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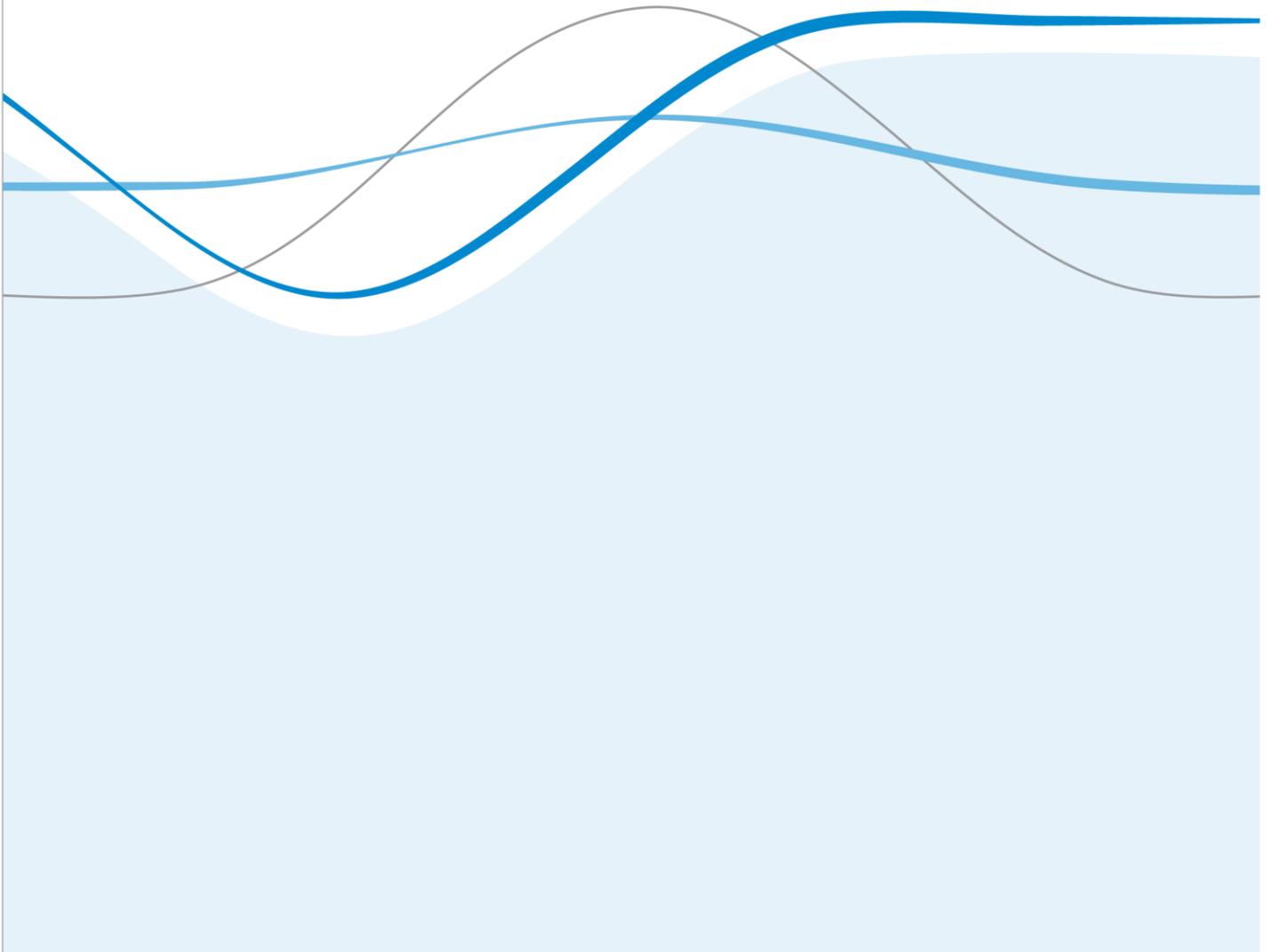
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EXECUTIVE SUMMARY

The measurement of quality of life in the context of spinal muscular atrophy (SMA) is challenging. This is because the disease is experienced by children and is rare, which makes data collection difficult. This Briefing reports on a symposium that outlined some lessons that can be learnt from the SMA context that might be more widely applicable.

Where evidence is lacking for new treatments, because of practical or methodological difficulties, there is a risk that patients remain unable to access cost-effective care. We identify a variety of ways in which current approaches to the measurement of quality of life in SMA may be inadequate. For example, it is unlikely that existing measures of health-related quality of life capture all that is important to patients and caregivers.

Based on the discussion, we highlight four possible strategies for improving the quantity and quality of data available to inform decisionmakers in the context of rare diseases:

- Bespoke data collection which is relevant to HTA decisionmakers;
- Simple economic modelling methods, which reflect the evidence available at the time of the assessment;
- Collaboration among the different parties involved; and
- Identifying what is 'good enough' to inform decisionmaking on use at the time of launch or of the health technology assessment process.

New approaches to research could facilitate health technology assessment processes and improve patients' access to cost-effective treatments for rare diseases.

1. INTRODUCTION

It is common to evaluate new treatments on the basis of their impact on quality of life, with patient-reported outcomes as the cornerstone of value. However, in the case of rare diseases, by definition, there is limited scope for collecting data from people who have experienced the disease or the treatment.

There are also practical and methodological challenges associated with capturing quality of life in paediatric populations. For children, it may be necessary to use proxy reporting (with a parent, for example). It can also be difficult to disentangle changes in quality of life that arise as a result of age-related or developmental changes, rather than because of a disease or its treatment.

Spinal muscular atrophy (SMA) is one disease in which these challenges play out. SMA primarily affects young children and has an estimated incidence of between 1 in 6,000 and 1 in 10,000 live births (D'Amico et al., 2011). Patients have significant medical expenditures; in Spain, for example, the cost per patient has been estimated to be around €34,000 per year (López-Bastida et al., 2017).

This Briefing reports on an Educational Symposium held on Sunday 11th November 2018 at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) European Congress in Barcelona, Spain. The symposium was introduced and moderated by Martina Garau from the Office of Health Economics and the speakers were:

- Huub van Rijswijck, Deputy Board Member, SMA Europe
- Julio Lopez Bastida, Professor, Universidad Castilla-La Mancha
- Andrew Lloyd, Director, Acaster Lloyd Consulting Ltd.
- Josie Godfrey, Director, JG Zebra Consulting

Huub van Rijswijck provided the perspective of a carer, as a father of a 13-year old son with SMA type 3, providing insights from the patient's perspective. Julio Lopez Bastida described his work in evaluating health-related quality of life in informal care settings across European countries. Andrew Lloyd provided an overview of methods for quality of life measurement. Josie Godfrey described the perspective of health technology agencies and identified key gaps in evidence requirements for decisionmakers.

Section 2 draws principally on insights from Huub van Rijswijck regarding the value of treatment in the context of SMA and rare diseases more broadly. Section 3 outlines some of the challenges associated with collecting the *right* data in this context, drawing especially on the content of presentations delivered at the symposium by Josie Godfrey and Julio Lopez-Bastida. Section 4 considers the possibility of new approaches, building on recommendations by Andrew Lloyd, and makes recommendations for future research. Section 5 concludes.

2. UNDERSTANDING THE VALUE OF TREATMENT FROM A PATIENT PERSPECTIVE

In order to understand the value of treatment for SMA, the impact of the disease on quality of life needs to be estimated. Quality of life can be affected by many disease-related and non-disease-related aspects of life, from marriage and parenthood to diagnosis and receipt of therapy. There are various dimensions within quality of life that might be considered important in the context of SMA. Huub van Rijswijck highlighted six

aspects of quality of life that are relevant to children experiencing the effects of SMA and other rare diseases:

- Comparison to what is perceived as normal
- Ability to participate
- Level of self-care and autonomy
- Physical health
- Self-esteem and recognition
- Coping and hope

Providing the patient's perspective, Huub van Rijswijck outlined the impact of SMA as being most felt when children have support needs that establish them as 'different' from other children. For example, children may have frustrations at school and require volunteers to assist with learning or self-care. An offer to go to a class adapted for children with special educational needs may be refused – for example – because of the desire to be 'normal'. This may impact on development.

According to a Dutch proverb, "man suffers most from the suffering he fears". Hope and fear can be important. In this respect, local and national funding and reimbursement decisions can have a real impact on quality of life as patients and carers can face desperation. This can also be exacerbated by uncertainty and inconsistency across different jurisdictions and different populations. Huub van Rijswijck suggested that pharmaceutical companies' pricing strategies could have a similar effect.

It is also important for patients to be able to maintain self-esteem and feel recognised by decisionmakers. Patients desire to be treated as human beings rather than cost centres, and policymakers can impact on quality of life in their behaviour. It is also possible to create false hope. In the case of Spinraza, this was experienced in the broad labelling by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (Prakash, 2017), but narrower recommendations by health technology assessment (HTA) agencies restricting treatments for certain groups. For example, while the National Health Care Institute (ZIN) in the Netherlands did recommend Spinraza, it was only recommended for children under nine and a half years old.

Huub van Rijswijck highlighted the fact that – for some people with SMA – there is no treatment available. Children (and caregivers) have to cope with (the idea of) future states, as well as coping with the irreversible deterioration of the motor neurons and loss of motor functions. In this case, lack of treatment can be devastating because it limits the ability to cope.

According to van Rijswijck, the goal of treatment in SMA is not to achieve clinical improvements, but rather to achieve stability by halting further dying of motor neurons and loss of motor functions. Therefore, it is important to value treatment in these terms. Generally speaking, trying to measure *improvements* in health status is not useful in the context of a progressive disease.

The value of treatment for SMA cannot be characterised exclusively in terms of functional status or physical health. While these are undoubtedly important, both in terms of their direct experience and their impact on other aspects of quality of life, there are other dimensions that ought to be characterised. These include children's (and caregivers') ability to participate and be similar to their reference group, to maintain autonomy and self-esteem, and to have hope and the ability to cope.

3. COLLECTING THE RIGHT DATA FOR HTA DECISIONMAKERS

Having identified some of the aspects of quality of life that *could* be affected by SMA, it is important to consider what data are available to support this and, if the available data are insufficient, what data ought to be collected.

3.1. Burden of disease

Julio Lopez Bastida described his work on the Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe (BURQOL-RD) project, which sought to quantify the health-related quality of life of patients suffering from 10 rare diseases and of their caregivers (López-Bastida et al., 2016). As a part of this observational study, caregivers were enrolled through SMA patient associations in France, Germany, Spain, and the UK. Primary caregivers completed online questionnaires that included socioeconomic questions, a proxy version of the EQ-5D-3L (EuroQol Group, 1990), Barthel Index (Mahoney and Barthel, 1965), duration of time spent on informal care, and the Zarit Caregiver Interview (Zarit, Orr and Zarit, 1985). The informal caregiver could be any relative or friend who carried out the usual caregiving activities, without having received training in doing so.

In this study, the mean average EQ-5D index score (utility value) was 0.22, and the mean average visual analogue scale (EQ VAS) score was 61.6[1]. This compares with mean paediatric utility values reported for other diseases of, for example, 0.50 in severe cerebral palsy and 0.89 in severe bilateral vision loss (Carroll and Downs, 2009). Thus, the severity of SMA is clearly reflected by the EQ-5D index. However, the relatively high EQ VAS responses imply that respondents are valuing the individual's current health status in a way that differs from the societal valuation that was applied to estimate the EQ-5D index. This could arise due to adaptation or the influence of different methods and warrants further research.

Figure 1 shows the distribution of responses across 'no problems', 'moderate problems', and 'severe problems' within each of the five dimensions of the EQ-5D-3L – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression – across the four countries included in the study. The results clearly demonstrate that, in all countries, SMA commonly has an impact on mobility, self-care, and usual activities, and that this impact often corresponds to individuals being confined to bed, unable to wash or dress themselves, or unable to perform usual activities. The impact on pain/discomfort and anxiety/depression is less common and severe, but non-negligible. These results suggest that the EQ-5D-3L is at least partially suitable for characterising the functional impact of SMA. However, the results do not provide insight into whether the measure would be responsive to the effects of treatment.

Figure 2 and Figure 3 characterise the burden of SMA for caregivers, by country and by disease type. The data include estimates of time spent by caregivers (per day) on basic activities of daily living (BADL) and instrumental activities of daily living (IADL). In all countries, the average time spent on caregiving per day exceeds eight hours. The average for type I SMA is around 13 hours per day. These estimates demonstrate a

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[1] EQ-5D index scores are on a 0-1 scale where 1 is 'full health' and 0 is a health state of equivalent value to being dead. EQ VAS scores are on a 0-100 scale where 100 is 'best imaginable health state' and 0 is 'worst imaginable health state'.

major burden for caregivers but are comparable to those identified in the context of other rare conditions (see, for example, Angelis et al (2015)). This burden should be considered in the evaluation of any treatment that might affect informal care needs.
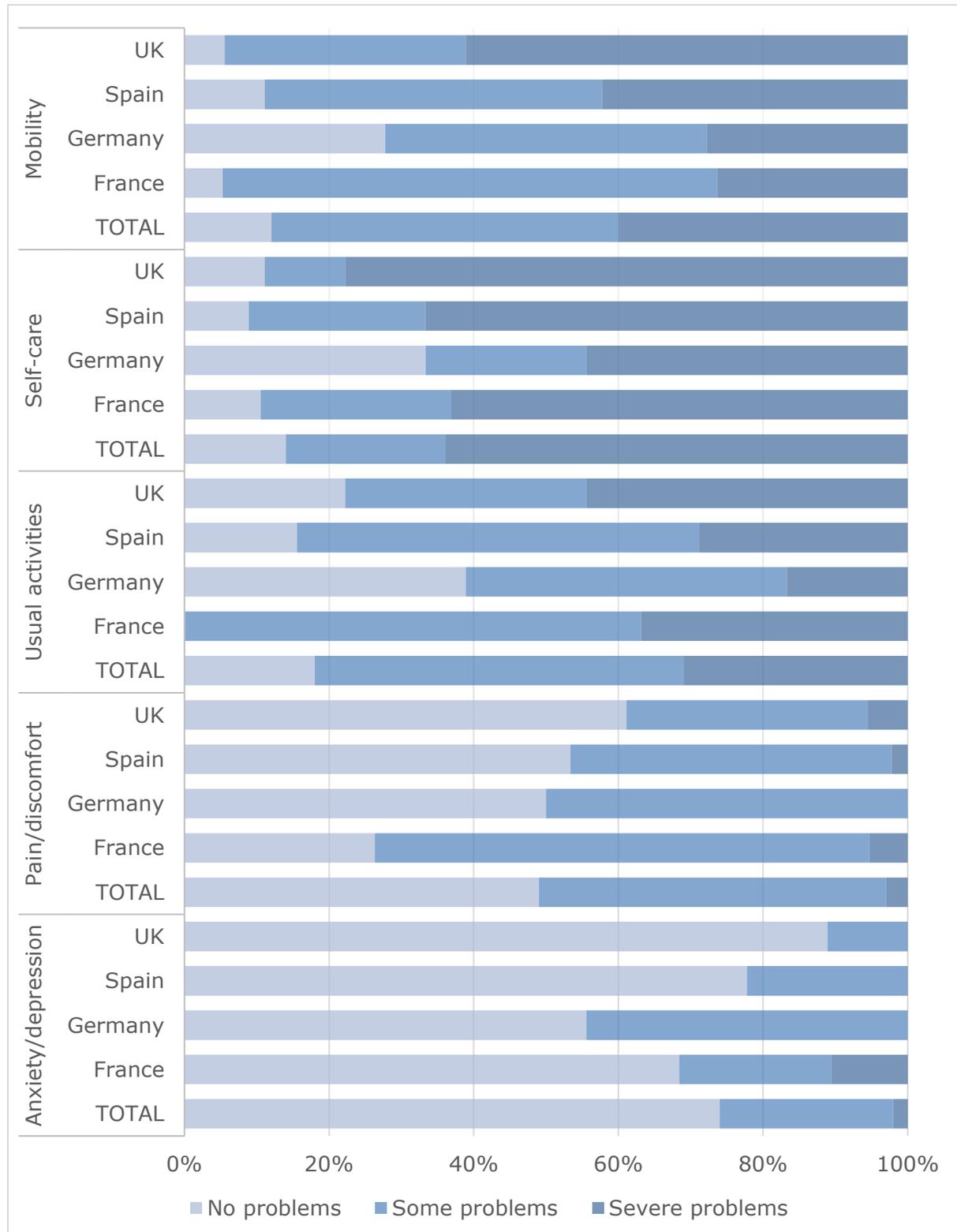

Figure 1: Frequency of proxy response levels on the EQ-5D-3L for people with SMA (López-Bastida et al., 2016)
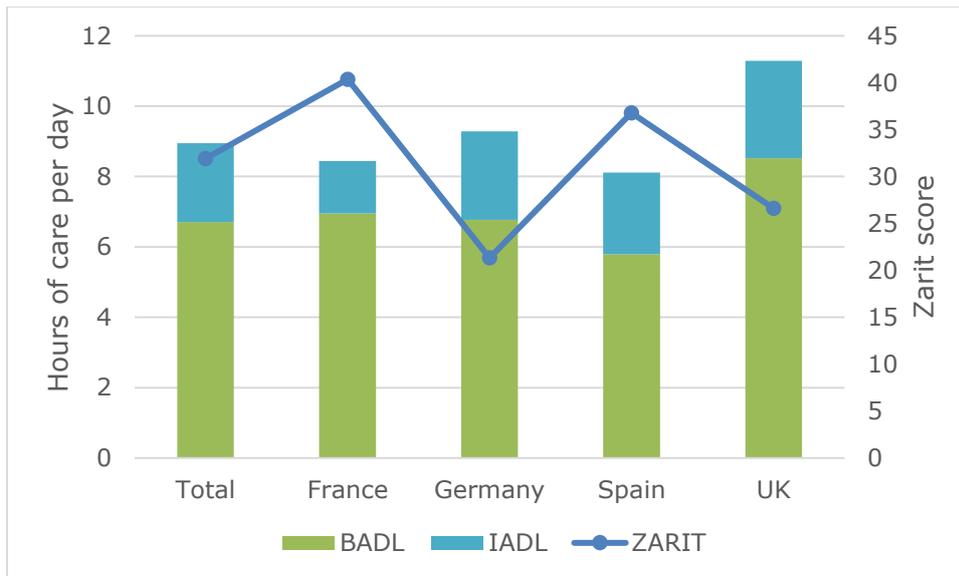
Figure 2: Caregiver burden by country (López-Bastida et al., 2016)
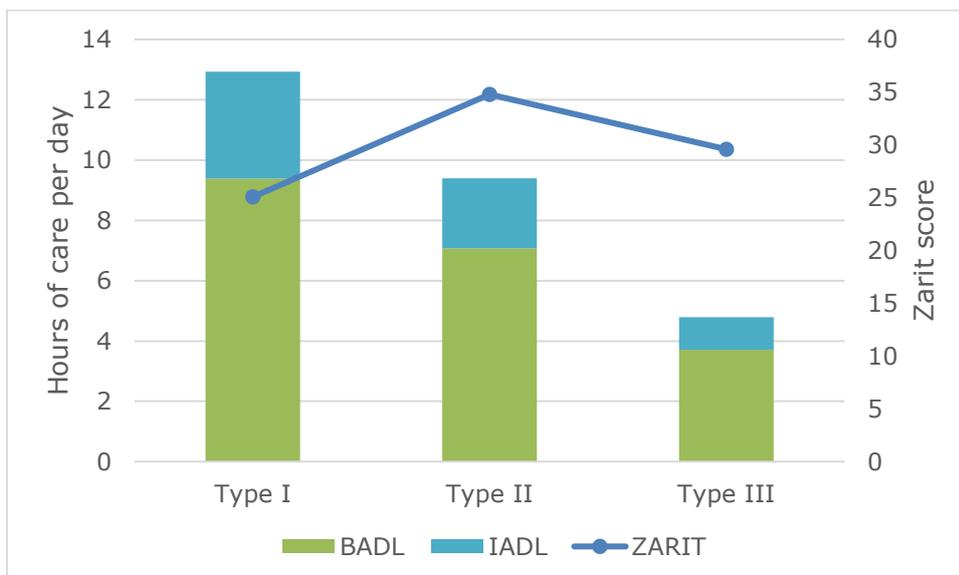
Figure 3: Caregiver burden by type (López-Bastida et al., 2016)

3.2. Inadequacy of existing measures

SMA can emerge early in life. The impact of interventions at this early stage may be a very important source of value. However, as Andrew Lloyd pointed out, most measures are simply not valid for self-completion in the context of children younger than seven years. The EQ-5D-Y (Wille et al., 2010) and CHU-9D (Stevens, 2010), for example, are not recommended for use with children under seven years old (Canaway and Frew, 2013; Janssens et al., 2015).

Measures that have been shown to be valid in younger children, such as the PedsQL (Varni, Seid and Rode, 1999), can be used to generate utilities (as required for health technology assessment) using mapping functions (Khan et al., 2014; Lambe et al.,

2018). However, there are fundamental limitations to the validity of these approaches (Brazier et al., 2010) and, as a result, mapping functions are often subject to criticism.

The absence of preference-based measures for younger children gives rise to a reliance on proxy measurement, which can be problematic. Proxy responses have been shown to be insensitive to pain and other subjective phenomena (Eiser and Morse, 2001), and children's and adults' preferences can differ (Ratcliffe et al., 2016).

Health technology assessment agencies require that health states and treatment effects are characterised in terms of utility values, which are often determined on the basis of generic measures such as the EQ-5D. It is therefore important that data – such as those reported by Lopez Bastida et al (2016) – are available to researchers. These data preclude an exclusive reliance on life expectancy, which is often the focus in evaluating treatments for children. However, most self-reported measures of health-related quality of life are not likely to reflect those effects that do not manifest as changes in functioning, such as the impact of hope and fear identified by Huub van Rijswijck. There may, therefore, be justification for the use of condition-specific or other more inclusive outcome measures.

It is important to note that there can be difficulties with any self-reported measures of quality of life. During his presentation at the symposium, Huub van Rijswijck posed a question to the audience: "How are you doing?" People are reluctant to answer such a question with honesty. This tells us something about a reliance on self-reporting and what van Rijswijck described as the 'Facebook effect'. There are two aspects to the 'Facebook effect'. First, individuals are assessing their quality of life with a 'status update' relating to their health *in the present moment*. Therefore, focus may be on present functional status rather than considering how expectations about the future may be affecting quality of life. Indeed, children may find it difficult to think about the future. Second, the way in which individuals respond to questions about quality of life is partially influenced by the people around them (Sneeuw, Sprangers and Aaronson, 2002). Patients are aware of how their self-assessments of health might impact on family or caregivers, and this may be especially true for children.

The gradual nature of functional decline in SMA, as motor functions are steadily lost, may also make current self-reported measures insensitive to change. This could occur due to adaptation. However, there are also acute events that may impact on quality of life, such as falls and other accidents, which might lead to hospitalisation. The timing of data collection may, therefore, be crucial. These challenges are not unique to SMA and apply beyond the context of rare diseases in general.

Previously, we identified some of the impacts that SMA can have on caregivers. The biases that we have described in self-reporting may also apply to proxy responses from caregivers, particularly if they learn to adapt to their circumstances. Julio Lopez Bastida argued that, for caregivers, the impact of caregiving needs to be measured in health, labour, and social dimensions. A person being sick can mean that a whole family is affected in a variety of ways.

3.3. What agencies need

Josie Godfrey emphasised the point that agencies are focussed on reducing uncertainty in their decisions. Broadly speaking, the question that HTA agencies seek to answer about a new treatment is '*is it value for money?*'. Agencies seek confidence in the use of resources.

In the case of SMA, the overarching challenge for HTA is not an abundance of the wrong outcomes data, but rather an absence of relevant data. For example, the National Institute for Health and Care Excellence (NICE) in England would take caregiver burden into account if these data were available.

For the majority of rare diseases, including SMA, a perfect model of either the natural history of the disease or of health state values is likely to remain unrealistic. As Josie Godfrey stated; no matter what, there are always going to be gaps in the evidence base for rare diseases, especially when compared to other disease areas. Therefore, the outstanding question for agencies, to inform decisionmaking on use at the time of launch or of the HTA process, is not necessarily '*what is the right data?*' but '*what is enough?*'

4. ADOPTING NEW APPROACHES

Each of the presenters at the symposium provided suggestions for ways in which quality of life measurement in SMA could be improved. Here, we provide an overview of some of the key recommendations that arose from the discussion.

4.1. Bespoke data collection

There is a need to consider bespoke approaches to data collection in SMA and other rare diseases, both in terms of the outcome measures used and the research methods employed.

Julio Lopez Bastida argued that there is a need to develop condition-specific health-related quality of life instruments for SMA patients. These might take into account the kinds of dimensions that are not included in generic preference-based measures such as the EQ-5D. Generic and condition-specific measures can be used together to provide a better understanding of the nature of quality of life in SMA. Huub van Rijswijck argued that quality of life measures in the context of progressive disease should be designed to account for the impact of knowledge about the future. For example, in SMA, that might include explicit identification of the expected time to losing the ability to walk, to go to the toilet independently, or to breathe without support. The impact of these expectations on quality of life can be identified using questions about domains of psychological wellbeing, such as hope.

Huub van Rijswijck argued that outcome measures used with children should recognise their agency; children don't wish to be treated as non-humans. Outcome measurement for SMA could be developed with reference to existing approaches to expanding value to incorporate concepts beyond functioning and health status (Garrison, Kamal-Bahl and Towse, 2017). There is a need to develop a deeper understanding of quality of life for SMA patients and their caregivers.

Andrew Lloyd argued that it is important to triangulate methods. Small surveys can be used to collect key quality of life data from patients, where very little exists. Vignette research can be used to ask larger samples of people without SMA to value health states defined in terms of the condition. Mapping studies can be used to transpose data from condition- or symptom-specific measures into more generalisable outcomes. Future efforts should not disregard the collection of proxy data and the collection of quality of life data from small samples. Furthering this work can help researchers to understand biases at play in quality of life measurement and to identify valid methods for the estimation of health state utility values, including mapping from clinical endpoints.

Vignette research may have a valuable role to play where there are significant challenges in recruiting participants into quality of life research studies.

Even with bespoke measures, low prevalence makes recruitment extremely difficult. Yet, as Andrew Lloyd pointed out, there are several strategies that could garner more success in data collection. In particular, routine data collection in clinical settings provides an opportunity for better representation of the patient population. Clinical data registries can supply evidence associating quality of life outcomes with treatment pathways.

4.2. Simple modelling methods

Typically, health technology assessments are supported by a cost-effectiveness model, which characterises – in a simplified way – the natural history of a disease and the costs and consequences of introducing a new treatment within this model. Disease progression is characterised as changes in disease severity and the occurrence of particular events. In SMA, this might be the achievement of motor milestones.

Clinical trials might not be capable of capturing information on all states that are important within the disease model. Many trial-based studies do not collect any quality of life data at all. Often, triallists are not considering the HTA process. Without trial-based data, modellers can turn to other types of published evidence, such as might be collected in observational studies. However, as Andrew Lloyd pointed out, evidence is lacking in the context of rare diseases such as SMA.

There is a drive for more complex cost-effectiveness models that better represent patient heterogeneity and variation in practice. However, more complex models require more specific data parameters, which might not be attainable in the context of rare diseases. Therefore, the development of simple models (in consultation with experts) could facilitate more robust modelling with realistic data requirements.

4.3. Collaboration

Given the difficulty in identifying research participants with rare diseases, collaboration among different stakeholders is crucial. This can operate on a variety of levels and provide opportunities for more effective data collection and more valuable research. Researchers working in the context of SMA may also learn from research in related disease areas, where similar challenges are experienced.

Engaging with patient organisations is critical and better engagement with clinicians can support ongoing research partnerships. Collaborations can help to ensure that data are collected at the earliest opportunity in the path from the development of new treatments to use in practice.

The pharmaceutical industry also has a responsibility to support these endeavours. Companies should be encouraged to capture more and better quality of life data. Andrew Lloyd suggested that early advice programmes could support this goal and that organisations such as ISPOR can serve an educational role. Josie Godfrey highlighted the possibility of sharing data and other forms of collaboration between companies and other stakeholders. Project HERCULES, which is a collaboration between seven companies developing treatments for Duchenne Muscular Dystrophy and other stakeholders, represents a good example that could be followed for other rare diseases.

HTA agencies and regulators can also work with companies to facilitate the generation of evidence to reduce uncertainty in critical areas. Managed access agreements may have a role but should not be seen as a solution in all cases. Fast-track HTA processes leading

to early access may pose a risk to data collection if speed is prioritised over evidence generation.

International collaborations are also an important way to enable cost-effective opportunities for the identification of more patients. Variation in local practice and management pathways make generalisability a challenge, yet these can be identified and understood as part of the interpretation of the findings.

4.4. Identifying what is 'good enough'

Andrew Lloyd outlined standard practices in the evaluation of health technologies and the significance of decisions in this context; if money is spent on a new treatment, then less must be spent on other treatments in other disease areas. With treatments that have a high incremental cost, this is particularly pertinent. Perfect data will never be available, and yet decisions still need to be made.

Efforts should be directed towards understanding what is 'good enough' for decisionmakers. This applies to all aspects of data collection and analysis. Many trials in the context of rare diseases are single-arm studies. As Josie Godfrey pointed out, for a high proportion of rare diseases, there are no treatments available. This further exacerbates the challenge of evaluating alternative management strategies because there is no standard of care against which to evaluate new treatments. These challenges make it difficult to identify the profile of controls and to understand the counterfactual. There is no consensus on methods for identifying treatment effects under these circumstances. A variety of issues also arises in measuring quality of life in children. For example, when is proxy reporting unreliable or otherwise inadequate? Researchers and decisionmakers should work together to specify evidentiary requirements that are 'good enough' in the context of treatments for rare diseases.

5. CONCLUSION

An absence of evidence is not evidence of absence, and yet, in practice, this distinction is not always recognised. Where evidence is lacking for new treatments, because of practical or methodological difficulties, there is a risk that patients remain unable to access cost-effective care.

We have discussed a variety of ways in which current approaches to the measurement of quality of life in SMA may be inadequate. Collaboration is key to achieving the goal of creating more and better evidence to facilitate health technology assessment of new treatments for rare diseases.

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