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Comparison of the United Kingdom and United States approaches to approval of new neuromuscular therapies

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Abstract

Many novel therapies are now available for rare neuromuscular conditions that were previously untreatable. Hereditary transthyretin amyloidosis and spinal muscular atrophy are two examples of diseases with new medications that have transformed our field. The United States and the United Kingdom have taken disparate approaches to the approval and coverage of medications, despite both providing incentives to develop therapies targeting rare diseases. The US requires less evidence for approval when compared with medications for common diseases and does not have a mechanism to ensure or even encourage cost-effectiveness. The Institute of Clinical and Economic Review provides in-depth cost-effectiveness analyses in the US, but does not have the authority to negotiate drug costs. In contrast, the UK has maintained a similar scientific threshold for approval of all therapies, while requiring negotiation with National Institute for Health and Care Excellence to ensure that medications are cost-effective for rare diseases. These differences have led to approval of medications for rare diseases in the US that have less evidence than required for common diseases. Importantly, these medications have not been approved in the UK. Even when medications meet traditional scientific thresholds, they uniformly arrive with high list prices in the US, whereas they are available at cost-effective prices in the UK. The main downsides to the UK approach are that cost-effective medications are often available months later than in the US, and some medications remain unavailable.

KEYWORDS
cost-effective, neuromuscular disease, orphan drugs, rare disease

Abbreviations: 3,4-DAP, 3,4-diaminopyridine; AChR, acetylcholine receptor; ALS, amyotrophic lateral sclerosis; ALSFRS-R, Amyotrophic Lateral Sclerosis Rating Scale—Revised; CADTH, Canadian Agency for Drugs and Technologies in Health; CHMP, Committee for Medicinal Products for Human Use; CDR, Common Drug Review; DMD, Duchenne Muscular Dystrophy; FDA, US Food & Drug Administration; FDASIA, Food & Drug Administration Safety and Innovation Act; EMA, European Medicines Agency; HFMSE, Hammersmith Functional Motor Scale—Expanded; hATTR, hereditary transthyretin amyloidosis; ICER, Institute of Clinical and Economic Review; LEMS, Lambert-Eaton myasthenic syndrome; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG, myasthenia gravis; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PMO, phosphorodiamidate morpholino oligomer; QALY, quality-adjusted life-year; QMG, quantitative myasthenia gravis; RCT, randomized controlled trial; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

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The objectives of this activity are to: 1) Understand the differences between the US and the UK in the approval process for drugs for rare diseases; 2) Understand and be able to explain to patients some of the reasons for high drug costs for new drugs in the US; 3)Be able to understand costs as well as benefits for new drugs for neuromuscular diseases, and to balance costs and benefits when prescribing these medications.

I have no conflicts of interest

1 | INTRODUCTION

The United States recognized the need to incentivize treatments for rare diseases in the early 1980s, specifically naming amyotrophic lateral sclerosis (ALS) and muscular dystrophy as two conditions (among many) lacking available treatments.[1] The European Union (EU), of which the United Kingdom was a member until recently, followed suit in 1999 by passing legislation to encourage development of treatments for rare diseases in stating that "patients suffering from rare conditions should be entitled to the same quality of treatments as other patients."[2] These pieces of legislation paved the way with significant incentives to pharmaceutical companies to develop and bring to market treatments for these rare diseases. There is little doubt that these incentives have led to more therapies for patients with rare diseases and financial benefits to pharmaceutical companies. Orphan drug sales currently total ~$140 billion (~15% of total worldwide pharmaceutical sales) per year, with expected exponential growth over the next several years.[3] Rare diseases affect only ~3.5% to 5.9% of the population, signifying that pharmaceutical companies make a disproportionate amount of money on orphan drugs compared with other medications.[4] Importantly, the US and UK have developed divergent approaches to medication approval and coverage for rare diseases, resulting in fundamental differences in the availability of medications and costs of treatment. In this review we summarize the two different approaches while also providing examples of how these approaches have affected availability and cost of new neuromuscular therapies in the two countries.

2 | THE UNITED STATES APPROACH

The Orphan Drug Act of 1983 provided a financial incentive for pharmaceutical companies to develop and bring to market novel medications for rare diseases based on a prevalence of less than 200,000 individuals in the US (~60 cases per 100 000 individuals).[1] The law provides market exclusivity for 7 years compared with the usual 5 years for medications, while also providing tax credits on clinical trials, availability of federal subsidies for clinical trials, and reduced or waived regulatory fees.[5] To achieve orphan designation, pharmaceutical companies are required to prove scientific rationale and disease prevalence. The US currently has over 5500 medications approved under orphan drug status.[6]

Patients with severe, life-threatening diseases who lack adequate treatment are often willing to accept more cost and risk to try novel treatments, even if efficacy data are limited and costs may be high. In response to pleas from advocates for patients with rare diseases and a desire to increase available treatments, the US Food & Drug Administration Safety and Administration Act (FDASIA) was signed into law in 2012. This law expanded the ability of the US Food & Drug Administration (FDA) to assist pharmaceutical companies in the development and subsequent FDA review of "breakthrough therapies" with preliminary evidence supportive of substantial improvement over currently available therapies for patients with serious or life-threatening diseases.[7] Goals of the FDASIA were to promote innovation, increase stakeholder involvement, and enhance the safety of the drug supply chain. The approval process has evolved over many years, with the FDA requiring less data, encouraging use of surrogate measures, and shortening the review time for approval of treatments for rare diseases. In fact, nearly half of new drug approvals are based on a single clinical trial, instead of the two or more that used to be the standard.[8] Although this has significantly shortened the time to approval for new therapies, it has also demonstrated the FDA's willingness to approve medications with less efficacy data and use of surrogate measures rather than survival or improved patient outcomes. The benefits of earlier access to a medication must be weighed with the potential that patients will be exposed to medications that have less favorable benefit to risk profiles than anticipated or even to medications that are not efficacious.[9] In addition, there is increasing evidence of pharmaceutical company abuse of the Orphan Drug Act through repurposing of already available medications for narrower indications to gain the lucrative protections and exclusivity benefits afforded to orphan drugs.[10] The US approach to orphan drug approval has led to a lower scientific standard compared with that used for medications for common diseases.

The FDA has no role in determining pricing of a pharmaceutical product before or after approval and there are no universal mechanisms to guide sustainable health system costs. One shortcoming of the US health-care system is the inability to control costs of therapies.[11] The Institute of Clinical and Economic Review (ICER) was founded in 2006 as an independent, nonpartisan group to objectively evaluate prescription medications within the framework of "health-benefit price benchmark" with an ultimate goal of helping the US evolve toward a system of fair pricing, equal access, and a sustainable health system. ICER uses the quality-adjusted life-year (QALY) as a measure of disease burden accounting for the quality and quantity of life lived as a measure of health effectiveness vs cost-effectiveness.[12,13] However, the use of QALYs in rare disease is challenged by several factors, including: limited long-term effectiveness data in young populations with previously untreatable conditions; shorter duration clinical trials with limited randomized or head-to-head trials; and difficulties in measuring the burden of illness on family caring for children.[14,15] The ICER Value Assessment Framework takes into account the long-term value and the short-term affordability with a health-benefit price benchmark of $100 000 to $150 000 per QALY. However, it should be noted that this threshold is subjective and may not fully account for the value of novel therapies for rare diseases.[13] ICER provides this information to key stakeholders, including drug manufacturers, patient advocacy groups, provider groups, government entities, and health insurance plans. The FDA approval of treatments for rare diseases considers only the scientific evidence for efficacy and safety and does not consider ICER guidelines or cost-effectiveness of novel medications. Once approved, medications are priced by the pharmaceutical company. Given that cost-effectiveness is not considered, the US approach to orphan drug approval has led to availability of many novel therapies at high list prices (Figure 1).

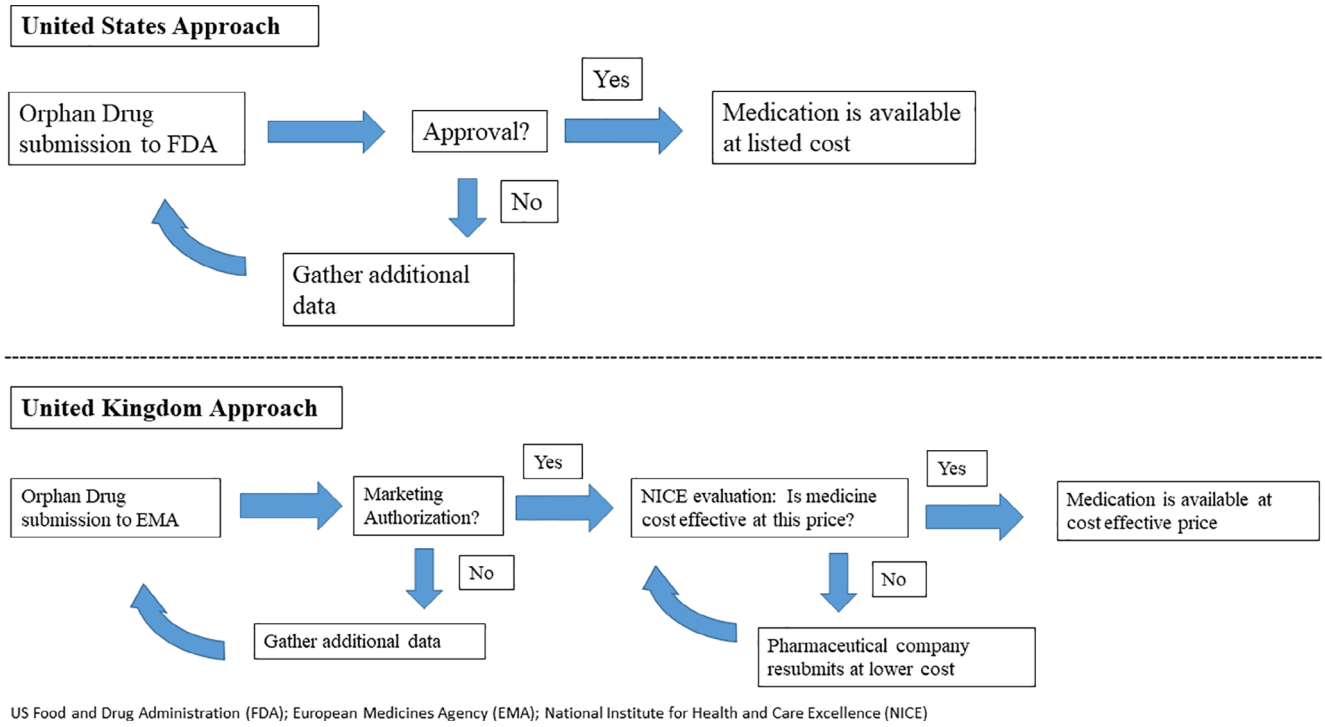

FIGURE 1 Divergent pathways from data submission to initial approval and availability of novel treatments

3 | THE UNITED KINGDOM APPROACH

The EU passed legislation in 1999 with the goal of increasing development and availability of novel medications for rare diseases.[2] The EU allows for 10 years of market exclusivity and uses a prevalence of 5 per 10 000 individuals in the European community for orphan drugs. In addition to the requirement of the treatment indication for a rare disease, the EU requires that the condition is considered life-threatening or seriously debilitating *and* that there is no satisfactory current method of diagnosis, prevention, or treatment. This distinction provides a slightly higher bar to qualify for orphan drug status compared with the US. The EU has over 100 approved orphan drug therapies for rare diseases.[16] The European Medicines Agency (EMA) has been the primary regulatory and approval agency for medications in the EU, including the UK, until very recently. Similar to the FDA, the EMA has also received more frequent submissions without high-quality randomized controlled trials (RCTs), but approves fewer medications and takes longer when approval is provided.[17] The UK approach to drug approval for rare diseases has led to a similar scientific standard compared with that used for approval of medications for common diseases.

Once the EMA approves a medication for use, it receives a marketing authorization; however, it is not commercially available until additional decisions on pricing are made. In the UK, the pharmaceutical company must then submit data to the National Institute for Health and Care Excellence (NICE) for cost-effectiveness evaluation. Based on review of the evidence for impact and an incremental cost-effectiveness ratio of below £100,000 per QALY, NICE then determines whether to recommend the medication.[18] If recommended, the medication will then be covered under the National Health Service (NHS) constitution; however, if a medication is not recommended, then it is not available on formulary and the company will need to resubmit an application with a lower cost of treatment. This process often leads to a period of negotiation between the pharmaceutical company and NICE during which the medication is approved but not available in the UK. The UK's approach to the cost of drugs for rare diseases has led to the approval and availability of only cost-effective medications, although sometimes with a delay of months while negotiations occur (Figure 1). One downside to this approach is that medications that may be clinically effective, but not cost-effective, are unavailable for treatment of neuromuscular diseases. Another downside is the delay from EMA approval to availability for clinical use. Next, we provide examples of new neuromuscular therapies to demonstrate how the US and UK approaches have led to key differences in approval, cost-effectiveness, and availability of these medications.

4 | HEREDITARY TRANSTHYRETIN AMYLOIDOSIS

Until recently, hereditary transthyretin amyloidosis (hATTR) had few treatments aside from liver transplant. Phase 3 trials for patisiran and inotersen were published in 2018.[19,20] The APOLLO study was a phase 3 RCT comparing patisiran with placebo and demonstrated a clinically significant difference in modified Neuropathy Impairment

Score + 7 (mNIS+7) measure at 18 months as well as secondary measures of the Norfolk Quality of Life–Diabetic Neuropathy scale and 10-meter walk test.[19] The Neuro-TTR trial was a phase 3 RCT of inotersen over a 15-month period that also demonstrated a clinically significant difference on the mNIS+7.[20] An indirect comparison showed that patisiran appears to demonstrate higher efficacy than inotersen.[21]

The FDA approved patisiran in August 2018 and inotersen on October 22, 2018.[22,23] Patisiran and inotersen were both priced at $450 000 annually in the US. However, the ICER cost analysis, using a threshold of $150 000 per QALY, indicated that inotersen should be priced at $25 379 annually and patisiran at $46 488 annually for each treatment to be considered cost-effective (Table 1).[24]

The EMA approved patisiran in August 2018 and inotersen in July 25, 2018.[25,26] In the UK, the initial list price for both treatments was £300 000. However, NICE declined coverage at this cost and both pharmaceutical companies were required to negotiate a confidential commercial agreement to achieve a lower acceptable cost per QALY gained (between £80 730 and £125 256 per QALY for patisiran and £96 697 per QALY for inotersen).[27-30] Agreement was reached with NICE in July 2019 for patisiran and April 2019 for inotersen.

The US and UK approaches both led to approval of these highly effective therapies; however, in the US, these medications have high retail prices, whereas in the UK the medications are available at cost-effective prices. The downside to the UK approach is that there was an initial delay in availability of patisiran and inotersen of 9 to 11 months compared with the US (Table 2).[24,29-35]

TABLE 1 Comparison of annual United States drug costs to the threshold cost for cost-effectiveness

Orphan drug medication	Annual price to achieve $150 000 per QALY	Annual cost (US$) at time of FDA approval
Patisiran	$46 488	$450 000
Inotersen	$25 379	$450 000
Nusinersen	$64 800	$375 000[a]
Onasemnogene abeparvovec	$899 000	$2 100 000[b]
Risdiplam	NA	$340 000
Deflazacort	$31 700	$89 000
Eteplirsen	–[c]	$300 000[d]
Golodirsen	–[c]	$300 000[d]
Edaravone	$4350[e]	$145 000
Eculizumab	NA	$500 000
Amifampridine	NA	$375 000

Abbreviations: FDA, United States Food and Drug Administration; NA, not applicable; QALY, quality-adjusted life-year.
[a]First-year cost: $750 000.
[b]One-time cost.
[c]Value-based price benchmark unable to be calculated in the absence of evidence demonstrating clinical benefits.
[d]Price will vary by patient weight.
[e]Calculated based on the Common Drug Review of the Canadian Agency for Drugs and Technologies in Health (*Pharmacoeconomic Review Report: Edaravone*).

5 | SPINAL MUSCULAR ATROPHY

The most severe form of spinal muscular atrophy (SMA) demonstrates progressive loss of motor function and is universally fatal without recently available treatments.[36]

Nusinersen is an antisense oligonucleotide drug that modifies pre-messenger RNA splicing of the *SMN2* gene and subsequently promotes increased production of full-length SMN protein. Multiple randomized phase 3 trials, including ENDEAR and CHERISH, demonstrated significantly improved motor milestones and event-free survival.[37,38]

Mendell et al studied the effects of functional replacement of the mutated *SMN1* gene using a single dose of intravenous adeno-associated virus vector, known as onasemnogene abeparvovec.[39] Fifteen patients with the SMA1 were included in this phase 2 trial with

TABLE 2 Neuromuscular orphan drug therapies

	Regulatory approval		Cost-effective		Available	
Orphan drug medication	US	UK	US	UK	US	UK
Patisiran	Yes	Yes	No	Yes	Yes	Yes
Inotersen	Yes	Yes	No	Yes	Yes	Yes
Nusinersen	Yes	Yes	No	Yes	Yes	Yes
Onasemnogene abeparvovec	Yes	Yes	No	Yes	Yes	Yes
Risdiplam	Yes	No	No	NA	Yes	No
Deflazacort	Yes	No	No	NA	Yes	No
Eteplirsen	Yes	No	No	NA	Yes	No
Golodirsen	Yes	No	No	NA	Yes	No
Edaravone	Yes	No	No	NA	Yes	No
Eculizumab	Yes	No	No	NA	Yes	No
Amifampridine	Yes	No	No	NA	Yes	No

the primary outcome of safety, and secondary outcome of time until death or permanent ventilator assistance. Impressively, all 15 patients were alive and event-free at 20 months of age, when compared with 8% survival in a historical cohort.[39,40] Given the natural history of SMA is never sitting and a 90% fatality rate at 2 years of age, the fact that 11 of 15 treated patients regained head control and independent sitting and 2 regained the ability to walk for years is remarkable. The therapy proved to be safe in this small study, showing only elevated serum aminotransferase levels without other liver enzyme abnormalities, which was attenuated by prednisolone treatment. A phase 3 trial awaits completion.

Risdiplam is a small-molecule *SMN2* splicing modifier that binds two sites in *SMN2* pre-messenger RNA, which results in correcting the splicing deficit of *SMN2* and subsequently increased levels of full-length SMN protein. Risdiplam was studied in 180 nonambulatory patients with SMA2 (71%) and SMA3 (29%). Risdiplam demonstrated a clinically meaningful and statistically significant difference in motor function compared with placebo.[41-43]

Nusinersen, onasemnogene abeparvovec, and risdiplam were approved by the FDA in December 2016, May 2019, and August 2020, respectively.[44-46] ICER evaluated the use of nusinersen and onasemnogene abeparvovec in SMA.[31] They noted nusinersen does not meet traditional cost-effectiveness thresholds in any population. The review also noted nusinersen was more cost-effective in the presymptomatic population, but even in this population the cost would have to be reduced to below $65 000 per year to meet a threshold of $150 000 per QALY. In later-onset SMA, nusinersen cost over $8 million per QALY gained given that there is no evidence to demonstrate life extension in this population and the benefits of treatment translate to only small improvements in quality of life compared with best supportive care. Onasemnogene abeparvovec also failed to meet established cost-effectiveness thresholds ($247 000 per QALY), but it was much closer to cost-effectiveness than nusinersen (Table 1). The efficacy of onasemnogene abeparvovec is only based on a single, small, phase 2 study.

The EMA approved nusinersen and onasemnogene abeparvovec in May 2017 and May 2020, respectively, although onasemnogene abeparvovec is authorized for use in the EU under "conditional authorization," which means the company will be required to provide new evidence and the EMA will review this information annually.[47,48] Risdiplam is not currently authorized for use by the EMA, but in February 2019 it was granted orphan designation.[49] NICE concluded that nusinersen should be recommended as an option for treating presymptomatic and symptomatic SMA types 1, 2, and 3.[32] Onasemnogene abeparvovec appears to be on the cusp of formal approval by NICE for use in the UK.[50,51]

The US and UK approaches both led to approval of nusinersen and onasemnogene abeparvovec, whereas risdiplam is only approved in the US. All three medications are available in the US. Nusinersen is currently available in the UK, and onasemnogene abeparvovec is approved by the EMA and just received NICE approval. Access to these medications occurred months earlier in the US, but the UK appears to have negotiated a cost for nusinersen and onasemnogene abeparvovec that will support long-term cost-effectiveness and availability. Moreover, patients with SMA in the UK currently lack access to risdiplam (Table 2).

6 | DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) presents in early childhood as progressive muscle weakness associated with cardiopulmonary complications. For many years, only glucocorticoids were available as treatment.[52,53]

An RCT comparing deflazacort, prednisone, and placebo demonstrated that deflazacort and prednisone were superior to placebo over 12 weeks in measurements of muscle strength and function.[54] Participants were then randomized to receive either deflazacort or prednisone for an additional 40 weeks. No differences in strength or function were observed, but deflazacort was associated with less weight gain and fewer psychiatric adverse events, whereas cataracts and growth delays were more frequently reported.

Several novel therapies have recently become available, including exon-skipping therapies that result in dystrophin restoration (eteplirsen, golodirsen, viltolarsen). Exon-skipping therapies are known as phosphorodiamidate morpholino oligomers (PMOs), which are designed to bind to pre-mRNA, alter the splicing process, and skip the targeted exon from the mature mRNA sequence with a goal of increasing dystrophin expression.[55,56] A 12-week, open-label, phase 2 study evaluated the safety and tolerability of eteplirsen in 19 ambulatory DMD patients between the ages 5 and 15 years, with a deletion amenable to exon 51–skipping therapy. There were no clear drug-induced adverse events, and the secondary outcome revealed a dose-dependent significant increase in dystrophin expression.[57] A subsequent 48-week study randomized DMD boys with amenable deletions to exon 51 skipping to 30 or 50 mg/kg eteplirsen or placebo for 24 weeks.[58] After 24 weeks, patients on placebo were switched to receive either 30 or 50 mg/kg eteplirsen in an open-label extension study in which muscle biopsies were obtained before treatment and at 48 weeks. Eteplirsen treatment resulted in significant improvement in dystrophin expression in muscle biopsies and improved 6-minute walk test compared with patients who were initially on placebo.[59] Golodirsen and viltolarsen induce exon 53 skipping and have also demonstrated increased dystrophin staining after treatment without evidence of improvement in patient-oriented outcomes in randomized trials.[60,61]

Importantly, none of the PMOs have undergone a phase 3 trial to evaluate clinical effectiveness, and most recent studies have included a significant open-label period without blinding. Outcome measures have included evaluation of pre- and posttreatment dystrophin expression in muscle and comparisons to historical cohorts.

In the US, all the aforementioned therapies are now available. Deflazacort was approved by the FDA in February 2017 to treat DMD patients 5 years of age and older.[62] The FDA granted accelerated approval of the exon-skipping therapies based on the surrogate endpoint that is thought to predict clinical benefit, although the FDA

is now requiring the pharmaceutical companies to conduct a clinical trial to confirm each treatment's clinical benefit with the threat that, if they do not verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the therapy.[63-65] ICER evaluated the long-term cost-effectiveness of the aforementioned therapies, and noted that the annual treatment cost for a 40-kg patient was $550 for prednisone, $81 400 for deflazacort, and $1 002 000 for eteplirsen.[33] The incremental cost-effectiveness ratios comparing deflazacort with prednisone ($361 000 per QALY) is beyond the range of the commonly accepted thresholds of $50 000 to $150 000 per QALY despite favorable assumptions about treatment effects (Table 1). With regard to eteplirsen and golodirsen, a value-based price estimate was not available given the absence of evidence proving clinical benefit. At the current pricing, PMOs are not cost-effective, even assuming positive effects on clinical outcomes.

Eteplirsen was not approved by the EMA in May 2018, and again in September 2018 after re-examination. The EMA cited that the Committee for Medicinal Products for Human Use (CHMP) was concerned that the study only involved 12 patients, did not compare treatment vs placebo beyond 24 weeks, there was no meaningful difference between eteplirsen and placebo in the 6-minute walk test, and the methods for comparing results of the studies with historical data were not satisfactory for showing effectiveness.[66] Similarly, golodirsen and viltolarsen have not been approved by the EMA.

In summary, the US approach has led to the approval of deflazacort and the PMOs. Deflazacort has comparable efficacy to prednisone, but it is not cost-effective. The evidence for PMOs is based on surrogate markers of disease, so the evidence does not meet traditional scientific thresholds. The UK approach has prevented access to deflazacort and PMOs (Table 2).

7 | AMYOTROPHIC LATERAL SCLEROSIS

ALS has long attracted intense interest from researchers to develop effective therapies. Edaravone, a free-radical scavenger, was initially developed for use in acute ischemic stroke in Japan in the early 2000s.[67] The first phase 3 trial failed to show a significant difference in the primary endpoint of the Amyotrophic Lateral Sclerosis Rating Scale—Revised (ALSFRS-R) between the treatment and placebo groups.[68] A post hoc analysis of a subpopulation of well-defined early-stage ALS patients without respiratory involvement suggested a possible benefit.[69] Using strict inclusion criteria, another phase 3 trial demonstrated a small, statistically significant slowing in the rate of decline; however, a higher proportion of patients in the placebo arm were in stage 2 ALS, indicating more severe disease at time of enrollment.[70] Edaravone places significant burden on ALS patients and caregivers with the need for port placement, time commitment for frequent infusions, and transportation to infusion centers (although infusions can be done at home for some patients) that are difficult to measure.[71] However, other adverse events were rare in the clinical trials.[72]

Edaravone was approved by the FDA for treatment of all patients with ALS in May 2017 under the orphan drug designation.[73] ICER has not yet published a review of edaravone. However, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a Common Drug Review (CDR) for edaravone in 2019, finding that edaravone likely extends life expectancy by 2 to 5 months and increases quality-adjusted life expectancy by 1 to 3 months, similar to riluzole.[34,74] However, the incremental cost-effectiveness ratio for edaravone compared with the current standard of care was $1 957 000 per QALY gained and would need to be reduced in price by ~97% to be cost-effective (Table 1).

The manufacturer of edaravone filed for EU approval via the EMA, but ultimately withdrew the applications. At the time of EMA withdrawal in May 2019, the CHMP provisional opinion was that edaravone could not have been approved, citing the following concerns: (1) the drug's lack of demonstrated efficacy to increase median survival, breathing, and muscle strength; (2) selection of stage 1 and 2 ALS patients in the phase 3 trial; (3) no improvement in patients switched from the placebo group to the edaravone group; and (4) short duration (24 weeks) for assessment of the primary endpoint. The CHMP held the opinion that the benefits of edaravone did not outweigh its risks due to lack of proven effectiveness.[75,76]

In summary, the US approach has led to the approval and widespread availability of edaravone, which has one positive and one negative clinical trial, potential harms related to frequent intravenous infusions, and high costs contributing to complex treatment discussions between providers and ALS patients.[77] In contrast, the UK approach has not allowed access to edaravone until further studies are performed to establish efficacy and cost-effectiveness (Table 2).

8 | MYASTHENIA GRAVIS

Myasthenia gravis (MG) has many effective therapies, but an estimated 10% to 15% of all cases are considered refractory and do not respond to typical therapies such as pyridostigmine, corticosteroids, or steroid-sparing agents, or require ongoing intravenous immunoglobulin or plasma exchange.[78]

Eculizumab is a humanized monoclonal antibody against human complement component 5 (C5) protein, which inhibits terminal formation of the membrane attack complex and destruction of the postsynaptic muscle membrane. The randomized, double-blind REGAIN phase 3 trial comparing eculizumab with placebo failed to meet its primary efficacy endpoint of change in the Myasthenia Gravis Activities of Daily Living (MG-ADL) total score after 26 weeks.[79] However, most other prespecified secondary efficacy endpoints, including change from baseline Quantitative Myasthenia Gravis (QMG) score, were significantly improved compared with placebo. The open-label REGAIN extension study demonstrated improvement in mean MG-ADL score and a considerable number of patients achieved minimal manifestation of disease status.[80] Despite REGAIN not meeting its primary efficacy endpoint, the positive results on several secondary measures and the results of the open-label extension trial indicate that eculizumab likely has a role for refractory AChR-antibody–positive generalized MG patients.

The FDA approved eculizumab for MG in October 2017. Cost is currently a barrier for use of eculizumab in refractory generalized MG patients, given its list price of approximately $500 000 per patient per year.[81] ICER has not performed a cost-effectiveness evaluation to date. However, CADTH analysis of eculizumab is associated with an ICER of $1 505 712 per QALY gained and has a 0% probability of being cost-effective at current cost.[35]

The EMA approved eculizumab for MG in August 2017.[82] However, the pharmaceutical company has not submitted an evidence submission to NICE and thus eculizumab had its appraisal terminated.[83] As a result, eculizumab is not available in the UK for refractory, generalized MG.

In conclusion, the US and UK approaches both led to approval of this likely effective therapy for refractory MG. In the US, eculizumab is available, but its high list price likely means that it is not cost-effective. In the UK, physicians do not have access to a potentially effective option for refractory MG when other options fail, but the health system avoids the high costs of this medication (Table 2).

9 | LAMBERT-EATON MYASTHENIC SYNDROME

3,4-Diaminopyridine (3,4-DAP, amifampridine), a potassium-channel blocker, has been the mainstay of treatment for Lambert-Eaton myasthenic syndrome (LEMS) for nearly 40 years. Several RCTs demonstrated that 3,4-DAP is safe and significantly improves QMG score, isometric muscle strength, and compound muscle action potential amplitudes on electrodiagnostic testing in LEMS patients.[84-86] A 2011 Cochrane Review concluded there was moderate- to high-quality evidence supporting the use of 3,4-DAP in LEMS patients.[87] Two RTCs of amifampridine, a phosphate salt form of 3,4-DAP, demonstrated significant improvement in baseline QMG score and Subjective Global Impression score without serious adverse effects.[88,89]

3,4-DAP was initially available in the US and UK through compounding pharmacies under a "compassionate use" investigational new drug program. The base form was relatively inexpensive—previously available at a cost of ~$1600 per year. The FDA approved amifampridine in 2018 with orphan drug status.[90] Amifampridine was then priced at $375,000 per year in the US, a 23 000% increase compared with the previous annual cost.[91] A cost-effectiveness analysis is not yet available from ICER.

In 2009, the EMA granted a marketing authorization under exceptional circumstances for amifampridine for the treatment of LEMS on the basis of sufficient clinical safety and efficacy data of 3,4-DAP.[92] After EMA approval, the annual price of 3,4-DAP rose from £730 in the UK to an estimated £29,448, leading to NICE denying approval for amifampridine on the grounds of: (1) insufficient evidence demonstrating clinical improvement in trials; and (2) an exponential price increase with the phosphate formulation, leaving UK patients to scramble to acquire the drug.[93]

Recently, a different pharmaceutical company received FDA approval for amifampridine for treatment of pediatric LEMS patients with pricing at $80 per 10-mg pill, with anticipated yearly cost estimates of $175 200 to $292 000, depending on dose, leading to speculation that this medication may be used off-label in adult patients.[94]

In summary, the US and UK approaches both led to approval of this efficacious therapy. In the US, the cost has increased by 23 000% without advancement in the treatment of patients with LEMS. The availability of amifampridine through a second manufacturer may result in a less costly alternative in the US, but this remains to be seen, and even the less costly version appears unlikely to meet reasonable cost-effectiveness thresholds. In the UK, the dramatic increase in price has led to withdrawal of this symptomatic treatment for LEMS patients, leaving them scrambling to find a replacement for this previously cost-effective treatment (Table 2).

10 | CONCLUSION

To advance treatments for rare diseases, it is essential to continue to research and develop medications. However, to sustain healthcare systems and make treatments widely available, the approval of these medications needs to be made in a thoughtful and cost-effective manner. The US and the UK have approached the approval and coverage of medications for rare diseases in very different ways. The US exhibits a different standard for approval for rare diseases, such as requiring fewer RTCs and the use of surrogate measures when compared with approval for treatments of common diseases. This has permitted access by patients in the US to medications such as PMOs for DMD and edaravone for ALS. PMOs have been approved based mainly on increased dystrophin staining and not on RCTs demonstrating efficacy on patient-oriented outcomes. Similarly, edaravone has been approved after one larger negative randomized clinical trial and one smaller positive randomized clinical trial. Clinical benefits for edaravone may apply to only a small subset of patients with ALS; this may be offset by chronic infusion risks and considerable patient time commitment. In contrast to the US, the UK has asked for more data for PMOs and edaravone before approval. PMOs and edaravone are currently unavailable in the UK. Medications for hATTR amyloidosis and SMA are available in both the US and UK, but are approved at cost-effective prices in the UK due to the requirement to demonstrate cost-effectiveness before widespread availability. In the US, ICER can only point out that these medications are not cost-effective without the ability to rein in costs through negotiation. The primary downside to the UK approach is that these efficacious medications are available months later, but the trade-off is more sustainable costs. Eculizumab and 3,4-DAP are examples of medications that are available in the US, but not in the UK, solely because of cost. Eculizumab likely has clinical benefit for a subset of refractory MG patients. However, many effective therapies already exist for MG and it is not cost-effective at its current price. 3,4-DAP was available in the US and UK at relatively low cost for many years, but with orphan drug status the price increased dramatically causing the UK to no longer cover this medication,

whereas the US has continued to allow access despite this increased cost. Overall, the UK approach has limited access to medications that do not meet traditional scientific thresholds used for common diseases and medications that do not meet cost-effective thresholds, while allowing coverage of cost-effective medications for hATTR amyloidosis and SMA. By comparison, the US has approved the use of multiple neuromuscular medications with less evidence than required for common diseases and none of the medications discussed meet cost-effectiveness thresholds.

CONFLICT OF INTEREST

There are no conflicts of interest.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated. Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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