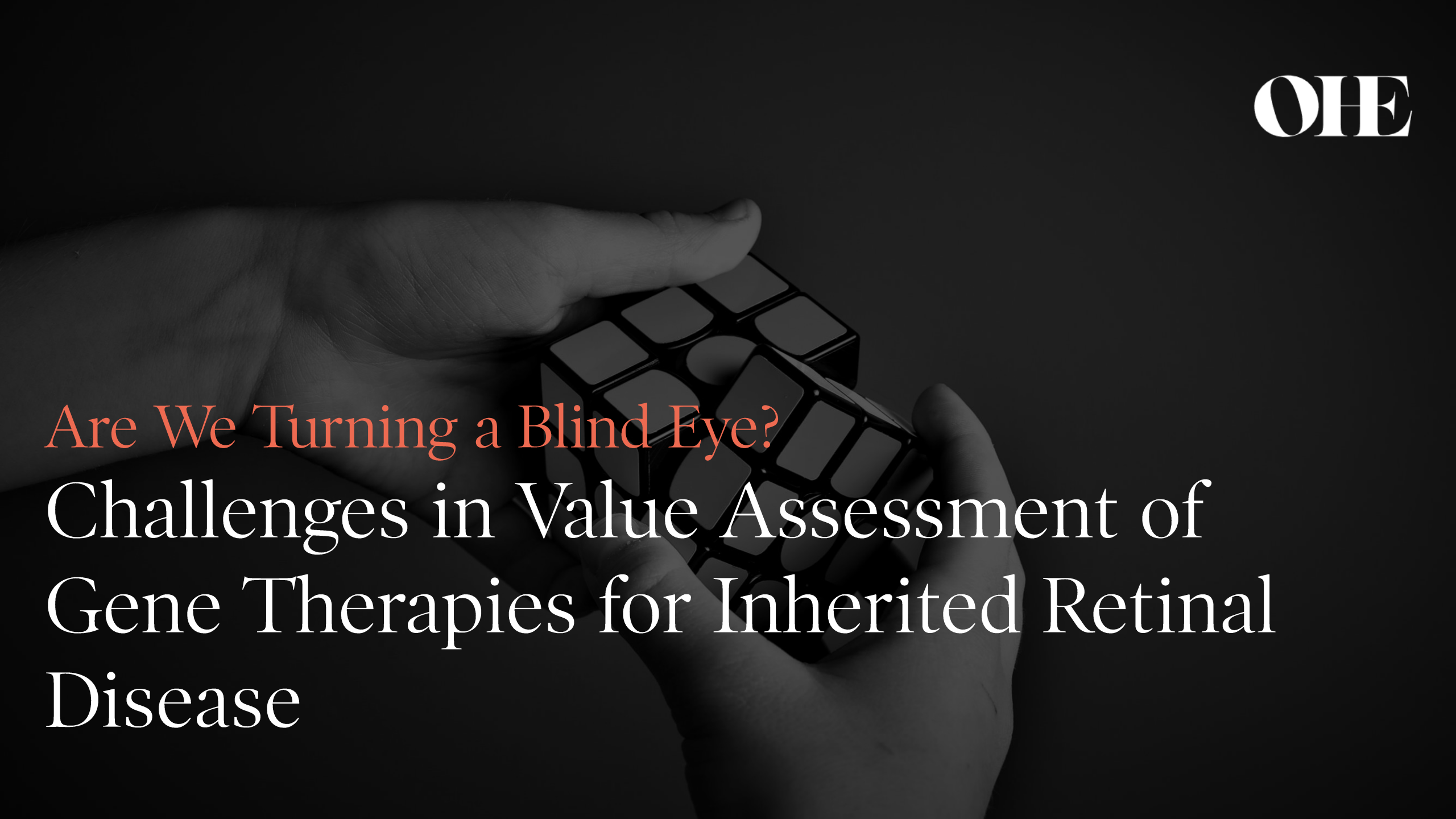


OHE

Are We Turning a Blind Eye?

Challenges in Value Assessment of Gene Therapies for Inherited Retinal Disease

Speakers & Agenda

Lotte Steuten
OHE

Welcome

Avril Daly
Retina International

A patient's perspective

Simon Brassel
OHE

Selected key challenges and considerations

Jennifer Lee
Janssen Pharmaceuticals

An industry's perspective

Caroline Bregman
NICE

An HTA agency's perspective

Retina International

What is the value and impact of gene therapies for patients living with Inherited Retinal Degenerations.

A Patient Community Perspective

November 8th, 2022. ISPOR – Vienna.

Avril Daly. Retina International.

Gene and Cell Therapy – addressing Europe's challenge?

Gene and Cell therapy has the potential to;

- To treat rare, inherited and complex diseases
- To change lives and address significant unmet need
- Reduce burden of disease on patient and carers
- Can improve the delivery of care and treatment by reducing burden
- Address growing societal inequalities
- Ultimately reduce cost

Retina International

Impact of Inherited Retinal Dystrophies - IRDs

- The prevalence and impact of IRDs at a national and global level has remained largely undocumented.
- The socioeconomic burden of IRDs, in addition to their impact on wellbeing and mental health, has been felt by patients, health advocacy organisations, health care providers, and scientists the world over.
- Studies undertaken by RI to understand the Social and Economic Impact of IRDs on the individuals affected and society at large demonstrated a significant burden, on wellbeing, mental health, access to education and employment as well as productivity.
- Yet in the context of VALUE IRDs are measured in their cost to the healthcare system, which highlights the challenges this community faces in accessing treatment.

Retina International

Assessing Value -
Looking at the healthcare system alone is not enough.

Experience of the IRD Community:

- Inherited Retinal Dystrophies are unlike other rare conditions- those living with vision impairment are not patients. They are not sick – but live with a degenerative disease that affects their wellbeing,
- Health systems costs are the lowest of cost types when conducting a socio-economic analysis of the impact of vision loss of inherited retinal conditions.

Cost is in Social Care – Social Services – Access to Education, Employment and impacts mental health.

- High rates of depression, anxiety and financial stress.
- Impact on education, employment and productivity losses.
- Impact on caregiver.
- Intangible costs.

This is recognized in other patient communities who do not solely rely on health care to provide support

Retina International

IRD Counts The Cost.

In 2019 a patient led study on the burden and economic impact of IRDs in the ROI and UK from a societal perspective found that:

- 33.8% (16m Euro) IRE
- 38.4% (138,1 STG) UK

were attributed to Wellbeing

- 9.4m Euro
- 114,1m Pounds Stg

were attributed to Productivity Costs

50,7% of people living with an IRD in ROI and
40,2% in UK
were not in paid employment

In both regions IRDs result in 9.6% loss of **productivity while at work.**

Retina International

Assessing degenerative disease

- Adaptations occur as sight degenerates
- But - does this mean safety?
- The view on health-related quality of life from parents and affected individuals differ

Retina International

Is it possible to ‘Prevent’ an IRD?

- Where a confirmatory Genetic Test is available it is possible to diagnose and understand how XLRP is likely to progre
- Early intervention has the potential to halt or slow down the degeneration of the retina, leading to longer life with visual function and functional vison resulting in changes that impact the course of a life.
- Preventing disease is a key pillar of national health care systems.

Patients living with XLRP are troubled by questioning the value of preventing a devastating genetic disease.

Retina International

Thank You.

Retina International

Outline

XLRP – What is it and what are its distinct properties?

Gene Therapies – Why may HTA be generally challenging?

Deep Dives – Broader Value & Discounting

Lessons learned elsewhere

Audience Poll

Selected Key Challenges and Considerations when Evaluating Gene Therapies

Simon Brassel
Principal Economist
OHE

Disclaimer

I am an employee of the Office of Health Economics, a registered charity and Independent Research Organisation, which receives funding from a variety of private and public sector sources.

XLRP – What is it and what are its distinct properties?

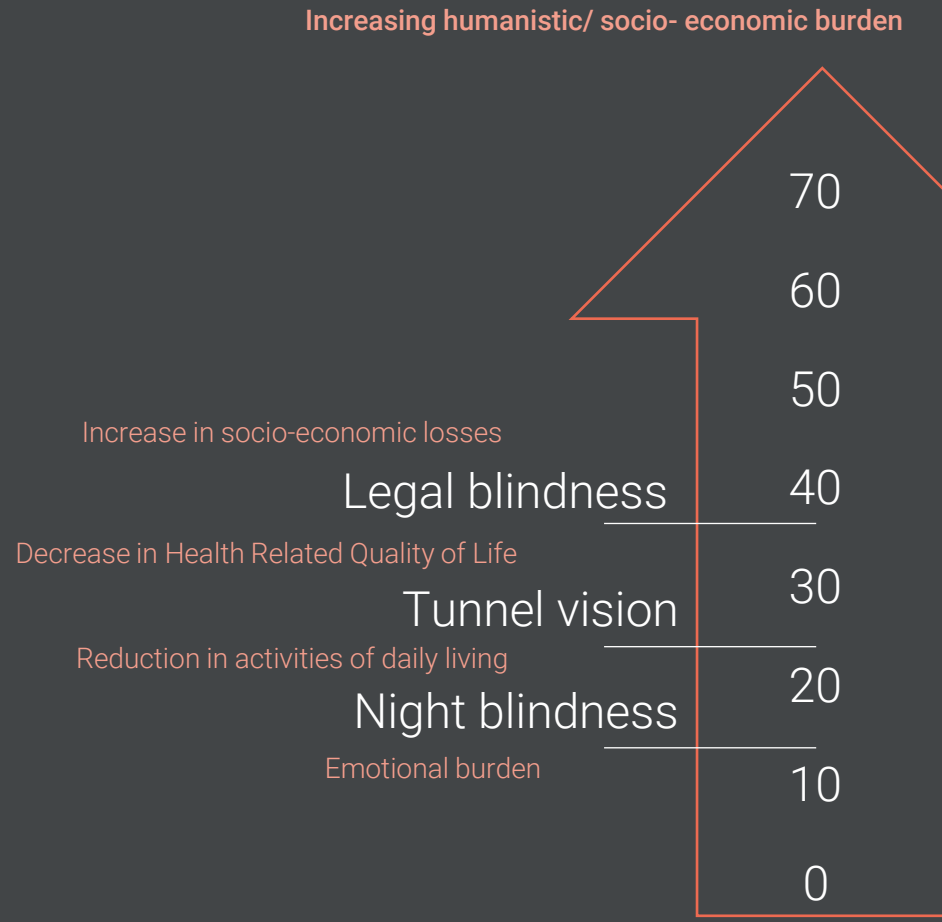
The distinct properties of X-linked retinitis pigmentosa (XLRP)

INCURABLE | RARE | CAUSES BLINDNESS

- ✓ Severe form of retinitis pigmentosa (RP), an inherited retinal degenerative disorder
- ✓ Affects ~ 1 in 15,000 people
- ✓ Defect in RPGR gene (located on the X-chromosome) causes retinal cells die over time, primarily in males
- ✓ Results in a progressive degeneration of the retina and consequent loss of vision

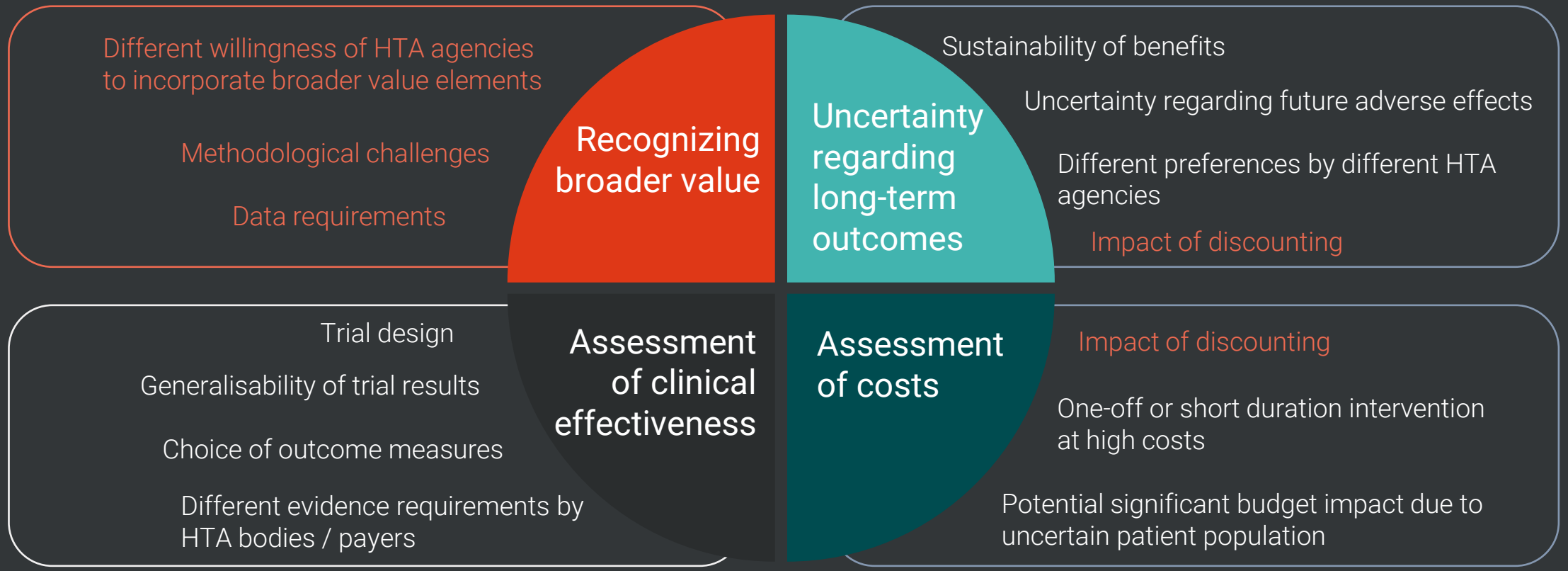
SLOWLY PROGRESSING | SIGNIFICANT HUMANISTIC AND SOCIO-ECONOMIC BURDEN

- ✓ First symptoms present itself in first decade of life
- ✓ Symptoms gradually worsen until subjects are declared legally blind in fourth decade of life



Gene Therapies – Why may HTA be generally challenging?

Overview of challenges for HTA of gene therapies

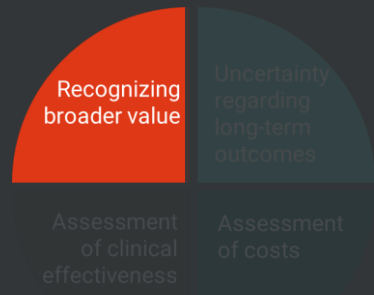


Adapted From: Besley et. Al (2022), Huygens et al. (2021), Drummond et al. (2019)

Deep Dives – Broader Value & Discounting

Deep Dive

Challenges in recognising the broader value of a gene therapy targeting XLRP



The Value Generation-Recognition Gap for Novel Gene Therapies in European HTA Systems using X-linked Retinitis Pigmentosa as a Case Study

OHE OFFICE OF HEALTH ECONOMICS janssen Johnson & Johnson

Jennifer Lee[1], Jake Hitch[2], Simon Brassel[2], Jacob Petersen[1], Tom Denee[3], Martina Garau[2], Lotte Steuten[2]

Table 2. Value generation-recognition gap for a gene therapy for XLRP

Country	Patient quality of life	Patient length of life[1]	Net health care costs[2]	Carer quality of life	Patient productivity	Carer productivity	Disease severity[3]	Insurance value	Scientific spillovers	Value of hope[4]
UK	◆◆◆			◆◆	◆◆◆	◆◆	◆◆	◆◆	◆	◆
Netherlands	◆◆◆			◆◆	◆◆◆	◆◆	◆◆	◆◆	◆	◆
France	◆◆◆			◆◆	◆◆◆	◆◆	◆◆	◆◆	◆	◆

Note: [1]XLRP has a limited impact on life expectancy (see table 1), [2]Uncertainty about pricing and long-term health service use by XLRP patients makes the impact on net costs too uncertain to assess its importance as a value driver/detractor, [3]The severity modifiers used by NICE and ZIN are both based partly on proportional QALY shortfall (PS) but there are no estimates of the PS for XLRP patients so it is unclear how the severity of XLRP would be operationalised if at all

Recommended for reference/base case economic evaluation

Recommended for sensitivity analysis

Not recommended in economic evaluation but could potentially be considered deliberatively

◆ The number of diamonds indicates the importance of each element as a value driver for an XLRP gene therapy. One, two, and three diamonds represent limited, moderate, and significant value drivers respectively.

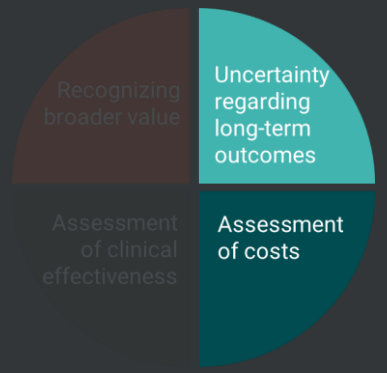
VALUE ELEMENTS INCONSISTENTLY CONSIDERED

- ✓ Potentially large losses in patient & carer productivity not captured with health system perspective
- ✓ Carer QoL losses often not captured and challenges who's QoL matters
- ✓ Unclear if existing mechanisms to capture severity of disease would be triggered

VALUE ELEMENTS RARELY, IF EVER CONSIDERED

- ✓ Potential insurance value due to genetic nature of disease
- ✓ Unclarity regarding scientific spillovers
- ✓ Debate around importance of value of hope (Peasgood et al. 2022)

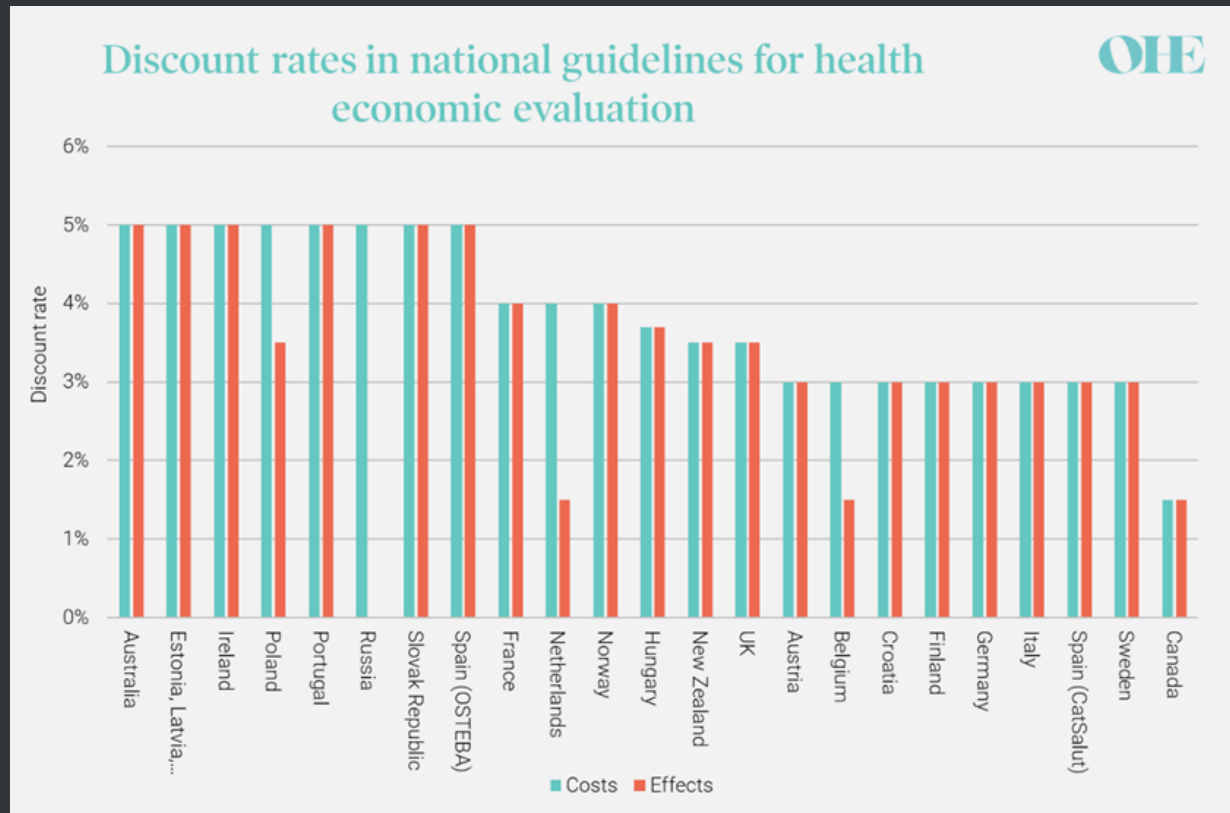
Deep Dive
The effect of discounting on a gene therapy targeting XLRP



- Large effect expected due to long delay between intervention and prevention of main outcome

- Experience Luxturna (Huygens et al. 2021):
  - NICE: lowering the discount rate from 3.5% to 1.5% reduced ICER by 43%.
  - ZIN: Using a discount rate of 4% for both costs and effects as opposed to 4% for costs and 1.5% for effects increases the ICER by 81%

- Alternative discounting approaches as solutions?
  - Equal vs. Differential
  - Constant vs. Stepwise vs. Hyperbolic vs. Time-shifted



Lessons learned elsewhere

Programme	Technologies	Relevance
Project Hercules • a **multinational collaboration** (e.g. patient organisations, clinicians, academics, pharmaceutical companies, Health Technology Assessment agencies) **to build a better evidence base** for Duchenne Muscular Dystrophy (DMD).	Multiple (must target) DMD	
Mechanism of Coordinated Access (MoCA) initiative ▪ a **mechanism** for European countries **to collaborate on access for patients** with rare diseases to OMPs via a voluntary, dialogue-based approach, with flexible interactions between key stakeholders to agree on the value of OMPs	Orphan Drugs	
HTA for Immunization Programs ▪ **Research** on pros and cons **for inclusion of broader value** ▪ **Impact of discounting** ▪ **Flexibility**	Vaccines	
NICE AMR Pilot • **Willingness** to (try to) assess different value elements • **Pragmatism** through deliberative decision making	Antibiotics	

It’s Time for a Poll!

WHERE DO YOU SEE THE BIGGEST CHALLENGES FOR THE VALUE ASSESSMENT OF GENE THERAPIES?

Advance to next slide for the poll

Are We Turning a Blind Eye? Challenges in Value Assessment of Gene Therapies for Inherited Retinal Disease

Industry perspective

Jennifer Lee, EMEA Therapeutic Area Market Access Leader, Immunology, Retina, Cardiovascular & Metabolism, and Value Optimizers

08 November 2022

Janssen Cardiovascular & Metabolism
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

What are the opportunities for gene therapies and how can we make gene therapies a reality in Europe and ensure patient access?

The opportunity of gene therapies

- Transformational field of therapy
- Paradigm shift for healthcare systems
- Impacts beyond direct health care system

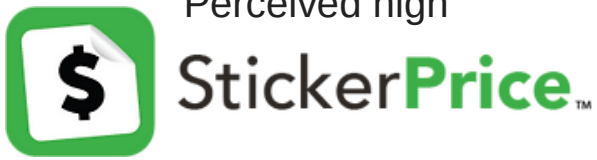
Making gene therapies a reality in Europe

- Policy frameworks and HTA methodologies to be updated
- New national and EU policy solutions
- Innovative approaches to reimbursement and payment models

Janssen Cardiovascular & Metabolism
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Multiple challenges exists in value assessment frameworks of gene therapies for inherited retinal diseases, including XLRP

Perceived high



..as it's a one-time treatment

How to demonstrate

QUALITY OF LIFE

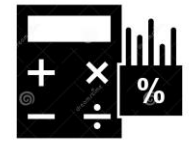
..as XLRP is slow progressing with little change expected; benefits are likely to be seen by carers

COST

QALY

Social care

Minor cost offsets in healthcare sector – mostly wider societal benefits



Discount Rate

Why discount benefits as the benefit increases with age?

Janssen Cardiovascular & Metabolism

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

But how can this be the case, when the goal is to stop people from losing their vision, even before they become symptomatic? Would society not value this goal?

Assessing patient QoL and carer QoL and carer costs for XLRP is challenging but is the key value element

Patient QoL

- XLRP is a slowly progressive disease
- Deteriorating visual impairment impacting daily life, increased risk of injuries
- Impact on educational, family and life planning

Carer QoL and carer costs

- XLRP impacts the QoL of carers, their earnings and productivity
- If child/adolescent with XLRP - large burden on parents and later a potential spouse

Assessing QoL

- Due to slow progress, patients attenuate to their condition
- Currently available general HRQoL measures are inadequately sensitive

Industry role

Develop new, adequately sensitive PROs including HRQoL measures in collaboration with patients, clinical experts, academia and regulators

If PROs including adequately sensitive HRQoL not timely available, generate utility data using robust study approaches

Life-long durability of effect of one-off gene therapies is challenging to demonstrate at launch

Patient access

- Patient access to a therapy benefitting patients, carers, healthcare systems, and broader society life-long

Further data collection

- Further RWD collection
- Long-term follow-up from trials continued

Optimize data-package at launch

- Natural history studies + long-term trial follow-up
- Develop and validate relevant surrogate endpoints

Clinical trial data

- Limited long-term clinical trial data in the younger, asymptomatic population at launch, given that regulators such as EMA require evidence of a treatment effect in the older, symptomatic population in order to achieve regulatory approval

A gene therapy for XLRP

- XLRP is a rare slow progressing disease with first visual impairment symptoms in childhood developing into legal and full blindness decades later

Conclusion

Durability of effect for gene therapies and acceptance of RWD

Discounting of particular importance for gene therapies

Value recognition gap in HTA

Holistic approach with a broad local societal perspective, including novel value elements

Deliberative & Flexible HTA processes that are fit for purpose

Patient QoL and Carer QoL

Patient access

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Challenges in Value Assessment of Gene Therapies for Inherited Retinal Disease

8 November 2022

Caroline Bregman

Senior Scientific Adviser

NICE Scientific Advice

NICE National Institute for Health and Care Excellence

Cell and gene therapies recommendations by NICE to date

Technology	NICE recommendations
Talimogene laherparepvec (Imlygic)	TA410: Recommended with PAS
Autologous human corneal epithelial cells containing stem cells (Holoclar)	TA467: Recommended with PAS
Autologous chondrocytes	TA477 & TA508: Recommended
Darvadstrocel (Alofisel)	TA556: Not recommended
Tisagenlecleucel (Kymriah)	TA554 & TA567: Recommended within the CDF
Axicabtagene ciloleucel (Yescarta)	TA559: Recommended within the CDF (review ongoing)
Autologous anti-CD19-transduced CD3+ cells (Tecartus)	TA677: Recommended within the CDF
Strimvelis	HST7: Recommended
Voretigene neparvovec (Luxturna)	HST11: Recommended with commercial arrangement
Onasemnogene abeparvovec (Zolgensma)	HST15: Recommended with managed access agreement
Atidarsagene autotemcel (Libmeldy)	HST18: Recommended with commercial arrangement

Challenges in ATMP evaluations

General uncertainty in the evidence

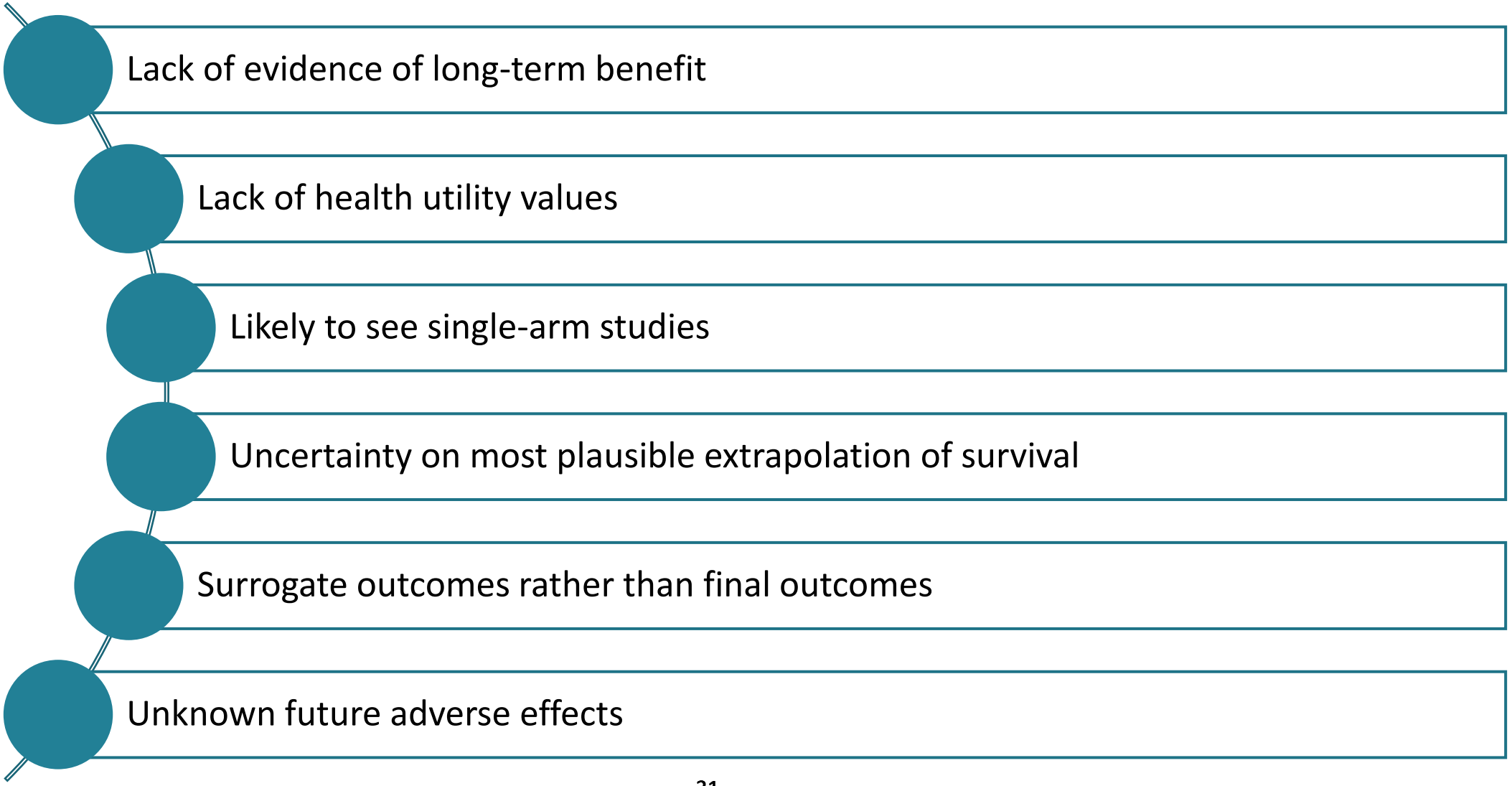
Costs of service delivery

Identifying the appropriate comparator

Concerns over adverse events

NICE

Evidence uncertainty in ATMP evaluations



NICE

How to address the challenges

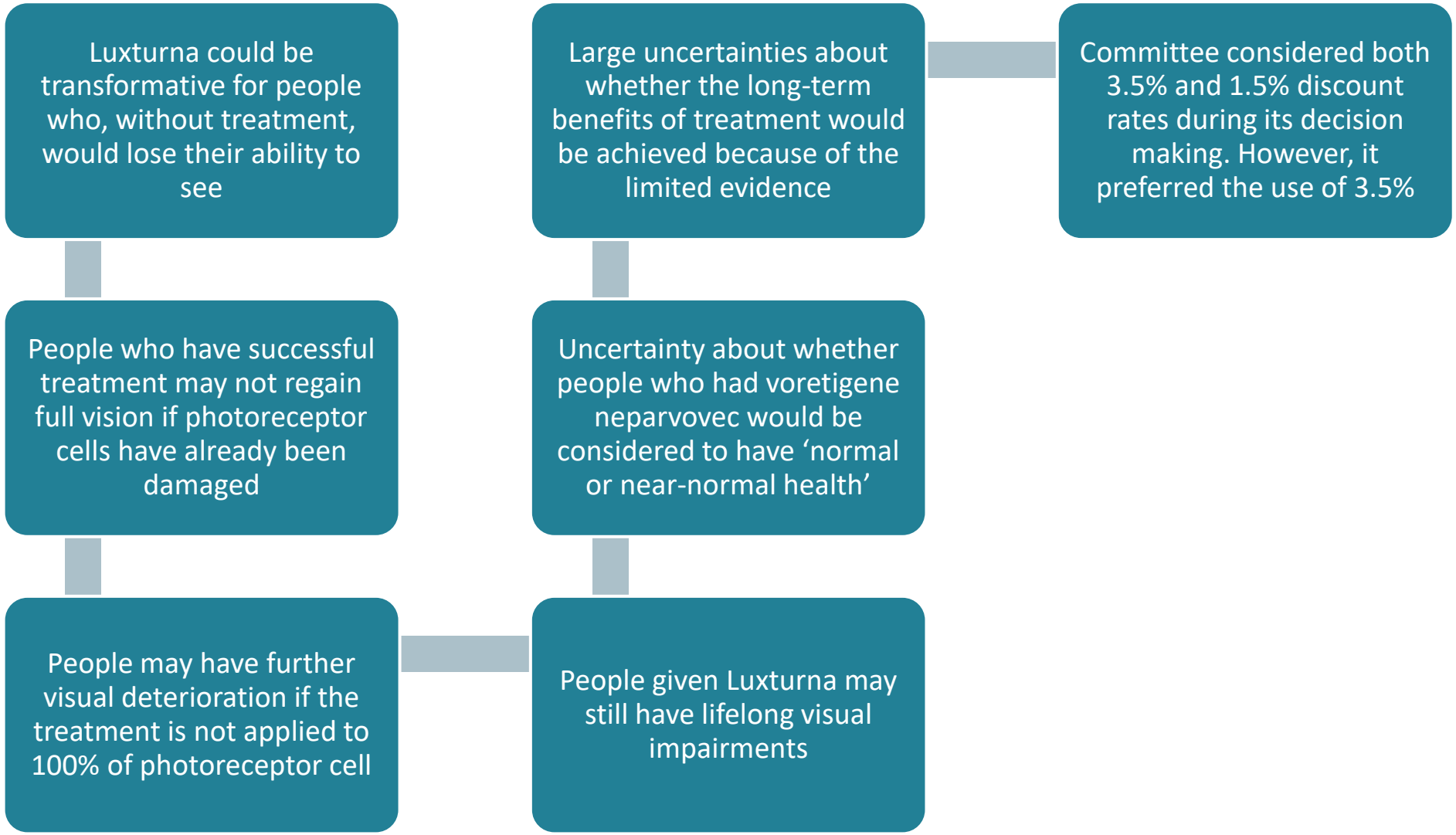
Methods review did not find features that are unique to ATMPs

But challenges are more commonly seen with these types of technologies

- **Changes in NICE's methods:**
  - Severity modifier
  - Better characterisation of uncertainty
  - Use of additional type of evidence beyond randomised controlled trial
  - Cure proportion modelling considered as an option
  - Apportioning costs

HST11: Voretigene neparvovec (Luxturna) for treating inherited retinal dystrophies caused by RPE65 gene mutations

HST11 Voretigene neparvovec: discount rate



Voretigene neparvovec: Other factors

Very large **emotional effect** of RPE65-mediated IRD on families and carers. It noted that there is a substantial financial impact on families in which parents have to give up work to provide care and because of the costs of home adaptation.

With sustained vision, children would be able to **attend mainstream school**, retain their independence, take part in social activities and achieve their full potential.

Treatment with Luxturna would **reduce the expenditure incurred by non-NHS government departments** that provide support for families affected by vision loss.

There was a **high unmet need** in people with RPE65-mediated IRD, and that Luxturna is a step change in the treatment of this condition.

Support initiatives for ATMPs

Accelerated Access Collaborative

- Unique partnership
- Designation supporting rapid national uptake

Innovative Licensing and Access Pathway (ILAP)

- Aims to accelerate the time to market, facilitating patient access to medicines

- NICE Scientific advice
- NICE Office for Market Access
- Patient engagement
- Managed access

NICE

It’s Time for a Poll!

WHERE DO YOU SEE THE BIGGEST OPPORTUNITIES IN OVERCOMING CHALLENGES FOR THE VALUE ASSESSMENT OF GENE THERAPIES?

Advance to next slide for the poll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Q&A