Financing Hope: Persons Living with Rare Diseases in Singapore

Introduction

In the metropolitan city-state of Singapore, where modern infrastructure and advanced healthcare systems meet diverse societal needs, the plight of families dealing with rare diseases often remains overshadowed. This case study delves into the life of little Devdan,[1] a 22-month-old child who, unlike his peers, cannot stand or toddle due to spinal muscular atrophy (SMA), a severe congenital genetic condition affecting his nerves and muscles. Devdan's journey is not just a personal narrative; it serves as a lens through which we examine the broader challenges and opportunities of financing rare disease treatments in Singapore. Through his story, this case study seeks to explore the intricacies of healthcare financing, the role of community support, and the policy implications of rare disease treatment in a high-performing healthcare system like Singapore's.

Background

Devdan's Story

At just a month old, Devdan was different from other children his age. He had poor muscle tone and difficulties breathing, sucking and swallowing. He was later diagnosed with SMA, a condition that, if untreated, progressively weakens muscles and can lead to severe physical disabilities.[2] The prognosis without treatment was grave: increasing progressive proximal muscle weakness and paralysis, potentially leading to total immobility and serious feeding and breathing issues, which could be fatal.

Whilst being cared for by a multidisciplinary team of doctors and allied health professionals at the National University Hospital (NUH), Devdan's parents researched and enquired with his doctors about the possibility of administering Zolgensma®, a revolutionary but incredibly expensive gene therapy. Dubbed "the most expensive drug in the world,"[3] Zolgensma®, which costs around S$2.9 million, offers a potentially curative, one-time treatment for children with SMA. Despite its high cost, based on clinical trial data,[4] Zolgensma® is potentially life-altering as it can retard disease progression or prevent disease development if used prior to symptom onset. Administered once and intravenously, it may spare Devdan from a lifetime of alternative ongoing treatments.

Nonetheless, the staggering cost of Zolgensma® posed an immense financial challenge for Devdan's parents, Mr. Dave Devaraj, a civil servant, and Ms. Shu Wen, an interior designer. In response, a fundraising campaign was initiated by the charity platform Ray of Hope. In an extraordinary display of community solidarity and

[1] "Please Give Devdan A Second Chance of Life", *Ray of Hope*, August 3, 2021, https://rayofhope.sg/campaign/please-give-devdan-a-second-chance-of-life.html (cited 15 Dec 2023).
[2] Adele D'Amico, Eugenio Mercuri, Francesco D Tiziano and Enrico Bertini, "Spinal Muscular Atrophy", *Orphanet Journal of Rare Disease* 6, no. 71 (2011).
[3] Mark Nujiten, "Pricing Zolgensma – The World's Most Expensive Drug", *Journal of Market Access & Health Policy* 10, no. 1 (2022).
[4] Linda P Lowes et al., "Impact of Age and Motor Function in A Phase 1/2A Study of Infants with SMA Type 1 Receiving Single-Dose Gene Replacement Therapy", *Pediatric Neurology* 98, (2019): 39-45.

This case was written by Ng Qin Xiang and Clarence Ong under the guidance of Associate Professor Jeremy Lim Fung Yen, Saw Swee Hock School of Public Health, National University of Singapore and has been funded by the Lee Kuan Yew School of Public Policy. The case does not reflect the views of the sponsoring organisation nor is it intended to suggest correct or incorrect handling of the situation depicted. The case is not intended to serve as a primary source of data and is meant solely for class discussion.

generosity, anonymous donors raised S$2.87 million in 10 days, demonstrating the power of crowdfunding and collective action in Singapore.[5]

Cost of Treating SMA

Prior to the advent of gene therapy, Risdiplam® stood as the sole alternative treatment for SMA officially registered and approved by the Health Sciences Authority (HSA) in Singapore. For those undergoing this treatment, it necessitates a daily oral regimen that extends throughout their lifetime. At present, the average annual cost of Risdiplam® in public healthcare institutions in Singapore is approximately S$375,000.[6] There are no further subsidies by the government and SMA treatment is not currently covered by the Rare Disease Fund (RDF).

The new kid on the block is Zolgensma®, which has only recently been approved by HSA under the Register of Class 2 Cell, Tissue or Gene Therapy Products for use in Singapore.[7] Before April 2023, it could only be imported under the special access route. Zolgensma® is priced, according to the manufacturer Novartis, at 50% less than the calculated value-based pricing benchmarks, including the 10-year cost of conventional SMA therapy.[8] Novartis described this as a "balanced approach", considering the costs of chronic care for SMA patients and the resources expended for research and drug development.

Setting Up the Rare Disease Fund (RDF)

In January 2018, the Singapore government began mulling over the possibility of establishing a separate fund to better support children with rare diseases and their families.[9] Policy discussions culminated in the creation of the RDF, launched in July 2019, to fund five medicines used for the treatment of three rare disease conditions.[10] With an initial endowment of S$70 million, the charity fund operates by combining government-matching contributions with community donations: for every S$1 donated by the public, the government contributes S$3 (3-to-1 matching). According to the Senior Minister of State for Health, Mr Edwin Tong, the donation matching approach was adopted to galvanise the larger community to "jointly support these patients and their families as part of our caring and inclusive society".[11] The policy's focus on collective action and

[5] Hedy Yang, "Nearly $2.9 Million Raised in 10 days to Treat S'pore Baby with World's Most Expensive Drug", *The Straits Times*, August 16, 2021, https://www.straitstimes.com/singapore/health/nearly-29-million-raised-in-10-days-to-treat-spore-baby-with-worlds-most-expensive.html (cited 15 Dec 2023).

[6] "Prescription Costs for Evrysdi for Spinal Muscular Atrophy", *Ministry of Health*, March 22, 2023, https://www.moh.gov.sg/news-highlights/details/prescription-costs-for-evrysdi-for-spinal-muscular-atrophy.html (cited 15 Dec 2023).

[7] "Register of Class 2 Cell, Tissue or Gene Therapy Products", *Health Sciences Authority*, December 15, 2023, https://www.hsa.gov.sg/ctgtp/ctgtp-register.html (cited 16 Dec 2023).

[8] "AveXis Announces Innovative Zolgensma® Gene Therapy Access Programs for US Payers and Families", *Novartis*, May 24, 2019, https://www.novartis.com/news/media-releases/avexis-announces-innovative-zolgensma-gene-therapy-access-programs-us-payers-and-families.html (cited 16 Dec 2023).

[9] "Govt Looking at More Help for Children with Rare Diseases", *Today,* January 9, 2021, https://www.todayonline.com/singapore/govt-looking-more-help-children-rare-diseases (cited 15 Dec 2023).

[10] Lee Qing Ping, "New Hope for Patients with Rare Diseases with the Launching of a New Fund", *The Straits Times,* July 2, 2019, https://www.straitstimes.com/singapore/new-hope-for-patients-with-rare-diseases-with-the-launching-of-a-new-fund (cited 15 Dec 2023).

[11] "Rare Disease Fund to Provide Financial Support to Singaporeans with Rare Diseases", *Ministry of Health,* July 2, 2019, https://www.moh.gov.sg/news-highlights/details/rare-disease-fund-to-provide-financial-support-to-singaporeans-with-rare-diseases (cited 15 Dec 2023).

shared responsibility mirrors the core principles of the "Many Helping Hands" approach, a community-based framework that encourages collaboration among stakeholders to address social welfare issues.[12]

Although the RDF's initial focus was directed towards five specific treatments, its non-restrictive framework allows for future expansion to include a wider range of conditions and therapies. In November 2019, the RDF was expanded to cover Pompe disease, a rare inherited neuromuscular disorder where patients can incur medical expenses in excess of S$500,000 each year.[13] Two years later, the RDF was extended to support the treatment of Mucopolysaccharidosis type VI as well.[14] As of 2023, the RDF covers five conditions and seven medications,[15] and has helped relieve the medical financial burden of nine Singaporean patients.[16] It is important to note that the scope of the RDF caters to a relatively small percentage requiring additional financial assistance for high-cost treatments. Other avenues, such as *Medisave*, *MediShield Life*, and *MediFund*,[17] exist to assist the majority of individuals with rare diseases by covering treatments and medical bills. However, the extent of financial support available through these avenues for such individuals remains limited and subjected to annual caps.

As of the conclusion of the fiscal year 2022, the RDF had a reported total of S$143 million.[18] There have been numerous calls to expand the scope of the RDF to cover more illnesses. In 2021, Member of Parliament (MP) Cheryl Chan called for the RDF to be extended to cover the treatment of Neuroblastoma and Krabbe disease, which are among the 10 most common rare diseases afflicting young children in the world.[19] She further added that patients with rare diseases outside the list of approved conditions and medication, unfortunately, faced nothing but "the strictest of processes and a flat rejection". While there remains a strong desire and momentum to support life-saving treatments for various rare diseases, the truth is that the healthcare financing system "is not designed to support such high-cost treatments".[20] The government's position, as

---

[12] Abdullah Tarmugi, "Statement by Mr Abdullah Tarmugi", *National Archives of Singapore Library,* March 10, 1993, https://www.nas.gov.sg/archivesonline/data/pdfdoc/at19950310s.pdf (cited 15 Dec 2023).

[13] Yuen Sin, "Rare Disease Fund Now Covers Pompe Disease, a Rare Inherited Neuromuscular Disorder", *The Straits Times,* November 3, 2019, https://www.straitstimes.com/singapore/health/rare-disease-fund-now-covers-pompe-disease-a-rare-inherited-neuromuscular-disorder (cited 15 Dec 2023).

[14] "Rare Disease Fund Extends Support to Another Rare Disease with $6.7 million gift", *KK Women's and Children's Hospital,* August 19, 2021, https://www.kkh.com.sg/news/giving-philanthropy/rare-disease-fund-extends-support-to-another-rare-disease-with-67-million-gift (cited 15 Dec 2023).

[15] "Rare Disease Fund", *KK Women's and Children's Hospital*, 2023, https://www.kkh.com.sg/giving/Documents/Rare-Disease-Fund/index.html (cited 15 Dec 2023).

[16] Jean Iau, "9 Singaporean Patients Helped by Rare Disease Fund since 2019", *The Straits Times,* April 11, 2023, https://www.straitstimes.com/singapore/9-patients-or-04-per-cent-of-those-who-suffer-from-rare-diseases-helped-by-fund-since-2019 (cited 15 Dec 2023).

[17] Medisave is a national medical savings scheme which helps individuals put aside part of their income into an account to meet their future hospitalisation, day surgery and certain outpatient expenses. MediShield is a catastrophic medical insurance scheme which helps Medisave account holders meet the cost of treatment for serious or prolonged illnesses. Medifund is an endowment fund that serves as a safety net to help needy Singapore citizens who are not able to pay for their heavily subsidised medical care at restructured hospitals.

[18] "Size Annual Income and Expenditure of Rare Disease Fund", *Ministry of Health Singapore*, October 4, 2023, https://www.moh.gov.sg/news-highlights/details/size-annual-income-and-expenditure-of-rare-disease-fund (cited 15 Dec 2023).

[19] Justin Ong, "Rare Disease Fund Should Cover More Illnesses, Benefit More People: MP Cheryl Chan", *Today*, August 3, 2021, https://www.todayonline.com/singapore/rare-disease-fund-should-cover-more-illnesses-benefit-more-people-cheryl-chan.html (cited 14 Dec 2023).

[20] Zhaki Abdullah, "Support for Treatment of Rare Illnesses, Regardless of Cost, Must Be Carefully Reviewed: Ong Ye Kung", *The Straits Times,* November 14, 2022, https://www.straitstimes.com/singapore/health/support-for-treatment-for-rare-illnesses-regardless-of-cost-must-be-carefully-reviewed-ong-ye-kung (cited 15 Dec 2023).

explained in a Parliamentary reply, is that increasing donations, particularly from high-net-worth individuals, foundations, and corporate sponsors, remains the key approach to securing additional funds for patients and their families.[21]

Problem

Through the case study, we see that the care and treatment of SMA, a rare and life-threatening genetic disease, presents a significant challenge, both medically and financially. SMA carries with it a dire prognosis for affected children, especially those with the most severe form, who historically have not lived past the age of two years.[22] This scenario changed with the introduction of Zolgensma®, an innovative gene therapy approved by the United States Food and Drug Administration (US FDA) in 2019 and recently by the HSA in Singapore. The treatment, which corrects the genetic defect in SMA, significantly improves muscle movement, function, and survival rates. However, it comes with a hefty price tag of around S$2.9 million for a single dose.

Although the RDF is a national charity fund aimed at providing long-term financial support to Singapore Citizens with rare genetic diseases who require high-cost treatments, it is currently restricted to only seven medications for five conditions,[23] compared to more than 20 approved novel medications by the US FDA for rare diseases.[24] Patients who have other forms of rare diseases and require medications not covered by the RDF, thus have to turn to charity organisations or crowdfunding. In fact, only nine Singaporeans, which translates to only 0.4% of some 2000 to 3000 local Singaporeans diagnosed with rare diseases, have received help from the RDF since its inception.[25]

This growing dependency on public charity for funding critical treatments potentially risks eroding confidence in the capability of Singapore's healthcare system to adequately provide for all its citizens, particularly those grappling with rare diseases. After Devdan, the following year saw two more infants, Zayn[26] and Shamel,[27] requiring crowdsourcing for funds for Zolgensma® through similar means. Relying on public goodwill and individualised crowdfunding for rare disease treatment are unlikely to be sustainable in the long run. Some children affected by SMA may also succumb to their illness before raising sufficient funds necessary for advanced treatment.[28] Although the number of individuals diagnosed with SMA in Singapore is relatively small (about 40 to 50 according to a MOH parliamentary reply in March 2023[29]), the broader implications of financing such treatments are significant, given the continued advancements in medical innovation and the likelihood of more such therapies becoming available in the future. There are also some 2000 to 3000

[21] Goh Yan Han, "More Ill Children Can Get Help with More Donations to Rare Disease Fund Says Koh Poh Koon", *The Straits Times,* August 2, 2021, https://www.straitstimes.com/singapore/politics/parliament-more-ill-children-can-get-help-with-more-donations-to-rare-diseases (cited 15 Dec 2023).
[22] D'Amico, Mercuri, Tiziano and Bertini, "Spinal Muscular Atrophy".
[23] "Rare Disease Fund".
[24] Ong, "Rare Disease Fund Should Cover More Illnesses".
[25] Iau, "9 Singaporean Patients".
[26] Loraine Lee, "Baby in NUH ICU with Severe Disease, Parents Hope Raise S$3 million for 'World's Most Expensive Drug'", *Today,* August 23, 2022, https://www.todayonline.com/singapore/baby-icu-nuh-spinal-muscular-atrophy-severe-disease-fundraiser-expensive-drug-1975686 (cited 15 Dec 2023).
[27] Jean Iau, "Parents of 17-Month-Old with Rare Genetic Condition Race to Raise $3 million for Treatment", *The Straits Times,* February 5, 2023, https://www.straitstimes.com/singapore/parents-of-17-month-old-with-rare-genetic-condition-race-to-raise-3-million-for-treatment (cited 15 Dec 2023).
[28] Kayla Wong, "14-Month-Old Baby Rayyan with Rare Genetic Disorder Dies", *Mothership,* January 1, 2021, https://mothership.sg/2021/01/rayyan-baby-passed-away/.
[29] "Singaporeans Diagnosed with Spinal Muscular Atrophy and Cost of Treatment", *Ministry of Health*, 22 March 2023, https://www.moh.gov.sg/news-highlights/details/singaporeans-diagnosed-with-spinal-muscular-atrophy-and-cost-of-treatment (cited 14 Dec 2023).

Singaporeans living with other chronic rare diseases who require the same, if not greater support with the substantial costs of treatment.

In addressing rare diseases, it is crucial to establish a suitable financing structure to avoid creating a schism between families who can afford these treatments and those who cannot. Health systems should provide equitable treatment access for all patients, regardless of the rarity of their condition. Beyond SMA, how can healthcare systems fund the care of patients with chronic rare diseases? Can insurance mechanisms help defray the hefty costs, or can the RDF grow and reach more patients?

Comparative Analysis

It is important to clarify that the comparative analysis includes countries of similar high-income status, ensuring a fair assessment and relevant insights for Singapore. Given the intricacies within the rare disease policy ecosystem, our analysis is confined to the processes of listing and reimbursing orphan drugs, as well as any special funding mechanisms available for such drugs. Consequently, government initiatives focusing on advancing research and development (R&D) for new orphan drugs, elevating awareness and diagnostic capabilities for rare diseases, and the influence of rare disease advocacy groups' social and political capital are not within the scope of this discussion.

Australia's Approach to Rare Disease Funding

A national single-payer funding system, *Medicare* serves as the publicly funded universal health insurance scheme in Australia, supplemented by the Pharmaceutical Benefits Scheme (PBS), which aids in covering expenses for certain medications and treatments. The Pharmaceutical Benefits Advisory Committee (PBAC), an independent expert body appointed by the government, employs specific criteria, including cost-effectiveness, to assess a medicine's eligibility for inclusion in the PBS.[30] While the consideration of cost-effectiveness is pivotal for managing budgets, it poses a challenge in evaluating drugs for rare diseases due to their limited evidence base on effectiveness and higher pricing, influenced by extensive research costs and reduced competition in smaller markets.[31] Accordingly, Australia established the Life-Saving Drugs Program (LSDP) in 1995 as a complementary initiative to the PBS. The LSDP aims to broaden access to high-cost drugs intended for treating rare diseases, acknowledging the unique challenges posed by such medications within the healthcare landscape. As of 2023, 17 medicines are subsidised via the LSDP.[32]

Risk-sharing agreements are commonly used by the PBS and LSDP to manage certain risks and uncertainties with new orphan drugs. Sponsors may voluntarily propose risk-sharing agreements with are captured through a legal deed of agreement that is negotiated between the sponsor and the Government. Some financial risk share agreements can be class deeds where sponsors share the risk based on market share. While such mutual agreements remain confidential, the majority of agreements are likely to be financial-based agreements which

[30] "AMWG Interim Report to Government – Attachment A", *The Pharmaceutical Benefits Scheme,* July 2008, https://www.pbs.gov.au/info/general/working-groups/amwg/amwg-interim-report-attachment-a (cited 15 Dec 2023).
[31] "Drugs for Rare Diseases: A Review of National and International Health Technology Assessment Agencies and Public Payers' Decision-Making Processes", *Canada's Drug and Health Technology Agency,* January 25, 2023, https://www.cadth.ca/drugs-rare-diseases-review-national-and-international-health-technology-assessment-agencies-and (cited 15 Dec 2023).
[32] "About the Life Saving Drugs Program", *Department of Health and Aged Care,* April 1, 2023, https://www.health.gov.au/our-work/life-saving-drugs-program/about-the-lsdp (cited 15 Dec 2023).

include price-volume, rebate or discount-based schemes.[33] However, a hybrid of financial and outcome-based agreements is also possible.[34]

Specifically, for the LSDP however, the usage of outcome-based risk-sharing agreements are referenced.[35] These agreements allow funding under the condition that ongoing data collection assesses the medicine's impact on the disease. Price adjustments may occur if emerging data suggests the medicine's efficacy differs from initial assumptions. In the past, LSDP mirrored PBS by implementing a policy to progressively reduce medicine prices on specific listing anniversaries.[36] However, as of June 2022, this policy within LSDP has been discontinued.[37] For orphan drugs under the LSDP, periodic reviews 24 months post-listing remain a crucial aspect of assessing medication usage, clinical benefits, and financial impacts.[38] Recommendations post-review may involve modifying eligibility criteria, adjusting risk-sharing arrangements, altering data collection scopes, referring the medication to PBAC for PBS listing consideration, or even removing it from the LSDP listing.[39]

In 2022, Zolgensma® was approved by listing under the PBS, saving approximately 20 patients AUS$ 2.5 million.[40] In the following year, the scheme was expanded to include pre-symptomatic babies as well, thus extending the subsidy to an additional 15 babies.[41] A cost-minimisation approach was taken, where PBS received a substantial unlisted discount from the sponsor.[42] An outcome-based risk-sharing agreement was also established, which encompassed an unspecified rebate on the cost over at least five years, following circumstances of a patient's death and the failure to meet certain developmental milestones.[43]

United Kingdom's Approach to Rare Disease Funding

The National Health Service (NHS) stands as the United Kingdom's (UK) publicly funded healthcare system, operating on the core principles of universality and free access to care for all, regardless of nationality or

---

[33] Haitham W Tuffaha and Paul A Schffham, "The Australian Managed Entry Scheme: Are We Getting it Right?", *Pharmacoeconomics* 36, no. 5 (2018): 555-565.

[34] Christine Y Lu et al., "Patient Access Schemes in Asia-pacific Markets: Current Experience and Future Potential", *Journal of Pharmaceutical Policy and Practice* 8, no. 6 (2015).

[35] "Procedure Guidance for Medicines Funded through the Life Saving Drugs Program (LSDP)", *Department of Health and Aged Care,* July 1, 2018, https://www.health.gov.au/sites/default/files/documents/2021/11/procedure-guidance-for-medicines-funded-through-the-life-saving-drugs-program-lsdp.pdf (cited 15 Dec 2023).

[36] Chim L, Salkeld G, Kelly P, Lipworth W, Hughes DA, et al. "Societal Perspective on Access to Publicly Subsidised Medicines: A Cross Sectional Survey of 3080 Adults in Australia." *PLoS One* 12, no. 3 (2017).

[37] "Ensuring the Future Sustainability of the Life Saving Drugs Program (LSDP)", *Department of Health and Aged Care,* 2020, https://www.health.gov.au/sites/default/files/documents/2020/10/ensuring-the-future-sustainability-of-the-life-saving-drugs-program.pdf (cited 15 Dec 2023).

[38] "Procedure Guidance for Medicines Funded through the Life Saving Drugs Program (LSDP)".

[39] Ibid.

[40] "Improving Access to Medicines – New Medicines Added to the Pharmaceutical Benefits Scheme", *Department of Health and Aged Care,* May 2022, https://www.health.gov.au/sites/default/files/documents/2022/03/budget-2022-23-new-medicines-added-to-the-pharmaceutical-benefits-scheme.pdf (cited 16 Dec 2023).

[41] Mark Butler, "Life changing gene therapy for babies with spinal muscular atrophy", *Department of Health and Aged Care,* October 23, 2023, https://www.health.gov.au/ministers/the-hon-mark-butler-mp/media/life-changing-gene-therapy-for-babies-with-spinal-muscular-atrophy (cited 16 Dec 2023).

[42] "Public Summary Document – November 2020 PBAC Meeting with May 2021 Addendum", *Pharmaceutical Benefit Scheme,* May 2021, https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2021-05/files/onasemnogene-abeparvovec-psd-may-2021.docx (cited 16 Dec 2023).

[43] "Public Summary Document – November 2020 PBAC Meeting with May 2021 Addendum and September 2021 Addendum", *Pharmaceutical Benefit Scheme,* September 2021, https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2021-09/files/onasemnogene-abeparvovec-psd-september-2021.docx (cited 16 Dec 2023).

immigration status. As a single-payer system, it covers primary, emergency, and compulsory healthcare at no cost to individuals. Within the NHS framework, the National Institute for Health and Care Excellence (NICE) evaluates health technologies based on evidence-based assessments of their effectiveness, safety, and cost-effectiveness. NICE's role is to ascertain if proposed healthcare expenditures within the NHS offer superior value compared to alternative treatments. Their evaluation involves analysing the cost and benefit of new treatments relative to existing ones, often considering interventions costing less than £20,000 per Quality-Adjusted Life Year (QALY) as cost-effective, allowing some flexibility up to £30,000 per QALY.[44] Notably, once NICE approves a treatment, the NHS is mandated to provide funding for it.

Specific to rare diseases, gaining approval for expensive orphan drugs often faces hurdles due to insufficient evidence for smooth endorsement by the NICE. In 2021, England's Rare Disease Framework aimed to address this inequality by refining the technology approval process.[45] The changes within the Highly Specialised Technologies (HST) Programme give more weight to health benefits in severe conditions, offer flexibility when evidence generation is challenging, and offer a higher cost-effectiveness threshold of £300,000 per QALY.[46] Additionally, the Innovative Medicines Fund (IMF), modelled on the reformed Cancer Drugs Fund (CDF), supports early access to promising treatments for any condition, including rare diseases.[47] With a £340 million annual grant, the IMF provides interim funding for drugs with uncertain clinical and cost-effectiveness. Data collection via trials and studies aims to fill evidence gaps. Negotiations on pricing occur within a value-based framework to strive for cost-effectiveness.[48] However, drugs not deemed superior or cost-effective compared to existing treatments during this evaluation may not receive additional funding. Manufacturers would then bear the financial responsibility for patient access if NICE does not recommend the drug.[49] The approach, though the timeline of patient funding is uncertain, seeks to incentivise high-risk, potentially breakthrough treatments by attracting innovative manufacturers to invest in substantial therapeutic advancements.

Zolgensma®'s successful listing as a subsidised drug under the NHS in 2021 served as the inspiration for the creation of the IMF.[50] A confidential commercial discount was agreed upon, which potentially lowered the Incremental Cost Effectiveness Ratio (ICER), allowing Zolgensma® to be approved under the HST Programme. An outcome-based risk-sharing agreement was set up, linking payment for the drug to substantial clinical

[44] Christopher McCabe, Karl Claxton and Anthony J Culyer, "The NICE Cost-Effectiveness Threshold: What It Is and What That Means", *PharmacoEconomics* 26, no. 9 (2008): 733-44.
[45] "England Rare Diseases Action Plan 2022", *Department of Health and Social Care,* February 2022, https://assets.publishing.service.gov.uk/media/62191cf0d3bf7f4f0ec9b6bf/England-Rare-Diseases-Action-Plan-2022.pdf (cited 15 Dec 2023).
[46] "Health Technology Evaluation Manual", *National Institute for Health and Care Excellence,* February 1, 2022, https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation (cited 15 Dec 2023).
[47] "The Innovative Medicines Fund Principles", *National Institute for Health and Care Excellence,* June 6, 2022, https://www.england.nhs.uk/wp-content/uploads/2022/06/B1686-the-innovate-medicines-fund-principles-june-2022.pdf (cited 15 Dec 2023).
[48] "Defining Value-Based Healthcare in the NHS", *Centre for Evidence-Based Medicine,* April 2019, https://www.cebm.net/wp-content/uploads/2019/04/Defining-Value-based-healthcare-in-the-NHS-Final4-1.pdf (cited 15 Dec 2023).
[49] Aris Angelis et al., "The Innovative Medicines Fund: A Universal Model for Faster and Fairer Access to New Promising Medicines or a Trojan Horse for Low-Value Creep?", *Journal of the Royal Society of Medicine* 116, (2023):324-330.
[50] Michelle Roberts, "Innovative Medicines Fund Launched to Fast-Track Drugs", *BBC,* June 7, 2022, https://www.bbc.com/news/health-61709542 (cited 16 Dec 2023).

advancements. The payment spans five years, and if the therapy falls short of delivering expected clinical outcomes, a partial refund will be issued.[51]

United States' Approach to Rare Disease Funding

The United States' approach involves a combination of federal and state programmes, private insurance, pharmaceutical company initiatives, and non-profit organisations. A signature initiative is the Orphan Drug Act of 1983, which was signed into law and provides incentives such as tax credits for clinical research, grant funding, assistance in clinical research design, and seven years of market exclusivity upon drug approval for drugs used to treat rare (or orphan because they have been typically neglected) diseases,[52] although some have criticised this to be overly lucrative for drug manufacturers.[53] The US National Institutes of Health (NIH), particularly through the National Center for Advancing Translational Sciences (NCATS) and its Office of Rare Diseases Research (ORDR), also plays a significant role in funding and conducting research on rare diseases. The Rare Diseases Clinical Research Network is an initiative that involves collaboration between the NIH, patient advocacy groups, and clinical researchers. Suffice to say, all these efforts ensure constant innovation and a steady pipeline of drug development to change the disease course of rare disease sufferers.

In the US, private health insurance is a major contributor to covering the costs of treatments, including those for rare diseases.[54] However, coverage and out-of-pocket costs can vary significantly and the health systems can be challenging to navigate. An analysis of out-of-pocket spending on orphan drugs from 2013 to 2018 also found an increasing trend (almost doubling from 2013 to 2018) and a higher burden on payers and families despite private insurance coverage.[55] Parents and guardians of children with SMA have also reflected drawn out processing coverage decisions by insurance companies, a lack of transparency in the claims and preauthorisation processes and being dependent on employment insurance for coverage.[56]

In terms of government-funded health insurance programmes (*Medicaid* and *Medicare*), they provide coverage for certain individuals, including those with disabilities and the elderly. They may cover some treatments for rare diseases, depending on the state and specific policy details. In particular, the Affordable Care Act (ACA), also known as Obamacare, has provisions that impact rare disease patients, such as prohibiting insurance companies from denying coverage due to pre-existing conditions, which includes many rare diseases.[57]

Also worth mention is the numerous non-profit organisations in the US that provide support for rare disease research and advocate for patients.[58] These organisations often fundraise to support research, increase awareness, and assist patients with accessing and affording treatments.

---

[51] Reinaldo Guimaraes, "New Challenges in Health Technology Assessment (HTA): The Case of Zolgensma", *cien Saude Colet* 28, no. 7 (2023): 1881-1889.

[52] Shailin Thomas and Arthur Caplan, "The Orphan Drug Act Revisited", *JAMA* 321, vol. 9 (2019): 833-4.

[53] Côté André and Bernard Keating, "What is Wrong with Orphan Drug Policies?" *Value in Health* 15, vol. 8 (2012): 1185-91.

[54] Kao-Ping Chua and Rena M Conti, "Trends In Orphan Drug Spending And Out-Of-Pocket Spending Among US Children, 2013–18", *Health Affairs* 39, vol. 10 (2020): 1806-11.

[55] Chua and Conti, "Trends in Orphan Drug Spending", 1806-11.

[56] Tai L S Pasquini, Sarah L Goff and Jennifer M Whitehill, "Navigating the US Health Insurance Landscape for Children with Rare Diseases: A Qualitative Study of Parents' Experiences" *Orphanet Journal of Rare Diseases* 16, vol. 1 (2021): 1-4.

[57] "Protecting Patients in State-Regulated Insurance", *National Organization for Rare Diseases,* https://rarediseases.org/policy-issues/state-regulated-insurance (cited 16 Dec 2023).

[58] Debbie Drell, Ashanthi De Silva and Cornelia Lee, "What Rare Disease Patient Advocacy Groups Are Doing to Mitigate the Effects of Disparities", *Advances in Pulmonary Hypertension* 21, no. 2 (2022): 35-43.

South Korea's Approach to Rare Disease Funding

In South Korea, healthcare revolves around the National Health Insurance Service (NHIS), a public insurance programme managed by the Ministry of Health and Welfare.[59] South Koreans with adequate income contribute to insure themselves and their dependents in this single-payer system. Introduced in 2000, the Mandatory Designation System necessitates all hospitals and clinics to be designated medical care institutions, obligated to provide services to participants in the NHIS, encompassing nearly the entire population.[60] South Korea made a pivotal shift in its National Health Insurance (NHI) drug reimbursement system in 2007, transitioning from a negative to a positive listing approach.[61] Post-2007, only drugs with confirmed cost-effectiveness became eligible for reimbursement. As a result of this change, obtaining reimbursement for orphan drugs where statistically verifying clinical outcomes is challenging, became more arduous. Between 2007 and 2020, South Korea saw the launch and approval of 168 orphan drugs, with 94 of them making it onto the reimbursement formulary.[62]

When considering reimbursement pathways for orphan drugs without alternatives, three potential pathways exist. For orphan drugs classified as essential drugs (ED) or falling under pharmacoeconomic waiver (PEW) categories, submission of a pharmacoeconomic study is not necessary. Instead, these drugs can be listed by referencing the listed prices of the same drug in the A7 countries.[63] For ED drugs, the average adjusted price in the A7 country sets the reimbursable price, while for PEW drugs, it is the lowest price among the adjusted A7 country prices.[64] ED classification hinges on meeting four criteria: alternative availability, disease severity, patient count, and clinical efficacy. As for PEW drugs, they must simultaneously demonstrate clinical necessity, and evidence challenges, and be listed in over three A7 countries to qualify. The risk-sharing agreement (RSA) pathway is specifically designated for anticancer drugs and orphan drugs lacking alternatives or therapeutically equivalent options.[65] However, within this subset, only those drugs addressing life-threatening critical diseases are eligible to pursue the RSA route. In each pathway, the price for reimbursement gets decided by a committee at the Health Insurance Review and Assessment Service (HIRAS), where price negotiation with the NHIS to agree on its budget impact ensues.[66] At present, no special fund for rare disease medications exists in South Korea although some conditions and drugs are covered under the NHIS.[67]

Specific to Zolgensma®, authorities in South Korea studied the results of the available clinical trials and found convincing long-term therapeutic effect that was maintained more than seven years after one dose

[59] Boyoung Jeon and Soonman Kwon, "Effect of Private Health Insurance on Health Care Utilization in a Universal Public Insurance System: A Case of South Korea", *Health Policy* 113, no. 1 (2013): 69-76.
[60] Young Joo Song, "The South Korean Healthcare System", *Japan Medical Association Journal* 52*,* no. 3 (2009): 206-209.
[61] Seung-Lai Yoo et al., "Improving Patient Access to New Drugs in South Korea: Evaluation of the National Drug Formulary System", *International Journal of Environmental and Public Health 16,* no. 2 (2019): 288.
[62] "RHealth Insurance Review and Assessment Service: National Drug Formulary", *Wonju,* 2020, https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA030014050000 (cited 15 Dec 2023).
[63] The A7 countries include the US, the UK, Italy, Germany, Japan, Switzerland, and France.
[64] Seung-Lai Yoo et al., "Improving Patient Access to New Drugs in South Korea: Evaluation of the National Drug Formulary System", *International Journal of Environmental and Public Health* 16*,* no. 2 (2019): 288.
[65] Yoo et al., "Improving Patient Access", 288.
[66] Sungju Kim, Hyunyoung Cho, Junhong Kim, Kyungmin Lee and Jong Hyuk Lee, "The Current State of Patient Access to New Drugs in South Korea under the Positive List System: Evaluation of the Changes since the New Review Pathways", *Expert Review of Pharmacoeconomics Outcomes Research* 2, no. 1 (2021): 119-126.
[67] Sung-Shil Lim et al., "The Cumulative Incidence and Trends of Rare Diseases in South Korea: A Nationwide Study of the Administrative Data from the National Health Insurance Service Database from 2011–2015", *Orphanet Journal of Rare Diseases* 14, no. 1 (2019): 1-6.

administration of Zolgensma®.[68] As such, since August 2022, the drug Zolgensma® is covered under the NHIS and patients who require it only have to pay 5.98 million won (around S$6200) despite the drug's marketed price of 2 billion won (around S$2.2 million).[69] Patients who receive the drug must consent to a five-year follow-up for regular evaluations of response as part of the government's effort to continually re-evaluate the usefulness and cost-effectiveness of insured drugs.

Comparison with Singapore's Approach

Singapore's approach to rare disease medication access focuses on budgetary impact, resembling South Korea's practice of exempting certain orphan drugs from cost-effectiveness analysis. There are shared challenges in conducting such analyses for high-cost, rare disease drugs given the infrequency of rare diseases. However, Singapore's system, unlike South Korea's, appears slow in adding drugs to its whitelist and lacks a transparent benchmark for selecting orphan drugs within its RDF. Internationally, countries like Australia, the UK, and South Korea also utilise distinct risk-sharing agreements, which Singapore's framework does not currently emulate. Additionally, the RDF's reliance on public goodwill and donations admittedly creates funding instability, and the absence of an early access mechanism or a real-world data monitoring system for orphan drugs prolongs approval processes, contrasting with practices elsewhere. This inadvertently results in inequities in Singapore, particularly for patients with non-listed rare diseases.

Policy Options

Risk-Sharing Agreements with Biomedical and Pharmaceutical Companies

To address the high costs (and current uncertain long-term efficacy) of treatments for rare diseases like SMA, Singapore can benefit from implementing risk-sharing agreements with pharmaceutical companies. This approach involves the government or healthcare providers negotiating with drug manufacturers to agree on terms that link the payment for the drugs to their performance in the real world or to specific outcomes. Given the paucity of long-term effectiveness data for treatments for rare diseases, making future payments conditional on the actual health outcomes and cost savings achieved would be a financially prudent approach for governments.

The core advantage of this model lies in its potential to make expensive therapies more accessible while managing financial risks. These agreements can be structured in various ways, such as paying for a drug only if it meets certain efficacy benchmarks or spreading the cost over time based on continued patient benefit. This strategy aligns the interests of public healthcare systems, patients, and pharmaceutical companies, ensuring that payment is contingent on the actual value provided by the treatment. Moreover, a payment-by-instalment method, which has been contemplated elsewhere, helps to spread the cost of these high-priced therapies over a period of time, thereby easing the immediate impact on healthcare budgets.[70]

Drugs for rare diseases are currently reimbursed in a growing number of developed countries, and various efforts have been made to address the high cost of Zolgensma® and other gene therapies, including discussions on pricing models, reimbursement strategies, and innovative payment arrangements to ensure patient access and affordability. Such arrangements are not new, and outcome-based rates, tied to short- and long-term outcomes of patients post-treatment, have been successfully established for other high-cost

[68] Kim Yun-Ni, "Ultra-Expensive SMA Drug Zolgensma to Get Insurance Benefits from August", *Korea Biomedical Review,* July 21, 2022, https://www.koreabiomed.com/news/articleView.html?idxno=14205 (cited 16 Dec 2023).
[69] Marianne Chang. "Korea's 1st Gene Treatment for SMA Zolgensma Gets Insurance Benefits", *Korea Biomedical Review,* August 1, 2022, https://www.koreabiomed.com/news/articleView.html?idxno=14296 (cited 16 Dec 2023).
[70] Troyen A Brennan and James M Wilson, "The Special Case of Gene Therapy Pricing" *Nature Biotechnology* 32, no. 9 (2014): 874-6.

treatments such as Luxturna® in the US.[71] In fact, risk-sharing agreements to mitigate investment risk for high-cost drugs are growing at an annual rate of 24% since 2012.[72] Such agreements also benefit from the involvement of various stakeholders such as patients, healthcare providers, payers, policymakers, and manufacturers. In the case of Zolgensma®, a risk-sharing agreement could involve initial partial payment, with subsequent payments contingent upon the drug demonstrating a certain level of effectiveness in patients. Similar to the South Korean approach, such agreements also encourage pharmaceutical companies to invest in long-term studies and data collection to validate the effectiveness of their products.

Nonetheless, outcome-based pricing shifts some financial risks to drug manufacturers, who may only receive full payment upon proven effectiveness of the treatment. This risk might lead to higher initial pricing or reluctance from manufacturers to engage in further research and development of therapeutics for other rare diseases. Likewise, outcome-based pricing models require certain alterations in traditional healthcare insurance practices, which may be resistant to change due to established protocols and risk aversion. Defining reasonable outcomes that accurately reflect the effectiveness of the treatment can also be a challenge, especially when it comes to gene therapies where studies are still ongoing and long-term effects are not yet fully understood.[73] The added administrative burden for healthcare providers and insurers to keenly track and monitor patient outcomes could also potentially impact the overall efficiency of the healthcare system.

Despite these challenges, the potential benefits of risk-sharing agreements in managing the financial burden of expensive rare disease treatments make them a compelling option for Singapore. They offer a pragmatic approach to balancing cost, access, and innovation in healthcare.

Creating A Rare Disease Investment Fund

Modelled after the proposal by Massachusetts Institute of Technology (MIT) Sloan School of Management Professor Andrew Lo and "The Rare Disease Fund Act of 2019" tabled to the United States House Financial Services Committee,[74] the RDF could be redesigned as an investment fund, where it would involve a mix of private investments, supported and encouraged by government backing. The idea is that by utilising the securitisation technique, the fund can effectively pool various assets and sell them off to investors, thereby attracting a larger pool of capital than typically available to biotechnology and pharmaceutical startups. The Singapore government could offer guarantees on certain securities, making them more attractive to investors to innovate new drugs and thus reducing their risk and eventual costs.

A key thrust behind such an investment fund would be to bridge the gap in early-stage drug development, often referred to as the "valley of death"[75] in biomedical research and development. This phase, characterised

[71] "Spark Therapeutics Announces First-of-their-kind Programs to Improve Patient Access to LUXTURNA™ (voretigene neparvovec-rzyl), a One-Time Gene Therapy Treatment", *Spark Therapeutics*, January 3, 2018, https://sparktx.com/press_releases/spark-therapeutics-announces-first-of-their-kind-programs-to-improve-patient-access-to-luxturna-voretigene-neparvovec-rzyl-a-one-time-gene-therapy-treatment/ (cited 14 Dec 2023).

[72] Alex Watt, "Risk-Sharing Agreements are Growing at a Rate of 24%", *Pharmaceutical Technology,* February 10, 2023, https://www.pharmaceutical-technology.com/pricing-and-market-access/risk-sharing-agreements/#?cf-view (cited 16 Dec 2023).

[73] Shuo Yang et al., "Long-Term Outcomes of Gene Therapy for the Treatment of Leber's Hereditary Optic Neuropathy". *EBioMedicine* 10, (2016): 258-68.

[74] "A Financial Public Private Partnership to Cure Rare Diseases", *MIT Sloan School of Management*, August 16, 2019, accessed https://mitsloan.mit.edu/centers-initiatives/mit-gcfp/a-financial-public-private-partnership-to-cure-rare-diseases.html (cited 14 Dec 2023).

[75] Marcus C Parrish, Yuan Jin Tan, Kevin V Grimes and Daria Mochly-Rosen, "Surviving in the Valley of Death: Opportunities and Challenges in Translating Academic Drug Discoveries" *Annual Review of Pharmacology and Toxicology* 59, (2019): 405-21.

by high risk and a lack of funding, is where many promising treatments falter, especially given the idiosyncratic risk from issues with the drug pipeline and systematic risk from prevailing economic conditions.[76] By providing essential funding at this critical stage, research into rare disease treatments could grow to a point where they can attract more traditional forms of venture capital and also enjoy certain economies of scale. By providing partial guarantees or other forms of financial support, the government effectively helps to de-risk these investments, making them more attractive and feasible for the private sector.

Singapore is ideally positioned to create and trial a national registry and research fund for rare diseases, owing to our strong standing in biomedical research, good reputation among pharmaceutical firms, advanced medical capabilities, and expertise in conducting clinical trials and long-term patient monitoring.[77] A recently inaugurated cell therapy facility, spanning 2,000 square meters and encompassing four translational laboratories and a quality control laboratory adhering to good manufacturing practice standards, has been established to cater to the growing need for cell and gene therapy locally, thereby enhancing access for patients who require these novel therapies.[78]

Nevertheless, private investors and companies typically expect a return on their investment. Given the high risk and long development timelines associated with rare disease drug development, achieving sufficient returns to attract and retain investors could be challenging. Such an investment fund runs the risk of misalignment between investor expectations and the social goals of the fund. Investors may prioritise projects with higher potential returns, which may not always align with the most urgent public health needs. Effective collaboration between various stakeholders (government, private investors, pharmaceutical companies, and research institutions) is difficult to achieve. Moreover, the government's role in providing financial guarantees can be complex and politically sensitive. The government must also ensure that the companies and investors involved have good credit histories and proof of credit worthiness as such an investment fund ultimately involves using public funds to underwrite private investment risks, which may not always be politically or publicly acceptable.

Resolution

There is a happy ending to Devdan's story. In just 10 days, a substantial sum of S$2.87 million was raised through the efforts of approximately 30,000 donors via the Ray of Hope crowdfunding platform.[79] In the last news update, the treatment markedly improved Devdan's feeding issues and motor abilities, enabling him to stand and walk with assistance, and even engage in activities such as tricycle riding, achievements that far surpassed the initial expectations of his grim medical prognosis. This fundraising effort, which is one of the largest for an individual beneficiary in Singapore, underscores the potential of collective action in addressing the financial barriers associated with high-cost medical treatments. At the same time, it also raises important considerations regarding the sustainability and scalability of such crowdfunding efforts in the broader context of healthcare financing.

---

[76] Richard T Thakor et al., "Just How Good an Investment is the Biopharmaceutical Sector?" *Nature Biotechnology* 35, no. 12 (2017): 1149-57.

[77] Raj Thampuran and Kong Hwai Loong, "The Biomedical Sciences: Research for Better Health" in *The Singapore Research Story*, ed. Hang Chang Chieh, Low Teck Seng and Raj Thampuran (Singapore: World Scientific, 2016), 101-33.

[78] Zhaki Abdullah, "New Manufacturing Facility, Task Force Set Up as Singapore Ups Game in Cell and Gene Therapy", *The Straits Times*, August 5, 2022, https://www.straitstimes.com/singapore/health/new-manufacturing-facility-task-force-set-up-as-s-pore-ups-game-in-cell-and-gene-therapy (cited 15 Dec 2023).

[79] Theresa Tan and Nadine Chua. "'It's a Miracle': Boy Treated with $3m Drug Donated by Public Can Now Walk with Support", *The Straits Times*, January 19, 2022, https://www.straitstimes.com/singapore/community/its-a-miracle-boy-treated-with-3m-drug-donated-by-public-can-now-walk-with-support (cited 15 Dec 2023).

While no country has effectively addressed this challenge of financing rare diseases, majority have acknowledged that fairness of access is a moral obligation of public health systems. Given the rarity and substantial expense of treatments for rare diseases, the most feasible solution seems to lie in improving national healthcare insurance schemes.

Discussion Questions

1. What are the key challenges faced by the Rare Disease Fund in Singapore?
2. How does Singapore's approach to rare disease funding compare with other developed countries such as the United States, the United Kingdom, Australia, and South Korea?
3. What potential policy options could be explored to improve the RDF and make rare disease treatments more accessible in Singapore?
4. How can healthcare insurance mechanisms contribute to the funding of rare disease treatments?
5. What role do ethics and equity play in the decision-making process for rare disease funding?

Exhibits

Table 1. A Comparison of Rare Disease Funding Approaches for Singapore, Australia, the UK, US and South Korea

Aspect/Country	Singapore	Australia	United Kingdom	United States	South Korea
Healthcare System	Mixed financing system (premiums, deductibles, co-insurance and co-payment)	Regionally administered, universal public health insurance programme (Medicare)	Publicly funded (NHS)	Mixed public and private	National Health Insurance Service
Funding Model for Rare Diseases	RDF, public donations, government matching	Medicare, PBS, LSDP	NHS, HST Programme, IMF	Private insurance, Medicaid/ Medicare	NHIS, positive listing approach
Treatment Coverage	Limited to very specific conditions and medications	Subsidises high-cost drugs for >10 rare diseases	Evaluates treatments for cost-effectiveness, funds approved and NICE-recommended treatments	Various programmes and insurance coverages, large number of ongoing clinical trials	Covers certain orphan drugs based on cost-effectiveness analyses
Cost of Treatment	High	Low	Low	Varied, often high and dependent on employment insurance	Low
Challenges	High reliance on public donations, limited RDF scope	Balancing budget and access to rare disease drugs	Complicated health technology assessment process; less than 50% of centrally authorised rare disease treatments are routinely funded	Complex insurance system, high out-of-pocket costs	Stringent criteria for rare disease drug reimbursement
Sustainability	Questionable, dependent on continuous public support	Relatively stable with government support	Government-backed, but dependent on NICE evaluation and recommendations	Varies widely, dependent on insurance and government programmes	Stable but selective in coverage

Abbreviations: IMF, Innovative Medicines Fund; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; HST, Highly Specialised Technologies; LSDP, Life Saving Drugs Program; PBS, Pharmaceutical Benefits Scheme; RDF, Rare Disease Fund