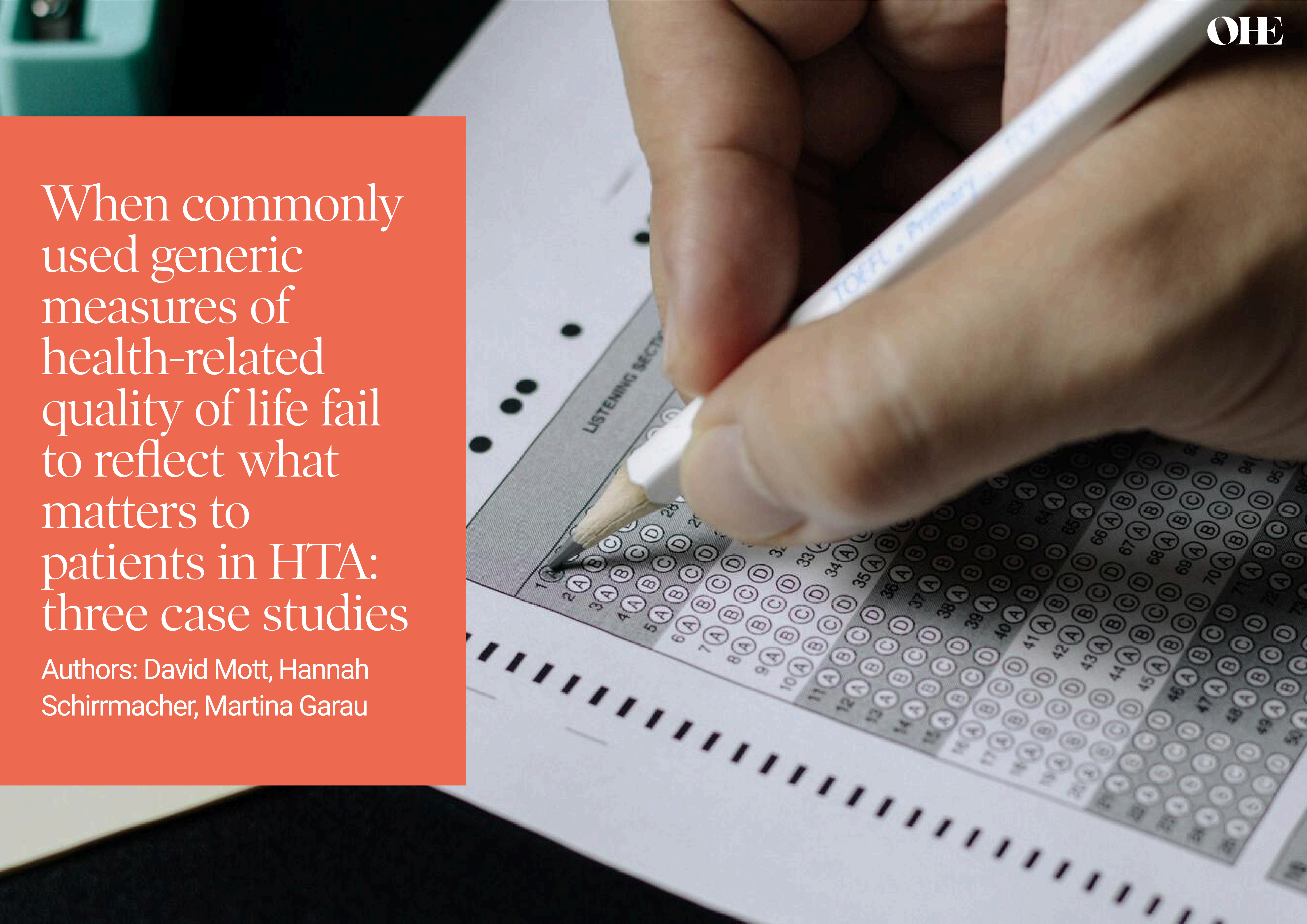

When commonly used generic measures of health-related quality of life fail to reflect what matters to patients in HTA: three case studies

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Introduction

Generic preference-based measures are often used for capturing patients' health-related quality of life (QOL) to assess quality-adjusted life years (QALYs) in health technology assessment (HTA), which informs coverage/reimbursement decisions.

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These measures – the most commonly used of which is the EQ-5D – seek to provide an overall picture of the patient's QOL and are applied across all health conditions. EQ-5D instruments capture five dimensions of health:

- Mobility
- Self-care
- Usual activities
- Pain/discomfort
- Anxiety/depression

Generic measures can be useful in certain contexts for comparing QOL across different health conditions. However, generic preference-based measures do not always capture all the dimensions of QOL that are important to patients. An earlier OHE report provides an overview of QOL measures, their advantages and limitations.

This interactive summary report provides three case studies exploring examples of health conditions where the EQ-5D has been shown to, or is likely to, perform sub-optimally in reflecting the dimensions of QOL that matter to patients.

This report focuses on the measurement of QOL specifically, and therefore does not consider broader outcomes (e.g., wellbeing) or broader elements of value that are of relevance to patients (e.g., spill over effects, productivity impacts, the value of hope).

Case Study One

Multiple Sclerosis

THE CONDITION

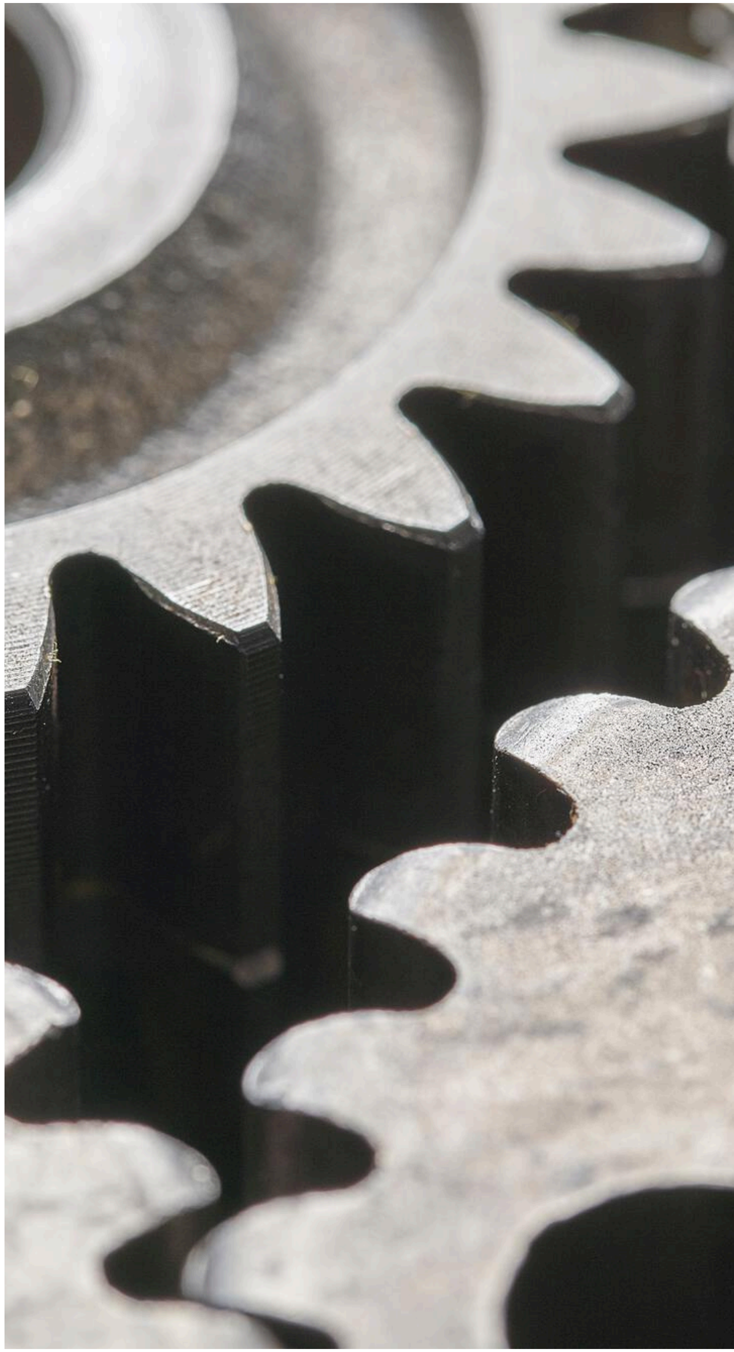
- Multiple sclerosis (MS) is a chronic, neurological disease that significantly impacts patients' level of functioning.
- In 2017, up to 913,925 people (362.6 per 100,000 population) were estimated to live with MS in the United States.
- Patients with MS experience various symptoms including visual impairment, bladder dysfunction, depression, fatigue, movement disorders, and cognitive impairment. Of these symptoms cognitive difficulties, and fatigue are believed to be among the most common.
- In addition, patients' symptoms and functioning are unpredictable and can fluctuate over time.
- There are currently several disease-modifying treatments available for the treatment of MS as well as a range of treatments to manage symptoms. However, while there are a range of treatment options, each with their own benefits and drawbacks that each patient must consider, there is still no cure for MS.

IMPORTANT DIMENSIONS OF HEALTH THAT MIGHT BE MISSED BY EQ-5D

- Fatigue
- Vision
- Bladder dysfunction
- Cognition

EQ-5D PERFORMANCE IN PEOPLE WITH MS

- The EQ-5D may fail to reflect the entirety of QOL in MS by not including domains such as fatigue and cognition.
- However, evidence in people with MS suggests that fatigue and cognition are correlated with other EQ-5D domains, such as usual activities and anxiety/depression. Therefore, EQ-5D may indirectly capture some of the impacts of fatigue and cognition. However, separate fatigue or cognition dimensions would likely be needed to capture the impacts adequately.
- Furthermore, it has previously been suggested that the EQ-5D inadequately captures elements of sensory deprivation, including vision and other aspects of QOL, such as bladder problems, tingling/numbness and balance/dizziness, all of which are relevant for people with MS.
- The EQ-5D has also been shown to be unable to differentiate between patients who are mildly and moderately disabled, suggesting that EQ-5D might not accurately represent the QOL of people with MS.
- Furthermore, a tendency for people with MS to report no problems – known as ceiling effects – was identified on the mobility and self-care items of the EQ-5D.



CAPTURING CHANGES IN QOL OVER TIME

- People with MS experience fluctuations in their symptoms, with moment-to-moment fluctuations as well as longer-term, weekly, and monthly changes possible.

- When people complete questionnaires about their QOL, they are expected to adhere to the 'recall period' used in the questionnaire. The recall period is the time period that they are asked to consider when assessing their QOL. For example, the EQ-5D asks respondents to assess their health 'today'.

- It has been suggested that short recall periods, such as EQ-5D's, could result in changes in QOL being missed if the patient is not experiencing symptoms in that particular time period, which may be the case with MS where symptoms fluctuate.

- To deal with this issue, a recent study developed an 'ambulatory assessment' version of the EQ-5D where MS patients rate their health on mobile devices three times a day over the course of a week.

- The ambulatory assessment version was found to be effective in capturing within-day and day-to-day health fluctuations (i.e., improved responsiveness), providing important information beyond that which would be captured with the standard questionnaire. However, this version of the EQ-5D has not yet been adopted by decision makers.

ASSESSMENT OF MS TREATMENTS IN PRACTICE

- In the UK, NICE has conducted thirteen technology appraisals for MS treatments. The potential limitations of using EQ-5D in the context of MS were recently acknowledged during the NICE methods review.
- In a recent NICE appraisal for an MS treatment, the committee acknowledged that improvements in cognitive processing might not be fully captured by the EQ-5D. Failing to capture the full benefits of treatments in this way could contribute to negative funding decisions.
- In the US, two assessments for MS treatments have been made by ICER. In the first assessment the MS Coalition, comprised of nine patient advocacy groups, noted that the utilities used "may not be as generalisable as might be desired".
- As EQ-5D data are typically used in HTA, despite the evidence of its flaws in this population, it could be argued that many past appraisals/assessments have failed to capture the full range of outcomes that matter to people with MS in QALY calculations.

Case Study Two

Alzheimer’s Disease

THE CONDITION

- Alzheimer’s disease (AD) is a progressive, neurological disease that causes damage to the brain.
- Dementia is a general term for a decline in mental ability and develops because of damage to the brain by diseases such as AD.
- Symptoms of AD include memory loss and problems with thinking, problem-solving, or language. Patients may also suffer from changes in mood, such as becoming anxious or depressed. These symptoms are mild to begin with, but get worse over time.
- An estimated 6.2 million people aged 65 and older were living with AD in the United States in 2021.

IMPORTANT DIMENSIONS OF HEALTH THAT MIGHT BE MISSED BY EQ-5D

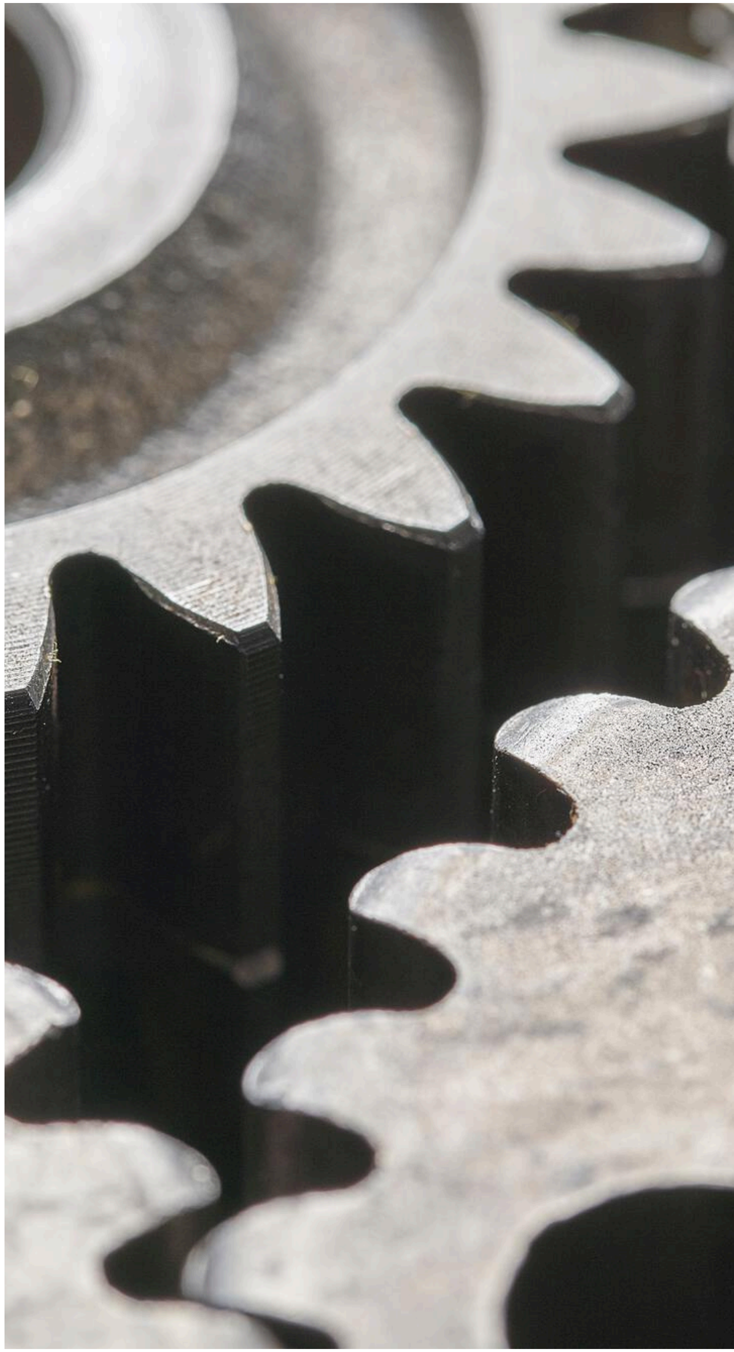
- Memory loss
- Cognition (problems with thinking, problem-solving, or language)
- Fatigue
- Incontinence
- Hearing problems

EQ-5D PERFORMANCE IN PEOPLE WITH DEMENTIA

- Concerns have been raised about the applicability of EQ-5D in this population (i.e., some evidence suggests that the measure lacks 'content validity'). For example, it has been suggested by both patients and carers that other dimensions of health that are not included as dimensions in EQ-5D (such as those listed in the previous section) are relevant in this context.

- Condition-specific measures have been designed that focus more specifically on outcomes that are important to people with Alzheimer's disease, such as QOL-AD. EQ-5D responses have been shown to be correlated with QOL-AD scores, indicating that EQ-5D does, to some extent, capture outcomes important to patients.

- However, EQ-5D has been shown to suffer from ceiling effects in this population. A ceiling effect is where respondents report that they have no health problems, even though they are suffering from a health condition. Improvements in health from new treatments cannot be captured if people report that they have no problems prior to receiving treatment. Thus, ceiling effects can make new treatments appear less effective.



PROXY RATINGS AND CARER QOL

- For people with more severe dementia, particularly individuals limited in their ability to make judgements and give accurate responses, a proxy, such as a carer, may be asked to complete the EQ-5D on their behalf. Proxy versions of EQ-5D questionnaires are available, which contain the same five dimensions as in the self-complete versions.

- On the one hand, the use of a proxy respondent may be helpful in avoiding some of the issues caused by self-reporting, e.g., ceiling effects that could be caused by patients perceiving their wellbeing as higher than those around them do.

- However, given the nature of the generic measures, proxy respondents are typically required to assess some unobservable aspects of the patient's health, such as their level of pain, discomfort, anxiety, and depression. Therefore, carers may be unable to accurately capture an individual's QOL across these items, and the validity of the proxy assessment may therefore be questioned.

- Several studies have assessed the reliability of the EQ-5D between respondents assessing the same individual, finding that patients typically provide higher ratings compared to their carers and that this is most evident on unobservable dimensions. More recently, a systematic review concluded that this type of reliability was moderate for EQ-5D in dementia, and that this was also the case for a range of other generic preference-based instruments.

- Furthermore, caring for patients with AD can have a significant impact on the QOL of a carer. Carer QOL can be measured using similar instruments to those used to capture patient QOL. However, one study found that EQ-5D may not be the optimal way to measure the QOL of people who care for AD patients, due to the focus on physical health.

ASSESSMENT OF AD TREATMENTS IN PRACTICE

- Few appraisals have been completed in the context of AD because there are so few treatments. A 2011 NICE appraisal for four treatments for AD accepted EQ-5D data, despite its potential limitations in this population.

- More recently, an ICER evidence report details that the utility inputs used were based on a 1999 study that used proxy-reported Health Utilities Index Mark II (HUI2) data, rather than EQ-5D.

Case Study Three

Sickle Cell Disease

THE CONDITION

- Sickle cell disease (SCD) is an inherited, chronic disease that affects the red blood cells. SCD is characterised by regular infections, anaemia, and recurrent painful vaso-occlusive events that require frequent hospitalisations.

- An estimated 100,000 people are currently living with SCD in the United States, although the exact number is unknown. SCD occurs among about 1 out of every 365 Black or African American births in the United States.

- Patients with SCD are expected to live 22 fewer years and have about half the quality-adjusted life expectancy of that of an individual without SCD.

- Structural racism can have a substantial negative impact on people with SCD, particularly in the United States.

IMPORTANT DIMENSIONS OF HEALTH THAT MIGHT BE MISSED BY EQ-5D

- Fatigue
- Pain (due to fluctuations)

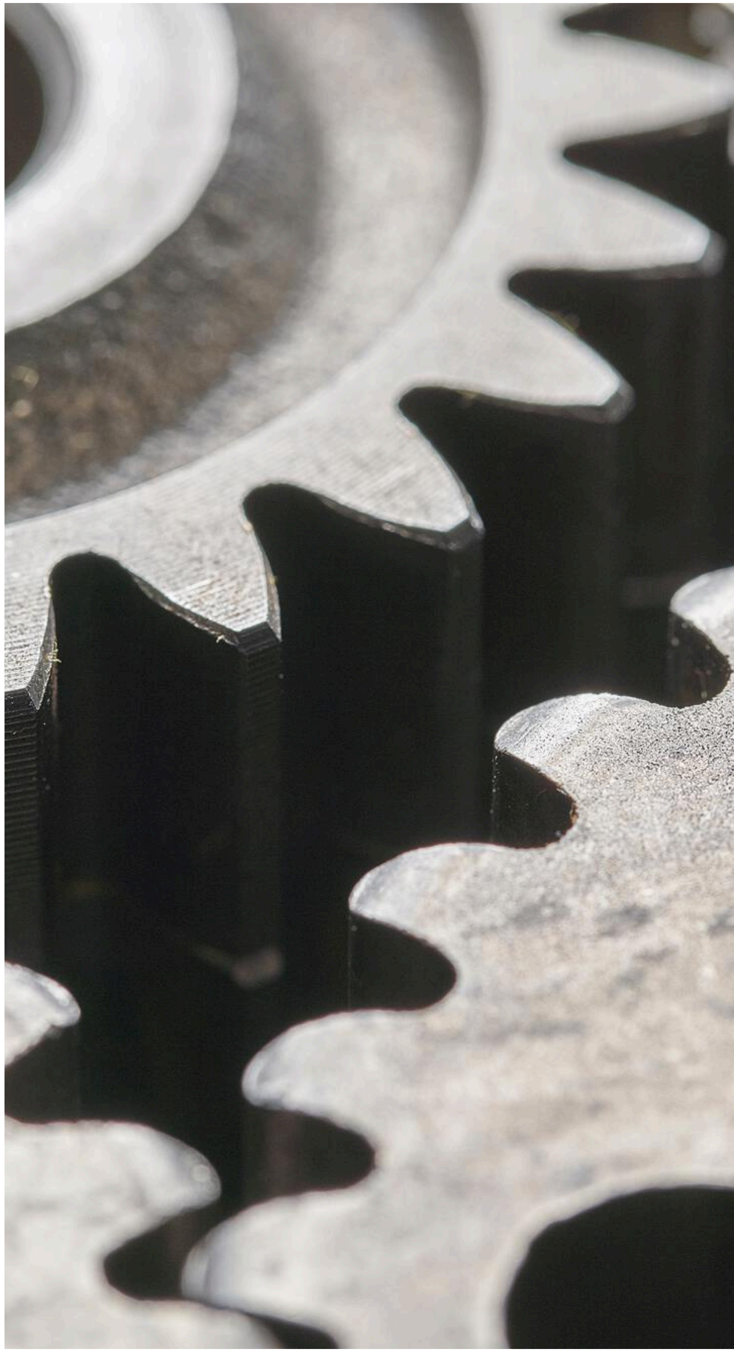
EQ-5D PERFORMANCE IN PEOPLE WITH SCD

- Relatively little research has been conducted to test the validity of different measures of QOL in people with SCD. This lack of research may in part be a reflection of the lack of research funding for SCD relative to comparable diseases, such as cystic fibrosis.

- As vaso-occlusive crises do not occur daily, and EQ-5D asks about your health ‘today’, the instrument may fail to accurately reflect the pain status of people with SCD. Treatments that help to alleviate pain in people with SCD may appear less effective as a result when QOL is measured using EQ-5D.

- Fatigue is a characteristic of SCD that is not captured explicitly by the EQ-5D and therefore, as is the case in MS, the EQ-5D may lack validity in the SCD population.

- Unlike in MS, no studies have examined whether fatigue is adequately captured elsewhere on EQ-5D in the SCD population.



CAPTURING CHANGES IN QOL OVER TIME

- The EQ-5D may fail to capture the impact of the recurrent painful vaso-occlusive events (known as pain crises) that affect people with SCD due to its recall period.

- Whilst EQ-5D does capture pain and discomfort, it assesses health ‘today’, and therefore it could fail to capture the impact of pain crises on the QOL of people with SCD.

- In contrast, the Adult Sickle Cell Quality of life Measurement information system (ASCQ-Me; a condition-specific measure) asks questions about the frequency of crises over the past 12 months, and specific questions about patients’ most recent crisis.

- Similar to the approach tested in MS patients (the ambulatory assessment), more frequent completion of the EQ-5D may effectively improve its responsiveness and could be useful in capturing the impact of these pain crises.

ASSESSMENT OF SCD TREATMENTS IN PRACTICE

- To date, there have been few appraisals for SCD as few treatments are available. An ICER assessment was conducted in 2020, and the evidence report stated that:

> Since decreasing pain crises should increase quality of life there continues to be important uncertainty about whether these new therapies impact quality of life or whether the instruments used in the clinical trials were not sufficiently sensitive to detect that improvement.

- The EQ-5D-5L was one of the instruments used in the relevant clinical trials, alongside the Brief Pain Inventory, the SF-36, and the Sickle Cell Disease Severity Measure (a condition-specific measure).

- In response to ICER's report, patient organisation Sick Cells released an infographic describing what ICER had missed from the perspective of patients and carers, which included the effects of fatigue on quality of life.

- Why You Need To Share Your Sickle Cell Story with ICER Infographic (click on logo to view)

SICK CELLS

Conclusion

CONCLUSION

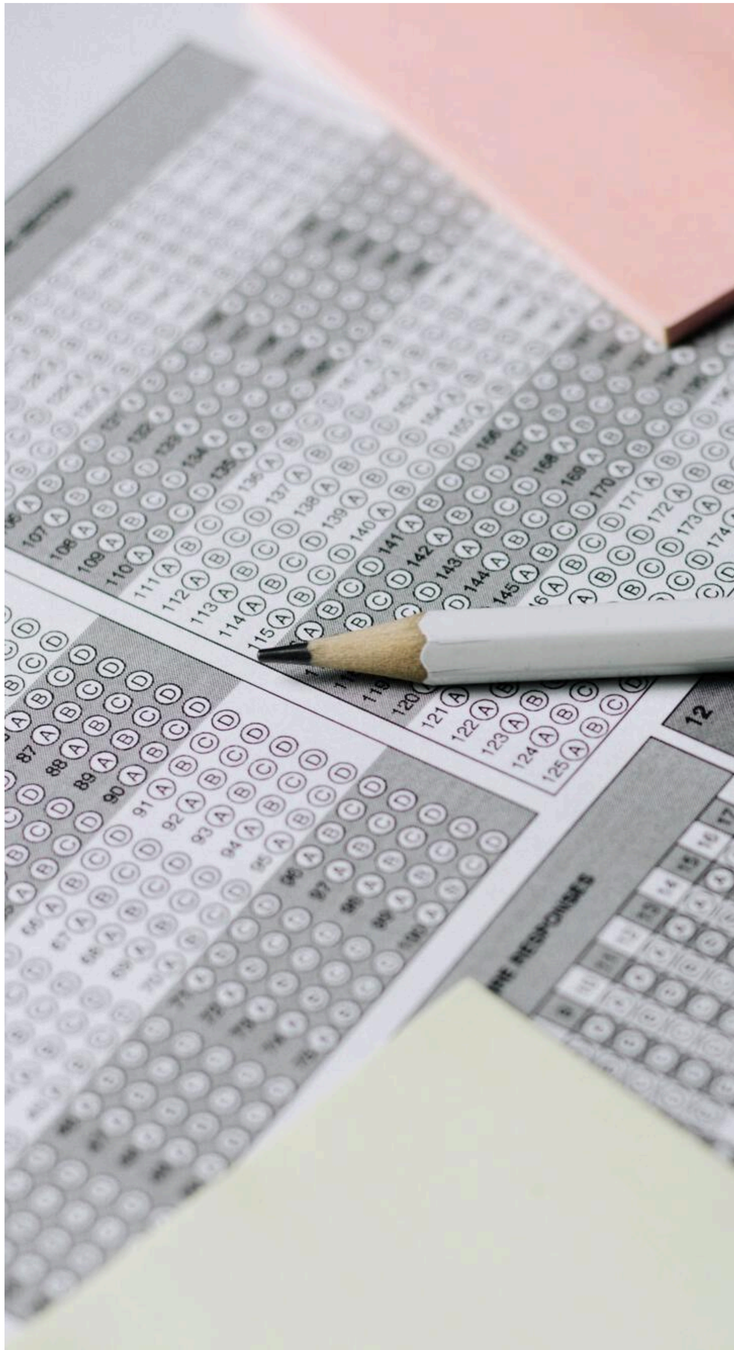
- There are health conditions where we might expect the EQ-5D to perform poorly, and these case studies explored some examples.

- There is a considerable evidence base indicating that EQ-5D has limitations in the MS and AD populations. In the SCD population, there are several reasons why EQ-5D is likely to perform poorly, which have been raised by patient groups. However, further research is required in this population.

- Whilst decision makers may seek consistency between HTAs (through the use of the same QOL measure), if the measure does not adequately capture changes in the QOL of patients, then the full benefits of new treatments could be underestimated, which could lead to suboptimal decision making.

- HTA agencies often require clear evidence to justify the acceptance of alternative measures to the EQ-5D, such as robust psychometric analyses that test the performance of the EQ-5D in the specific condition of relevance.

- Where such evidence exists, and QOL gains are to be estimated (e.g. to estimate QALY gains for HTA), there are several alternatives which have been summarised in an earlier OHE report. Each of these alternatives have their advantages and disadvantages, and therefore the most appropriate approach to use can vary depending on the context.



Thank you for reading

When generic measures fail to reflect what matters to patients

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