ISPOR Conference, Washington DC, USA, May 2022

Issue Panel Report

Are we capturing the multidimensional value of rare disease therapies through the QALY[1]?

Key points from panellists

- Alicia Granados - Rare diseases not only have small, heterogeneous populations but there is a paucity of clinical knowledge about optimal outcomes to study and high unmet need for effective treatment of severe conditions. This makes generation of evidence to inform cost utility analysis based on cost/QALY extremely challenging.

- Ariel Beresniak – The QALY requires a multiplicative calculation derived from multi-attribute utility theory that requires four key assumptions to be met, which have never been validated.

- Michael Drummond - The QALY is a useful measure to evaluate quality of life and survival, but other aspects of value may also be important for rare disease therapies. Aspects such as the severity of disease, insurance value, real option value and equity are particularly important.

- Sheela Upadhyaya - Cost/QALY can be a useful tool in appraisals, but flexibility is needed to account for severity of the disease and uncertainties that may arise due to the nature of the condition. Different types of evidence are needed to inform the determination of value of rare disease therapies and identify benefits not captured in the QALY.

- Durhane Wong-Rieger - To patients, the QALY seems like a tool to deny people living with rare diseases access to treatments. It was not designed for the case of rare diseases and in many cases the cost/QALY estimates are so far above traditional thresholds it is hard to see how commercial agreements will ever be made. So the QALY really impacts patients lives and a new approach is needed for rare disease treatments.

[1] Quality Adjusted Life Year

Contents

Glossary

HEOR	Health Economics and Outcomes Research
HSUV	Health State Utility Value
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
QALY	Quality Adjusted Life Year
QoL	Quality of Life
WDC	Washington DC
WTP	Willingness to Pay

About ISPOR

ISPOR was founded in 1995 and is the professional society for health economics and outcomes research. ISPOR is an international, multistakeholder, not-for-profit organisation dedicated to advancing health economics and outcomes research (HEOR) excellence to improve healthcare decisions. The Society is the leading source for scientific conferences, peer-reviewed and MEDLINE®-indexed publications, good practices guidance, education, and HEOR resources in the field. Its strategy is designed to improve the science, education, and global engagement of its members and the HEOR community through scientific and research excellence, member engagement, education and training, communication and collaboration, and organizational values.

An abstract for this Issue Panel was judged by reviewers from the ISPOR membership and selected for presentation at the US conference on 18 May 2022 as an in-person session.

Status of this report

This report has been prepared by Karen Facey PhD and approved by all presenters to become a public record. It presents each panellist's views, and the accuracy of statements are their responsibility. A consensus has not been developed as the purpose of this panel was to present and share different stakeholders' perspectives.

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Are we capturing the multidimensional value of rare disease therapies through the QALY?

1. Introduction

Alicia Granados MD, PhD: Global Scientific Advocacy Head, Medical Affairs - Rare Diseases, Sanofi

Dr Granados drew on her experience as a leader, of those using and doing HTA, in the Spanish and international health systems (World Health Organisation), and now industry, to give a personal perspective about whether the QALY captures the multi-dimensional value of rare disease therapies.

In the week prior to the panel session, Dusetzina published an article in the New England Journal of Medicine about the high cost of cancer drugs in the U.S. Medicare program, concluding that without access, even cures are ineffective. This is an important statement that all stakeholders need to consider, particularly for rare diseases.

Evidence generation and interpretation is challenging and complex in rare diseases, due to the nature of the diseases, which are mainly of genetic origin and that display substantial clinical heterogeneity in their presentation and progression – making choice of outcomes difficult, particularly when using standard statistical approaches. Traditional approaches force selection of a primary endpoint, "putting all the eggs of the analysis in one basket", thereby relegating other, potentially relevant endpoints, to secondary testing. Furthermore their low prevalence and sparse geographical distribution of patients means it is difficult to run clinical trials and include patients, as by definition the sample size is small. Thus the evidence generated is considered to be insufficient, or low quality, by some health systems to invest in new treatments.

Cost utility analyses based on determination of the Incremental Cost Effectiveness Ratio (ICER), or cost/Quality Adjusted Life-Year (QALY) are used by some decision makers. These analyses seek to measure the value for money of a rare disease therapy compared to the current standard of care. Recommendations are often made taking account of a willingness to pay (WTP) threshold that is aligned to the value of other therapies in the health service

The question for this panel is whether a QALY can capture all the aspects of value for a rare disease therapy.

The use of the QALY has been challenged by aspects ranging from equity and ethical issues to scientific validity. So, this panel includes key stakeholders who can explore the challenges of using the QALY to make decisions about the reimbursement of rare disease therapies. The barriers and enablers that could facilitate methodological alternatives or complementary sources of evidence in the decision-making processes will be also discussed.

Before their input, a polling question was used with the audience:
Are we capturing the multidimensional value of rare disease therapies through the QALY?

n=20, 75%=no, 15%=yes, 10%=unsure.

2. Analytical perspective – Is the QALY calculation valid?

Ariel Beresniak MD, MPH, PhD: CEO Data Mining International, Geneva, Switzerland

Dr Beresniak stressed that establishing the value of innovative treatments for rare diseases raises many issues; mainly as a result of the methodological limitations and challenges associated with generating reliable evidence from a small number of patients.

The main advantage of the QALY is its simplicity, and the main disadvantage of the QALY is its simplicity.

The QALY is based on a simple multiplicative formula of the time multiplied by the utility. So, 2 years * 1 utility is considered the same as 4 years * 0.5 utility. If we apply that analogy to cooking a steak on the barbecue, will the steak taste the same if we grill the steak for 3 minutes at 200C vs grilling it for 6 minutes at 100C?

The calculation of the QALY could lead to divergent results from identical databases depending on the choice of units. For example, consider the situation where QALYs are used to determine the location of the next ISPOR meeting. There is a choice of two days in Washington DC (WDC) or one day in Miami and we value warm temperatures. This shows how ISPOR offices in Europe, basing their calculations on Centigrade would make different conclusions to those in the US offices using Fahrenheit.

QALY = Time x Temp (°C)

- WDC 2 days x 5 °C = 10 QALY
- MIAMI 1 day x 25 °C = 25 QALY

MIAMI is the best location (more than double the QALYs)

QALY = Time x Temp (°F)

- WDC 2 days x 41 °F (= 5 °C) = 82 QALY
- MIAMI 1 day x 77 °F (=25 °C) = 77 QALY

WASHINGTON DC is the best location

This is a counter example of the theory and Karl Popper, the famous philosopher of scientific reasoning argued that if you find one counter example of a theory, it destroys that theory.

The QALY is derived from multi-attribute utility theory and requires four key underlying assumptions (hypotheses) to be met, as outlined by Pliskin et al. (1980)[2].

Hypothesis H1: The preferences of an agent are expressed by Standard Gamble with interval utility.
Hypothesis H2: Z and T are mutually independent utilities.
Hypothesis H3: The agent is only slightly neutral to risk in probabilities on standard gambles where lots belong to T.
Hypothesis H4: The agent's time-trade-off rate g is constant.

So, before using the QALY to inform decision-making these assumptions should be tested to ensure they are valid, but this is never done in practice.

[2] Pliskin JS, Shepard DS, Weinstein MC. Utility functions for life, years and health status. Oper Res. 1980;206–23.

The European Commission funded FP7 research project, ECHOUTCOME, tested the scientific validity of these four QALY assumptions using mathematical and experimental explorations. A survey of 1361 subjects in four countries found that not one assumption (hypothesis) required for the QALY was validated. Hence it concluded that the QALY formula is not scientifically valid and can lead to divergent results from the same data (Beresniak, 2014) and so alternative robust HTA methodologies are needed to assist decision-making.

In terms of rare diseases, according to the EU definition of <5/10,000, there are more than 7,000 rare diseases, which affect 4% of the population worldwide. More than 80% of rare diseases are of genetic origin, 75% occur in children and they contribute to 30% of childhood deaths. So if we really intend to use a QALY to assess the value of rare disease therapies, there are a range of challenges in addition to the general concerns about the methodological limitations of the QALY formula.

- Poor sensitivity of generic patient-reported outcomes (PROs) such as EQ5D in rare diseases
- Survival criteria are difficult to assess in chronic rare diseases that do not cause early death
- There are challenges in capturing PROs in children, so this raises ethical issues.

The main defence for use of the QALY is that it is not perfect, but it is "useful"…

However, consider this argument in relation to an aeroplane. Would you accept to fly in a plane that does not have a perfect altimeter over the Swiss Alps? Would you risk your life? This is relevant because when QALYs are used to evaluate treatments, they can impact the lives of patients.

Robust alternative approaches for establishing the value of rare disease therapies are:

- Cost-effectiveness analyses (cost per clinical outcome) – although such analyses do not enable cross disease comparison, these could be explored in epidemiological analyses
- Cost-benefit analyses (cost by complication avoided)
- Small sample effectiveness analyses
- Resampling (Jackknife, Bootstrap)
- Bayesian analyses
- Non-parametric (distribution free) statistical tests
- Burden of disease studies
- Multi-criteria analyses – allowing qualitative and quantitative analyses (responder / non responder profiles)
- Budget impact simulations.

Q: If there is such a strong scientific argument to challenge the use of the QALY, why do you think it is still being used?

The QALY was first used in Australia about 30 years ago, so decision makers are familiar with it, and it is simple to use. Furthermore, as different results can be obtained from the same inputs, it is easy to manipulate results for supporting any point of view in the frame of pricing/reimbursement negotiations. The QALY could be considered as a toy for the "watchdog" of the healthcare system and if you take it back the watchdog might bite.

3. Economic perspective – Does the QALY reflect all the relevant aspects of value?

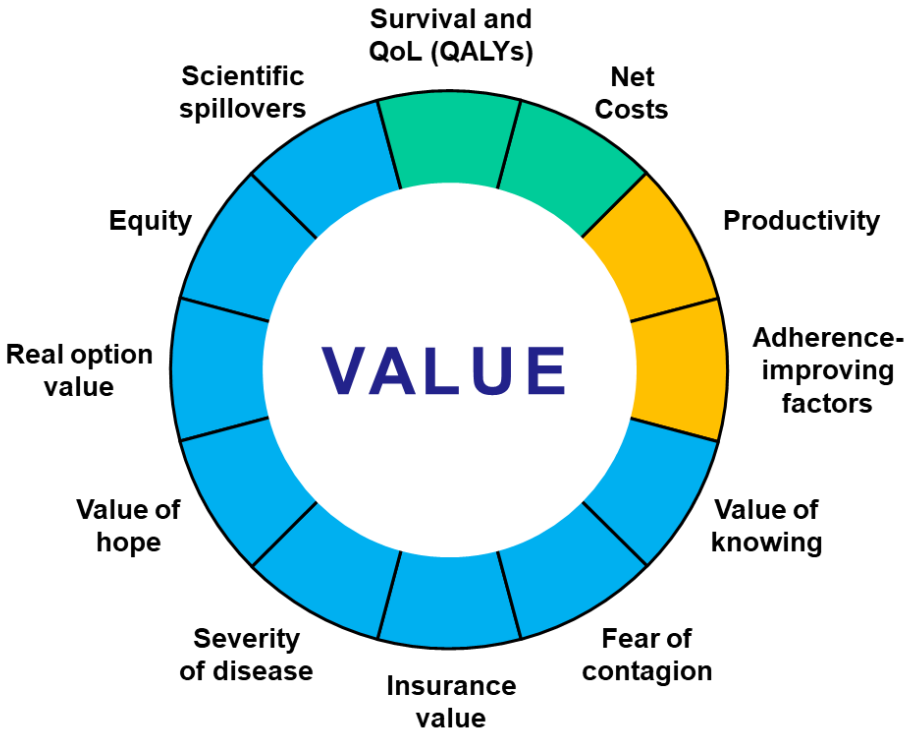
Michael Drummond, PhD: Professor of Health Economics, University of York, England and Bocconi University, Italy.

Professor Drummond, noted that Dr Beresniak had discussed some of the problems associated with the internal validity of QALYs, this presentation would consider some of the problems associated with external validity.

The ISPOR Taskforce report "Defining Elements of Value in Health Care - A Health Economics Approach" depicted the elements of value that may be considered from a payer or health plan perspective. This "flower of value" was adapted in Drummond et al.'s paper exploring the analytic considerations associated with applying an economic evaluation reference case to gene therapy.

Elements of Value according to ISPOR Task Force
Drummond M, et al. Value Health. 2019;22(6):661–668.

Figure adapted from Lakdawalla DN, et al. Value Health 2018;21:131–139



- Core elements of value
- Common but inconsistently used elements of value
- Potential novel elements of value

The figure shows that most payers/decision-makers consider survival and quality of life, alongside net costs of treatments (including savings). Some may also consider productivity and factors that improve adherence to therapy (such as improved route of administration if that may improve quality of life or survival). However, the flower shows that there are a range of other factors that could contribute to how a healthcare intervention is valued.

For example, a treatment which treats a severe disease may be valued more highly than one that treats a mild disease. Some other aspects of the value flower are more contentious, such as the value of hope and insurance value.

So, there are a range of relevant factors that could contribute to a choice in healthcare and, taking Dr Beresniak's example, you may choose Miami as the meeting destination if you value beaches, but Washington if you value museums, and neither of those is related to the main purpose of the meeting. Considering the value flower, other elements that seem of most relevance for rare disease therapies are considered in the following table.

Severity of disease	♣ There is some evidence that society places a higher value on health gains for people with serious illnesses. ♣ Most rare diseases are severe, and we know that some HTA bodies take this into account.
Insurance value	♣ Individuals place a high value on therapies being available for potentially catastrophic illnesses, even though it is not likely they would need them. ♣ For example, grandparents may value treatments of diseases that lead to death in childhood, if their children are of child-bearing potential.
Real option value	♣ Some therapies may provide a bridge until better therapies are available. ♣ For example, the value of a last line cancer treatment may appear to be small, but it could extend the patient's life long enough to give them the opportunity to receive a newly developed treatment in future.
Equity	♣ Society may be willing to pay more for a therapy that will treat a group of people that are not well served by current treatments. ♣ There are 1000s of rare diseases that have no disease specific treatments and rely on best supportive care.

Such a broader value framework (beyond survival and quality of life) would need to be applied consistently across all health technologies (not just rare disease therapies), but it is likely that many of these aspects will affect the valuation of rare diseases to a greater extent than that for more prevalent diseases.

Moving to other considerations of external validity. It is important to consider how QALYs play out when used to inform appraisals of rare disease treatments.

Bocconi University led work in the EC-funded IMPACT HTA project Work Package 10 to develop an appraisal framework suitable for rare disease treatments. One workstream evaluated issues related to use of PRO measures (PROMs) to determine quality of life in considerations of added benefit and development of health state utility values (HSUVs) for economic models.

One study by Nicod et al. (2021) reviewed all NICE appraisals of rare disease treatments (in the Technology Appraisal and Highly Specialised Technologies programmes) that were not related to cancer. Six of the 24 appraisals did not include any kind of PROM. HSUVs were derived through data collection (7/24 cases), mapping from another QoL measure (6/24), vignettes (5/24), published literature or other methods (6/24), with some using a combination of methods. In only four cases were EQ-5D data generated alongside clinical trials, which would be regarded as the gold standard approach by many. Few of the measures

demonstrated significant changes, due to lack of sensitivity, lack of face validity, short-term data, or implausible health states. Similar problems were observed with generic or disease group PROMs. So even though it is important to evaluate QoL in rare diseases, it is challenging.

These findings were compared with appraisal reports available for these 24 rare disease treatments in three other countries. This found that 61% of the reports from France and 16% of reports from Germany did not include any discussion of QoL evidence, despite their systems focusing on the determination of added therapeutic benefit. Meanwhile in the Netherlands, where there is evaluation of cost effectiveness, 38% of the reports did not include QoL evidence. When QoL data were reported, they were deemed inconclusive. The main reasons for this were that no statistically significant differences were determined, the evidence was considered explanatory, QoL was a secondary endpoint, the PROM was not validated or considered clinically relevant.

This shows that the QoL data submitted to support demonstration of value for RDT were not considered relevant or did not demonstrate any effect, not only in England (when using QALYs), but in other HTA systems with different approaches for assessing the value of treatments.

Q: The understanding of evidence in the field of rare diseases is complex. What other arguments, methods or tools could we use?

The health systems that seem to take a broader view of value, considering some of the other elements of the ISPOR flower are those that have some form of supplementary process. We need to explore the issues of equity more and whether we should do more for those who are unfortunate. Would we give a premium to those who have a catastrophic illness? Governments have focused on about socio-economic equity (e.g. due to deprivation), but some of the other aspects of value outlined in the value flower need to be considered. This requires a shift from horizontal equity (treating everyone the same) and vertical equity (treating unequal's, unequally – e.g. rare diseases).

4. HTA perspective – The use of the QALY in appraisal deliberations

Sheela Upadhyaya: Rare Disease and Rapid C-19 Strategic Adviser, National Institute for Health and Care Excellence (NICE), England.

Mrs Upadhyaya presented the impact of the recent changes to NICE methods and process for technology appraisals as outlined in *NICE health technology evaluations: the manual, January 2022* (the Manual) that might be of particular relevance to determining the value of rare disease therapies. These changes have been developed with extensive work across a range of taskforces over several years and cover all forms of technologies – both medicines and devices, for diseases of all prevalence. However, during this process, the issues faced in determining the value of rare disease therapies has been raised and in particular the challenges of using the QALY to demonstrate patient benefit.

The key aspects of the recent changes that are of most relevance to appraisal of rare disease therapies are shown in the following diagram.

Severity of disease	**Consideration of different types of evidence**	**Flexibility to accept uncertainty in specific situations**	**Commercial and Managed Access**
Calculation of future health lost by patients on standard care, by evaluation of QALY shortfall Resulting in weighting of up to 1.7x	Emphasis on a comprehensive evidence base, including real-world, qualitative, and expert elicitation	NICE appraisal committees will have flexibility where there is still some uncertainty because of challenges in collecting evidence to recommend technologies for children, or when they are highly innovative or complex	NICE appraisal committees can recommend managed access where significant uncertainties exist that can feasibly be resolved by data collection

The severity decision modifier has replaced the end of life modifier, and this will give appraisal committees additional quantitative evidence to consider as part of their deliberation.

In addition, the new methods guidance emphasizes the potential for consideration of other forms of evidence beyond that used in a traditional QALY calculation to better understand the nature of the condition and treatment impacts. So this could answer the moderator's last question. For example, the methods now include more guidance about when vignettes could be used, when expert elicitation could be used etc.

Rare diseases come with a wide range of uncertainties because most have childhood onset and historically children did not live long enough to achieve long term outcomes. The Manual clearly characterizes different forms of uncertainty that arise in appraisal and deliberative appraisal processes, with recognition that some are particularly challenging for rare diseases.

All NICE appraisal committees can now make a recommendation for additional data collection to provide a bridge for patient access whilst seeking to resolve important uncertainties through a Managed Access Agreement. This requires negotiation on the commercial arrangements and a structured approach to real-world data collection to inform a re-appraisal of value at the end of the agreement.

The Manual states clearly that appraisals are based on evaluations of clinical effectiveness and value for money. However it also states that degree of need and desirability to promote innovation need to be taken. These are particularly important for rare diseases. Furthermore, appraisal committee recommendations must consider the health system's obligations for equality and human rights, which are highly relevant for people living with rare diseases. Committees can also consider broader social considerations, uncaptured benefits (particularly as described by clinicians and patients) and costs/benefits outside health. So all these are areas that can bring flexibilities into the deliberation of the appraisal committee, rather than strict application of WTP threshold.

Looking at the ISPOR flower, NICE is trying to improve its consideration of severity and equity. But other elements of value need to be set in the context of the whole health system, where there is a fixed health budget. If that budget was to expand it would encroach on budgets that affect other provisions in society, such as education or policing.

The new NICE methods and processes for appraisal were launched in February 2022 and are being implemented for scoping new appraisals. As they are implemented, they will be reviewed to explore their impacts and feedback will be sought from stakeholders to improve processes. There has also been a commitment for modular updates to take account of new situations and developments. Potential topics for update include:

- processes to facilitate rapid entry to a Managed Access Agreement
- managing technologies with multiple indications
- appraisal processes for digital, genomic and antimicrobial technologies
- methodological updates, such as consideration of the societal value of health benefits in severe diseases and health inequalities.

Mrs Upadhyaya noted that her personal view was that the QALY should be used as a tool not a rule. There needs to be clear understanding of where the QALY falls short (uncaptured benefits) within a well-structured decision making framework that aids committee members to develop their recommendations with flexibility and transparency. To achieve this, comprehensive evidence to support all decision making domains is needed that includes broader social considerations.

5. Patients' perspectives – The impact of the QALY on patient lives

Durhane Wong-Rieger, PhD: President and CEO, Canadian Organization for Rare Disorders, Canada.

Dr Wong-Rieger began by stating patients' views that the QALY has never captured the multi-dimensional value of rare disease treatments. QALYs are useless for most therapeutic assessments. Mrs Upadhyaya suggested they are a starting point, but a starting point for what?

The QALY was never designed for rare diseases, it was designed to compare a new therapy with an existing therapy to show incremental benefit. However, for most rare diseases there are no existing therapies. In rare diseases a new treatment is often high cost due to the complexities of development and when that is compared to best supportive care, the differential cost is high, so it is hard to prove value for money.

The QALY can be seen as an economic tool, or a political tool but to patients it feels like it is an easy way to say no, because a health budget might be overwhelmed. It is important to consider the impact of using the QALY on patients, particularly those with rare, severe, progressive diseases that have no other alternative therapies as shown in the following three cases.

"Catch-22" for a patient with atypical hemolytic uremic syndrome (aHUS) and one transplanted kidney

- 2006: Failed kidney transplant; rare disorder (aHUS) destroys RBCs.
  - Second transplant failed
- 2013: Soliris® given regulatory approval but as it's a very rare disease, trials are small, so not recommended by CADTH due to insufficient evidence of clinical and cost effectiveness. ICER = Ca$940,084/QALY (compared to standard threshold of CA$50,000)
- 2016: Funding approved for Soliris, only in patients without transplant.
- Surgeon will not transplant unless patient receives Soliris.
- 2019: Patient gets approval for Soliris and gets on transplant list
- 2021: Patient gets transplant and Soliris.
- 2022: Patient continued access not guaranteed due to mandatory 6-month reviews.

Dimensions of value
Disease: Rarity, severity, identifiability, life-threatening, health distribution, alternatives
Treatment: Efficacy, magnitude of benefit, safety profile, innovation profile, societal impact, distribution of health
Population: Societal impact, distribution of health, socio-economic policy
Socioeconomic: Societal impact, distribution of health, socio-economic policy, industrial and commercial policy, legal
Other: Diagnosis feasibility, treatment provision, cost-effectiveness

12-year seeking access to cystic fibrosis treatment

Kalydeco®
2013 Works well for a small number of cystic fibrosis patients with specific G551D mutation; but there were major uncertainties and very high ICER of $2 - $9 million/QALY.
2014 CF additional mutations; ICER = $850,932 - $1.2 million/QALY.
There was a belief that it worked well, and committees indicated that they wanted to say yes, but it costs too much and a need for commercial negotiations. However, those negotiations take time and patients with cystic fibrosis may not survive that long.
Trikafta®
For this combination treatment, coverage of the population was much wider, thus increasing budget impact, but uncertainties, particularly in long-term outcomes remained.
Submitted ICER vs. BSC = $358,597/QALY - $531-195/QALY
CADTH reassess: ICER vs. BSC = 1,1067,215/QALY - $1,911,977/QALY

Patient Priorities

- ♥ Access to (individually) necessary medicines/devices
- ♥ Timely access to "more effective and safer"
- ♥ Participation in clinical trials (access, experience)
- ♥ Affordable access (co-pays)
- ♥ Trusted oversight
- ♥ Urgently needed HTs (diagnosis, life-threatening, severe, emergency conditions) with "early stage" therapies and on-going monitoring

Spinal Muscular Atrophy (SMA) – those left behind

Type 1 SMA is a devastating disease in babies. By the age of 6 months they may be unable to roll over, have a feeding tube, they are likely to need a wheelchair, and most will die by the age of 6 years old. SMA can also be a slowly progressive disease with muscular disabilities that occur in mid adulthood.

Spinraza® was approved for patients under 18, due to lack of controlled trials and data in older age groups.
Consider the case of the woman with SMA, who works as a spinal cord social worker and who is not deemed to have severe disease because it is slowly progressing. Her disease is progressing to the point where she cannot walk unaided, cannot roll over in bed. She is not eligible to receive Spinraza® in Canada. However, it would be available to her in England, where access has been granted subject to collection of real-world data. Instead, Canada requires clinical trials that are going to be impossible to do based on small numbers, challenges of recruitment, long timeframe needed to demonstrate outcomes, and the fact that other countries are approving on basis of RWD collected.

Submitted ICER
SMA1 $665,570/QALY; SMA2 $2.1 million/QALY; SMA3 $2.9 million/QALY
HTA Committee (CDR) ICER
SMA1 $9.2 million/QALY; SMA2 $24.4 million/QALY; SMA3 $7.4 million/QALY (WTP=$50,000)

Zolgensma® : Is a one-off gene therapy that is hoped to be curative.
ICER = $334,040/QALY. Would require a price reduction of 90% to make it cost effective against standard threshold. Approved only for children aged 6 months or younger.
Consider this case of twins, who were not diagnosed in newborn screening, and living in a rural area they did not receive their SMA diagnosis until they were 18 months old so were not eligible for treatment with Zolgensma®. They received Spinraza® but would prefer to receive the gene therapy given the challenges associated with the intrathecal injection and hope of cure. Furthermore, the saving associated with not having to administer nusinersen would mean the funding for Zolgensma® would be recouped within 10 years.
Eventually a clinical trial was found that would provide Zolgensma®, but only one child was granted access. The treating clinician argued that this was unethical, and the child was given the therapy in compassionate access.

These and other patients' experiences show that the QALY is not fit-for decision-making purposes and does not capture the multi-dimensional value of treatments for people living with rare diseases. Furthermore, many disease-specific PROMs don't capture value adequately, either. So, if we want to make sure every patient has a fair chance, we must come up with something different, which is based on the patient's real-world experience and outcomes.

6. Discussion

Dr Granados thanked the panelists and invited questions from the audience.

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Dr Granados reflected that she had heard about methodological issues, budget issues and moral issues with the use of the QALY but questioned why there is so much scrutiny on the 20% of the healthcare budget relating to medicines, of which only 1.4% is for rare diseases, when 80% of healthcare expenditure is not reviewed (OECD, 2015).

Professor Drummond outlined that money spent on healthcare needs some sort of scrutiny to support health system sustainability. A range of mechanisms are used to improve in health system efficiency. For example, in hospitals tariffs relating to Diagnosis Related Groups are used, but HTA is a good system for determining whether good value for money is being achieved with health technologies.

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Dr Deborah Marshall, University of Calgary, Canada, asked why an appraisal approach beyond the cost/QALY should only be used for rare disease therapies (however we define rare, or ultra-rare)? Do we need a separate value flower for each type of condition?

Mrs Upadhyaya indicated that the challenges seen in rare diseases push us to think differently about methodologies that might work better. This can provide a test bed that is rolled out for other situations.

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