light perception”), reducing the HSU value. This finding aligns with the increased suicide rates associated with severe vision impairment reported in the literature thus highlighting the importance of including methods for valuing WTD health states (105).
Adaptation to vision loss in IRD, where patients may adjust to progressive impairment over time, could be influenced by the inclusion or exclusion of WTD states in utility valuation, particularly given the severe psychological impact of this condition. In this study, the cTTO) methodology incorporated WTD states, resulting in 14% of evaluations being rated as WTD, most frequently for the "hand motion to no light perception" health state (41%, Table 7). This inclusion likely captured the profound distress associated with total vision loss, aligning with literature on increased suicide rates among individuals with severe vision impairment. Participants from the general population, who lack personal experience of adaptation to IRD, may overestimate the negative impact of severe health states when WTD valuation is permitted, leading to lower mean utility values (e.g., 0.20 for the most severe state, Table 9) compared to studies excluding WTD (e.g., 0.33 in O'Brien et al., 2023, Table 9). Conversely, excluding WTD states might mask the true extent of perceived burden for IRD, as it restricts respondents to a minimum utility of zero, potentially underrepresenting the severity for those who view total blindness as worse than death. For IRD, a condition with lifelong progression often starting in childhood, adaptation by patients may reduce perceived disutility over time, a nuance that general population valuations without WTD might miss. Thus, including WTD states, as done here, likely provides a more comprehensive reflection of societal perceptions of IRD severity.

HSU values are used to inform the estimation of QALY’s in CUAs required for HTA. HTA agencies prefer estimates of HRQoL or utility from the within-trial evidence from patients (using generic or disease-specific utility instruments), however in the absence of such data or where there are particular health state impacts for a condition that are not well captured by existing generic instruments, direct elicitation of utility weights by the general public, via TTO methods for example,

are acceptable (111). Direct elicitation based on the general population in their own country is requested because resources allocated for health technology in countries such as Australia and the United Kingdom come from the public such that preferences should reflect their own society (102, 129). However, there is a resource burden, in terms of time and money, associated with conducting TTO studies and notwithstanding the differences in the HSU for the most severe visually impaired health state ("Hand motion" to "no light perception"), a similar study using the same health state vignettes conducted in the UK produced HSU's similar to those in the present study. This study therefore supports the consideration of the HSU's from this study in CUA conducted in other countries with similar cultures and HTA processes as in Australia.

One of the criticisms of the vignette approach is that it may not accurately reflect the extent to which patients learn to cope with and adjust to their disease (130). For instance, elements of adaptation might be expected among patients with IRD considering that they live their whole lives with the deteriorating condition and do not know of anything else. Vignettes may also lead people to focus specifically on certain aspects of the description and could place undue weight on a specific descriptor (99). There are however criticisms with other HRQoL instruments such as generic instruments lacking sensitivity to vision loss (EQ5D), and that the use of vision-specific instruments (National Eye Institute Visual Function Questionnaire, NEI VFQ) focus on physical rather than social or personal aspects of HRQoL (87, 131, 132). There is also the problem of collecting HRQoL data from other diseases that may not accurately reflect that circumstances of patients with IRD may have a different impact upon HRQoL. For example, generic instruments showed a greater impact of glaucoma (a disease the impacts peripheral vision) on mental rather than physical aspects of QoL, and vice-versa for age-related macular degeneration (a disease diagnosed later in life that affects central vision and thus the ability to conduct tasks day to day). This was attributed to patients with early stages of glaucoma (in whom there is minimal functional impairment), worrying about blindness that affects their mental QoL, while physical aspects of QoL remain relatively unaffected (131, 132). Patients with RPE65-mediated IRD are impacted from birth and suffer loss of central vision and peripheral vision as well as night blindness therefore vignettes that adequately represent

changes in this RD that has limited HRQoL and utility data were important. The health state development for this study was based on patient and carer testimonials, supported by qualitative findings from previous research to comprehensively represent the spectrum of disease and its daily impact on patients with IRD (30, 104). For example, the health states in the current study provide the context to living with impaired vision due to IRD that included limitations to everyday activities such as commuting and socialising in the day and the nighttime and the increasing worry experienced from impending loss of vision due to the degenerative nature of the condition.

The adaptations made to the health state vignettes have some strengths and limitations that should be considered when interpreting the study results. Best practice guidance on the development of health state vignettes suggests that uncertain statement such as “you may feel” should be avoided because respondent interpretation of such statements may vary (107). However, by rewording such statements and presenting such emotional impacts as certainties, as occurred in this study, means the vignettes may no longer be a reasonable representation of the typical experience of an IRD patient, It is important to note that although the updated health state descriptors were not revalidated with patients or clinicians, the similarity of the resulting HSU’s with those from the UK study indicates that the changes to the HS’s didn’t impact on the respondent interpretation.

Despite the development of vignettes that reflect real life experience of patients, the utility values from this study do not represent all IRDs. IRDs are a large group of clinically heterogeneous conditions such that visual acuity, visual field and night vision may not deteriorate in parallel as they are presented in the vignettes, but rather at different trajectories than is reflected in the health states. Furthermore, some IRD’s do not affect VA, VF and night vision for example, cone dystrophies typically present with progressive loss of visual acuity, photophobia and colour vision disturbance (133). The potential difference in utilities between different IRD’s could be explored in future research.

IRD is detected in early childhood with vision deteriorating over the patient's life (11). The average age of patients receiving VN for RPE 65 mediated IRD in clinical trials was 15 years and the product is available to children over the age of 3 years (10). The current study was however restricted to adults and this can be an issue for the comparability of these values and their use in EEs, and it raises the question of whose values should be sought when valuing children's health (102). While there is the argument that the adult general public as taxpayers and potential beneficiaries from publicly funded healthcare should be the source of valuations, it can be argued that children are also beneficiaries of healthcare services and older children may contribute financially through tax system. However, research indicates that TTO tasks are unreliable in young, adolescent, populations because they have difficulty in understanding and interpreting the TTO tasks (134). In addition, adolescents have been found to underestimate the effects of mild, moderate, and severe vision loss upon HRQoL compared with patients with actual vision loss, and thus are not good patient surrogates for utilities used in cost-utility analysis (135).

The utility values elicited in this study for IRD health states exhibit a notably larger variation, with standard deviations (SD) ranging from 0.26 for "moderate impairment" to 0.58 for "hand motion to no light perception" (Table 6), compared to existing literature where SDs typically range from 0.08 to 0.29 (Table 9). This variation, approximately twice as large in the most severe health states, may be attributed to the inclusion of WTD states in the cTTO methodology or the vignette approach, which while detailed, elicits varied interpretations of impairment impacts. The implications of this large variation are significant for EEs. High variability in utility estimates introduces uncertainty into QALY calculations, potentially affecting incremental cost-effectiveness ratios (ICERs) and decision-making in HTA. It suggests a need for sensitivity analyses in EEs to account for this uncertainty, as well as larger sample sizes in future TTO studies (incorporating a WTD state) to stabilize estimates.

The feasibility of conducting valuation studies online via VC interviews has been challenged for two reasons (136). The first being that the iterative procedure in the TTO task is complex, which is why face-to-face interviews have traditionally been used, and thus VC interviews may result in poor

quality data. Second, despite the advantage of greater geographical reach and more rapid data collection, requirement for VC interviews can pose a barrier preventing older people, less educated people, diseased populations and less technically skilled from being sampled. Indeed, the sample enrolled in this study shared demographic characteristics consistent with the Australian population generally but there was a higher proportion of participants with degree-level or higher education qualifications compared with the general population (47% vs 31%, **Table 5**) in the study. However no significant differences in HSU by education were observed in the regression analyses **(Table 8**). Moreover recent research demonstrates that VC administered interviews provides equivalent data quality to face:to:face interviews and that VC as a mode of administration does not impact on TTO interview task duration, number of moves or proportion of specific responses (123, 136).

There are some limitations to discuss. The study had a sample size of 109 which is in line with the UK TTO study but may be considered a limitation due to it being smaller than other TTO utility studies (90, 136). This study intended to replicate a prior TTO study conducted in the UK as closely as possible. Consequently, images representing visual impairment in each health state were not presented to participants; only text descriptions of each health state were provided, which could be a further limitation of this study. In addition, because the health states describe impairment associated with either VA or VF changes, the HSU's will need to be applied to specific IRDs with caution because the health states cannot necessarily be attributed to various levels of VA and VF impairment. Finally despite developing an interviewer script and training the interviewers, interviewer effects were detected in regression analyses with a single interviewer, who had conducted over half of the interviews, positively impacting the HSU's across the health states **(Table 8**).This reinforces the need for continuous data monitoring and checks during data collection as recommended in TTO protocols (112). Protocol compliance by interviewers is also a possible limitation that can lead to poor comprehension of the valuation task by the respondent. The HSU order in a small proportion of the sample (10%, 11/109) was not logical, that is at least two of the five HS's were not clearly ordered in terms of severity and the difference in HSU was greater than 0.05, which may signal poor comprehension and task misunderstanding. However, the average

interview duration (44.2 minutes) is greater than what is expected for 5 HS's as according to standard QC measures respondents generally take 5 minutes to complete each TTO task. This indicates that interviewers spent sufficient time explaining the task to participants and participants had time to ask questions (122, 124). Furthermore, only four respondents (4%) were classic "non-traders", which was a QC measure of task comprehension used in the study. Otherwise non-trading occurred in 28 (26%) interviews, similar to other TTO studies, most commonly for 1 HS only (12%) and generally in the mildest HS, moderate vision impairment, on the basis that it did not impact much on HRQoL (**Supplementary Table 24 and Table 25**, Appendix 2)(137).The percentage of non-trading, as a measure of possible interviewer effects, indicates respondents had a reasonable understanding of the task.

Conclusion

This study provides valuable information on HSU's across a range of IRD health states from the Australian general population perspective. Overall, our findings provide important insight into the perception of vision loss with health state utility values. These utility values were elicited using a method and sample that may allow the resulting values to be incorporated into EEs for HTA purposes in Australia and other countries, with similar cultures and HTA processes, in assessing the value to society of new technologies for IRD.

Appendix 7 reviewer updates to Chapter 4 Research study 3

Caregiving for patients with IRD.

Abstract

Purpose

Rare genetic conditions, mainly affecting children, pose significant challenges for caregivers due to their complex and continual healthcare requirements. Considering unrelated healthcare costs and the emotional strain experienced by caregivers is essential for assessing the cost-effectiveness of treatments for these diseases. This research explores the implications of caring for an individual with an IRD on the caregiver's life and how this impact evolves as the patient ages.

Method

Semi-structured interviews were conducted face to face or virtually with seven caregivers using a guided script. Audio recordings were transcribed verbatim. Employing a mixture of inductive and deductive analytic approaches a thematic analysis was conducted. A medical resource burden survey captured the time commitment of caregivers attending healthcare appointments for patients with IRD.

Results:

The results highlighted the multifaceted nature of their support roles across various life stages. Caregivers provided critical assistance with daily activities while also adapting to the changing needs of patients with IRD. They reported emotional challenges, alongside a strong sense of duty and obligation in fulfilling their caregiving responsibilities. Many caregivers struggled to relinquish control, regarding it as both a necessity and a responsibility because of the limits on the individuals they care for. The need for social support emerged. Furthermore, their caregiving duties often led to significant personal and employment-related sacrifices, emphasising the critical need for more structured support and resources for caregivers. Overall, the findings reveal the layered emotional and practical challenges experienced by caregivers of patients with IRDs, underscoring the importance of acknowledging and addressing their well-being.

Conclusion:

This study underscores the significant emotional, social, and economic challenges faced by caregivers, advocating for tailored support systems and increased recognition of caregiver burden in research, policy, and practice. Additionally, it emphasises the integration of caregiver burden into HTAs to provide a comprehensive assessment of the social value of new technologies for IRDs.

Introduction

Taking care of an ill or disabled individual imposes a well-documented burden on the caregiver (138-142). The caregiving burden encompasses the emotional, physical, and financial strains experienced by those providing care to patients, which can significantly impact their quality of life (QoL). It is suggested that health intervention reimbursement decisions should be viewed in the context of the entire family and that integrating caregiver burden into HTA's can capture a more comprehensive picture of the costs and benefits associated with a health intervention(143, 144).

Rare genetic conditions are predominantly diagnosed in children and pose substantial challenges to caregivers due to the complexity and ongoing nature of health service needs (1, 77). The possibility of lifelong caring, limited capacity for independent living and lack of treatment options means paediatric rare genetic conditions have a large impact on families and caregivers (77, 145, 146).

IRDs constitute a group of clinically and genetically heterogeneous degenerative conditions in which gene mutations cause a progressive loss of photoreceptor cells and an impairment for visual function. Individual IRDs are rare and gradually lead to an irreversible visual decline including potentially to blindness (58, 62, 147, 148). As the disease progresses and visual function becomes increasingly impaired, patients with IRD adapt however support is still needed and is largely provided by unpaid community-dwelling caregivers, usually friends or family members (30).

Capturing the impact on the caregiver in an EE is critical for therapies that may offer long term benefits allowing patients with a rare disease (RD) to live a relatively normal life and potentially

alleviate caregiver burden (9). Inclusion of nonrelated healthcare costs and consequences of IRDs, such as alleviating the emotional stress of seeing a close relative or friend suffering from a serious condition and time spent in providing informal care, have been shown to have profound effects on whether a therapy is deemed cost-effective (74, 149).

The aim of the research is to investigate how caring for a person with an IRD impacts the carers' life, and how that impact changes as the person being cared for gets older.

Methods

This is a mixed-methods study, comprising semi-structured interviews with caregivers and a survey related to attending vision related medical appointments with those who are being cared for (**Supplementary Table 26 and Table 27**, Appendix 4). The theoretical framework used to explore the humanistic burden of IRD on caregivers is phenomenology. Phenomenology is concerned with in-depth understanding of the participants' lived experiences and the meanings the participants perceive of those experience (150).

To assess the time commitment of caregivers attending healthcare appointments for patients with IRD, participants were required to complete and return a medical resource burden survey before the interview, (**Supplementary Table 27,** Appendix 4).

Sample size, recruitment and ethical consideration

Determining if a sample size is adequate in qualitative research is relative, since the events and experiences are the focus of the research rather than the individuals (151). The intent of the recruitment process in this study was to reach theme saturation in the qualitative interviews with respect to identifying the factors that impact caregivers of patients with IRD and how these factors change as the patients with IRD grow older. Prior to study start ethics approval was obtained (UTS HREC ETH23-8979).

Evidence suggests the majority of themes from a focus group discussion are identified after 3 focus groups (of 5-6 participants each), and among individual interviews little new information is gained beyond the first five to six interviews (152). As such we originally planned to recruit 20 participants to enable 3-4 focus groups. A minimum of 3 caregivers was required to host a focus group, otherwise interviews were planned to be held individually.

Caregivers residing in Australia were invited to participate if they were an unpaid caregiver and the person being cared for (for example child, husband, wife, parent, family member) had received a diagnosis of IRD before 18 years of age (regardless of the IRD subtype), are English speaking, and had or currently have an active role in IRD care. Caregivers were required to attend an online virtual interview, or a face to face focus group. Because of the low prevalence of individual IRD's the study recruited a convenient sample that relied on carer voluntary participation (147).
The study was advertised to carers via vision related patient organisations (Retina Australia, Vision Australia, Cure Blindness Australia). Due to the slow recruitment of volunteers through patient organisations a new recruitment strategy was implemented after obtaining ethics approval. Suitable caregivers were identified from a panel of individuals who had previously indicated a willingness to participate in research studies by market research agency (Ekas marketing research Australia). Written informed consent was obtained from the participants and they were asked to complete a medical resource utilisation form. Participants were compensated $100 and up to $50 for travel or parking costs (if they attended face to face focus group). The sampling of panels of individuals who had volunteered to conduct research using the inclusion criteria presented above continued and interviews conducted until the emerging theoretical themes were saturated.

At the beginning of each focus group/ interview, participants were informed that the session would be recorded. The interviewees were made aware they could stop the interview at any time they needed. During the interviews supports were planned in case the researcher perceived discomfort or distress of the interviewee. These supports included: discontinuation of the interview or referral for support; neither were required by those participating in the study.

Interviews and data analysis

A semi-structured interview guide based on open-ended questions captured the participants' experiences of caregiving how it has changed over time across all aspects of life (physical, mental, financial and social) (**Supplementary Table 26,** Appendix 4). The interview questions were formed based on literature describing carer burden (142, 153). Prior to initiation of caregiver interviews, the appropriateness and order of the interview questions were discussed within the research team. In-depth semi-structured interviews with open-ended questions grouped as general impact, medical management, family life, worry, social, physical/emotional and financial were undertaken by two researchers (RDL, MF). An open and naïve approach was used in the interviews to explore the participants' responses by asking probing questions, e.g. by using mirroring and paraphrasing (154, 155). The interviews were conducted by the first two authors (RDL and MF), who had no former relationships with the participants prior to study commencement. All interviews were audio recorded and transcribed verbatim by MF using otter.ai. To ensure accuracy, MF reviewed each transcript by replaying the audio recording and checking the text word for word, manually correcting any errors.

A qualitative thematic analysis was used to identify and analyse themes in the interview transcripts (156, 157). Data analysis was performed iteratively using three methodological principles: maintaining an openness to the phenomenon of interest, identifying and exploring preconceptions, and maintaining an ongoing reflective attitude guided the phenomenological approach to data analysis.

Researchers read and re-read the quotations line-by-line to familiarise themselves with the data prior to coding. Coding of the first transcript was conducted following review of the transcript line-by-line by two researchers (MF and RDL) and coding the data together, discussing and reconciling, and refining the coding throughout the process to generate a codebook. The three remaining transcripts were coded by a single researcher (MF) with any new codes added to the code book. No new codes were generated after the third transcript. Upon completion of coding the transcripts, 42

codes were generated. Coded data were reviewed in relation to each other and sorted into preliminary themes. Themes were identified systematically by the researchers using a combined deductive and inductive approach which allows the exploration of a-priori themes **(Table 10**), but also leaves space to discover other unexpected aspects of the participants' experience (142, 158, 159). The interpretation of themes was discussed and agreed by the research team. Because of the low sample size, it was agreed among the researchers that codes generated from at least 2 individual responses would constitute a theme. In the final stage a narrative description with extracts for each theme was compiled by one researcher (MF), this was discussed and agreed for each theme by all researchers. NVivo 12 software was used for data storage, coding and mapping.

Responses to the medical resource questionnaire were summarised using descriptive statistics. The survey data are presented for two categories of caregiver, those who care for persons less than 18 years and those who care for those ≥18 years with the intention of identifying whether there are obvious differences in the frequency of visit and types of health care required by children and adolescents compared with adults to better understand the time commitment required from caregivers across the life span of the patient with IRD

Table 36 *A-priori themes and subthemes used for deductive analysis*

Major theme	Positive subtheme/code	Negative impacts subtheme/code
Coping	Social support Normalisation Appreciating child's resilience	Avoiding glaucoma related thoughts Emotional detachment Blaming health professionals
Emotional well-being	Managing fleeting anxiety Feeling hopeful or grateful Feeling proud of child	Feeling anxious or scared Feeling shocked, guilty or regretful Feeling low or helpless
Medical and social support	Medical care becomes routine Positive reinforcement with child Community establishment	Perceived that treatment is hurting child Overprotective of child Fear of schoolyard bullying
Social well being	Relationship teamwork Connecting with other carers Sharing experience	Relationship conflict Trouble caring for other children Social isolation
Clinical and familial control	Acceptance of disease outcomes Trusting the child to be autonomous Confidence in managing disease	Wanting a cure Attending appointments with adult child Worried about others caring for child
Family planning	Gaining knowledge of future risk Confident in detecting condition Planning ophthalmic follow ups	Worried about future children or grandchildren Not wanting more children Self blame for genetics

Source: Knight LSW, Ridge B, Staffieri SE, Craig JE, Prem Senthil M, Souzeau E. The Caregiver Experience in Childhood Glaucoma: An Interview Study. Ophthalmol Glaucoma. 2022;5(5):531-43(142).(142)

Medical resource survey and data analysis

The medical resource burden questionnaire asked caregivers to report, "*Approximately how often they attend appointments with healthcare practitioners specifically for or related to IRD with the person care(d) for*"? Caregivers selected one of seven options for frequency of visits from never to weekly across ten categories of health care. Formal statistical comparisons of the medical resource burden between the two groups, those who care for persons less than 18 years and those who care for those ≥18 years, was not conducted due to the small sample of caregivers in the study, However, comparing the number of caregivers attending medical visits and the frequency provides some indication of the time commitment borne by caregivers.

Data Quality (Trustworthiness, Dependability, Transferability)

Quality in qualitative research can be evaluated from the aspects of clarification and justification, procedural rigour, sample representativeness, interpretative rigour, reflexive and evaluative rigour and transferability (160). In terms of rigour, the main concept of this study was well defined, and the design, sampling and choice of data collection method of this project were in line with the desired outcome of the study. The interview questions were formulated in a way that addressed the research concepts and questions. To achieve consistent content, the same researcher asked the same questions during interviews.

Confidentiality

Participants were assured their data were de-identified (anonymised) and their experiences were used only for the research purposes of this project. Participant responses were recorded using an anonymised identification number. Electronic data were stored in the primary analysts (MF) folder on the secure University of Technology OneDrive. Data will be retained for a minimum of five years and then deleted.

Results

Participant characteristics

Six caregivers were identified through the market research agency and two responded to an advertisement in a Retina Australia newsletter. One participant withdrew consent while organising the focus group such that a total of seven eligible caregivers were interviewed between May and December 2024. A face-to-face interview was conducted with a group of three caregivers, a videoconference with a group of two caregivers and two videoconference meetings with single participants. The interview times ranged from 35 mins to 100 mins. Four caregivers reflected on caregiving of children and adolescents (n=4) aged 5-17 years, and three reflected on caregiving of adults (n=4) aged 35 to 86 years (noting one parental caregiver had two adult children with an IRD, **Table 11**). The persons cared for were diagnosed with kerataconus, retinitis pigmentosa, cone/rod dystrophy and rod dystrophy. The age range of the caregivers was 40 – 71 years, and most caregivers were parents with children affected with IRD (n=5) while one was a daughter caring for her father and the other had been a friend who had been volunteering to assist a patient with IRD for over 10 years.

Table 37 *Caregiver focus group participant demographics*

Sociodemographic characteristics of the caregivers, n=7	
Gender,	
Female	5
Male	2
Age group of persons cared for,	
0-18 years	4
19-37 years	1
38-55 years	1
55-73 years	0
>74 years	1
Caregiver relationship	
Parent	5
Child	1
Friend	1

Seven overarching themes were generated, five themes established based on the deductive coding and two themes were established using an inductive process. The themes, codes and concept for each code are presented in **Table 12**.

Table 38 *Major themes identified for caregivers in the study*

Major theme (coding type)	Codes	Concept
Coping (deductive theme)	• appreciate persons resilience • adapting or accepting situation • normalisation or learning to cope	Caregiver coping i.e. adapting to the caregiving situation
Emotional well-being (deductive theme)	• fear of hereditary impact on oneself • feeling anxious or scared • feeling exhausted • feeling fearful • feeling hopeful or grateful • feeling low, despondent, discouraged or sad • managing emotional side • feeling shocked guilty or regretful • self-blame for IRD • feeling unprepared or ill equipped • worry about the future • frustration • positive reinforcement of person cared for • reward from caring • impact on own health	Caregiver emotional well being (positive and negative feelings associated with being a caregiver)
Medical and social support (deductive theme)	• worry about lack of autonomy • advocating for self or IRD person • attending appointments • community or family support network • getting medical appointments or care for IRD person	Caregiver getting medical and social support for IRD person
Social well being (deductive theme)	• relationship conflict • resolve conflicts or disagreements caused by or involving IRD person impact on family • competing needs	Caregiver social well being (impact on immediate and extended familial and extrafamilial relationships)
Relinquishing control (deductive theme)	• acceptance of disease outcomes • change living habitat or arrangement • lack of trust in others caring • looking for a cure or treatment • trusting IRD person to be autonomous	Learning to accept the IRD persons condition and their actions and helping the RD person adapt
Need for support (inductive theme)	• desire for help or support for caregiver. • feeling forgotten • feeling taken for granted • lack of support • impact on life • impact on work • financial impact	Caregivers expressed a need for help for themselves and did not feel they were receiving support.
Duty (inductive theme)	• protective or avoidance • responsibility or dependence • unrelenting constant demands • preparing for independence	Most caregivers felt obliged to assume their caregiving roles, viewing it as a necessity rather than a choice. Caregivers expressed felling they have no alternative but to fulfill the caregiver role.

- Theme 1 – caregiver coping

Caregivers (2/7) highlighted the resilience of the individuals they care for, emphasising their ability to normalize their condition which is a positive coping mechanism. They recognise and commend the person's resilience in managing life despite challenges presented from vision loss. For instance, a caregiver spoke proudly of their teenage son acknowledging that despite having to forego playing a sport and even missing out on sporting scholarship, the son showed strength in handling his disease outcomes "*(father) So he had to give all that up and watch his class mates continue. So that was just part of it. That was explained to him. But I think he's taken it all in his stride quite well*". Similarly, another caregiver described the friend they were caring for who was in their third decade of life, as having adapted to her conditions, noting she had continually adjusted to her condition since birth. The caregiver celebrated the strength and resilience of the person cared for, reflecting she was living an outgoing life, recognising she was thriving in the face of adversity "(*friend) she's just had to become adjusted to…She's very outgoing…maybe because it has been since birth. She doesn't know any different*"

All (7/7) caregivers expressed a positive focused coping strategy of accepting of the IRD condition in the person they cared for. Accepting the condition was consistent among caregivers but it was evident that they are constantly adapting to the changing needs of the patient with IRD and dealing with the consequences of deteriorating vision. Caregivers of younger children find hope in their ability to adapt to the condition and witness their resilience, illustrated by a caregiver settling in and taking their child's condition as normal. "(*father) We…settled…..in and take it as normal and take a look how he goes now*". Caregivers of middle-aged patients with IRD acknowledge the limitations of deteriorated vision and recognised the individuals' efforts to help themselves but they expressed there was an ongoing need to step in and provide guidance and support. "(*mother) mum, you know there's nobody and I've got to pick my daughter up at three o'clock from school …so can you come*". Caregivers of elderly individuals noted an increase in the assistance they were providing over time and the requirement to take a more directive role because of the diminished capabilities in the aged person, "(*daughter) he was going himself to the public hospital but he fell on public*

*transport … now he's got a private appointment because the delay (in public) was too long for a period of time…. I go with hi*m".

Caregivers often found themselves managing the frustrations of the person they care for, particularly as age and deteriorating vision present new challenges, such as instances where the individual may resist assistance and inadvertently face difficulties due to their limited vision " (*mother) he wouldn't let me hold his arm, and he would run into people…And I'd be saying, he can't see you, trying to apologize to people and smooth it over*" and "(*daughter) this level of frustration because…his independence has gone….I seem to get the blame for a lot of things*". These examples illustrate the complex emotions and adaptive strategies employed by caregivers as they support patients with IRD through various stages of life (161).

- Theme 2 - Emotional well-being of the caregiver

There was a mix of positive and negative feelings experienced by the caregiver. Almost all caregivers (6/7) conveyed a sense of anxiety regarding a variety of challenges associated with the disease including the initial diagnosis, uncertainty about the progression of the disease, concerns about the patients with IRD being unable to travel from one place to another or potentially harming themselves due to vision loss, or the responsibility of ensuring the patient with IRD can attend appointments.

"(*father) The worry that worry is always on the back of your mind. The worry is not something like you're going to show 24/7 Yeah, but in the back of my mind, I'm always concerned, ….maybe he's going to fall, maybe he's going to miss his steps. … let's say something is very simple, two minute, instant, noodles, .. need a hot water.. whether it's a water in the cup and put it in the microwave or use a kettle into the container, as a normal person, this is a very simple task. But for him We are always worried that .... maybe misjudge with the hot water and its going to burn him*"

While a couple of caregivers (2/7) expressed feeling optimistic and hopeful for younger patients with IRD "(*father) we just have to stay positive and show him the positive side to life….hopefully there*

will be some sort of solution for our sons future….as long as you have a healthy outlook…without good eyesight I think he can still have an enjoyable life", a caregiver of patients with IRD who were middle aged described an emotional journey that had been dynamic from to very despondent times to positive and hopeful times *"(mother) he really straightened out…first time in his life…would have been about 30 or so…I saw the potential*"

Overall, however, most (5/7) caregivers expressed a sense of sadness and feeling regretful at opportunities lost as they witness the impact of vision deterioration on the lives of patients with IRD. They mourn the lost opportunities and dreams that the patient with IRD may experience. For example, a caregiver of a young teenager expressed sadness at the thought of their child not experiencing certain aspects of a typical teenage life, "(*father) can't drive a car, it limits a lot of options for him… your freedoms are.. limited … there's a lot of things you won't be able to experience*". As the age of patients with IRD increases and vision loss deteriorates further, so does the weight of the sadness felt by caregivers, as exemplified by a mother's profound sorrow and feeling helplessness in the face of her child challenges "(*mother) just so tragic, and you know, as a mother, it's just heartbreaking, and there's nothing that I can do to make that any better*". Even in the late stages of life, caregivers continue to express deep empathy and sadness for the person they care for, acknowledging the cumulative impacts of the gradual loss of abilities "(*daughter)he's going through all these changes, and they're stacking up… its tough because everything is slowly being taken away…I feel sorry for him*".

- Theme 3- Medical and social support by the caregiver

The four caregivers (4/7) of younger patients with IRD volunteered the overwhelming experience of the diagnostic process, actively seeking treatment, and attending multiple medical appointments with different doctors within the same specialty seeking a variety of opinions " (*mother) we went from 2 therapies a week to 6 …then he had the next drop in vision, and life has really changed since that drop in vision. You didn't have to worry about him because he could see enough to know. But now there's a lot of safety concerns. There's a lot of trips to hospital because he has misjudged*

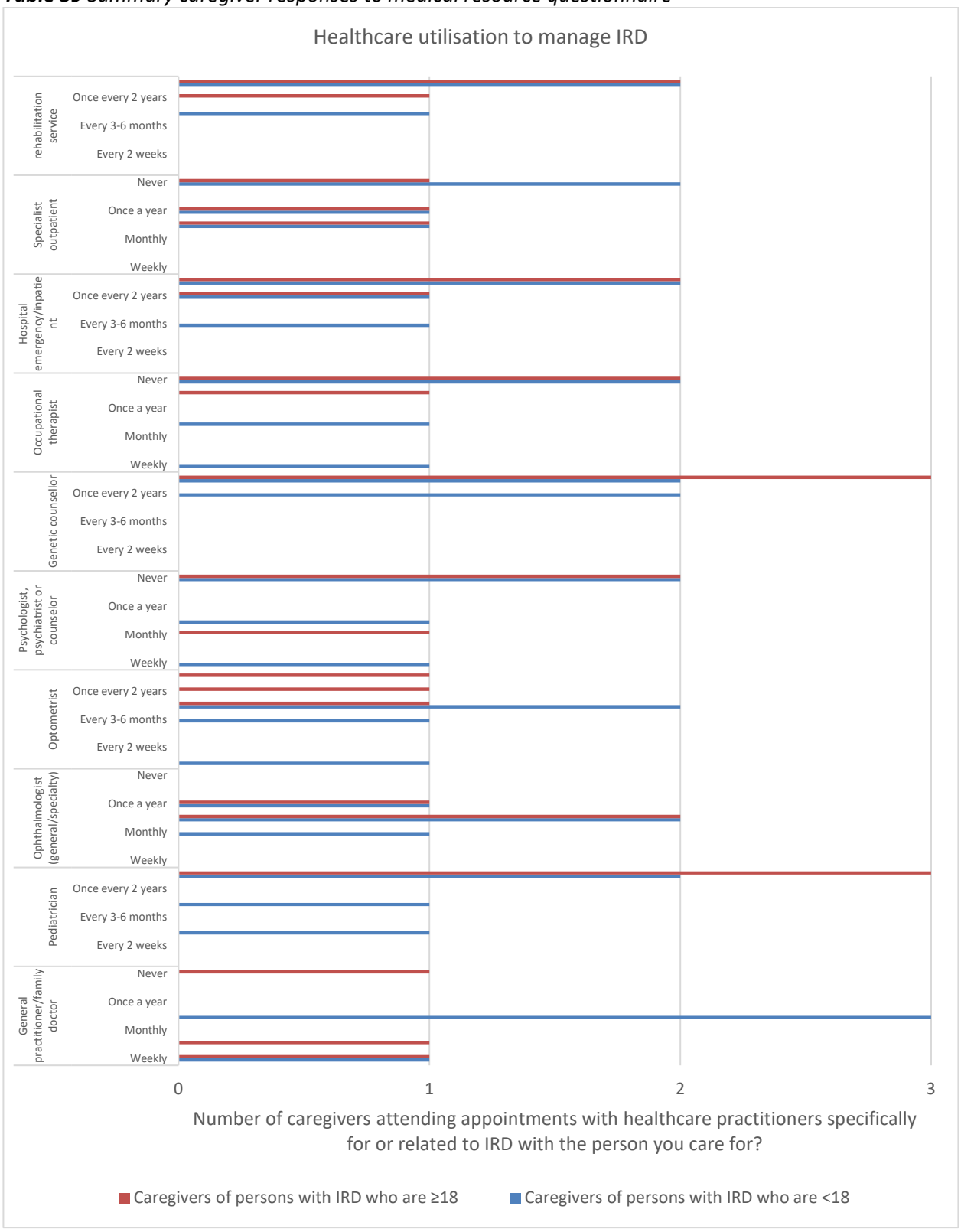
something". This contrasted with the experiences of caregivers of middle age to older patients with IRD who either did not mention the diagnostic journey (3/7) or reflected on it briefly and factually without conveying a sense of having been overwhelmed "(*mother) was the first one diagnosed, we were all, everyone in the family was checked and we had no sign of it. We had no family history of it. And when, two years later, when (second son) turned 10, I recognised the early symptoms of night blindness, and knew that he must have it. So now I have these two sons with retinitis pigmentosa*"

All caregivers were focused on providing support for the medical needs of the patients with IRD, recognising that these needs extend beyond the IRD itself, as some individuals also required medical support for other co-existing health conditions. For instance, multiple (5/7) caregivers expressed concerns about the emotional well-being of the patient with IRD, indicating the need for psychological and psychiatric support in addition to medical care "(*mother) he is in denial. He doesn't .. want to become highly visible…. he internalises. So that's why we're seeing a psychologist, and we're going to have to see a psychiatrist, and he's becoming a loner*". Caregivers also emphasised the challenges and time-consuming nature of medical appointments and treatments, reflecting the significant commitment involved in supporting the patient with IRD "(*friend) You know, seeing the ophthalmologist you've got a certain time and then of course the appointment never runs on time. So you know you've got that wait and then depending on what assessments they do, that can take time you know, waiting for dilating drops, etc, etc. split lamps so that can take I allow myself a good day*". Additionally, they describe the practical measures taken to assist with medication management, such as organising and labelling medication to ensure safety and minimise errors due to the individual's visual impairment "(*daughter) I have to double check everything. I've got to read all the prescriptions to make sure … ticked every box*".

A summary of the response to the medical resource burden associated with IRD questionnaire are presented in **Table 13**. One caregiver of a child or adolescent did not respond to the question about attending rehabilitation services with the person who has an IRD such that there were only three

responses for this cohort and this category. The most frequently attended medical appointment for IRD by caregivers was to the GP (6/7 caregivers attending every week to every 3-6 months) and ophthalmologist (7/7 caregivers attending visits monthly to annually). Overall, respondents expressed a similar burden attending medical appointments with children and adolescents as for adults specifically for or related to IRD thus inferring a similar time commitment for medical support from caregivers irrespective of the age of the patient with IRD.

Table 39 *Summary caregiver responses to medical resource questionnaire*



All caregivers were also actively involved in providing diverse support to help those with IRD navigate daily life. For example caregivers described the need to provide transportation to and from school, facilitating educational support in younger and middle aged patients with IRD or assisting middle aged patients with IRD with shopping task or general mobility due to in some cases the reluctance to use a cane due to pride " (*mother) I still do basically everything I used to do when he was a toddler*." For instance, the caregiver of a school aged person sought educational support outside of school through a tutor due to the illness affecting the child's confidence and relationships at school.

Caregivers of older patients with IRD expressed the need to learn new skills themselves to assist in navigating computer systems for example to assist the patient with IRD due to the lack of timely or co-ordinated support from universities. They also commented that providing housing support on and off over many years as one of the largest impacts they faced. These instances underscore the ongoing assistance provided by caregivers for older patients with IRD in ensuring access to education opportunities and housing as well as the additional effort required of caregivers to address the shortfall of existing support.

"(*mother) mate used to help…getting transport from A to B, help with technology…technology is a huge issue…he uses an iPhone which is probably best for blind people, and he uses it well, but these things never work the way they should…there's always difficulties*" and "(*mother)requires so much support with just getting food in, getting to places…, and all of the technology related things that you have to do these days*."

The NDIS is a system that aims to provide support for people with a disability and allows people to stay at home and receive care. Few caregivers (3/7) stated they had to get involved in the person they cared for seeking support from the Australian National Disability Insurance Scheme (NDIS; https://www.ndis.gov.au/). Those seeking support from the NDIS on behalf of the patient with IRD felt like victims of a system that claims to assist but often complicates matters, requiring them to navigate progressively challenging obstacles. Reflecting on the struggle to maintain NDIS care for a

middle-aged son with IRD and comorbid health issues requiring 9-10 hours of support, one caregiver described the smooth process of allied health organising the NDIS package that became very stressful for her to then renew, "(*mother) So after being in hospital with all the allied health people. He got a fabulous NDIS package at the end of that, because it was all coordinated through them. That was very good. But a year later, they chopped it when it was due to be redone …a battle that went on for seven or eight months…very stressful*". Another caregiver was annoyed that vision support only started when vision had substantially declined and that it took over 12 months to assess a claim, "(*mother) They said that they don't support low vision. So even though at the time everybody knew that (son) would eventually go legally blind. NDIS will not step in until you hit that 6/60 marker. That's kind of like the tick on the box*". One caregiver who was balancing the care of her father with IRD and young daughter described feeling as though she was "(*daughter) drowning in things*" stated they didn't have time to explore NDIS for her father or caregiving respite.

- Theme 4- Social well-being of the caregiver

Two caregivers with children affected by IRD stated they had received or currently receive help from their own parents and were grateful for family support to share the caregiving responsibilities "(mother) when my mother was around, she was able to do a lot" "(*mother)She…did a lot of the heavy lifting in regards the boys…help that I needed when I was working*"

All caregivers who provided care for a family member (6/7) expressed that their caring responsibilities have negatively impacted on their own immediate family in some way. It is worth noting that, due to the small sample size, some non-significant findings between subgroups may be subject to a Type II error, where a real difference or effect exists but could not be detected. Nonetheless, of the five caregivers who had children, three expressed the challenges associated with parenting or providing attention to their other children. For example, one caregiver of a teenager reflected on her daughters increased household contributions, …"(*mother) my daughter is making up for a lot. She is picking up my pieces where I am unable to cope…..she gets frustrated*", while another caregiver reflected on the impact on her unaffected son, "(*mother) my son, who is*

unaffected by RP… he has felt…overlooked quite a lot". A daughter caring for her elderly father noted that her husband had taken on a significant portion of their daughter's education which affected their families' dynamics, "(*daughter) My husband does a lot of our daughter's education stuff…there's a lot of stuff that we have to do… he attends most of those things, but he works full time. So, there's a lot of juggling*". One of the caregivers was a single parent so was particularly conscious of devoting attention to all of his children "(*father) he is one of five. So, I can't afford to spend too much time with just one…I've got to have broader vision to see that everybody else is happy to and traveling. They all have their own problems but not necessarily health problems. But as a father, you've got to make sure that they're all traveling well*"

Most caregivers (4/7) expressed a desire for interaction with a social network of individuals facing similar circumstances "(*daughter) where people that are going through the same thing we can connect with you know, even if you don't want to connect with them personally, you can see group hopes, and you know, maybe this has gone on all you know, have you noticed, someone is experiencing this*". They emphasised the need for support and assistance, with one caregiver of a school aged child expressing they needed help noting they are part of the "*sandwich generation*" who also needed to care for their aging parents thus acknowledging that the situation may become more challenging with time. Most of the caregivers (4/7) were unaware of a support group for families of individuals with similar eye conditions and expressed a desire for a network or group they could connect with to share experiences with other facing similar challenges. "(*father) I just don't I already know if there are any support groups out there, you know, for family of from people who have this type of eye conditions, if there's some sort of a network, or if there is some sort of a group*". Again, the limited number of respondents means some differences in awareness or need for support between subgroups may not have reached significance in our study and could represent a Type II error.

- Theme 5- Relinquishing control

Parental caregivers (5/7) found it challenging to relinquish their role and trust patients with IRD to become autonomous. For example, one caregiver of an adolescent was encouraging their son to

self-administer eye drops but felt compelled to remind his son to administer the drops for fear of the disease progressing. Another caregiver of an adolescent stated explicitly that it was their responsibility to provide care "(*father) But it's our children? I personally think, it's, it's, it's our responsibility as a parent to give our son support*". This might imply a reluctance to encourage independence or may relate to the act of being a parent. One caregiver of a middle-aged patient with IRD reflected on their realisation, "(*mother) It took a long time for each of them to accept that they really needed, needed to acknowledge that they were blind …I spent years trying to make them do what I thought they should be doing to improve things. And of course you can't, we can't control what anyone else does, and that was a very hard lesson for me*." Letting go of control seemed to depend on how well the person being cared for managed their vision loss and how strongly the caregiver felt responsible for their care.

All carers understood the clinical progression of the condition would limit the abilities of the person being cared for or expressed that it had already imposed limitations on the patient with IRD such as giving up contact sports, loss of driver license, reduced interactions and connection with peers, unable to go food shopping unassisted and loss of job. Helping the person they cared for adapt mentally to the limitation was mentioned by all caregivers, all stated that the person they cared for had or was receiving professional psychological support, in some cases at the bequest of the caregiver. A couple of caregivers (2/7) were particularly proud of how the person they cared for had adapted to the vision disorder and its implications stating they were "(*father)taking it in their stride quite well*" and were "(*friend)very outgoing….despite having these issues*". Although all carers were accepting of the condition, some (5/7) expressed feelings of regret due to the impact of the chronic deteriorating condition on the events that would otherwise be routine without the inherited retinal condition such as driving, or playing sports or games with their peers, or having a job. While all caregivers accepted the disease course was incurable and some expressed pride in the patient with IRD managing, one caregiver expressed being hopeful for a cure *"(father)we were looking for a cure or maybe some type of treatment… hopefully, there will be some sort of a solution for our sons future*".

- Theme 6 “Duty” theme

Most caregivers (5/7) felt compelled to take on their caregiving responsibilities, perceiving it as a necessity rather than a choice; some stating that they are the best qualified to provide care. There is a common subtheme of “Duty” or “obligation”, as they express a sense of having no alternative but to fulfill the role of caregiver. One caregiver of a teenager implied she had a duty to protect them because they had expressed fear of potential relocation to a nursing home or supported accommodation. An elderly mother of a middle aged patient with IRD described her duty in having to find alternative care arrangements for her son because she needed to plan for her own retirement highlighting *“(mother)it’s a big burden for him to try and get somebody else to take him on*”. A caregiver of their parent expressed the sense of duty as a family member, which was unfairly borne solely by them, noting that the responsibility is disproportionately placed due to her male siblings being too busy and less emotionally capable of understanding their parent’s needs, ”(*daughter) I feel like I'm a lone ranger,… two brothers, but they seem to be always busy. And it's always dumped on me*”

- Theme 7 Caregiver need for support

Parental caregivers (5/7) didn’t see themselves as caregivers, they see themselves as a parent or a child with a duty to support their family. Furthermore, some caregivers (4/7) expressed feeling overwhelmed by the immense responsibility placed upon them and that they felt forgotten and under supported. They highlighted their lack of formal training and qualifications, relying instead on their lived experiences to navigate daily challenges “(*daughter) all this stuff just fallen on our shoulders. And there's just not that … understanding or not even I might say acknowledgement, I don't want to be acknowledged but just something to say, is there anything you need as a caregiver .. there is the service or there is this group that you can chat to or something about it? That would be* good”.

Most caregivers (5/7) volunteered they needed for support for themselves. When government caregiver assistance was discussed one caregiver who lamented the difficult bureaucracy in getting NDIS support for her son found the process to gain caregiver assistance for herself cumbersome and stated, "(*mother)My path is already difficult. I don't need anyone injecting more difficulty, please. I want someone on my side*". A couple of caregivers expressed feeling that they were forgotten by their other family members who "always seem to be busy" and by health care professionals, with one suggesting, "(*daughter) I think it would be good that you know that medical professionals actually ask the carers, how are you going, you know, how's things at home its good that they focus on the patient? That's really good. Obviously, that's what they need to also think about, you know, is there any other outstanding circumstances that could affect you know, your dad, or your son, or your friends, you know, yeah, I just think that we sort of a bit forgotten*"

All of the caregivers (7/7) expressed they had changed their employment conditions to be able to undertake their caregiving role. Most caregivers (5/7) combined their employment and caregiving roles however two caregivers had ceased employment to maintain a caregiving role. Changes in employment conditions included being unable to return to work after the IRD diagnosis due to the frequency of medical appointments "(*mother) we still don't know if I actually will be able to return to work…has a therapist for everything… because they've realised they don't quite understand the trajectory we have to get as much in as possible to his vision memory now…. so that he will still recall it, even if he can't remember, it's really important*", or having to reduce full time work to part time work, requesting to maintain hybrid working conditions, "(*mother) I've pushed for hybrid .. so that I can be here .. supervising*", so that they can spend more time observing how their teenage son with IRD is coping and be there to assist, or one caregiver who increased their hours of work because his wife can only work casually because she is the primary caregiver "(*father) I work full time…. we just need to…take care of our children. My partner …she stays at home during the time…she can contribute more than myself, because, you know I work quite long hours*".

Discussion

This thematic analysis of interviews with caregivers of patients with IRD revealed several themes that highlight the multifaceted challenges and emotional experiences associated with caregiving in Australia, and their need for support. The themes revealed in the study corroborates prior research that has shown that caregiving of individuals with an IRD leading to visual impairment from a young age poses a substantial threat to a caregivers psychosocial well-being and continually does so as the patient with IRD ages and faces new challenges (142, 162). Our study is unique in that it included both working age and retired caregivers in Australia, and captured the experience of caring for children, adolescents, adults and elderly patients with IRD.

The emotional well-being of caregivers has been frequently highlighted in studies examining the impact of caregiving for individuals with visual impairment (VI) (66, 142, 163, 164). In this study, caregiver emotional well-being emerged as a dynamic construct, oscillating between positive emotions such as optimism and hope, and negative emotions including sadness and anxiety. Notably, anxiety was a dominant pervasive emotion reported by all caregivers. Anxiety among caregivers was largely attributed to the progression of vision loss in patients with IRDs and the accompanying responsibility of assisting with their evolving needs. This finding reflects what is known from the broader caregiver literature; the act of caring for an individual with VI has been well-document to negatively impact various domains of HRQoL, including physical (e.g. fatigues, sleep deprivation), psychological (suffering, anxiety, depression) and social (economic challenges, workplace disruptions, strained relationships) (66, 163, 165). This impact is cumulative, with HRQoL deteriorating as the duration of caregiving increases. For example, a recent study reported a negative association between caregiving duration and caregiver HRQoL, indicating that the burden of caregiving intensifies over time (166). Similarly, Braich et al. (2016) demonstrated a significant decline in caregiver HRQoL as the severity of VI in the care recipient increased, further underscoring the time -dependent burden (66).

Although this study did not specifically assess HRQoL, as noted above high levels of anxiety were observed among both parental and non-parental caregivers, spanning a wide age range of

individuals care for (5 to 86 years, **Table 11**). This highlights that the emotional toll of caregiving does not necessarily diminish as patients with IRDs transition to adulthood and adapt to vision loss. It's important to acknowledge that the similar impact on caregivers of both children and adults with IRDs may stem from the permanent and progressive nature of blindness, though this pattern might not apply to all chronic, degenerative diseases. Nonetheless the findings from this study challenges perceptions that caregiving burden for patients with IRD may lessen over time, an assumption that may have influenced HTA agencies to apply non-uniform caregiver disutility values-used to quantify the reduction in HRQoL-across caregivers of children, adults, and those of retirement age in the EE of a GT for IRDs (82). These insights emphasize the importance of gaining a deeper understanding of caregiver impact throughout a patient's lifetime to identify potential differences between childhood and adult caregiving contexts, and they call for a more refined approach to assessing caregiver burden in **EEs**, especially considering the enduring **emotional strain** reported by caregivers in varied situations.

Informal caregiver time costs have been estimated to constitute 16% and 14% of the total socioeconomic burden of IRDs in the United Kingdom and the Republic of Ireland, respectively (167). The time caregivers dedicate to supporting the medical needs of patients with IRDs encompasses a broad spectrum of activities, including attending medical appointments not only with ophthalmologists and optometrists but also with psychological services, occupational therapists, general practitioners (GPs), and visits to the hospital. The finding is consistent with prior research highlighting high rates of health care service utilisation (168-170). This caregiving responsibility extends across the entire lifespan of patients with IRDs. In this study, data from the medical resource use questionnaire revealed a comparable caregiving burden for children and adolescents as for adults, suggesting that the time commitment required for medical support does not substantially decrease as patients with IRDs transition into adulthood. This finding underscores that the time-related component of caregiver burden, which is often incorporated into EEs, remains significant regardless of the age of the person affected by IRD. The lifelong nature of IRDs implies that caregiving responsibilities may shift between different individuals over time, such as from parents to partners or children. This dynamic was reflected in the current study, where caregivers

included not only parents but also adult children. These findings raise important questions for EEs of IRD interventions, particularly regarding the appropriate number of caregivers to be considered and whether disutility values assigned in EEs to account for caregiver burden should differ over the life of the patients. Further research is needed to address these questions and to ensure that the full scope of caregiver burden is adequately captured in EEs.

Caregivers in this study highlighted the burden of supporting activities such as education, housing, as well as applying for social services. A particular challenge reported by some caregivers was navigating the National Disability Insurance Scheme (NDIS) in Australia. The NDIS aims to provide individualised funding for people with permanent and significant disabilities that affect their capacity to participate in daily activities. Caregivers expressed frustration with the narrow eligibility criterion for individuals with VI to be considered eligible for NDIS support. The eligibility for the NDIS requires a diagnosis of severe VI, defined as corrected VA of ≤6/60 (20/200) on the Snellen Scale in both eyes or VF of 10 degrees or less in the better eye, as assessed by an ophthalmologist (114, 171, 172). Caregivers expressed that patients with IRD experience significant challenges in daily living well before meeting the NDIS eligibility threshold for “Severe vision impairment”, a finding supported by published evidence (106). This criterion ignores that effective management of IRDs requires collaboration with experts knowledgeable about IRDs, including ophthalmology, neuropsychiatry, psychology, neurology, orthoptics, developmental therapy, occupational therapy, and/ orientation and mobility specialties early before patients experience severe VI because visual disorders in children can disrupt essential functions like bonding, cognition, motor skills and spatial awareness (173). Firstly, the restrictive NDIS eligibility criterion risks neglecting the broader spectrum of visual function deficits and the necessary therapies to prepare for severe VI. Secondly, caregivers pay out of pocket costs for IRD specialists up until the point that the NDIS eligibility threshold for “Severe vision impairment” is met placing a large financial burden on caregivers. Reducing bureaucratic barriers and ensuring timely delivery of support would help caregivers manage their responsibilities more effectively.

Moreover, caregivers felt there was an inadequate understanding of VI among NDIS staff, which required them to repeatedly explain the impacts of vision loss on the person they were caring for to justify requests for support services. For example there are various types and levels of VI that impact daily living differently, loss of VA where the eye does not see objects as clearly as usual is different to loss of visual field, where the eye cannot see as wide an area as usual without moving the eyes or turning the head; in addition most people who are "blind" have some usable vision that can help them move around in their environment and do things in their daily lives but is still significantly limiting (174). Two people may have the same visual acuity, but one may be able to use his or her vision better to do everyday tasks. This challenge to understand the complexity of vision is understandable because IRDs represent a diverse group of clinically heterogeneous conditions that impact the functional performance among individuals with VI differently (133). Public understanding of VI is limited, and recent research suggests that the effectiveness and fairness of the NDIS in providing vision rehabilitation services suffer due to complicated procedures and inadequate training for staff and local area coordinators (171, 175, 176). There is a need for improved resources that articulate the various types and stages of VI. Such resources could aid caregivers in explaining and securing essential services for individuals they care for. Family experts have highlighted that access to information is a critical coping mechanism for caregivers to manage stress (164). Addressing these gaps in understanding and resource availability may alleviate some caregiver burden associated with IRD's. In addition, policymakers should invest in specialised training for NDIS staff and local area co-ordinators to improve their understanding of VI, including the diverse clinical presentation of IRD's.

Two themes induced in the analysis: the sense of duty experienced by caregivers and their need for support, are consistent with the results of previous research about caregivers for patients with IRD conducted in Spain (162). Caregivers in this study highlighted accessing financial assistance and respite support through government programs was burdensome reflecting broader systematic inadequacies (https://www.carergateway.gov.au/). In addition, the interviews revealed that the informal caregivers have or are balancing paid employment with their caregiving responsibilities.

This finding is supported by research from the Household, Income and Labour Dynamics in Australia (HILDA) survey which shows informal caregiving reduces carers' workforce participation, with carers more likely to decrease working hours or leave employment altogether resulting in lower average earnings compared with non-carers (177, 178).Notably, this economic impact is often more pronounced for female caregivers, who constitute a significant proportion of informal carers and face additional financial challenges due to pre-existing gender-based inequities in income and workforce participation. Women are more likely to take on caregiving roles, which exacerbates the gender pay gap and limits their career progression, further entrenching financial inequity between men and women. Overall, this underscores the significant economic trade off associated with informal caregiving. While the NDIS aims to provide as much care as possible privately, through encouraging self-care, there is a substantial burden imposed on caregivers that needs to be acknowledged. Support for carers-such as financial assistance and access to short notice caregiving help-may influence the ability of working carers to effectively balance their work and caregiving responsibilities. Raising awareness about the critical role of informal caregivers, particularly the disproportionate challenges faced by women, could encourage greater governmental support tailored to address these inequities.

When incorporating caregiver impacts into EEs for IRD interventions, there is a risk of double-counting that needs to be managed to ensure accurate cost-effectiveness assessments (17). Double-counting can occur if the same burden is captured across multiple components of an EE, such as both the caregiver's disutility (reduction in health-related quality of life [HRQoL]) and indirect costs (e.g., productivity losses or time spent caregiving). This study's data reveals critical insights into this issue, as caregivers reported substantial emotional distress (Theme 2) and employment adjustments (Theme 7), which could be quantified as disutility in quality-adjusted life years (QALYs) and as societal costs in a broader perspective. If both are included without adjustment, the burden may be overestimated, potentially inflating the perceived value of interventions like VN by duplicating impacts on incremental cost-effectiveness ratios (ICERs). However, evidence suggests that income loss is only partly impacting utility scores such that the impact of double counting is negligible (231). Nonetheless to mitigate the risk of double-counting,

EEs should transparently categorize which aspects of caregiver burden are captured in each component—such as disutility for emotional impact and costs for time-related burdens. Sensitivity analyses should also test scenarios with and without overlapping elements to assess their influence on results.

The study data indicates that caregivers of IRD patients consider time pressures and constraints as significant factors impacting their QoL, a finding worth reporting as it intersects with both emotional and economic burdens. All caregivers (7/7) emphasized the substantial time commitment required for medical and daily support activities, such as attending appointments with general practitioners and ophthalmologists (Table 13) and assisting with tasks like transportation or technology navigation (Theme 3). This time burden directly influenced their QoL, as expressed in Theme 7 (Need for support), where caregivers felt overwhelmed and "forgotten" due to unrelenting demands. For example, one caregiver described "drowning in things" while balancing care for an elderly father with IRD and a young daughter, lacking time even to explore respite options like the NDIS. Another noted the stress of frequent medical appointments disrupting work and personal life, necessitating hybrid working conditions to supervise their teenage son. These reflections indicate that time constraints exacerbate emotional strain (Theme 2) and contribute to employment sacrifices (Theme 7), underscoring a critical dimension of caregiver burden that must be considered in EEs.

This study relied on the participation of caregivers who volunteered their time, which may introduce potential biases. It is possible that some participants, having experienced caregiving as a traumatic process, engaged in this study as a form of therapeutic outlet. Given the small sample size, this could have influenced the findings. Conversely, individuals who experienced significant trauma as a result of caring for someone with an IRD may have chosen not to participate, potentially due to the discomfort associated with revisiting distressing events. These factors may limit the generalisability of the findings to the broader population of caregivers of patients with IRD. However, the study's inclusion criteria were designed to create a focused yet diverse group of participants, specifically targeting unpaid caregivers with a variety of backgrounds and experiences. This approach sought

to capture diversity by recruiting caregivers with different relationships to those they care for (such as parents, children, or friends), spanning a wide age range of care recipients (from 5 to 86 years), and encompassing various IRD subtypes (including retinitis pigmentosa and cone/rod dystrophy)(Tabe 11). Additionally, geographic diversity was facilitated by offering both face-to-face and videoconference interviews, which enabled participation from caregivers across different regions of Australia. This diversity provides a rich representation of the lived experience of caregivers across different relationship types, disease profiles and timelines.

While the sample size for this study is relatively small (n=7), this is consistent with established guidelines and evidence in qualitative research that emphasize the importance of information richness over quantity of participants(179). Two studies provide strong methodological support for the adequacy of small sample sizes in qualitative studies when participants are carefully selected for their relevance to the research question and their ability to provide rich meaningful data (179, 180). Boddy (2016) argues that the determination of sample size in qualitative research is contextual and depends on the study's focus and methodological paradigm (180). For research grounded in constructivist approaches such as the current thematic analysis, small sample sizes are justified due to the depth and richness they provide. Similarly, Malterud (2015) emphasises that small, focused samples are particularly appropriate when the study employs a rigorous and detailed analysis plan (179). The rigorous design, clear focus on the "unpaid caregiver" with diverse participant characteristics in this study ensures that the sample provides rich and meaningful data, making it an ideal foundation for thematic analysis. Nonetheless, given the small sample size, caution is warranted in interpreting non-significant or comparable findings as definitive, since the study may be underpowered to detect true differences (i.e., there is an increased risk of Type II error).

Conclusion

Thematic analysis offers a robust qualitative approach for exploring complex, nuanced experiences of caregivers, particularly in the context of rare heterogeneous conditions such as IRDs. This study highlights the enduring emotional, social, and economic toll of caregiving for patients with IRDs,

emphasising the importance of tailored support systems and the need for greater recognition of caregiver burden in research, policy, and practice. It further advocates for the inclusion of caregiver burden over the patient's lifetime in EEs conducted for HTA s, ensuring a more comprehensive assessment of a social value of new technologies for IRDs. Notably, the limited sample size in this qualitative study could have obscured differences between caregiver subgroups or care contexts, increasing the likelihood of a Type II error. Additional studies with larger participant groups are needed to determine whether such differences are present.

Appendix 8 reviewer updates to Chapter 5 Research study 4

Stakeholder survey about broad elements of value in health technology assessment in Australia: industry and academia more similar than different.

Abstract

Objective

Researchers propose wider individual and societal benefits (or broad elements of value) be included in economic evaluations (EEs) of health technologies. This study investigates opinions of Australian stakeholders regarding the inclusion of broader value elements in reimbursement decisions for health technologies for rare diseases (RDs) in Australia.

Method

Stakeholders were invited via email to complete an online survey about their views on broader elements of value in HTA. Responses were summarised using descriptive statistics and compared using chi-square statistics.

Results

Forty-four respondents (academia (n=11), private sector (n=33)) completed the survey between October 2023 and May 2024. Only 27% of stakeholders agree the current information about the sources of value considered in reimbursement decisions is sufficient. Stakeholders consistently agree labour productivity (>50%), adherence (>80%), reducing uncertainty due to a new diagnostic (>70%), disease severity (>71%), value to caregivers (>70%), and equity (>70%) should be considered in HTA. The majority (>70%) agreed managed entry agreements (MEA), risk share arrangements (RSA), and multi criteria decision analysis (MCDA) be used in reimbursement decision-making for medicines for RDs. Significantly fewer academic stakeholders (40%) versus private sector (77%), believe an increased willingness to pay (WTP) threshold be applied to medicines for RD.

Conclusions

Academic and private sector stakeholders hold similar views when considering medicines for non-rare and rare diseases. Stakeholders favour considering more value elements in HTA than referred

to in the Pharmaceutical Benefits Advisory Committee (PBAC) and Medical Services Advisory Committee (MSAC) HTA guidelines. This study highlights further advice is needed on the factors considered in reimbursement decisions and how that would influence guidelines.

Introduction

EE is widely used in HTA to inform reimbursement decisions in healthcare (17, 46). As part of HTA, an EE assesses the incremental cost-effectiveness of a new therapy and the incremental cost-effectiveness ratio (ICER) is judged against an implicit or explicit "cost-effectiveness or willingness to pay (WTP) threshold," to help judge the efficient allocation of healthcare resources (16).
EEs can only include benefits for which adequate data are generated (181). Typically, only direct patient health benefits via health related quality of life (HRQoL) and survival (used to calculate QALYs) are considered in an EE (49). They can however adopt a wider, societal perspective and incorporate broader elements of value such as indirect non health benefits, like productivity gains, offered by a health technology (97, 144, 182). The perspective taken by decision makers is often outlined by HTA guidelines reflecting their country values and preferences, and they may be required to consider a government perspective only rather than the societal perspective (17, 49). Several studies suggest wider benefits to individuals and society should be included in EEs (45, 57, 183). An International Society for Pharmacoeconomics and Outcomes Research (ISPOR) special task force on value assessment recommend a series of broader value elements in HTA assessments (45). If HTA does not include the broader value of a therapy then treatments with wide ranging impacts may be undervalued and receive inappropriately high incremental cost-effectiveness ratios (ICERs) (182, 184). Some of the broad value elements suggested range from conventional concepts, such as adherence improving factors or disease severity, to novel elements of value such as scientific spillover (45).

RDs are a group of diverse diseases, characterised by low prevalence and often have severely debilitating symptoms that substantially affect the HRQoL of patients and their families (6, 77). EEs of medicines for RDs often produce high and uncertain ICERs, in part due to their high cost and

difficulty generating robust evidence supporting clinical efficacy due to small sample sizes, single arm studies, shorter duration of patient follow up and reliance on immature clinical evidence to inform modelling (6, 16). Different reimbursement agencies provide varying recommendations based on EEs of the same medicine for RD, partly because factors like disease severity and broader elements of value were considered, leading to greater acceptance of higher and uncertain ICERs (5, 7, 74). Additionally, some RD medicines have gained expedited access in cases of high unmet need through payment mechanisms like outcome-based managed entry agreements (MEA's) to address the financial risks associated with uncertain clinical evidence (7).

To improve the quality of EEs experts recommend an impact inventory to explicitly and transparently consider the broader health and nonhealthy impacts of a medicine (144). It is however noted that methods to include broad value elements into value assessment are unclear such that HTA agencies use different approaches (9, 185, 186). Two mechanisms to formally include broader elements of value into an EE are a multi criteria decision analysis (MCDA), or the deliberative process (187). The latter is used by reimbursement agencies such as the National Institute for Health and Care Excellence (NICE) in England and Wales and the PBAC and MSAC in Australia. However, deliberative processes have their shortcomings as the relative importance of various criteria varies between stakeholders, which elements of value contributed to the decision is not always clear and how the decision was reached is not always transparent (6, 39, 102, 187-189).

This study investigates the opinions of Australian stakeholders in the HTA process about the importance of various broader elements of value in EEs, transparency in reimbursement decision-making in Australia, and opinions on mechanisms to manage uncertainty associated with medicines of RDs.

Methods

A quantitative survey was conducted of stakeholders involved in HTA in Australia, representing academia, specialist consultants and the pharmaceutical industry. An invitation was emailed to

potential participants (including government agencies and representatives of patient organisations) via local professional societies such the member list of Medicines Australia (which includes Patient Advocacy groups, pharmaceutical company representatives) and at health economic events hosted by as ISPOR Australia Chapter (attended by government, pharmaceutical representatives and health economic consultants). Invitees were encouraged to forward the survey to other relevant colleagues. No responses from government agencies and patient representatives were received.

The survey was developed using the Qualtrics Survey platform and was completed between 02 October 2023 and 14 May 2024. Questions were based on the broader elements of value proposed by ISPOR and mechanisms suggested, and adopted, to manage uncertainty in value assessment (45, 188-190). The questions were discussed with an expert health economists experienced in HTA prior to implementation. Prior to initiation of the survey, the appropriateness and order of the questions were discussed within the research team. Pilot testing of the survey was conducted with internal and external members of the research team to assess comprehension. The survey comprised 32 questions across six sections (**Supplementary Figure 14**, Appendix 3) and was intended to take approximately 10 minutes to complete.

Because value elements are sometimes referred to by other names in the literature or the names may not represent the essence of what is considered, a brief description of each 'value element' was included in the survey (**Supplementary Figure 14**, Appendix 3).

Most questions sought agreement to statements on a 5-point Likert scale: 1=strongly disagree, 2=somewhat disagree, 3=neither disagree nor agree, 4=somewhat agree, 5=strongly agree (respondents could choose a sixth category 'Don't know'). Depending on the resulting number of respondents, and to ensure >5 minimum responses per category (for statistical testing), the categories ‘strongly agree’ and ‘somewhat agree’ were collapsed into one group ('Agree'), and the categories ‘strongly disagree’ and ‘somewhat disagree’ into another group ('Disagree'). The category ‘neither disagree nor agree’ or “don’t know” is henceforth referred to as ‘neither’ within the

text. The remaining questions asked participants whether they agreed with statements with response options 'yes', 'no' or 'not sure', and to nominate methods (via a free text field) to incorporate added value not currently utilised in EEs. Provided a response was not 'yes' the participant was reported to 'Agree'. A response “No” or “Not Sure” reflected that the participant did Not Agree with the statement

Five major categories of stakeholders were defined for respondents to self-allocate 1) pharmaceutical industry, 2) specialist consultants, 3) academia, 4) government agency and 5) representative of patient organisation. Responses to each question were summarised using descriptive statistics and reported for the cohort overall and by respondent categories separately. Test for difference between respondent categories were performed using chi-square statistics (5% significance level). The relative risk (RR) (academic group versus Private sector groups) and 95% confidence interval (CI) are estimated for each response.

Where no background demographics were reported for a participant who consented, their data were removed from the sample. If demographic data were reported but only partial survey response data was provided, participant responses were only included in those questions to which they contributed (thus the sample size varies per question). All analyses were performed using Excel on a MS Windows platform. This study received ethics approval in September 2023 (HREC REF NO. ETH21-6090).

Results

Forty-four respondents completed the survey from academia (n=11) and the private sector (n=33). The respondent categories were aggregated into 'academia' and the 'private sector' (pharmaceutical industry and specialist consultants). The sample was adjusted by excluding three respondents without demographic data. The majority of respondents in both groups had a post graduate degree (Masters 27/44, 61% or Doctoral 14/44, 32%) and the top three primary

qualifications were in health economics (28/44, 64%), pharmacy (11/44, 25%) and science (10/44, 23%). Mean (standard deviation, SD) years of experience was 7.3 years in academia and 14.3 years in the private sector (**Table 14**). Most (67%) in private sector held managerial roles compared with only 18% (2/11) of the academic group.

Table 40 *Background information for all stakeholders and by subgroup*

	Australian stakeholders (N=44)	***Australian stakeholder subgroups***	
		Academia (N=11)	***Private (consultants = 10, pharmaceutical industry=23)***
Years involved in HTA in Australia, mean	12.1 years	*7.3 years*	*14.3 years*
Position Managerial, n/N (%)	22/44 (50%)	*2/11 (18%)*	*20/33 (61%)*
Academic qualification, n/N (%)	14/44 (32%) Doctoral degree 27/44 (61%) Masters degree 3/44 (7%) Undergraduate degree	*8/11 (72%) Doctoral degree* *3/11 (27%) Masters degree*	*6/33 (18%) Doctoral degree* *24/33 (72%) Masters degree* *3/33 (10%) Undergraduate degree*
Area of academic qualification[a], n/N (%)	28/44 (64%) health economics 11/44 (25%) pharmacy 6/44 (14%) statistics 10/44 (23%) science 6/44 (14%) public health 7/44 (16%) business/economics/MBA	*9/11 (82%) health economics* *2/11 (18%) statistics* *1/11 (9%) science* *1/11 (9%) pharmacy* *1/11 (9%) public health*	*19/33 (58%) heath economics* *10/33 (30%) pharmacy* *9/33 (27%) science* *7/33 (21%) business/economics/MBA* *4/33 (12%) statistics* *1/33 (<1%) medicine* *5/33 (15%) public heath*

a. multiple disciplines reported per individual in some cases

Few (<30%) Australian stakeholders agree that the current HTA methods applied in Australia are adequate to appropriately assess the CE of all medicines or medicines for RD (**Table 15**). Despite the absence of a significant difference in responses between stakeholders, it is noteworthy that academic respondents were four times more likely (RR 4.36) to agree that the HTA methods used in Australia are adequate for all medicines, compared to their private sector counterparts. However, the substantial uncertainty surrounding this estimate is reflected in the wide confidence interval (range 0.84 to 22.79). The majority of stakeholders disagreed with the statement that the public information on reimbursement decisions in Australia provides sufficient information about which sources of value are considered and how they contributed to decision-making (73%; academia=55% versus private sector=80%, p=0.1031) (**Table 15**). It is important to emphasise the variation in response rates, despite the lack of statistical significance. Notably, academics were

twice as likely (RR 2.27) to concur that the publicly available information on reimbursement decisions is adequate compared with the private sector. Of the 24 respondents from the private sector who disagreed, 83% felt that while they knew which sources of value were considered, they did not know how they contribute to decision-making. Equal proportions of respondents from academia thought that either the sources of value considered were not known (33%) or did not know how they contributed to decision-making (33%).

The majority of stakeholders (70%; academic=50% versus private sector=77%, p=0.1110) agreed that having an explicit checklist on broader value considered beyond the QALY by decision makers would be more informative than what is currently published in Australia (**Table 15**). There is an imbalance in responses however, a RR of 0.65 suggests that the academic group were 35% less likely to agree than private sector stakeholders that a checklist may be more informative. Importantly, the 95% CI range (0.34 to 1.25) indicates uncertain precision of this effect.

Stakeholders were invited to explore mechanisms to facilitate expedited access to treatments for RDs, while effectively managing the uncertainties associated with cost-effectiveness analysis (CEA) and budgetary impacts (BI). This consideration is driven by the significant unmet need and the demand for accelerated access to such medicines. A description of the mechanisms were as follows: MEA, outcome based managed entry agreement that allows earlier market access but requires CEA review once additional outcome data are available. For example: clinical data from pre-specified study protocol for all patients subsidised or from existing planned or progressing studies [26]); MCDA, multicriteria decision analysis which involves a deliberative process where decision makers and stakeholders come together to define the problem and determine the criteria, weighting and evidence requirements for decision [24, 28]); RSA, financial risk share arrangement that financially subsidises based on medicine or patient performance. For example: a percentage rebate is paid if the number of treatments per patient or accepted duration of treatment is exceeded. Subsidy ceases if patients do not meet agreed clinical measures [26]); WTP, willingness to pay is

an increase in the ICER considered acceptable for treatments of RDs.

Most Australian stakeholders (>68%) agreed the four mechanisms (MEA's, financial risk share arrangements [RSA's], MCDA's and increased ICER's considered acceptable for treatments of RDs denoted as WTP), should be used in making reimbursement decisions about medicines for RD (**Table 2**). Over seventy percent (>70%) of academia and private sector respondents agreed that MEA's RSA's and MCDA should be used in making reimbursement decisions for medicines for RD in Australia **(Table 15**). Significantly fewer academic respondents (40%) compared with the majority of private sector respondents (77%) (p=0.0320) agreed that an increase in the ICER considered acceptable for medicines for RDs in Australia, should be used in decision-making.

Table 41 *Comparison between adequacy of HTA methods, sufficiency of public information and mechanisms for decision making*

Q: Do you think the current HTA methods applied in Australia are adequate to appropriately assess the cost effectiveness of all medicines? n/N (%) agree			
Total cohort	5/43 (12%)		
Academia	*3/11 (27%)*	*RR: 4.36 (95%CI 0.84, 22.79) p=0.06*	
Private sector	*2/32 (6%)*		
Q: Do you think the current HTA methods applied in Australia are adequate to appropriately assess the cost effectiveness of medicines for rare diseases? n/N (%) agree			
Total cohort	8/44 (18%)		
Academia	*2/11 (18%)*	*RR:1.0 (95%CI 0.24, 4.25) p=1.0*	
Private sector	*6/33 (18%)*		
Q: Do you agree that the current public information regarding reimbursement decisions in Australia provides sufficient information about which sources of value are considered and how they contributed to decision-making, n/N (%)			
Total cohort	11/41 (27%) agree	*Reasons for disagreement* 6/30 (20%) state we don't know which sources of value are considered 22/30 (73%) state while we know which sources of value are considered, we don't know how they contribute to decision-making 2/30 (6.7%) did not select a re	
Academia	*5/11(45%) agree*	*RR:2.27 (95%CI 0.87, 5.97) p=0.10*	*Reasons for disagreement* *-2/6 (33%) state we don't know which sources of value are considered* *-2/6 (33%) state while we know which sources of value are considered, we don't know how they contribute to decision-making* *-2/6 (33%) not sure*
Private sector	*6/30 (20%) agree*		*Reasons for disagreement* *- 4/24 (17%) state we don't know which sources of value are considered* *-20/24 (83%) state while we know which sources of value are considered, we don't know how they contribute to decision-making*

Q: Do you agree that an explicit checklist of sources of value beyond the patient QALY and whether they were considered by decision maker would be more informative than what is currently published in Australia? n/N (%) agree		
Total cohort	*28/40 (70%)*	
Academia	*5/10 (50%)*	*RR:0.65 (95%CI, 0.34, 1.25) p=0.11*
Private sector	*23/30 (77%)*	
Q: Do you agree the following mechanism, MEA should be used in Australia in making decisions about reimbursement of medicines for rare disease, n/N (%) agree		
Total cohort	*32/40 (80%)*	
Academia	*9/10 (90%)*	*RR: 1.17 (95%CI 0.88, 1.56) p=0.36*
Private sector	*23/30 (77%)*	
Q: Do you agree the following mechanism, RSA should be used in Australia in making decisions about reimbursement of medicines for rare disease, n/N (%)		
Total cohort	*33/40 (83%)*	
Academia	*9/10 (90%)*	*RR: 1.13 (95%CI 0.86, 1.48) p= 0.47*
Private sector	*24/30 (80%)*	
Q: Do you agree the following mechanism, MCDA should be used in Australia in making decisions about reimbursement of medicines for rare disease, n/N (%)		
Total cohort	*29/40 (73%)*	
Academia	*7/10 (70%)*	*RR: 0.96 (95%CI 0.60, 1.51) p=0.84*
Private sector	*22/30 (73%)*	
Q: Do you agree the following mechanism, WTP should be used in Australia in making decisions about reimbursement of medicines for rare disease, n/N (%)		
Total cohort	*27/40 (68%)*	
Academia	*4/10 (40%)*	*RR: 0.52 (95%CI 0.24, 1.14) p=0.03*
Private sector	*23/30 (77%)*	

Abbreviations: CI, confidence interval; MEA, outcome based managed entry agreement (defined as allows earlier market access but requires CEA review once additional outcome data are available. For example: clinical data from pre-specified study protocol for all patients subsidised or from existing planned or progressing studies [26]); MCDA, multicriteria decision analysis (defined as involves a deliberative process where decision makers and stakeholders come together to define the problem and determine the criteria, weighting and evidence requirements for decision [24, 28]); RR, relative risk; RSA, financial risk share arrangement (defined as with subsidy based on medicine or patient performance. For example: Percentage rebate if the number of treatments per patient or accepted duration of treatment is exceeded. Subsidy ceases if patients do not meet agreed clinical measures [26]); WTP, willing ness to pay (defined as increase the ICER considered acceptable for treatments of rare diseases).

The majority of all Australian stakeholders (>65%) believed that six of the eleven broader value elements recommended by ISPOR: labour productivity, adherence, reducing uncertainty due to a new diagnostic, severity of disease, value to caregivers, and equity should be considered in HTA of all medicines and medicines for RD (**Table 16**). Whereas few stakeholders agreed that the value of hope, real option value, scientific spillover, fear of contagion or insurance value should be considered **(Table 16**).

The degree of consensus between the stakeholder groups is demonstrated by a RR close to 1.0 accompanied by a narrow confidence interval. This indicates consensus between academia and private sector respondents on the majority of broader value elements agreed should be considered

in HTA of all medicines and medicines for RD in Australia, namely adherence, reducing uncertainty due to a new diagnostic, severity of disease, and equity. Furthermore, the analysis revealed no statistically significant differences in responses when analysed by sector (Table 16). Interestingly the likelihood of agreeing to include “Labour Productivity” in HTA of all medicines and medicines for RD in Australia is approximately 30% less in the academic respondents compared with private sector respondents. Also, the likelihood of the academic group agreeing to include “Value to caregivers” in HTA of medicines for RD in Australia (RR0.75) is 25% less likely than the private sector, yet the degree of concordance was greater when considering HTA of all medicines (RR0.86). In addition, the majority of both stakeholder groups did not agree that the Value of Hope should be considered in HTA of all medicines and medicines for RD in Australia (<43%), the likelihood of agreeing that it should be included was 50% lower in the academic respondents compared with private sector respondents (RR 0.46 and RR0.38, respectively). Each group was aware of methods to capture impacts on costs and outcomes for the broad sources of value, such as HRQoL measures, subgroup analysis and distributional cost-effectiveness analysis (DCEA) (**Table 1**7).

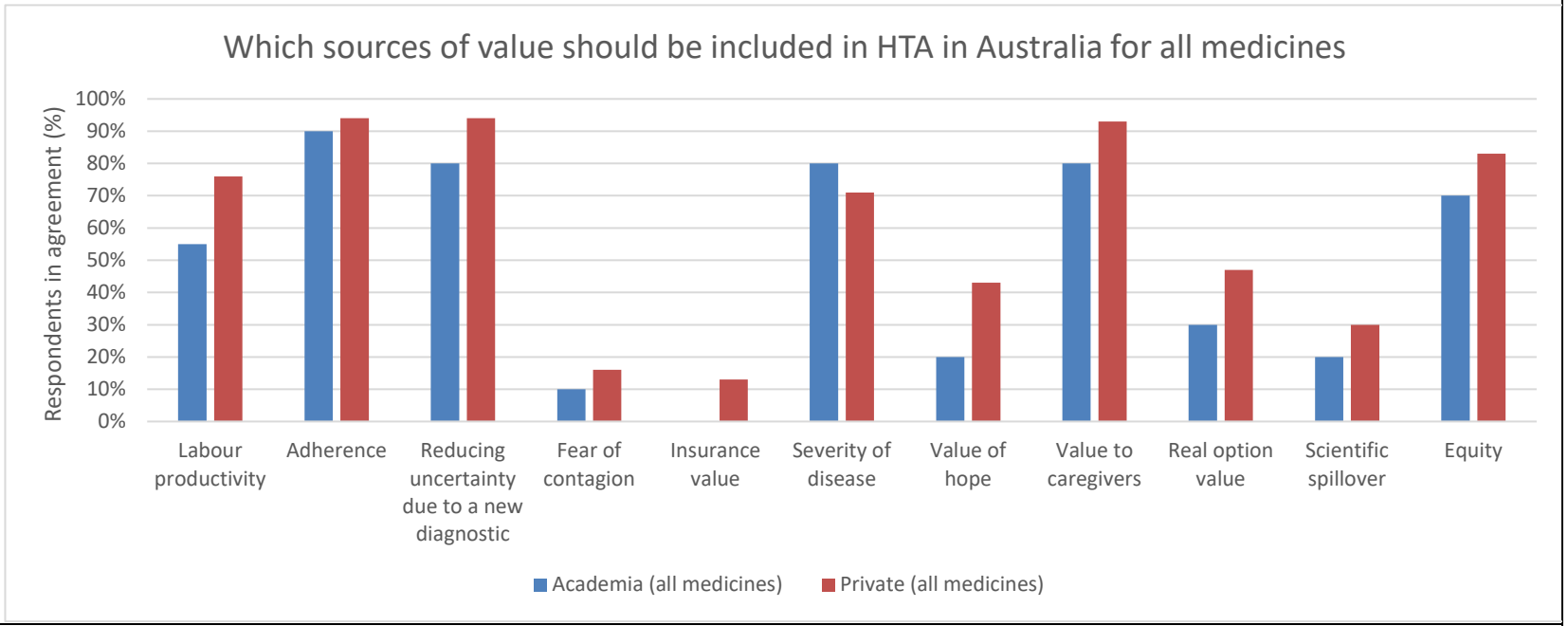
Table 42 *Comparison between sources of value that should be considered in HTA for all medicines and medicines for rare disease*

Broad elements of value	All medicines, n/N (%) agree				Medicines for rare disease, n/N (%) agree			
	Total cohort	*Stakeholder sectors*			Total cohort	*Stakeholder sectors*		
		Academia	*Private sector*	*RR (95%CI), p-value*		*Academia*	*Private sector*	*RR (95%CI), p-value*
Labour productivity	31/43 (72%)	*6/11 (55%)*	*25/32 (78%)*	*0.70 (0.40, 1.23), 0.1326*	26/40 (65%)	*5/10 (50%)*	*21/30 (70%)*	*0.71 (0.37, 1.39), 0.2508*
Adherence	39/42 (93%)	*9/10 (90%)*	*30/32 (94%)*	*0.96 (0.77, 1.20), 0.6877*	34/40 (85%)	*8/10 (80%)*	*26/30 (87%)*	*0.92 (0.66, 1.30), 0.6091*
Reducing uncertainty due to a new diagnostic	37/41 (90%)	*8/10 (80%)*	*29/31 (94%)*	*0.86 (0.62, 1.18), 0.2093*	34/40 (85%)	*7/10 (70%)*	*27/30 (90%)*	*0.78 (0.51, 1.19), 0.1250*
Fear of contagion	6/41 (15%)	*1/10 (10%)*	*5/31 (16%)*	*0.62 (0.08, 4.70), 0.6335*	4/40 (10%)	*1/10 (10%)*	*3/30 (10%)*	*1.0 (0.12,8.56), 1.00*
Insurance value	4/41 (10%)	*0*	*4/31 (13%)*	*ND*	6/40 (15%)	*1/10 (10%)*	*5/30 (17%)*	*0.60 (0.08, 4.54), 0.6091*
Severity of disease	30/41 (73%)	*8/10 (80%)*	*22/31 (71%)*	*1.13 (0.77, 1.65), 0.5751*	31/40 (78%)	*8/10 (80%)*	*23/30 (77%)*	*1.04 (0.73, 1.51), 0.8270*
Value of Hope	15/40 (38%)	*2/10 (20%)*	*13/30 (43%)*	*0.46 (0.13, 1.70), 0.1869*	9/40 (22%)	*1/10 (10%)*	*8/30 (27%)*	*0.38 (0.05, 2.64), 0.2744*
Value to caregivers	36/40 (90%)	*8/10 (80%)*	*28/30 (93%)*	*0.86 (0.62, 1.19), 0.2235*	35/40 (88%)	*7/10 (70%)*	*28/30 (93%)*	*0.75 (0.50, 1.14), 0.0533*
Real option value	17/40 (43%)	*3/10 (30%)*	*14/30 (47%)*	*0.64 (0.23, 1.78), 0.3558*	11/40 (28%)	*0*	*11/30 (37%)*	*ND*
Scientific spillover	11/40 (28%)	*2/10 (20%)*	*9/30 (30%)*	*0.67 (0.17, 2.58), 0.5397*	10/40 (25%)	*1/10 (10%)*	*9/30 (30%)*	*0.33 (0.05, 2.32), 0.2059*
Equity	32/40 (80%)	*7/10 (70%)*	*25/30 (83%)*	*0.84 (0.54, 1.30), 0.3613*	34/40 (85%)	*8/10 (80%)*	*26/30 (87%)*	*0.92 (0.66, 1.30), 0.6091*

Abbreviations: CI, confidence interval; ND, not determined; RR, relative risk

Note: The questions posed to participants were, "Rate the extent to which you agree or disagree that the following source of value should be considered in HTA of medicines in Australia", and then participants nominated if they were aware of methods to include each source of value in a cost-effectiveness analysis (presented in Table 5); a table of 11 value elements was then presented to participants and they were asked "Do you agree that the following sources of value should be considered in cost effectiveness analysis of a medicine for rare disease in Australia?" for each value..

Table 43 *Comparison between stakeholder groups regarding sources of value that should be considered in HTA for all medicines and suggested methods to include them into EEs*



Suggested methods related to assessment of costs or outcomes:						
Productivity: human capital approach, friction cost, willingness to pay study, patient preference, G method(191)	**Adherence:** persistence, discontinuations, observed utilisation within trial and post listing surveillance	**Reducing uncertainty**: decision tree/ Bayes revision node to capture test accuracy before modelling costs & outcomes in responders and non-responders,	**Severity:** utility study, ICER threshold, QALY weighting, scenario analysis (using results from complementary subgroups), specific funding pools	**Value of hope**: Utility studies (Time trade off, standard gamble and other preference based measures).	**Value to caregivers**: Productivity, indirect carer costs, CareQoL and other measures of utility	**Equity:** Threshold increase, equity weightings, funding for specific populations, subgroup analysis, distributional cost-effectiveness analysis

Discussion

This study examined views from academic and private sector stakeholders involved in HTA on which broad elements of value should be considered by decision makers in Australia, and mechanisms to mitigate uncertain cost effectiveness (CE) and budget impact associated with medicines for RDs.

The majority of respondents agreed that current public information regarding reimbursement decisions in Australia provides insufficient information about the consideration of sources of value in decision-making. Furthermore, the majority of respondents agreed that current HTA methods applied in Australia are inadequate to appropriately assess the CE of all medicines and medicines for RD. Australian reimbursement recommendations are made transparent to the public by publishing them online as public summary documents (PSDs) (69). They provide contextual information pertaining to each recommendation and although they are limited in terms of the amount of information published, they provide insight into the factors and trade-offs noted through the deliberative process in arriving at reimbursement recommendations (82). Transparency on which inputs are accepted (and under what conditions) by HTA decision makers is necessary because it enables stakeholders to collect relevant data to inform decision-making (72). This study highlights transparency on what was considered in PBAC and MSAC decision-making in the PSD needs further improvement. Of interest the participants in the Australia's recent HTA policies and methods review (referred to as the "HTA review") expressed concern that PSDs fail to adequately convey how certain evidence types impact health technology funding decisions (192). The HTA review findings are consistent with those from this survey.

More private sector stakeholders (77%) than academic stakeholders (50%) thought an explicit checklist of sources of value beyond the QALY and whether they were considered by decision maker, would be more informative than what is currently published in Australia. Private sector stakeholders, particularly those in the pharmaceutical industry, may have more interest in PBAC and MSAC decision-making than academics, as they depend on these decisions for medication funding (**Table 14**). Nonetheless, experts suggest a checklist for reimbursement decision-

making as a useful framework to standardise the consideration of sources of value, minimise bias and improve transparency (9, 45, 144, 193). The HTA review recommends that the Australian Government develop and support an explicit qualitative values framework to ensure HTA decisions consider broader value, enhancing transparency and consistency in funding health technologies (192). Importantly the recommendation states the framework should allow enough flexibility for the deliberation process itself to add value that is not pre-weighted and scored. Examples of explicit qualitative value frameworks and transparent reporting by HTA committees include the I.C.E.R. in the US that refers to "*Potential other benefits and contextual considerations*" such as health disparities, caregiver burden, or impact the entire "*infrastructure*" of care that committee members individually rate during deliberation (69). The I.C.E.R value framework is systematic regarding the factors incorporated into decision-making and explicitly reported (69, 194). NICE includes non-quantified additional health benefits such as to the health system (e.g. equity), and innovation (82, 102). The NICE final outcome describes how such "other factors" impacted decision-making (82).

Less than 20% of Australian stakeholders agree that fear of contagion and insurance value should be considered in HTA of all medicines or medicines for RD in Australia. Six broad value elements that most Australian stakeholder felt should be considered in HTA of medicines in Australia (labour productivity, adherence, reducing uncertainty due to a new diagnostic, severity of disease, value to caregivers, and equity) are recommended in several HTA guidelines whereas only two (severity of disease and equity) overlap with the 'less -readily quantifiable' factors quoted to "*influence*" PBAC decision-making in Australia (49, 195). Only one of the six broad value elements (equity) overlap with less -readily quantifiable' factors quoted to "*influence*" MSAC decision-making in Australia(99). The PBAC HTA guidelines highlight several factors considered during PBAC deliberations, such as the overall confidence in the evidence and assumptions presented, equity, severity, the capacity to target therapy, the existence of effective therapeutic alternatives, public health considerations, and any other pertinent factor influencing a medicine's suitability for listing on the PBS. The MSAC HTA guidelines highlight the following are considered during MSAC deliberation, equity, value of knowing, presence of

effective alternatives, and other relevant factors (including the impact on organisations, or the way in which organisational issues may create barriers or facilitators to the uptake of the new technology or efficiency of health care delivery, ethical concerns, and social aspects)(99). These qualitative assessments, along with CE and BI, may obscure the weight of each factor in reimbursement decisions. Additionally, while the guidelines assert that "*Supplementary analyses may be appropriate where the proposed intervention has important societal implications*"—thereby permitting the inclusion of broader values in supplementary CEA—the relegation of non-health benefits to supplementary analyses might result in them being overlooked in the decision-making process and omitted from the PSD.

A recent review of 53 HTA guidelines representing 52 countries revealed an average of 5.9 of a possible twenty-one societal and novel value elements were mentioned although the authors acknowledge simply recommending novel elements of value in HTA guidelines may not lead to them being incorporated into decision-making (49). Australian HTA guidelines outline a preferred approach for PBAC and MSAC submissions but allow alternative approaches if justified with data. Stakeholders can include alternative value elements in submissions, but decision-makers must transparently evaluate these. Transparency is crucial for pharmaceutical industry sponsors, as developing evidence is resource-intensive and can guide future evidence generation. Including well-supported broader value elements in decision-making acknowledges therapy benefits and aids patient access to medicines (5, 74, 185).

There are challenges quantifying some broad value elements, and a lack of consistent methodology for their inclusion in EEs as well as expertise in assessing the methodologic approaches (45, 49, 182). Both stakeholder groups were generally aware of methods to incorporate agreed-upon value elements into HTA of medicines. However, some elements like fear of contagion and insurance value lacked acknowledged methods. Suggested methods, within the CE framework, included preference-based methods, scenario analysis, and DCEA. Academics had higher method knowledge, indicating varying skill sets among stakeholders. This underscores the need for PBAC and MSAC HTA guidelines to provide guidance on data

and methods to support broader value elements, alongside improving transparency in decision-making. For example the Medical Services Advisory Committee (MSAC) in Australia includes the 'value of knowing' as a less quantifiable factor influencing decisions and offers technical guidance on evidence to support this element whereas the PBAC does not provide specific guidance on how to address less quantifiable factor influencing decisions (99).

The inquiry into proposed decision-making mechanisms for reimbursing medicines for RD in Australia was framed by the context that medicines for RD are generally expensive with limited evidence of clinical effectiveness, attributed to small, non-comparative clinical studies and lack of epidemiological data. RSA's and outcome based MEA's are existing mechanisms employed in Australia to subsidise medicines despite the lack of confidence in the evidence for a medicine (190). Most stakeholders agreed RSA's and MEA's should be used in making reimbursement decisions about medicines for RDs. RSA's described in this study are a practical financial arrangement that continues to subsidise a medicine only when treated patients meet specific clinical criteria, it also provides certainty around financial expenditure to the government despite patient population size uncertainty. Outcome based MEA's are challenging to implement in Australia due to the absence of infrastructure linking medicine utilisation and clinical outcomes, and thus most MEA's implemented in Australia to date are limited to reviewing the recommendation to reimburse a medicine once additional outcome data become available from a clinical trial that is underway (190, 196, 197). If MEA's are to be used to expedite access to medicines for RDs in Australia despite uncertain clinical evidence, handling challenges such as establishing infrastructure to support comprehensive data collection as well as price adjustments based on outcomes arrangements or product delisting due to suboptimal performance are some of the significant tasks for both payers and the pharmaceutical industry (190, 198).

The MCDA method referred to in this survey was a quantitative MCDA whereby stakeholder preferences are used to specify a value for each criterion, the values are weighted, and an overall score generated for each intervention (187). The use of quantitative MCDA in HTA is not

widespread but most Australian stakeholders responding to the survey believe it should be used to make reimbursement decisions about medicines for RDs in Australia (199). The formal structure of MCDA, avoids some of the issues in less structured deliberative processes, explicitly elicits decision makers preferences and allows for the inclusion of broader value elements important to stakeholders but not easily accommodated in standard CEA's (187, 189, 200). Two systematic reviews of quantitative MCDA found it useful for focusing discussion and reporting decisions transparently but found no evidence of improved decision-making quality or timeliness (193, 195). Importantly, weighting of the relative importance of various value elements would likely differ between stakeholders such as patients and payers (187). Consequently, the HTA review recommendation to develop a "qualitative value framework" that is neither pre-weighted nor pre-scored.

There was significant disagreement between the stakeholder groups regarding increasing WTP thresholds in making reimbursement decisions about medicines for RD. Among the many countries that use CEs to inform funding decisions (such as England and Wales, Australia, New Zealand, Canada, Sweden, the Netherlands, and others), only England and Wales, and the Netherlands use an explicit WTP threshold to make funding recommendations (43). The PBAC do not explicitly report a fixed WTP value to judge the acceptability of a medicine as CE, but revealed and stated preference studies of PBAC decision-making shows a preference for smaller ICERs to recommend a medicine (40, 201). The view from academic stakeholders aligns with surveys of the Australian general public which shows there is no WTP a premium for rarity although there is a case for paying more for drugs that treat severe conditions, or where there is no alternative treatment available (56, 202, 203). Nonetheless the PBAC have stated their willingness to accept a higher ICER in the face of significant uncertainty in the CE of a medicine for a RD (196).

A limitation of our study is the small sample size in this survey, and the unequal group sizes (academia, N=11; private sector, N=33). The timing of the survey, conducted during the recent HTA review in Australia, may have influenced participation, as stakeholders could have

experienced fatigue due to the extensive feedback collection during the review. Discrepancies in sample sizes may account for the lack of significant differences observed, as smaller samples increase variability and standard error, reducing estimate reliability and sensitivity to detect differences. Additionally, recruitment through email and professional societies may introduce selection bias, as it depends on self-selection by more engaged stakeholders. Nevertheless, the participants had considerable expertise, averaging between 7-14 years of HTA experience, predominantly with health economic qualifications (**Table 14**), making their opinions likely a reliable reflection of other health economists in Australia. The absence of data from critical groups, such as government policymakers and patient representatives, limits the generalisability of our findings. Further research to include insights from these groups and expand the sample size would be beneficial. There may be other value elements that stakeholders think should be considered in HTA of medicines in Australia beyond what was considered in this survey. Nevertheless, the broad value elements in the survey covers a wide range of value from societal elements (health impacts beyond the treated individual and costs beyond the healthcare sector such as productivity and scientific spillover), to novel elements (e.g., insurance value, fear of contagion and value of hope). Regardless, the list of broad elements of value are not intended to be final preferences of stakeholders.

Conclusion

The perspectives of Australian stakeholders in both the academic and private sectors were largely congruent, showing no significant differences between general medicines and those for RDs. Stakeholders from both sectors involved in HTA in Australia expressed concerns that current methods are inadequate for assessing medicines and that public statements lack transparency regarding which value sources influenced reimbursement decisions. There was consensus among both groups favouring the inclusion of more value elements in HTA decision-making than currently recognised in the PBAC and MSAC HTA guidelines, specifically advocating for the integration of six out of the eleven values from the ISPOR value framework.

The survey's findings offer valuable insights relevant to the Australian HTA review's recommendations, suggesting an explicit qualitative framework be developed, informed by public consultation and existing research. Additional research to gather perspectives from patients and decision-makers and to increase the sample size would be advantageous. This study underscores the necessity for enhanced guidance in reimbursement guidelines and for greater transparency in the publication of decisions related to the values influencing decision-making.

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