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EDITORIAL

Dramatic Innovations in the Treatment of Spinal Muscular Atrophy, But Many Unknowns Remain

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This supplement includes five papers that add to our understanding of the costs, health-related quality of life, and cost effectiveness of different treatments for spinal muscular atrophy (SMA), as well as patient preferences for treatment. SMA is a severe, inherited neuromuscular disease with an incidence of approximately 1 in 10,000 live births [1]. SMA has received increased attention with the recent US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approvals of the gene therapy Zolgensma®, described as 'the world's most expensive drug' [2], for paediatric patients with the severe SMA type 1 or up to three copies of the gene SMN2. SMA type 0 is typically associated with foetal or neonatal death, while SMA type 4 is the mildest form and typically emerges in adulthood. Patients with SMA type 1 are unable to sit unassisted and their life expectancy is not typically more than 2–3 years [3, 4].

The UK list price of Zolgensma® is £1.79 million per patient dose [5]. The UK's National Institute for Health and Care Excellence (NICE) has also approved Spinraza®, which has marketing authorisation for all SMA types, under a managed access agreement that sets the price at £75,000 per vial. This implies a treatment cost of £450,000 in the first year of treatment and £225,000 in subsequent years [6]. NICE subsequently declined to recommend a third treatment, Evrysdi®, which has a list price of £7900 per 60 mg vial [7, 8], but the manufacturer has very recently struck a deal with NHS England to make it available at a reduced price [9]. These are true disease-modifying therapies (DMTs) but come at unprecedented costs that must be weighed alongside the cost and quality-of-life burdens of SMA on patients, caregivers, health systems, and wider society.

In this supplement, a systematic review by Paracha et al. [10] reports substantially higher direct healthcare costs among infants with SMA relative to a matched sample of infants without SMA, as well as cost differences by SMA type. Type 1 patients have the highest annual direct costs but, as a result of their relatively short life expectancy, the lowest lifetime costs. However, they note that survival gains from DMTs are likely to increase the lifetime costs of persons with type 1 SMA. Likewise, they found a gradient in annual indirect carer costs by SMA type, with type 2 carers reporting the greatest indirect costs relative to types 1 and 3. Again, this suggests that the carer costs associated with SMA type 1 may move towards those of type 2, as treatments shift type 1 patients towards current type 2 patients. However, the authors emphasise that while many of the cost studies they identified stratify by SMA type, they do not stratify by mobility or breathing function, making it difficult to predict the full impact of DMTs on costs as patients experience changes in survival as well as function. They call for systematic cost studies that can track direct and indirect costs to understand the full impact of the new treatments.

Paracha et al. [11] make a similar observation around the difficulty of interpreting health state utilities. Their systematic review of health state utilities finds a wide mix of methodologies and perspectives. Elicitations used vignettes, discrete choice experiments, and generic health state descriptors, as well as a mix of patient and proxy perspectives. Together, these make it difficult to come to a generalisable understanding of the health-related quality-of-life burdens of SMA on patients. Most utility valuations used proxy-derived values based on motor function, and report ranges from 'worse than death' in type 1 SMA to 0.71 in type 3 SMA. A limited number of valuations were based on patient-derived values and reported utilities better than death for all SMA types. Most studies estimated utilities under best supportive care and therefore provide limited information about the impact of DMT on patient utility, but they do consistently demonstrate that SMA is associated with a substantial health-related quality-of-life burden on patients and carers. The authors note that this is an active research area, with nine new publications between 2019 and 2021,

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compared with just five up to 2019, but that the quality of most studies is moderate. Sample sizes are (unavoidably) small; there is a high risk of sample bias and loss to follow-up; there is heterogeneity in methods and samples between studies; and there is a lack of validated valuation sets for childhood versions of most generic health state descriptors. Together, these limitations mean that it is difficult to estimate the specific utility impact of SMA or new DMTs, and the authors call for researchers to more consistently integrate utility assessment into the design of clinical trials. They also note that many generic measures, and even some SMA-specific measures, are insensitive to aspects of functioning that are important to patients, including fine head and finger movements that could make a meaningful difference in quality-of-life by allowing independent control of, for example, a wheelchair.

A review of economic evaluations of SMA DMTs by Paracha et al. [12] notes how these limitations in estimates of both cost and utilities have led to inconsistencies between different economic models used in HTAs. They identify differences in model structure and functional endpoints; methods for indirectly mapping patient-reported outcomes to preference measures; and the inclusion of carer utilities. As noted earlier, there was also a lack of a clear association between costs and changes in patient functioning. Above all, they note the reliance of all models on critical assumptions around survival, utilities, and maintenance of functioning, given the absence of long-term clinical data. The authors call for registries to systematically collect long-term patient outcomes.

Beyond the methodological and data issues highlighted in the review, the NICE appraisal of Evrysdi® acknowledged challenges around the modelling of carer-related utilities in the context of SMA [6]. Specifically, it noted that removing carer utility from the model at the time of patient death perversely made life-extending treatment appear less cost effective. More broadly, this raises methodological and ethical issues about how to conceptualise and model the impact of SMA and similar conditions on carers. Most economic models conceptualise caring—even by family carers—as a disutility, perversely implying that extending patient survival has a negative impact on the well-being of family members. At the same time, however, it is important that improvements in functioning that can reduce the burden on carers are appropriately recognised and valued in economic evaluations.

The review of economic evaluations also raises the importance of measuring outcomes that are important to patients. As observed by Paracha et al. [11] , small changes in fine motor functioning that may not be captured by instruments such as the EQ-5D can be very valuable to patients. This emphasises the importance of understanding patient preferences for treatment and outcomes. This special issue includes two patient preference studies: one in the context of the UK [13] and one in a multicountry European context [14]. In both studies, respondents placed more value on improvements in motor function than improvements in breathing function. This result was somewhat unexpected and may reflect some degree of 'start point bias', as most respondents had better breathing function than motor function at the time they completed the discrete choice experiment, but it highlights the potential for unexpected preferences or value. These studies also reveal the challenges of understanding patient preferences in very young populations or where patients may have difficulty providing responses. In particular, caregivers responding on behalf of younger patients tended to express different preferences than adult SMA patients answering on their own behalf. Adult patients valued functional *maintenance*, whereas carers gave more value to functional *improvement*. This could reflect differences in the distribution of SMA type among the two groups—caregivers tended to respond on behalf of younger and more severe SMA patients—but it may also be the case that caregivers have an imperfect understanding of the preferences of the person for whom they are caring.

Such difference in the strength of patient and carer preferences echoes differences in the utilities of patients and carers described by Paracha et al. [11]. Many carers described the health states of those they cared for as 'worse than dead', while most patients described these states as having positive utility. This may be an extreme—indeed, fundamental—divergence in preferences between patients and carers, but it demonstrates the challenge of fully understanding and valuing the preferences of patients who may not be able to speak for themselves. It emphasises the importance of fully understanding patient values and preferences rather than having decision makers, or even carers, value treatment outcomes and processes on a patient's behalf.

The articles in this special issue highlight the costs and burdens of SMA, and especially the challenges to a full understanding of the value of emerging DMTs. These are expensive medicines, but rigorous assessments have demonstrated they can deliver value to patients, carers, health systems and society. However, important questions remain. The clinical benefit of these medicines has been demonstrated in short-term trials, but there is an absence of long-term evidence of effectiveness and safety. Such uncertainty is not unique to SMA treatments, but it is compounded by the substantial and often one-time cost of these medicines, raising the stakes of making the 'wrong' decision. Likewise, there is imperfect information on the costs they may help to avoid and the preferences of the patients they will treat. Information on costs and potential savings is not well aligned with functional outcomes that patients and clinicians understand, and utilities have been derived from small patient populations using a range of instruments and respondent

perspectives. Furthermore, utility instruments may not be sensitive to small gains in functionality that patients may value quite highly, while the discrete choice experiments suggest that the preferences of carers and decision makers may be an imperfect substitute for patient preferences. Together, these articles show that alongside the exciting progress in SMA, there are important questions outstanding.

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