Valuing Health:

Exploring potential drivers of reimbursement decision-making in health technology assessments for orphan drugs and rare diseases

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Abstract

Background: Principles underpinning distributive justice approaches adopted by a country have consequential effects on priority-setting in its healthcare system, including resource and funding allocation. There is currently inadequate recognition of most rare diseases as a cost to health systems despite their high economic and social burden. One way to approach this is to explore how 'value' is defined and measured in healthcare. HTA is one of the tools that have piqued the interest of many policy and decision makers to evaluate the clinical and economic value of healthcare technologies. However, many studies highlighted how conventional evaluation methodologies discriminate against those with rare diseases, as the high cost treatments are highly unlikely to be cost-effective within the traditional value assessment frameworks (VAFs). Research in this area also revealed critical differences in HTA methodologies across various countries. This study aims to investigate the drivers of positive recommendations for orphan drug indications so as to contribute to current understanding of how value assessment frameworks in HTAs can improve management of rare disease treatments and their specificities. **Methods**: In this study, 47 dossiers evaluation orphan drug indications were retrieved from six different HTA agencies (ACE, AiHTA, CADTH, NICE, ICER, ZIN) and reviewed against a checklist of 32 selected HTA evaluation factors. The dossiers were analysed for reporting frequencies and outcomes of assessment of these factors. Subsequently, the data collected was analysed for their association and strength of relationship with three variables 1. *HTA agencies* 2. *Financing systems* 3. *Recommendation decisions*, using Fisher Exact test and Cramér's V respectively. Correspondence analysis was also used to explore the association of HTA agencies with specific factors while multiple correspondence analysis was used to illuminate possible association between certain outcomes of assessment of particular HTA factors and recommendation decisions. A case analysis was also conducted to investigate differences in assessment of evidence across HTA agencies. **Results:** Only dossiers from NICE reported on all 32 factors in the checklist. Statistically significant differences in reporting frequencies were found for the highest number of factors i.e. 22 (out of 32) across *HTA agencies*, out of which, 18 showed stronger associations with the agencies, compared to *financing systems* and *recommendation decisions*. Only one (disease nature/severity) out of the nine factors that were found to be more commonly reported in rare disease treatment assessments, fall under ISPOR's 12 additional elements of value. MCA outputs suggest the effects of outcomes of assessment of six out of eight factors that were statistically significantly associated with *recommendation decisions*. **Conclusion**: Variations in HTA evaluations of orphan drugs in this study are more likely to be associated with agency-related specificities than financing systems or *recommendation decisions*. This has further provided the ignition for public authorities to relook at their HTA capacities for developing appropriate VAFs and other supportive systems to ensure timely access to orphan drugs, and foster international collaborative efforts.

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Content

List of Tables

List of Figures

List of Figures (continued)

Appendices

1 Introduction

Due to the high economic and social burden along with inadequate recognition of most rare diseases as a cost to health systems, they represent an important aspect to be addressed in public health[1, 2, 3]. It is especially crucial where legislations pertinent to orphan drugs and rare diseases are absent or work-in-progress areas in the health systems across the world. The lack of such national legislations may have a significant negative impact on a country's rare disease patients if the inadequacy of value assessment methodologies hinders accessibility and affordability[4]. In general, an orphan drug (also known as orphan medicines or orphan medicinal products) is commonly referred to as a drug or biological product that serves to prevent, diagnose or treat a rare disease or condition that is serious, debilitating or life-threatening[5]. This scope of definition is used by key drug regulatory agencies such as the EMA and FDA. Increasingly, many countries are beginning to take a step forward in identifying innovative drugs, such as rare disease treatments (RDTs) or orphan drugs, as well as advanced medicinal therapy products (AMTPs) i.e. medicines for human use that are based on genes, tissues or cells[6], as their strategic priority[7]. This has consequently led to a plethora of schemes and initiatives to promote research and development in this field. In the last few decades, countries across the globe have implemented different combinations of legislations, regulations and policies to inform decisions on value-for-money, availability and (market) accessibility of orphan drugs. Reference pricing i.e. the insurer or employer establishes a maximum contribution it will make towards the price of a drug or procedure and the patient pays the remainder, and Health Technology Assessment (HTA) are policies commonly used to obtain greater value-for-money from pharmaceuticals[8]. HTAs can be conducted by private or public agencies to summarise information about medical, economic, social and ethical issues associated with the use of a healthcare technology as well as other aspects, such as its impacts on the healthcare systems as a result of administering the intervention, and the cost implications for the patients[9]. HTA is said to be a superior strategy compared to reference pricing because it addresses both price and the appropriate indications for the use of the assessed technology along with the additional value achieved from additional costs[10]. However, although HTA conducted by private or independent agencies can be informative to policymakers, preference for advice from public HTA agencies still exists in several countries since national HTA agencies theoretically serve the public interest[11]. The decisions made by HTA agencies on the financial implications of new health interventions are predominantly based on economic analyses such as cost-effectiveness analysis (CEA)[12]. Data from CEA may be used in a budget impact analysis (BIA) to assess the affordability of adopting a new healthcare technology based on the given resources and budget constraints in a specific context[13]. These approaches to value assessment serve to inform decision-makers on the development of reimbursement policies for their healthcare systems. While some studies that report on cost-utility analysis align their definitions of 'value' with that of Porter's i.e. health outcomes obtained

per dollar spent, few were found to explicitly divulge their underpinning principles or concepts of establishing value[14]. Govaert et al.[15] further defined value as "health outcomes achieved that matter to patients, relative to costs of achieving those outcomes". Other definitions include "value for money expected from the treatment"[16] and "a combination of clinical benefits, side effects, and improvement in patient symptoms or quality of life in the context of cost"[17]. The swelling costs of health-related services and ever-widening inequalities in access to healthcare also stress the importance of justice as an ethical concern in this regard. With the myriad of 'value' definitions that have been conceptualised so far, what then qualifies as a just and fair system of value-based resource distribution? Are we a step closer, or a step further from this ideal?

These questions direct us back to how value is measured, perceived or even 'constructed'. Comparative studies, mainly in Europe, the United States of America (USA) and the United Kingdom (UK), that looked into the HTA criteria of assessment for orphan drugs revealed critical differences across the countries[18]. Even if the same criteria were used, some discrepancies still persist because of how these so-called benchmarks may be affected by country- or HTA agency-dependent factors, such as HTA capacities and methodological preferences[19]. To add, researchers are increasingly questioning the relative value of the special status, on the basis of prevalence of rare diseases in funding decisions[20]. The influence of political and societal perspectives on the concept of equity and considerations related to it are substantial[21]. Cross-country differences were also deemed to be driven by reasons such as heterogeneity in evidence appraised and the interpretation of the same evidence, as well as how the same uncertainties are perceived and handled. Even though there may be agreement in evidentiary requirements, how uncertainty in evidence may be considered acceptable may differ[22]. These may also be confounded by agency-specific preferences for assessing evidence, risk, value and stakeholder inputs. Different approaches in HTA and the way specificity of orphan drugs are dealt with render significant impact on the outcome of policy decisions or HTA recommendations across different countries. Studies [22, 23, 24] have also consistently highlighted the importance of transparency in assessment methods and hence, systematic policymaking to avoid or address differing decisions about the same drug[21]. For instance, high-income countries tend to increase the participation of stakeholders and enhance the transparency of processes, policy-making and regulations by systemising participation of various HTA institutions[25]. In Asia, some countries have quality assurance processes in place to strengthen the methodological rigour of their studies and ensure consistency across HTA evaluations[26]. In countries like Singapore and Thailand, in-house evaluations are sent to independent reviewers for validation of scientific rigour before being used to inform funding decisions. On the other hand, middle-income countries are associated with raising awareness, training and skill development for HTA staff, institutionalising the concept of HTA and

allocating resources for effective decision-making in their health systems[25]. Hence, HTA capacities may also significantly impact HTA recommendations across different jurisdictions. It is therefore crucial to understand regulatory and policy initiatives for orphan drugs that exist in countries and their differences to improve research and policy development for the treatment of rare diseases[4]. However, there is yet to be consensus on the definition of 'value', given the variety of contexts in which value assessment frameworks (VAFs) can emerge and to which they apply. Evident differences were also found in the interpretations of the concept of unmet medical needs. The quantification of these needs was deemed to be highly dependent on the scope and the value assessment framework (VAF) in which it is used based on different stakeholder preferences and responsibilities[27]. Contradictorily, many examples of efforts to apply value assessment were aimed at striking interventions with low value for their cost, off the list[14]. In a systematic review to assess existing practices of value assessment in healthcare, Seixas et al.[14] concluded that the actual practice of value assessment might be less developed than writing or publishing on this subject. Nonetheless, there is agreement that the rising awareness of the need to measure 'value' is intimately related to the financial pressures faced by healthcare systems around the world.

Appropriately considering differences across HTA practices in their respective contexts can influence conclusions on comparisons between international HTA recommendations[11]. According to research in the area of rare diseases, drug reimbursement decisions were found to be significantly associated with a treatment's cost-effectiveness, existence of a financial agreement, a health system built on social health insurance, the condition's incidence rate and socioeconomic characteristics of the country[28]. To further understand the drivers of positive recommendation for reimbursement of orphan drug indications and the extent to which value assessments were transparently reflected in HTA evaluations, this study analysed HTA dossiers across three key aspects that variations in assessment may exist based on literature i.e. HTA agencies, healthcare financing system and HTA recommendation decisions. The dossiers were retrieved from HTA agencies that (i) represent high-income countries[29] with either a single or multi-payer system in terms of their health financing model, and (ii) publish their evaluations in English. The documents were subsequently analysed against a list of HTA evaluation criteria (factors) developed from a targeted literature review, in addition to three elements (*disease severity, value of hope* and *equity*) out of the 12 that were proposed by The International Society for Pharmacoeconomics and Outcomes Research Special Task Force (ISPOR) as other considerations in assessing the value of new healthcare technologies[30].

The primary objectives of this study were to explore if

1. reporting frequencies of HTA factors are associated with (i) HTA agencies (ii) financing systems and (iii) recommendation decisions for the reimbursement of the assessed orphan drugs by six HTA agencies i.e. ACE (Singapore), NICE (the United Kingdom), CADTH (Canada), ZIN (the Netherlands), AiHTA (Austria) and ICER (USA);

2. recommendation decisions are associated with outcomes of evaluation of specific HTA factors for rare disease treatments (regardless of disease type and drug class); and

3. methodological variations exist in the utilisation of evidence by different HTA agencies, through a case analysis on Zolgensma (Onasemnogene abeparvovec), a gene therapy for the treatment of a rare disease called Spinal Muscular Atrophy (SMA).

Overall, the study aims to juxtapose HTA judgment decisions with current 'best' practices for the evaluation of (novel) orphan drugs so as to extend potential discussions on HTA capacities and how HTA agency- or country-specific preferences and methodologies, can influence recommendation decisions for the reimbursement of this class of treatments.

2 Background

2.1 Healthcare Systems

Arguments from egalitarian theories of distributive justice have been particularly predominant in shaping and justifying healthcare provision[31]. Advocates of this standpoint believe that healthcare provision should be organised in a way that allows individuals to access the standard or basic range of opportunities in society[31]. In other words, healthcare resources may be unequally distributed so that those with poor health status can receive the (additional) support they need. It is said that the most powerful concept that public health has to offer is universal healthcare coverage since it means that all citizens have access to the health services they need without financial hardship, thereby making health a reality for all[32]. This includes access to not only essential health services, but also health promotion and prevention, rehabilitation, as well as palliative care.

All health systems are built around attributes of efficiency, trustworthiness and affordability[33]. Each system can further be defined by three functional processes, namely, service provision, financing and regulation, which are respectively governed by principles of equity, financial protection, efficiency and quality[33]. Models of service delivery, financing and economic policy are ways in which healthcare

systems can be described[34]. While theoretical distinctions may be made between different models, it is noteworthy that in reality, a country's healthcare system cannot be adequately described by just one model because most of them adopt blended or mixed approaches[35]. Most literature refer to healthcare systems in terms of the four major models, the Beveridge model, Bismarck model (social health insurance), National Health Insurance model (statutory health insurance) and the out-of-pocket model[35,36]. The ***Beveridge model*** was first conceived in the UK based on a single-payer national system. Medical treatments are regarded as public services and are hence, financed and provided by the government for all citizens using funds raised through general taxation[33,36]. Providers of care belong to the public sector, either owned or controlled by central and regional governments in terms of service distribution and delivery, as well as provider payments[33]. Examples include Denmark, Ireland, New Zealand, and the United Kingdom. Compared to the Beveridge model, the ***Bismarck model*** (social insurance model) is a more conservative model in that it taps on an insurance system, known as sickness funds, largely financed jointly by employers, employees and private insurance funds[35]. The funding derived from employment taxes are held in separate funds specifically for the national health programme[33]. Examples include Austria, Belgium, France, Germany, Luxemburg, and the Netherlands. The ***National Health Insurance model*** (statutory health insurance), exhibits elements of the Beveridge and Bismarck models[37]. A universal and individually-focused model, the system is funded through a government-run insurance system which every citizen contributes to, and pays private-sector providers it uses[35]. The ***out-of-pocket (OOP) model*** represents a market-driven system that weighs on the question of ability to pay, thus the disparity between the rich and poor. Out-of-pocket payments comprise private transactions made by individuals to private providers, official patient cost-sharing like user fees or copayments, and informal payments[38].

Healthcare financing systems mobilise and allocate financial resources within the healthcare system to meet the health needs of the population, individually or collectively, often in view of expected future needs. The key sources of funds include out-of-pocket payments, contributions to social insurance funds, self-purchased private insurance (voluntary or compulsory/statutory), and taxation[35]. However, to reiterate, few countries adopt a single funding approach to finance their healthcare systems. In reality, many funding-based models are in fact, described to be 'mixed' or 'hybrid' models[35], as demonstrated by examples in Table 1.

Table 1. Types of healthcare funding systems in relation to predominant healthcare system models in example countries adopted and modified from the Health Policy Consensus Group[39]

Model	Funding system(s)	Countries
National Health System model (Beveridge model)	General taxation	United Kingdom
	Regionally allocated resources from taxes	Denmark[40]
National Health Insurance model (Statutory Health Insurance)	Province/Territorial taxation and Federal funding programme for province and territories[39]	Canada[41]
	General taxation (regional)[8] Voluntary private health insurance paid by individuals, with tax subsidies	Australia[42]
Social Insurance (Bismarck model)	Social health insurance paid by employer and employee, with multiple, noncompetitive, autonomous, third party payers (insurers)	France, Austria[43]
	Social health insurance paid by employer and employee, with autonomous, competitive third party payers (insurers)	Germany
	Compulsory social health insurance for basic care paid by individuals, with competitive third party payers (insurers) and government-defined benefit package	Switzerland[38]
	Compulsory social health insurance for catastrophic illness and long-term care and social health insurance for acute medical services paid by employer and employee	The Netherlands
Out-of-pocket	Individuals pay directly healthcare providers at the time of service use[9]	Rural regions of Africa, India, China[38] and South America[35]
Mixed systems	Voluntary health insurance predominantly paid by employers, with tax subsidies for employers and employees	United States
	Catastrophic health insurance and tax-exempt health savings account	Singapore[44]

Payer type, whether single or multiple, is a controversial topic for many countries looking into reforms of their healthcare systems[45]. Single- and multi-payer systems can be differentiated mainly by revenue collection, risk pooling, purchasing and social solidarity. In terms of revenue collection, a ***single-payer*** health system is generally described by universal and comprehensive coverage, where one organisation, usually the government, collects and pools revenues to purchase health services for the entire population i.e. the payer is a public entity. A ***multi-payer*** healthcare system, on the other hand, can be delineated by health coverage that is administered by two or more providers which can be in charge of doing so for

i.e. the payer is a public entity. A ***multi-payer*** healthcare system, on the other hand, can be delineated by health coverage that is administered by two or more providers which can be in charge of doing so for different groups of the population[45,46]. In this case, a certain level of competition along with basic principles of healthcare coverage, marked out by a governmental body, is assumed to exist. A single payer system may have a stronger purchasing position relative to the insurers in multi-payer systems due to the ability to take advantage of its monopsony (single buyer or sole purchaser) power. Nonetheless, multi-payer systems can emulate the single payer systems in terms of purchasing. For instance, with a centralised government body providing guidance through HTA, insurers within a multi-payer system can employ HTA for decision-making. Approval processes, insurance reimbursement policies and clinical development and application are three primary ways in which HTA can be used to ascertain value in order to inform allocation decisions[45]. However, since single-payer systems include all the insured within a single risk pool while multi-payer systems would pool at possibly varied levels of health risks[45], could varying tendencies for risk selection, as a result of how healthcare is financed, influence reimbursement mechanisms or policies in the context of HTA?

2.2 Value in healthcare

The growth in interest in HTA is spurred by the high stakes involved because, albeit contextual differences in its definition and application, it consolidates private and public interests in a process where outcomes are perceived through different lenses of key stakeholders[47]. However, there is currently no global consensus on how 'value' in healthcare should be defined or measured although the goal of value assessment is to advocate an efficient and equitable healthcare system[48]. Dimensions of healthcare technologies that are crucial for their assessment include *physical nature* e.g., devices, drugs, procedures, systems etc., *purpose* e.g., screening, diagnosis etc., and *stage of diffusion* i.e. where it is in its life cycle e.g., experimental, investigational[49]. Technologies can be evaluated for their cost and cost-effectiveness, social, legal, ethical and political impacts, patient-reported outcomes, real-world effectiveness, efficacy and safety[50]. One of the most commonly accepted meanings of 'value' is by Michael Porter, who defined it as 'health outcomes achieved per dollar' i.e. maximisation of objective gains in health in relation to a fixed amount of financial resources[51]. The 'economic perspective' of value, defined by Garrison et al.[52], distinguishes between 'gross value' as willingness to pay for an economic good and 'net value' subtracts the incurred opportunity cost to obtain the 'gross value', where the latter connotes allocative efficiency. The contextual sensitivity of the concept of 'value' is evident in how the value of health technologies varies due to, for instance, perspectives and evidence evaluated in HTA and the way societal values are considered, implicitly or explicitly. A systematic review of value assessment frameworks (VAFs) by Zhang et al.[48] grouped attributes of values broadly into health benefits, affordability, societal impact,

burden of disease, quality of evidence, cost-effectiveness, ethics and equity, unmet needs and innovation. They concluded that significant variations exist in defining and measuring 'value' and the 'gaps' regarding patient and/or public engagement in the framework development process. To add, existing VAFs can also aggregate multiple value attributes into a single index for decision-making purposes. 'Value' is thus, evidently contextual.

HTA has increasingly been used as a tool by many countries in Europe e.g., the Netherlands, Germany and Spain[53,54], as well as countries like Australia and Canada[55,56] to inform pricing and reimbursement decision- and policy-making in the health care sector for reasons such as healthcare cost control[57]. In Europe, regulatory processes have been harmonised with the European Medicines Agency (EMA) by the European Legislation[58]. The EMA plays a central role in HTA by working closely with HTA institutions to provide recommendations on medicines and other healthcare technologies that can be reimbursed by a European Union (EU) Member State's healthcare system[59]. In Asia, the adoption of HTA to evaluate clinical and economic value of healthcare technologies (drugs, services and procedures) has only picked up speed recently in a growing number of countries due to the pressing need to justify value-for-money while securing accessibility to care[60,61,62]. The lack of awareness with regards to HTA and country-specific epidemiological, clinical and health economics data, along with disjointed research efforts may have contributed to the initial slow adoption of HTA[60,63]. These were only introduced in Asia in the late 1990s when many countries in Europe, Canada and Australia had already institutionalised HTA[60]. Only recently, more Asian countries are starting to implement HTA for pricing and reimbursement decisions[53]. In the race to achieve value-for-money, the uptake of HTA to inform policy-making in the area of healthcare in Asia is undoubtedly gaining attention and traction for research.

2.3 Putting 'value' in perspective for rare disease treatments

If HTA is used to inform decision-making with regards to health policy and reimbursement to address rising costs of healthcare, limited healthcare resources and the need to improve consistency and quality of care[64], what are the implications of variations in the perspectives of 'value' and approaches to measuring it in the field of rare disease treatments (RDTs)? Factors driving the growth of HTA, such as those related to costs, value-for-money, benefits and risk of technologies, have motivated the adoption of 'in-house' approaches to address related issues[47]. Methodological choices made by HTA institutions may be directly influenced by legislation or formal agreements between an HTA institution and a decision-maker[65]. For instance, Denmark was found to place emphasis more frequently on patient-related and organisation aspects while most countries generally focus more on the clinical aspects of healthcare technologies[66]. More commonly, economic evaluation is preferred as a standard requirement in performing HTA for

many countries, such as the UK and Canada. The choice of methods and whether they are mandatory has cascading effects on the quality of evidence and subsequently, reimbursement decisions and patient access. There is largely a shared consensus in incorporating systematic and explicit approaches to assessing the quality of evidence and the strength of recommendations. This can help prevent errors, facilitate critical appraisal of these judgements and improve communication of this information[67]. Although variations in methods, approaches and standards may be grounded on reasons that stem from the purpose of tailoring to the local context of care or needs and could be immensely beneficial, clarity and transparency in the relationship between HTA and decision-making in each country must be made discernible to all stakeholders. Institutions are advised to review, revise or develop their internal guidelines description in order to achieve alignment of scientific and technical practices with other HTA institutions and hence, increasing the quality, quantity and efficiency in producing HTAs[65].

That said, why is it substantially crucial to produce 'good-quality' HTA, especially for RDTs? A VAF applying a standard economic evaluation framework would inappropriately treat orphan and non-orphan drugs equally due to its emphasis on cost-effectiveness as it ignores the impact of disease rarity on evidence and data uncertainty. This spirals into a somewhat inaccurate estimation of the intervention's actual health benefit in terms of e.g., Quality-adjusted-life-years (QALYs). Variations in HTA including the standards of references or guidelines used have evident impacts on patient access which depends on reimbursement decisions made by payers and HTA institutions following a drug's marketing authorisation. Reimbursement entails compensation or repayment i.e. how and how much payers are willing to pay for covered healthcare services and products on behalf of their members. The payer, public or private insurer, is generally referred to as the agents for their plan subscribers or members and negotiate prices and access to the technology[68]. Pricing and reimbursement practices vary across countries and types of healthcare services. A study by Allen et al.[64] to compare reimbursement recommendations by eight European HTA Agencies identified alignment between organisation structure of reimbursement systems and HTA recommendation but interestingly, *less* alignment between HTA processes and recommendations. Mandates, as well as political, social and population needs unique to a country explain the variations in HTA activities even if reimbursement recommendations are guided by similar principles such as, clinical efficacy and cost effectiveness, and necessity for patient input. To curb rising costs and at the same time ensure consumer-oriented healthcare, various payment models have emerged. With heightened emphasis on delivering 'value', pay-for-performance or value-based payment models have become part of the overall national strategy in some countries. These serve to incentivise provider performance by attaching financial incentives or disincentives that tie reimbursement to metric-driven outcomes to drive providers towards value-based care. However, the increase in uptake of HTA in

informing coverage decisions has made the processes required for patient access to new technologies more complicated. Variations in HTA practices due to the quality of evidence available and willingness to accept uncertainties or differing methods of assessment or priorities have resulted in discrepancies between HTA recommendations[69], especially when decision-making is decentralised, for instance, in countries like Italy[64]. Through the alignment of payment with value and quality, rising needs and combinations of treatment approaches such as in multidisciplinary care could potentially be addressed[70,71].

Heterogeneity in coverage recommendations and decision-making could also be explained by incorporation of social value judgements, which have recently been increasingly advocated by many studies in the field of rare disease since it captures value beyond standard clinical benefit assessment[72]. Rare diseases, generally referring to life-threatening or chronically debilitating conditions, are described to be caused mostly by genetic predispositions[73]. They are known to pose a high burden on patients since lifelong treatment and care is usually needed. Depending on severity, patients hampered by these diseases may, therefore, face limitations or difficulties with their social, educational and professional lives. Furthermore, such patients' inadvertent dependence on caregivers, such as family members, for daily tasks can curtail their professional or social activities since they spend a significant amount of time on care-related tasks[74]. Patients with rare diseases are also distressed by challenges they face in securing jobs with wages high enough to sustain additional high expenditure on treatment and care, as compared to patients with non-rare diseases[75]. Historically, due to the small market for orphan drugs and hence anticipated insufficient returns on investment in treatments like RDTs due to small groups of patients, patients with rare diseases were way underserved by commercial drug development since commercial viability of such drugs is highly questionable[75,76]. Under conventional frameworks of HTAs, orphan drugs or RDTs struggle to prove their cost-effectiveness due partly to impractical requirements from regulatory authorities[75]. Along with their high cost, this implies that funding (through reimbursement) and hence, patient access may be hindered. A recent retrospective study of medical and insurance records revealed that rare disease direct medical costs are estimated to be three- to five-fold higher than age-matched controls (patients with non-rare diseases) in spite of differences in payer mechanisms across healthcare systems[77]. Concerns about whether standard economic evaluation methods in HTAs adequately reflect societal values or preferences for the serious and/or life-threatening rare disease treatments and orphan drugs began to receive attention and are much debated on[78]. Recognition of the economic challenges and issues with valuing RDTs has gathered consensus in many countries that efforts to address the aforementioned issues are much needed. Legislations to stimulate orphan drug development have been found in jurisdictions such as the European Union (EU), the United States of America (USA), Singapore, Japan and Australia[79,80]. They share the same unpinning principle of equity in terms of access to treatment

and aim to improve commercial viability of orphan drug development by incentivising and rewarding innovation through measures such as grants and tax credits for research and clinical development, reducing fees for drug approval applications, granting entitlement for market exclusivity and eligibility for fast-track assessments. A study on cancer orphan drugs showed that there are more FDA approvals than EMA especially for subgroups of more prevalent cancers[81]. While the prerequisites for orphan drug designation are comparable between the USA and the EU, the EU demands demonstration of notable benefits in cases where the drug targets the same indication as one that is already existing in the market. Although such regulations are paramount in incentivising and fostering innovation, especially when an alternative treatment for the condition is not available in the market, the different approaches between international jurisdictions tend to translate into unpredictability for manufacturers in terms of likelihood their investment will lead to reimbursement. This is especially when new technologies tend to enter the market with inadequate outcome data but are required to demonstrate value-for-money to payers since many reimbursement schemes require evidence of cost-effectiveness and economic modelling. Such analyses usually encompass long-term outcomes which need to be modelled based on assumptions because of the lack of such data from clinical trials which adds another layer of uncertainty for payers. Variations in methodological approaches on evidentiary requirements and how uncertainties are perceived and dealt with and a number of contextually-sensitive reasons exist between international jurisdictions[82]. Since HTA processes are not harmonised across different jurisdictions, outcomes of reimbursement decisions may wind up different.

Since the implementation of The Orphan Drug Act in 1983 in the USA, continued efforts to raise public awareness and promote investment opportunities for rare diseases have followed suit in several countries. In Asia, rare diseases also present a challenge to medical care as an important public health issue and it is estimated that populous nations such as China and India each have approximately more than 70 million rare disease cases[83]. In circumstances where drug developers are not incentivised to manufacture orphan drugs, the need to import them would inadvertently lead to affordability issues given high prices on these ‘premium drugs’. Although China is actively promoting regulation in these areas, it is still lagging behind other countries with orphan drug legislation e.g., the USA or EU. Progress has also been witnessed in countries like Japan, South Korea, and Taiwan with the enactment of legislation and accompanying regulation in the area of rare diseases and orphan drugs[53]. With the current environment and complexities, understanding rare diseases and the (existing) regulatory frameworks that are required is crucial to initiate or improve accessibility and affordability of orphan drugs in Southeast Asia. While actual numbers of people suffering from rare diseases are mostly unknown, it is estimated to be about 9% of the region’s population[84]. Across Southeast Asia, there remains fundamental challenges from basic healthcare systems

to funding in the area of rare disease management. Lack of resources and adequate fundings impedes active research and active monitoring of rare diseases, as such, the true burden of these diseases may be underreported[84]. Singapore was one of the first few countries to introduce its own legislation recognising orphan drugs in 1991 amongst others like Japan (1993), Australia (1997), Taiwan (2000), Europe (2002) and South Korea (2003)[85]. HTA capability in Singapore was developed concurrently with its medical device regulation system in the 1990s and the first formal unit with HTA functions was established in 1995[86]. The country established The Agency for Care Effectiveness in 2015 to support the Ministry of Health Drug Advisory Committee in making evidence-based recommendations for the public funding of drugs through the employment of HTA. The Rare Disease Fund was introduced in 2019 to provide financial support to patients with certain rare genetic diseases[87]. Although the Agency for Care Effectiveness has developed standardised HTA methods and processes in line with international best practices to ensure consistency and robustness in methodologies, there is still currently lack of clarity in whether or how orphan drugs are assessed. Leveraging on best practices around the world and organisation of multi-stakeholders and regional approaches and strategies have been identified as opportunities for improvement and further development to address these issues[84].

With rare diseases gaining more attention on a 'leave no one behind' basis, decision makers are increasingly adapting reimbursement processes to account for specific characteristics of orphan drugs and rare diseases[88]. While some jurisdictions apply their formal or standard evaluation criteria, others decided to modify or include other criteria in their assessment[89]. This has led to the emergence of different VAFs for RDTs in effort to establish balance between prioritising standard efficiency criteria such as cost-effectiveness and unconventional criteria that elucidate other elements of value not captured in a regular framework[23]. The International Society for Pharmacoeconomics and Outcomes Research Special Task Force (ISPOR) proposed the inclusion of 12 elements for consideration in assessing the value of new health technologies to encourage broadening perspectives of what constitute 'value' in healthcare and to spur studies on the inclusion of the additional elements of value into a conventional cost-effectiveness analysis. Out of these 12 elements, four of them - *quality-adjusted-life-years*, *net costs*, *productivity* and *adherence-improving factors* - have been considered in conventional VAFs, while the eight others - *reduction in uncertainty*, *fear of contagion*, *insurance value*, *severity of disease*, *value of hope*, *real option value*, *equity* and *scientific spillovers* - are considered more novel in economic assessments. Most of these elements are theoretically well understood and have been included in VAFs but *equity* and effects of *scientific spillovers* require further theoretical development and consensus on their inclusion. These 12 elements form 'other considerations' that may also influence HTA processes in various different settings[18]. They serve to capture broader aspects of a treatment's value and the impacts of the condition on

patients that are not usually considered in routine HTA methods employing the use of clinical and economic evidence[90]. Augmenting a conventional CEA to consider the additional elements of value relevant to patients, beyond life years gained or improvements in quality of life and are not captured in Quality Adjusted Life Years (QALYs) i.e. a unit of measurement of health outcomes[91], can potentially lead to a CEA that is more fit-for-value[30]. Other possible approaches for valuation and inclusion of these elements include their integration in net monetary benefit calculation, inclusion as attributes of health state descriptions or as criteria in conceptual frameworks like multi-criteria decision-analysis, where drug appraisal is conducted according to an explicit but flexible set or combination of criteria[68]. Because of the high acquisition costs of RDTs and uncertainty in their cost-effectiveness, some researchers have proposed the use of separate approaches for RDT appraisal to facilitate more structured, consistent decision-making and better management of rare disease treatment specificities[92]. This is also considered more appropriate since evidence about an orphan drug's clinical value is rarely available at the time of marketing authorisation because of the sample size in clinical trials or low prevalence in the community[92]. Hence, reimbursement models aimed at capturing and assessing value appropriately are essential for RDTs[92]. To put things in perspective, reimbursement schemes between healthcare payers and medical product manufacturers are futile if capturing and assessing 'value' is not aligned between the key stakeholders whose decisions and deliberations place the life of rare disease patients at stake.

Researchers in the field of health policy have certainly instigated noteworthy arguments and insights, particularly those pertinent to appraisal criteria and their relevance for assessing orphan drugs 'holistically' and appropriately. This is to ensure that the frameworks used have been tailored to the peculiarity of not only the drugs but the diseases as well, and whether this class of technologies should have special reimbursement status[93,94]. For all that, there is undoubtedly a need to strike a balance between ethical and economic concerns and clarify what society wants and is prepared to accept as consequences[95,96].

3 Theoretical framework

The intersection between economics and ethics illustrates notions regarding societal expectations of how people should behave, a citizen's obligations to one's government and of course, policies that should be prioritised or pursued by a state or country[97]. The rising costs of healthcare services and vast (sometimes invisible) inequalities in access to healthcare illuminate the importance of justice as an ethical concern in healthcare. Treatments for life-threatening diseases such as rare disease treatments emphasise ethical imperatives for timely access because the societal value of these treatments may be shaped by ethical constructs and the right to life can very well encompass the right to health.

and human reason[97]. So who and what (reasons) determine or make value judgements in healthcare and what are the implications? Approaches to distributive justice by a country can have consequential effects on priority-setting in its healthcare system, including resource and funding allocation. Due to limited resources for healthcare, it is paramount that decisions are made to prioritise patient segments that are expected to yield the greatest benefits[98]. In healthcare, utilitarianism stipulates that whenever there is a choice between different but equally efficacious methods of treatment, patients' benefits should be maximised and the costs and risks minimised i.e. maximising aggregate health outcome of population Any other approach would be regarded as an unethical practice[97]. On the other hand, egalitarianism espouses equal distribution of certain goods such as medical care, yet it permits inequalities as long as it benefits the needy[99,100] i.e. minimising health differences by maximizing the welfare of those who are worse off. Arguments from egalitarian theories of justice have been particularly influential in shaping and justifying healthcare provision. To set the stage for this discussion, it is useful to begin with 'distributive justice' as defined by Beauchamp and Childress[100], as follow

> *"Fair, equitable and appropriate distribution determined by justified norms that structure the terms of social cooperation. Its scope includes policies that allot diverse benefits and burdens such as property, resources, taxation, privileges and opportunities."*

Indeed, allocation decisions are generally guided by objectives that call for different approaches. If society wishes to maximise benefits for the greatest number of individuals (utilitarianism), the cost–benefit ratio of rare diseases may be positioned less favorably to receive public funding as it would in an egalitarian approach, that aims to maximise equality of all individuals[101]. An egalitarian outcome may be grounded on attaining a determined threshold of health, an overall prioritization of the worst off, or amount of resources for each individual. In light of this, an egalitarian approach may offer a better foundation for public funding of orphan drugs development and treatment coverage for rare diseases[101]. Otherwise, the rule of rescue, or the capacity to intervene if a therapy becomes available, may also offer a value of hope in fund allocation to rare disease treatments using public funds[102]. A utilitarian objective is more inclined to dominate standard economic approaches to evaluating public healthcare interventions and HTA is one of such tools[103]. However, evidence[104,105] suggests that an egalitarian objective is a much more acceptable approach to most people in that many health interventions are aimed at reducing health inequalities such that there has been growing interest in the assessment of population-level equity considerations[106,107]. An example of a health system founded on egalitarian principles is the National Health System (NHS) of the UK. However, utilitarianism is actually at the heart of the NHS system and medical resource allocation because egalitarianism considers only needs and not probability of success (of e.g., treatments), length, or quality of life, unlike utilitarianism[108]. In the area of therapeutic pathways like

regenerative medicines, it has been argued that initiatives involving resource allocation to facilitate innovation in the field reflect a more utilitarian perspective than egalitarian notions, which are widely accepted as underpinning principles of many healthcare institutions[31]. Another budding approach explored in literature is liberal egalitarianism although rationing approaches based on personal responsibility is a prominent yet a controversial idea. Cappelen[109] pointed out that it is possible to assign a significant but limited role of individual responsibility in rationing healthcare resources. This in turn, helps policymakers make decisions in situations where cost-effectiveness of different alternatives and where the severity of illnesses are similar, or even when society wishes to assign some weight to responsibility for choice[109].

Ethics is considered a crucial element in HTA since its conception to inform policymakers on making value-for-money decisions[110]. HTA aims to provide relevant information to decision makers to maintain accessibility of the health care at the highest quality as possible while ensuring efficiency. One of the key elements of HTA is economic evaluation, which encompasses various approaches like cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis. These approaches consider and evaluate an intervention's value-for-money in comparison to other alternatives. In the context of HTA, the theoretical principles of economic evaluation seek to demonstrate and inform how best to allocate the health budget to maximise individual and social welfare[78]. However, neither theory nor practice of economic evaluation satisfactorily reflect social values. The assessment of individual and social welfare adopts the theory of preference utilitarianism, where individuals seek to maximise their utility defined by the strength of their preferences for different options. According to Richardson and Schlander[78], the Economic Welfare Theory "extends this assumption to the doctrine that social welfare is a function only of individual utilities" and they claimed that this is "commonly simplified to the utilitarian objective of maximising (unweighted) utilities". Richardson and Schlander[78] also highlighted that "there are significant problems with the theory of economic evaluation and its policy prescription that QALYs should be maximised". In its measurable forms, 'utility' does not take into account key individual preferences such as an aversion to uncertainty and the preference for greater protection against severe health states than provided when QALYs are maximised. Hence, conventional evaluation methodologies were said to discriminate against patients especially those with rare diseases and inadvertently require high cost services that struggle to establish their cost-effectiveness based on some of these traditional criteria that form the frameworks of value assessment in HTA[78]. Additionally, the HTA process itself can raise ethical questions with regards to consequences as a result of the choice of endpoints or comparators, and within economic evaluation itself[111]. However, it is generally recognised that ultra-rare, health-catastrophic conditions should be assessed against a higher cost-effective threshold. Drug pricing may also present potential ethical concerns due high manufacturing costs which in turn demand a high target price in order for manufacturers to achieve commercial viability given the rarity of the target disease of the treatment[101].

may also present potential ethical concerns due high manufacturing costs which in turn demand a high target price in order for manufacturers to achieve commercial viability given the rarity of the target disease of the treatment[101]. While HTA serves to inform or recommend as a guideline, the ultimate decision on reimbursement of health technology still lies on the payers, whether public or private.

As such, while health systems can be founded on some of these ethical approaches, they may not be the ***sole*** elements influencing the key drivers of HTA reimbursement-decision making or recommendations for reimbursement because of how complex the notion of 'what qualifies as a fair and just approach of resource distribution' is, just as are HTA evaluations. Although the concept of equity of access to healthcare forms the central objective of many health systems, research evidence on its concept, in terms of the nature and magnitude of inequities, remains difficult to interpret. This has resulted in ambiguities in decision-making pathways to ascertain whether inequities pose a sizable policy problem and how they can be best tackled[112]. This study sets out to illuminate further understanding in the dynamics behind (supposedly) ethical economic decisions using HTA evaluations of orphan drugs as a context of investigation and deliberation.

4 Methods

4.1 Search strategy: Creating the dataset

A HTA dossier or HTA-related document presents or records an analytical framework through which, at the minimum, a systematic review of clinical, epidemiological and health information pertinent to safety, efficacy, quality of life evidence is evaluated for a given disease area. Often, cost-effectiveness compared to available alternatives is used to ascertain and substantiate recommendation decisions for reimbursement. In this study, a targeted literature review was focused on dossiers documenting RDTs or orphan drugs evaluated from 2016 up to December 2021. This comprised 47 dossiers that were subsequently compared across six HTA agencies representing their respective countries. This includes Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada, Zorginstituut Nederland (ZIN) in the Netherlands, The Austrian Institute for Health Technology Assessment (AiHTA) in Austria; Agency for Care Effectiveness (ACE) in Singapore, The National Institute for Health and Care Excellence (NICE) in the UK and The Institute for Clinical and Economic Review (ICER) in the USA. The dossiers were downloaded from two key sources – The International HTA database (INAHTA) and respective webpages of the aforementioned HTA agencies. The international HTA database[113] provides free access to bibliographic information about ongoing and published HTAs commissioned or undertaken by HTA agencies internationally, including INAHTA members and non-INAHTA members. All aforementioned HTA agencies are INAHTA members (ACE, CADTH, AiHTA, ZIN and NICE) except

ICER. Where assessments, evidence or dossiers available were retrieved directly from INAHTA's 'International HTA database' landing page using the search function with NIH (National Library of Medicine) MeSH terms[114] 'Disease(s), Rare, 'Rare Disease(s)', 'Orphan Disease(s)' and 'Disease(s), orphan'. The dossiers were selected based on five main overarching criteria, alongside the consideration of relevant orphan drug regulations (Appendix A, Table 1), where the reports must, at the point of data collection for this study, document the assessment of a drug, treatment or technology that is:

(a) presented in English Language

As the primary aim of this study was to gain preliminary insights on the research area of interest on samples with directly accessible information, due to limited capacity for bulk translations of non-English reports given the stipulated duration for this research, the search strategy was focused on agencies with readily accessible or downloadable HTA reports published in English Language.

(b) approved with an effective/active orphan designation

This criterion was determined against Orphanet and the respective reference drug regulatory agencies. Orphanet is a Consortium of 40 countries within Europe and across the globe that aim to gather and improve knowledge on rare diseases for the betterment of diagnosis, care and treatment. It is supported by grants from the European Commission. For this criterion, Orphanet was used to determine if the drug assessed based on the respective HTA dossiers have an active designation as an orphan drug or equivalent. Specifically, Orphanet's database, 'Inventory of Orphan Drugs'[115], was used to run the search. Synonyms for the drug names e.g., generic and commercial or trade names, were used to run the search to verify the drug's status as an orphan drug. Outputs of the search include designation status in both Europe and the USA. Subsequently, the orphan drug statuses were cross-checked against databases from the respective health jurisdictions with designating authority, namely, The Food and Drug Administration (FDA) of the United States of America (USA), the European Medicine Agency (EMA) of the European Union (EU) and the Medicines & Health Products Regulatory Agency. Only drugs with 'active' designation status were included in the dataset.

The Food and Drug Administration (FDA)

The FDA in the USA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, and products that emit radiation. It also provides accurate, science-based health information to the public[116]. The FDA has the authority to grant orphan-drug designation to a drug or biological product that is indicated for preventing, diagnosing or treating a rare disease or condition. This designation process is separate from seeking approval or licensing, and is subject to the same

potential market exclusivity. A search was run through FDA's Orphan Drug Approval and Designation search engine[118] by using the drug names (and their synonyms) indicated on the dossiers. In order for the HTA dossiers, particularly from ICER, CADTH and Singapore, to be included in the dataset, the drug indication under 'Orphan drug Designation' must be a rare disease (according to FDA and/or Orphanet) and 'Orphan Drug Status' must reflect 'Designated/Approved'.

European Medicine Agency (EMA)

EMA is a decentralised agency of the EU responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU[119]. EMA's scientific committee provides independent recommendations on medicines for human and veterinary use. The Agency also evaluates marketing authorisation applications submitted through a centralised procedure that provides a basis for authorisation of medicines in Europe and is responsible for reviewing applications from sponsors for drug designations[119]. It assigns designation to drugs that are intended for treating, preventing or diagnosing life-threatening or chronically debilitating rare diseases, and demonstrate significant benefit for patients affected by those conditions[120]. Applications are deliberated by EMA's Committee for Orphan Medicinal products, whose opinion is then communicated to the European Commission for decisions on granting the orphan designation[120]. Following successful designation, the EU offers a range of incentives to encourage development of the designated medicines, such as fee reductions on services required, protocol assistance and market exclusivity once the medicine enters the market. A search was run through EMA's Orphan Drug Approval and Designation search engine[121] by using the drug names (and their synonyms) in the dossiers. In order for the HTA dossiers, particularly from ZIN, AiHTA (and CADTH, NICE and ACE), to be included in the dataset, the drug indication under 'Orphan Drug Designation' must be a rare disease (according to FDA and/or Orphanet) and 'Orphan Drug Status' must reflect 'Positive/Approved' or state explicitly that the drug was 'designated an orphan medicine', with an EU designation number, where applicable.

Medicines & Healthcare products Regulatory Agency (MHRA)

The MHRA regulates medicines, medical devices and blood components for transfusion in the UK, ensuring that they meet applicable standards of safety, quality and efficacy and their supply chains are safe and secure[121]. The MHRA reviews applications for orphan drug designation at the time of a marketing authorisation (MA) or variation applications[122]. All medicines that have been granted an orphan MA from the UK Licensing Authority will be listed on its Orphan Register. The Orphan Register[123] comprises 1. EU Marketing Authorisation (MA) converted into Great Britain MA in accordance with the Human Medicines Regulations (2012) i.e. where there is an existing EU orphan designation, the Great Britain MA continues in effect with the remaining period of orphan market

accordance with the Human Medicines Regulations (2012) i.e. where there is an existing EU orphan designation, the Great Britain MA continues in effect with the remaining period of orphan market exclusivity, and 2. products that have received an MA with orphan status on or before 1 January 2021 from the UK licensing Authority, the MHRA. An effective orphan designation is indicated by an orphan designation number. Products with orphan designation in the EU can be considered for a Great Britain orphan marketing authorisation while a UK-wide orphan marketing authorisation can only be considered in the absence of an active EU orphan designation. A search was run through the database, Orphan Register, using the drug names (and their synonyms) reflected on the respective HTA dossiers retrieved from NICE. In order for the shortlisted dossiers to be included in the dataset, the assessed drug indication must be included in what is reflected under 'Authorised orphan indication' in the Orphan Register (and/or in Orphanet) along with the drug's Great Britain Orphan designation number which indicate its status with an active designation.

Health Science Authority (HSA)

As the national regulator for drugs, innovative therapeutics, medical devices and health-related products, The Health Science Authority (HSA) in Singapore plays a vital role in ensuring they are well-regulated under high standards of safety, quality and efficacy[124]. Orphan drugs were previously regulated under the Medicines Act (Chapter 176), as Medicines (Orphan Drug) (Exemption) Order (1991)[125], one of the laws on which HAS regulates medical products in Singapore. After 1 November 2016, HSA consolidated existing regulatory controls into a single legislation, the Health Products Act (HPA) and the Medicines (Orphan Drug) (Exemption) Order was repealed. Currently, the HPA does not contain any specific definition of, or reference to orphan drugs or rare diseases[126]. As such, orphan drugs are regulated in the same way as other therapeutic products which are defined as 'health products intended for use in humans for a therapeutic, preventive, palliative or diagnostic purpose'[127]. However, hospitals can apply for approval to import unregistered therapeutic products for patients' use only when these therapies are considered 'life-saving' i.e. 1. There is an unmet medical need e.g., there is no registered treatment option 2. The patient's health will be clinically compromised without treatment with the unregistered product[121]. The Therapeutic Products Guidance from HSA provides that if a product is designated as an Orphan Drug by at least one reference drug regulatory agency or has been approved by at least one reference regulatory agency via an accelerated or fast track approval or approval under exceptional circumstances, the applicant should consult HSA before submission to seek advice of eligibility for verification evaluation route[128]. HSA's reference agencies are, namely, Australia Therapeutic Goods Administration (TGA), Health Canada (HC), US Food and Drug Administration (FDA), European Medicines Agency (EMA) via the Centralised Procedure, and

UK Medicines and Healthcare Products Regulatory Agency (UK MHRA)[129]. A search was run through the databases of FDA, EMA and MHRA using the search engine by keying in the drug names (and their synonyms) indicated in the HTA dossiers. In order for the HTA dossiers from ACE to included, drug indications under 'Orphan Drug Designation' must be a rare disease (according to FDA and/or EMA and or MHRA, and/or Orphanet) and 'Orphan Drug Status' must reflect 'Positive/Approved' or state explicitly that the drug was 'designated an orphan medicine'.

(c) indicated for a rare disease or condition

Orphanet was also used to determine and verify the 'rarity status' of the target indication of the drugs i.e. the assessed drug indication in the HTA dossier must be a rare disease. This was conducted by running a search of the indication i.e. disease or condition names and their synonyms in the database under 'Inventory, classification, and encyclopedia of rare diseases, with genes involved'. Outputs of the search include a detailed description of the disease. Information about the disease's prevalence and epidemiology was used to determine the rarity status in e.g., Europe, according to the EU Regulation on Orphan Medicinal Products (OMPs)[130] as 5 in 10,000. Only drug indications that target rare conditions defined by the respective reference authorities are included in the dataset. The terms 'rare disease treatments' and 'orphan drugs' were used interchangeably throughout this report.

(d) conducted between January 2016 to December 2021

This is determined by the publish date stated on the report or the report's landing page on the HTA agency's website. The period is defined on the basis of narrowing the scope of analysis within the most recent five years backdated from the time of data collection, given the stipulated duration to conduct this study.

(e) indicated 'completed' or equivalent in terms of publication status

Where reports are retrieved from the webpages of the respective HTA agencies, this is indicated as 'Assessment status: closed' for ICER, 'Project status: completed' for CADTH, 'published' along with dates for NICE, 'The National Health Care Institute has completed its assessment' and letter date for ZIN, the publish date for ACE and lastly, 'Project status: Completed' for AiHTA dossiers which were all first retrieved from INAHTA webpage.

As the HTA dossiers were retrieved from six different countries which may use different reference drug regulatory agencies, additional considerations were made to further determine if the HTA dossiers are suitable for inclusion based on ***criterion (b) and (c)*** as compiled in Table 2.

Table 2. Summary of HTA agency and justification for the reference agency used with regards to inclusion criteria (b) and (c)

HTA agency	Type of HTA dossier	Reference regulatory agency for criteria (b) and (c)	Justification(s)
ZIN	Advisory Letter to Prime Minister	EMA	The Netherlands is a country in the EU.
AiHTA	Horizon Scanning	EMA	Austria is a country in the EU.
ACE	Summary Report (Guidance)	EMA, FDA, MHRA	These three agencies have been listed by HSA as its reference drug regulatory agency.
NICE	Full report (Guidance)	MHRA, EMA	The Orphan Register comprises EU authorised and designated drugs.
ICER	Final Evidence Report	FDA	ICER synchronises their assessments with FDA drug approvals[131].
CADTH	Health Technology review reports	FDA	There is no existing orphan drug framework in Canada currently although Health Canada (HC) is an equivalent of FDA and EMA. This is thought to be attributed to Canadian's current access to the majority of the orphan drugs approved in the US due to the drugs being approved for sale or were available through the Special Access Programme[132].

Conclusions about HTA recommendations for reimbursement of orphan drugs were determined directly from the reported decision reflected in respective dossiers i.e. where it states '*(not)recommended for reimbursement or inclusion*' or equivalent e.g., '*not to be included*'. For ICER, it is taken to be a positive recommendation if their conclusions advised on the need for price or coverage revision as one of the key policy implications, such as '*...those who design health benefits need to recognize the seriousness of financial toxicity for patients and families and seek new approaches to eliminate this burden*' and '*...consider the treatment's broader benefits to patients and society while simultaneously working to maintain affordability of health insurance for all patients*'. AiHTA, ZIN and CADTH were selected as a source of HTA dossiers for Austria, the Netherlands and Canada respectively as no readily accessible reports could be retrieved from the other HTA agencies in the countries. Due to international reference to NICE's published guidances and the fact that no other relevant dossiers were found from other UK HTA agency's webpage or INHTA, dossiers from NICE were deemed to be representative of the country's drug regulation practices and included in the dataset. Based on the aforementioned inclusion criteria, relevant dossiers were found only from ICER for the USA.

4.1 Research design

This study mainly comprises a document analysis (including a case study) which was conducted using a self-developed criteria checklist comprising HTA evaluation factors to answer the aforementioned research objectives. The development of the evaluation factor list was based on three main studies, Maynou and Cairns[133], Yuasa et al.[134] and Whittal et al.[135]. Further cross references to Nicod et al.[136], Rawlins et al.[137] and Lakdawalla et al.[30] were also made with respect to the definitions of the factors, some of which were reworded to provide clarity and scope for the purpose of this study. An initial compilation of 42 factors were subsequently refined to a list of 32 variables stratified into the five main categories – 'economic evidence', 'clinical evidence', 'disease considerations', 'treatment considerations' and 'other considerations', as shown in Table 4. Reference to the IMPACT HTA WP10[138] (country vignettes to characterise country processes) was made in order to further define the scope of each variable to create a more focused checklist to analyse the data collected from the dossiers from each HTA agency. Each dossier was reviewed and analysed for the evaluated factor against the developed checklist. Based on what was reported or documented in each dossier, the information collected from the documents was transformed into nominal data coded or labelled with numbers for each HTA factor and recorded in two datasets. Where appropriately addressing the aforementioned research objectives, the data was analysed against three nominal variables which were also coded with numbers, shown in brackets i.e. (a) **HTA agencies** i.e. ACE (1); AiHTA (2); CADTH (3); ICER (4); NICE (5); ZIN (6) (b) **Financing systems** i.e. single payers (0); multi-payers (1) (c) **Recommendation decisions** i.e. not recommended (0); not recommended (1). Content analysis was conducted in the case study to elucidate identified discrepancies.

4.2 Data collection

The first dataset records the factor reporting frequencies reflected in the HTA evaluation of the drug for its indication. Each factor was deemed to be reported if it was explicitly mentioned or elaborated as a consideration in the decision-making process and subsequently labelled with '1', or if found otherwise, labelled with '0'. This procedure was consistently applied for all 47 dossiers (Table 1, Appendix B). In the second dataset, each variable was labelled with the numbers i.e. 0, 1 or 2 based on the researcher's comprehension of dossier information regarding the outcomes of factor evaluation or assessment. This process of sieving out relevant and appropriate supporting information was further guided by the independently derived **question** scoping each factor for the purpose of this study (Table 3). Each dossier was read at least once, first to gain an overall idea of the general structure and approach of the evaluation, and subsequently to quote evidence as to substantiate the decisions on labelling the levels within each variable (HTA factor) 0, 1 or 2 to specify the respective outcomes of factor assessment. Similarly, this procedure was repeated for all 47 dossiers (Table 1, Appendix C).

Table 3. Definitions and scope of the HTA evaluation factor (criteria) list

Category	Factor	Definition	Scoping Question
Economic Evidence	ICER framework for rare diseases	cost-effective assessment that incorporate societal perspectives e.g., ICER calculated from with modified societal perspective, contextual considerations that may lead to coverage and funding decisions at higher cost-effectiveness thresholds, caregiver utility scores etc.	Does a modified cost effectiveness analysis apply for assessment?
	Cost-effectiveness	cost-effectiveness estimate (represented as an ICER) compared to what is usually considered cost-effective use of resources i.e. cost per QALY gained based on current price level, compared to SOC or best supportive care	Is ICER considered cost-effective ie. within WTP or cost-effectiveness threshold at current price level?
	Budget impact analysis	A budget impact analysis evaluates whether the high-value intervention is affordable i.e. feasibility	Is treatment affordable for the healthcare system?
	Comparative effectiveness	Direct or indirect data / evidence that allow comparison of effectiveness between treatment and comparator	Could comparative effectiveness be assessed/concluded?
	Economic modelling	Methodology quality in terms of assumptions and inputs in economic models	Were there issues identified with the inputs and assumptions that question the validity of the models?
Clinical evidence	Study design	Uncertainty or issue of study type like RCT, double blind or design like single arm study	What were the concerns raised regarding the studies?
	Sample size	Uncertainty or issue of sample size in clinical trial	What were the concerns raised regarding the sample size?
	Additional/other evidence	Other evidence e.g, expert opinions, international consensus, other trials conducted	Where these evidence are considered, are they deemed valid for decision making?
	Clinical benefits	Observed benefits mainly in terms of therapeutic impact and consideration in clinical site	Is efficacy deemed overall clinically meaningful based on measured outcomes (if applicable, for all relevant subgroups/indications)?
	Safety	Patient risk caused by adverse events or side effects in clinical trial i.e. overall safety profile	Is the treatment deemed safe for patients (overall safety profile)?
	Population generalisability	Uncertainty or issue of target population for treatment, probability of generalization	Are results generalisable to most patients in routine or general clinical practice?
	Survival	Percentage of people in trials/study group who have avoided death (mortality) after a given period of time	Was survival highlighted as an important clinical outcome or required for consideration?
	Long-term effectiveness	Magnitude of clinical effectiveness/benefit based on clinical evidence of significant improvement in long-term outcomes for patients that is clinically significant and important for management of the disease	Does treatment improve long-term outcomes for patients?
	Quality of life	Clinical evidence of impact of treatment on generic health-related and/or disease-related quality of life	Does treatment lead to significant improvement to the quality of life?
Disease considera-tions	Available options/ alternatives	Problems related to alternative treatment compared to target treatment	Is current treatment/alternatives unavailable, limited, time-consuming, burdensome for patients and carers, not well tolerated, resulting in complications which impact QOL and mental well-being?
	Children	Special consideration given to quality of life of children	Are special considerations for children/pediatrics included in decision-making (with exceptions)?

	Disease nature	Severity of a disease determined based on its impact on mortality and quality of life.	Does disease rank high in terms of severity in its worst form?
	Rarity	Disease is considered rare based on contextual-specific definition	Is special consideration given to the rarity of the disease?
	Disease burden	Does disease have significant impacts on these aspects?	Is disease determined to have a significant burden?
	Unmet needs	Refers to clinical need or equivalent (e.g., therapeutic gap)	Does treatment address a therapeutic gap or unmet needs?
Treatment considera-tions	Indirect benefits	The indirect effects of health improvement like productivity in the workplace	Does treatment render indirect benefits to patients, family, caregivers etc.?
	Adherence-improving factors	Medical technologies that can improve patient's adherence to treatments and health outcomes that will then impact costs and effectiveness (e.g. simple dosing schedules, alternate routes of administration and combination treatments)	Does treatment improve adherence, thereby health outcomes?
	Innovation	A new technological innovation that demonstrates a benefit of an important nature	Is the treatment a new innovation of important benefits?
	Complex care pathway	Complex pathway for treatment to reach patient (delivery of specialised technology)	What is the impact of the treatment on the delivery of specialised health services?
	Managed entry agreement	A MEA is an arrangement between a manufacturer and payer/provider that enables access to reimbursement of a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize their effective use, or limit their budget impact. This variable collects the different types of MEA: financial, performance-based or a combination of both	Are MEAs or equivalent considered for decision-making?
	Patient access schemes	Patient access schemes are innovative pricing agreements proposed by pharmaceutical companies. They aim to improve cost-effectiveness and enable patients to gain access to high cost drugs and treatments	Are patient access schemes considered for decision making?
	Cost of treatment	Costs associated with disease management and treatments	Is the cost of treatment deemed costly ?
	Long-term financial risk	The impact of reimbursing treatment on the financial risk to public payers i.e. financial burden on the public healthcare system?	Does treatment present potential financial risks to public payers?
	Treatment duration	Duration of treatment	Is treatment lifelong?
Other considera-tions	Stakeholder persuasion	Patients and their advocates, such as patient communities, can weigh in the decision by explaining inadequately measured health-related quality-of-life or poorly reflected symptomatology during clinical trials	Are stakeholder inputs, where considered, valid for decision making?
	Value of hope	Technologies that provide an opportunity for a cure regardless of the mean outcome. For example, an ill patient may be willing to trade-off some survival for a small probability for a cure. Value of hope can be important for therapy with uncertain effects that cannot be predicted beforehand by diagnostic tests or assessments	Does treatment offer a value of hope?
	Equity	Equality considerations and social value judgements	Does recommendation/accessibility to treatment impact equity?

The definition of uncertainties and issues were adapted from the definitions elaborated by Yuasa[134]. Uncertainties are defined as unclear or insufficient clinical evidence that hindered the ability to obtain a solid judgment of the assessed technology reported by the HTA agencies. In this study, variables with level definitions specifying 'uncertainty' are deemed synonymous with 'limited' depending on the expression that is commonly used in dossiers with respect to communicating outcomes of assessment of a particular factor. Issues are defined as clinical factors that were expressed as being incorrect or problematic by the HTA agencies. These were identified by the exact and/or similar expressions in the dossiers. The full definitions of the levels for each variable are illustrated in Table 4.

Table 4. Variables (HTA factors) and their respective definition of levels

HTA Factors / Variables	**Level / value definitions**		
	0	1	2
Budget impact analysis; cost-effectiveness; other evidence; clinical benefits, safety; population generalisability; long-term effectiveness; quality of life, disease nature; unmet needs; indirect benefits; adherence-improving factors; long-term financial risk; treatment duration	No, uncertain or limited	Yes	Not mentioned
ICER assessment framework for rare diseases; comparative effectiveness; economic modelling; survival; children; disease burden; rarity; innovation; cost of treatment; stakeholder perspective; value of hope; equity	No	Yes	Not mentioned
Study design; sample size	Uncertain/limited	Issues	Not mentioned
Patient Access Schemes (PAS); Managed Entry Agreement (MEA)	No	Yes	Recommended
Available options / alternatives	No options	Limited/issues	Not mentioned
Complex care pathway	Negligible, uncertain/limited	Increased burden/ complexity	Not mentioned
*Recommendation decisions (for reimbursement)	Recommended	Not recommended	Not mentioned

*The terms 'recommendation decisions' and 'reimbursement decisions' both refer to reimbursement or financial coverage by payers, and may be used interchangeably in this paper, where appropriate and relevant to the content discussed.

4.3 Data analysis

The number of dossiers reporting each factor was recorded and calculated as a proportion out of the total number of dossiers from each agency (i.e. relative frequency) since the number of dossiers from each agency included in this study is different. Distribution analysis of reported HTA factors across the agencies were further stratified according to the aforementioned categories. This facilitated a categorical or thematic approach to summarise the HTA factor reporting frequencies. Descriptive statistics was used to illustrate the frequencies and distribution of the respective factors. Statistical analyses were carried out using STATA MP 17.0, Minitab 18 and DisplayR. Cross-tabulations were conducted for subsequent Test of Independence (Chi-Squared and Fisher Exact) to explore variable associations elaborated in the aforementioned study objectives.

(i) Fisher Exact and Chi-Square Test of Independence

As the first objective of this study was to determine whether HTA factor reporting frequencies vary significantly across the three variables (a) HTA agencies (b) types of financing systems (single- versus multi-payers) and (c) recommendation decisions, associations were explored using Fisher Exact and Chi-Square Test of Independence using STATA MP 17. A significance level where $\alpha = 0.05$ (based on a two-sided test) was used in this study since the sample size is 47 and 5% is conventionally used across literature[139]. Where $p < 0.05$, the null hypothesis stating the independence between the two variables was rejected, and that they are not independent was concluded. Where expected values are below 5 in the cross-tabulations, Fisher Exact test was used to determine statistical significance of the differences in reporting frequencies of HTA evaluation factors and recommendation decisions across (a) HTA agencies and (b) Financing systems. Chi-Squared values and the degrees of freedom were used for subsequent analysis of the strength of association between variables and interpreted using Cramér's V.

(ii) Cramér's V

Cramér's V was used as a measure of effect size for Chi-square Test of Independence. Because of the nature of the data collected for this study, where each variable of interest was assigned a value of 0 and 1 for analysis of reporting frequencies and 0, 1 or 2 for analysis of outcomes of assessment of each factor, Cramér's V was deemed suitable for exploring the strength of the relationship between the variables. The use of Cramér's V facilitated an analytical focus on factors with reporting frequencies that were found to be **strongly** associated with (a) *HTA agencies* (b) *Financing systems* and (c) *Recommendation decisions*. Generally, Cramér's V ranges from 0 to 1, where 0 implies no relationship and 1 implies perfect association. There are various rules of thumb for interpreting Cramér's V as an effect size for the Chi-Square Test of Independence. An approach based on the degrees of freedom[140] was applied in this study. In two by two tables, Cramer’s V has the same value as a measure of association called phi, where

the phi coefficient is similar to Pearson correlation coefficient, ranging from -1 to 1. Where negative Cramer's V arose as a result of a two by two contingency table, the absolute value was recorded in this study and interpreted as follows, in Table 5.

Table 5. Interpretation of Cramér's V on strength of associations between categorical variables based on degrees of freedom according to Chi-Square Test of Independence

Degrees of freedom (d.f)	**Interpretation of Cramér's V on strength of associations between variables based on d.f**			
	Negligible	Small (weak)	Medium (moderate)	Large (strong)
1	0 < 0.10	0.10 < 0.30	0.30 < 0.50	0.50 or more
2	0 < 0.07	0.07 < 0.21	0.21 < 0.35	0.35 or more
3	0 < 0.06	0.06 < 0.17	0.17 < 0.35	0.29 or more
4	0 < 0.05	0.05 < 0.15	0.15 < 0.25	0.25 or more
5	0 < 0.05	0.05 < 0.13	0.13 < 0.22	0.22 or more

(iii) Correlation analysis (CA)

CA analyses a two-way contingency table and focuses on exploring relationships between two sets of variables. Based on results of Fisher Exact test across (a) HTA agencies (b) Financing systems and (c) Recommendation decisions, CA was conducted for the variable that showed the highest number of HTA factors demonstrating statistically significant and strong associations so as to explore their relationships further as an extension of the first study objective. CA was performed using Minitab 18 and DisplayR was used to produce a correspondence biplot (using principal normalisation) and interpreted along with the statistical output of the analysis. Distances between the origin and (i) row (ii) column labels were used to determine their distinction from others i.e. the closer they are to the origin, the higher the likelihood that they are indistinct from each other. To improve the interpretability of the association shown in CA in terms of the relative angles to the origin between the row (agency) and column (factors) labels, a moon plot was created using DisplayR with the *row normalisation* option. The smaller the angle connecting the row and column labels to the origin in the moon plot, the higher the likelihood they are associated. The size of the fonts on the moon plot represents the distance between column labels and the origin. Deductions made from the CA and moon plot were also subsequently compared with the raw data and statistical results from Fisher Exact and Chi-square Test of Independence, to make relevant and appropriate conclusions.

(iv) Multiple correspondence analysis (MCA)

MCA is an extension of correspondence analysis (CA) to analyse the pattern of relationships in observations between more than two categorical variables. As part of the second objective of the study to explore whether recommendation decisions were influenced by specific outcomes of assessments of the selected HTA factors, MCA ((*method(joint)*; *norm(principal)*) was conducted using STATA MP 17 to develop further insights. Associations between observations recorded for the outcomes of evaluation (*MCA categories*) for HTA factors with statistically significant differences in reporting frequencies across (a) HTA agencies and (b) recommendation decisions were plotted as a means of visual representation. The results were interpreted based on the statistical output of the analysis and an MCA plot. Points that are farther away from the origin of the MCA plot indicate *categories* that are more influential. Points on opposite sides of the plot indicate that a dimension contrasts these categories. For consistency in the scope of the analysis, the following was applied for both CA and MCA in this study:

- The inertia (*inert*) for a component describes the amount of variation the component explains.
- The inertia (*inert*) for a column describes how much the values for that category differ from the expected value under the assumption that none of the categorical variables are correlated
- The column correlation (*corr*) value represents the contribution of the component to the inertia of the column. Correlation values range from 0 to 1. It is used to interpret each component in terms of its contribution to column inertia. Values close to 1 indicate that the component accounts for a high amount of inertia. Values close to 0 indicate that the component contributes little to inertia
- The contribution (*contr*) of each column category to the inertia of each component

(v) Case study

The last objective of this study was to illuminate and extend current understanding on variations in outcomes of assessment of HTA factors with respect to how evidence was used and assessed against standards or criteria specific to HTA agencies and their evaluations. The aim was to investigate the presence of methodological variations such as evidentiary requirements across HTA agencies. With growing attention on patient access to treatments for neuromuscular disorders[141], spinal muscular atrophy was selected as a case analysis since dossiers evaluating Zolgensma® were included and available from three HTA agencies in this study. A document study was conducted to further analyse the information reported in the dossiers from CADTH, NICE and ICER by comparing the factor assessment outcomes for each HTA evaluation factor. Synonyms or similar words and phrases pertinent to the assessment of the HTA factors were bolded while each agency's judgment was underlined for comparison purposes. Factors that were found to have different outcomes of assessment were further analysed to deliberate understanding on how (evidence-based) clinical or scientific value

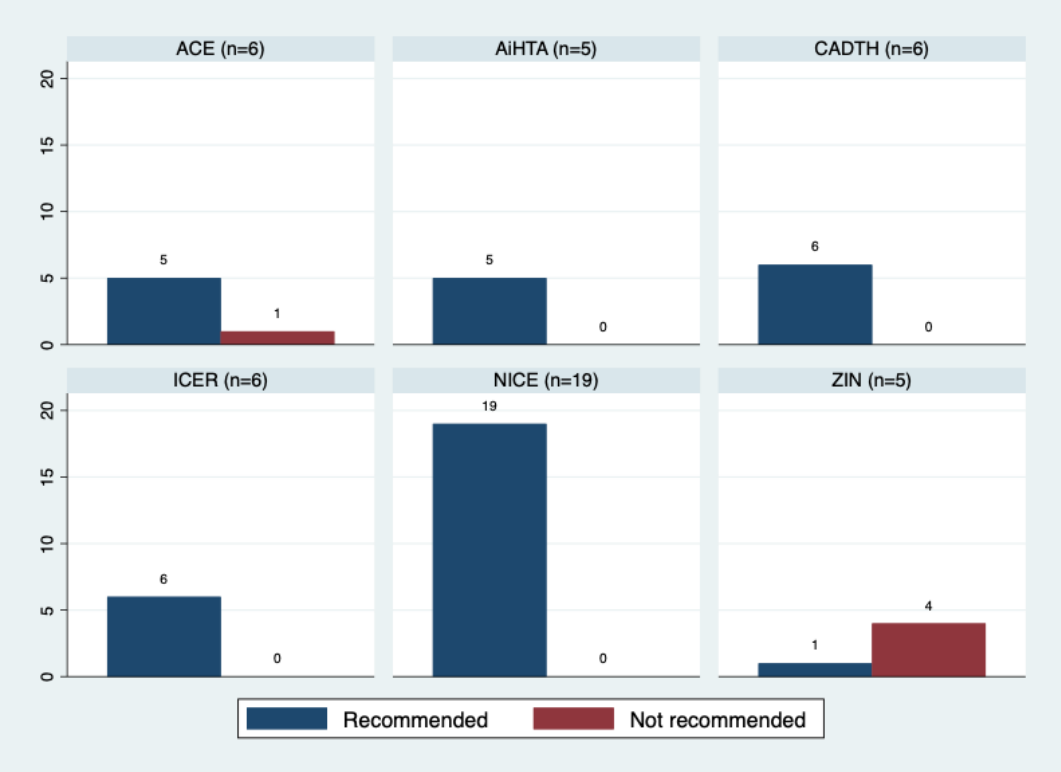
judgment are made. This serves to particularly explore possible explanations for variations despite the evaluation or utilitsation of the same body of evidence, since in these cases, preliminarily speaking, the differences did not seem to be associated with the HTA recommendation decisions made by the agencies, at least based on the scope and data collected in this study.

5 Results

5.1 Recommendation decisions across HTA agencies (Appendix A, Table 2)

Figure 1 summarises frequency distribution of recommendation decisions across HTA agencies. Five out of all 47 dossiers (10.6%) across all HTA agencies did not have a positive recommendation for reimbursement. All dossiers from CADTH, NICE, AiHTA reported positive HTA recommendation for reimbursement and for ICER, all dossiers advised on ensuring affordability with respect to pricing and insurance coverage reviews i.e. all ICER dossiers were considered to have positive recommendation in this aspect. One out of six and four out of five dossiers from ACE and ZIN respectively, did not report a positive recommendation. Fisher Exact Test revealed statistically significant differences in recommendation decisions ('recommended' and 'not recommended') across HTA agencies ($p < 0.001$) and that the two variables are strongly associated ($\chi 2 = 29.8$; Cramér's V = 0.80).

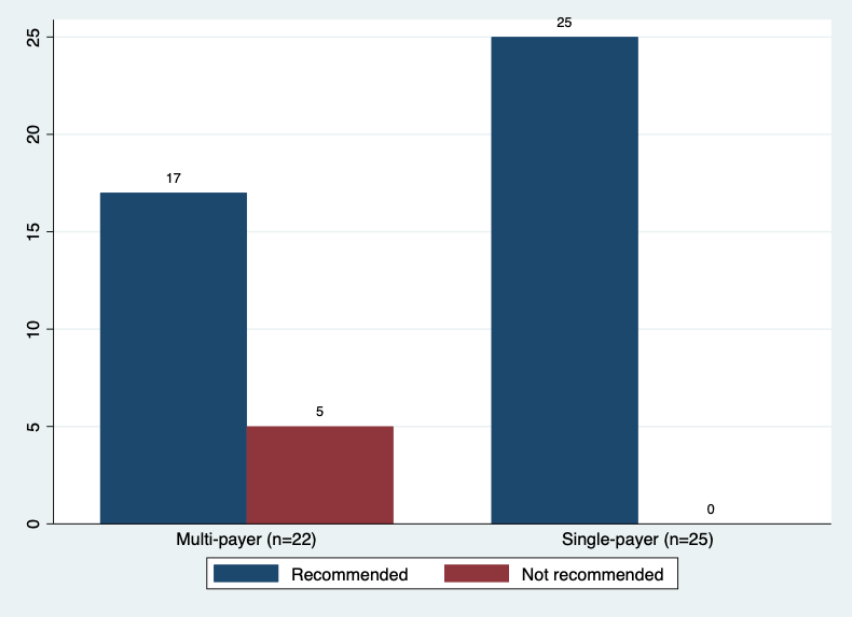
Figure 1. HTA recommendation decisions from 47 dossiers across HTA agencies



5.2 Recommendation decisions across financing systems (Appendix A, Table 2)

Figure 2 shows that, across financing systems, all 25 dossiers (100%) from single payer systems and 17 out of 22 dossiers from the multi-payer systems (77.3%) concluded with positive recommendations. Fisher Exact Test was statistically significant (p = 0.02) i.e. significant differences in recommendation decisions were found between single- and multi-payers. The two variables were deemed to be moderately associated ($\chi 2$ = 6.36; Cramér's V = 0.37).

Figure 2. HTA recommendation decisions from 47 dossiers across financing systems

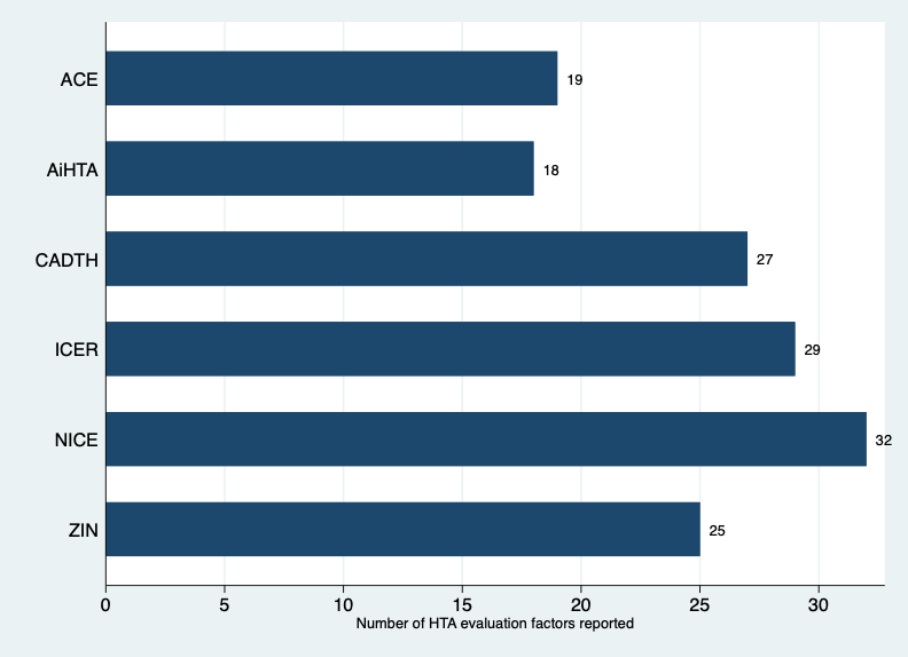


5.3 HTA evaluation factors reported across HTA agencies (Appendix A, Table 3)

(i) Frequencies

A total of 32 HTA evaluation factors were included in the checklist, out of which, five were classified under 'economic evidence', nine under 'clinical evidence', six under 'disease-related considerations', nine under 'treatment-related considerations' and three under 'other considerations'. Overall, all 32 factors were reported in dossiers from NICE, 29 from ICER, 27 from CADTH, 25 from ZIN, 19 from ACE and 18 from AiHTA. It is also noteworthy that not all factors out of these were reported in each dossier. For instance, a range of 17 to 23 factors were reported in CADTH's dossiers, 3 to 18 by ZIN, 3 to 14 by ACE and 14 to 17 by AiHTA (Appendix B). The least number of factors were reported in dossiers from ACE and AiHTA where HTA is used to inform inclusion in Drug Subsidy List in Singapore and Horizon Scanning in Austria respectively. The total number of factors reported across all dossiers from each of the agencies are summarised in Figure 3.

Figure 3. Number of factors reported (out of a total of 32) across HTA agencies



(ii) Test of Independence

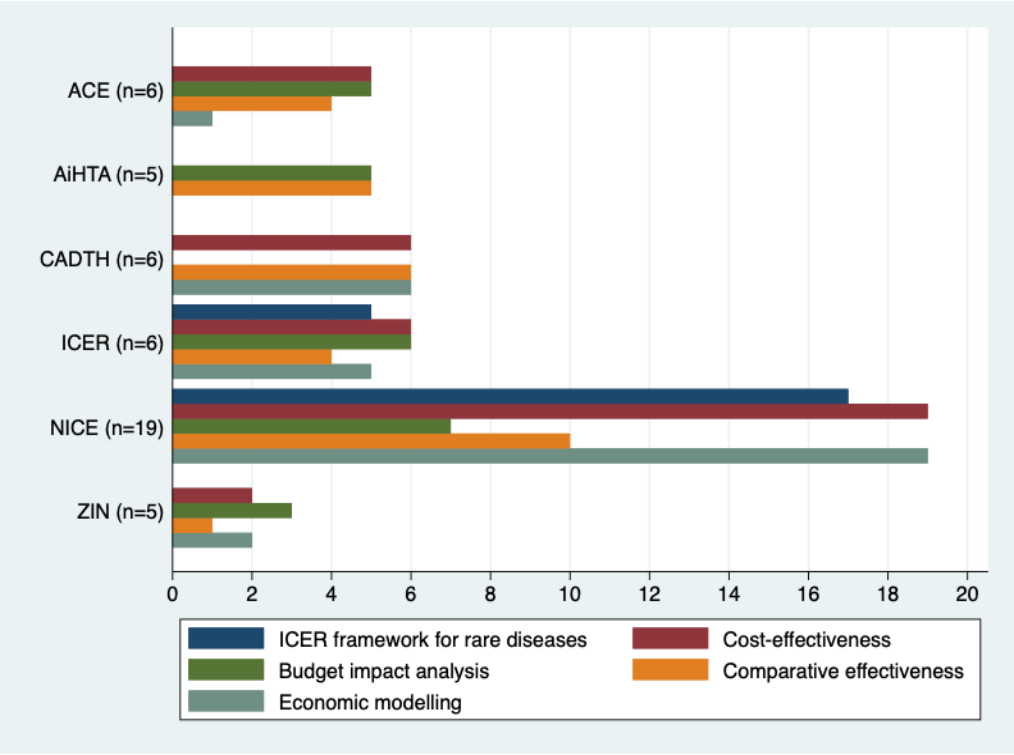
Results of Fisher Exact Test on the reporting frequencies of the HTA factors across HTA agencies and financing systems were recorded in Table 6 according to the categories the factors fall under.

(a) Economic evidence (Table 6a)

Out of the six agencies, only NICE and the ICER applied a HTA assessment framework specially adjusted or modified for rare diseases and reported all five factors in their evaluation of economic evidence. Figure 4 summarises reporting frequencies of factors under evaluation of economic evidence. 'Comparative effectiveness' was reported across all HTA agencies and in the highest proportion of dossiers (100%) from CADTH and AiHTA. 'Cost-effectiveness' was reported by all agencies except AiHTA. 'Budget impact analysis' was reported by all agencies except CADTH, and in all of ZIN's dossiers. 'Cost-effectiveness', 'comparative effectiveness' and 'economic modelling' were reported in all CADTH's dossiers, 'budget impact analysis' and 'comparative effectiveness' in all AiHTA's dossiers, 'cost-effectiveness' and 'economic modelling' in all NICE's dossiers, and 'cost-effectiveness' and 'budget impact analysis' across ICER's dossiers. Out of the five factors, statistically significant Fisher Exact results ($p < 0.05$) were found for the reporting frequencies of 'cost-effectiveness', 'budget impact analysis' and 'economic modelling' across HTA agencies and financing systems. The three factors were shown to be strongly associated with HTA agencies and financing systems based on Cramér's V (Table 5). While reporting frequencies of 'comparative

effectiveness' were statistically different between HTA agencies, it was not significant between the two groups of financing systems. Association between financing system and 'comparative effectiveness' was also found to be of moderate strength according to Cramér's V. Four out of five factors present statistically significant differences in reporting frequencies across HTA agencies.

Figure 4. Number of dossiers reporting factors under 'economic evidence' across HTA agencies



(b) Clinical evidence (Table 6b)

Out of the six agencies, only dossiers from the single-payers, CADTH and NICE, reported all nine factors in their evaluation of clinical evidence, compared to multi-payer systems. As shown in Figure 5, out of the nine factors, 'safety', 'clinical benefits', 'quality of life', 'survival' and 'population generalisability' were reported by all HTA agencies. In terms of proportion of dossiers reporting the factors in the evaluation of clinical evidence across HTA agencies, 'clinical benefits' and 'quality of life' were reported in all dossiers from AiHTA, CADTH, ICER and NICE, 'long-term effectiveness' and 'safety' in all dossiers from AiHTA, CADTH and NICE. 'Study design', 'sample size' and 'long-term effectiveness' were reported by all HTA agencies except ACE. 'Quality of life' was most frequently reported amongst dossiers from ZIN and ACE. Under clinical evidence, reporting frequencies for 'additional/other evidence', 'clinical benefits', 'population generalisability', 'long-term effectiveness' and 'quality of life' were found to be statistically significant across both HTA agencies and financing systems.

Table 6a. HTA factors reported across HTA agencies and financing system for economic evidence (*statistically significant i.e. p < 0.05)

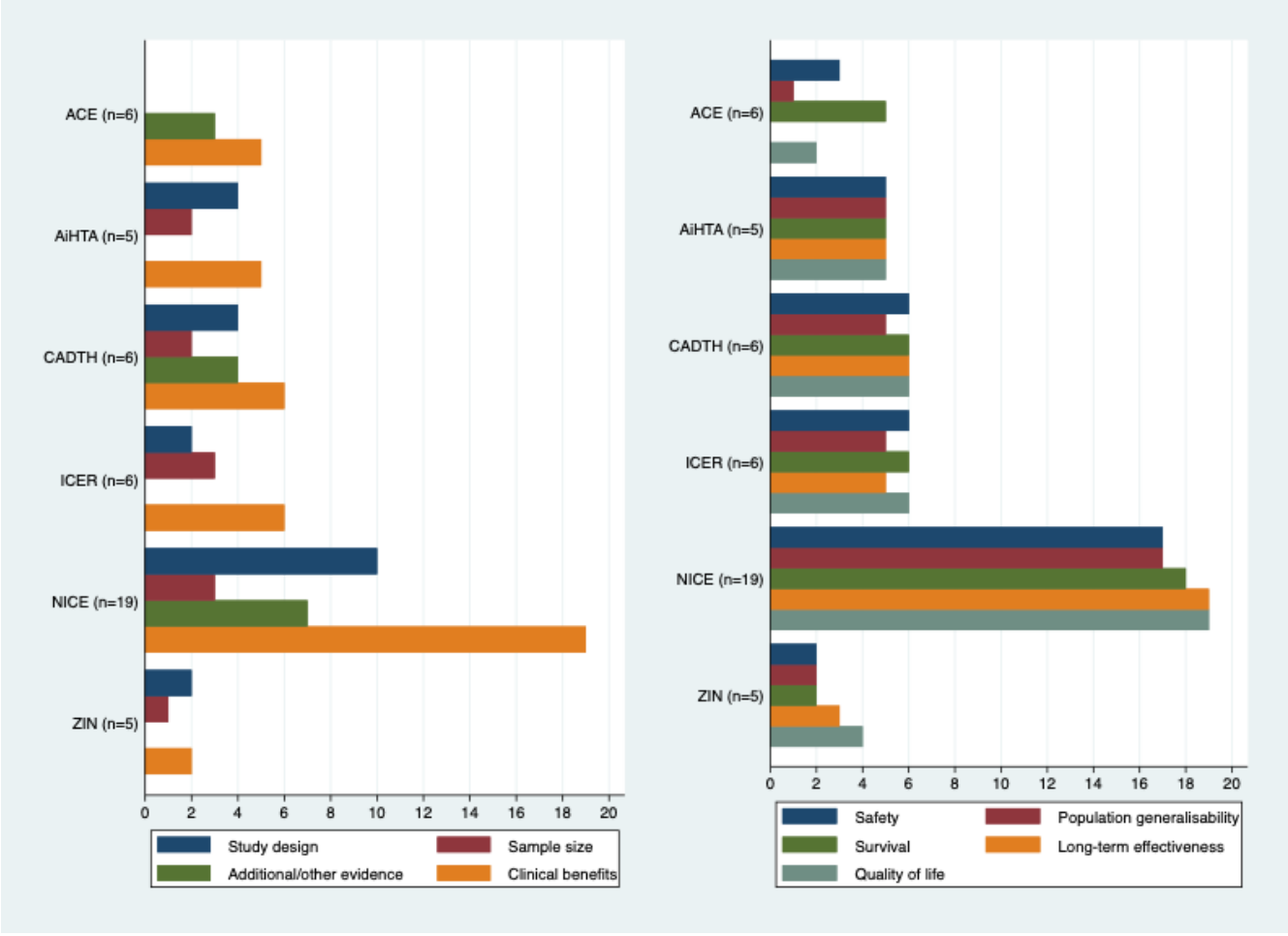
Test of Association	**Factors under evaluation of economic evidence across *HTA agencies*** (d.f = 5)				
	ICER assessment framework for rare conditions	Cost-effectiveness: value-for-money	Budget Impact Analysis	Comparative effectiveness	Economic modelling
$\chi 2$ (Cramér's V)	3.08 (0.26)	31.88 (0.82)	20.89 (0.67)	11.47 (0.49)	33.29 (0.84)
Fisher Exact (p value)	1.00	<0.001*	<0.001*	0.04*	<0.001*
	Factors under evaluation of economic evidence *across financing systems* (d.f = 1)				
$\chi 2$ (Cramér's V)	1.84 (0.20)	14.44 (-0.55)	16.13 (0.59)	0.0007 (0.00)	22.66 (-0.69)
Fisher Exact (p value)	0.49	<0.001*	<0.001*	1.00	<0.001*

Table 6b. HTA factors reported across HTA agencies and financing system for clinical evidence (*statistically significant i.e. p < 0.05)

Test of Association	**Factors under evaluation of clinical evidence across *HTA agencies***								
	Study design	Sample size	Additional/ other evidence	Clinical benefits	Safety	Population generalisability	Survival	Long-term effectiveness	Quality of life
$\chi 2$ (Cramér's V)	9.23 (0.44)	5.95 (0.36)	12.31 (0.51)	20.89 (0.67)	15.21 (0.57)	18.13 (0.62)	15.65 (0.58)	33.87 (0.85)	24.56 (0.72)
Fisher Exact (p value)	0.09	0.26	0.03*	0.003*	0.02*	0.003*	0.04*	<0.001*	<0.001*
	Factors under evaluation of clinical evidence across *financing systems*								
$\chi 2$ (Cramér's V)	1.81 (-0.20)	0.35 (0.09)	5.16 (-0.33)	4.97 (-0.33)	3.08 (-0.26)	5.14 (-0.33)	2.48 (-0.23)	12.65 (-0.52)	6.36 (-0.37)
Fisher Exact (p value)	0.24	0.73	0.03*	0.04*	0.12	0.04*	0.17	<0.001*	0.02*

Except for 'long-term effectiveness', which was found to be strongly associated with both HTA agencies and financing systems, the other four aforementioned factors were strongly associated with HTA agencies but moderately associated with financing systems. Statistically significant differences across HTA agencies were also ascertained for 'safety' and 'survival'. Although these two factors were strongly associated with HTA agencies, they were weakly associated with financing systems. Heterogeneity in reporting frequencies for seven out of nine factors revealed statistically significant differences across HTA agencies, out of which five of them may be associated with the types of healthcare financing system.

Figure 5. Number of dossiers reporting factors under 'clinical evidence' across HTA agencies

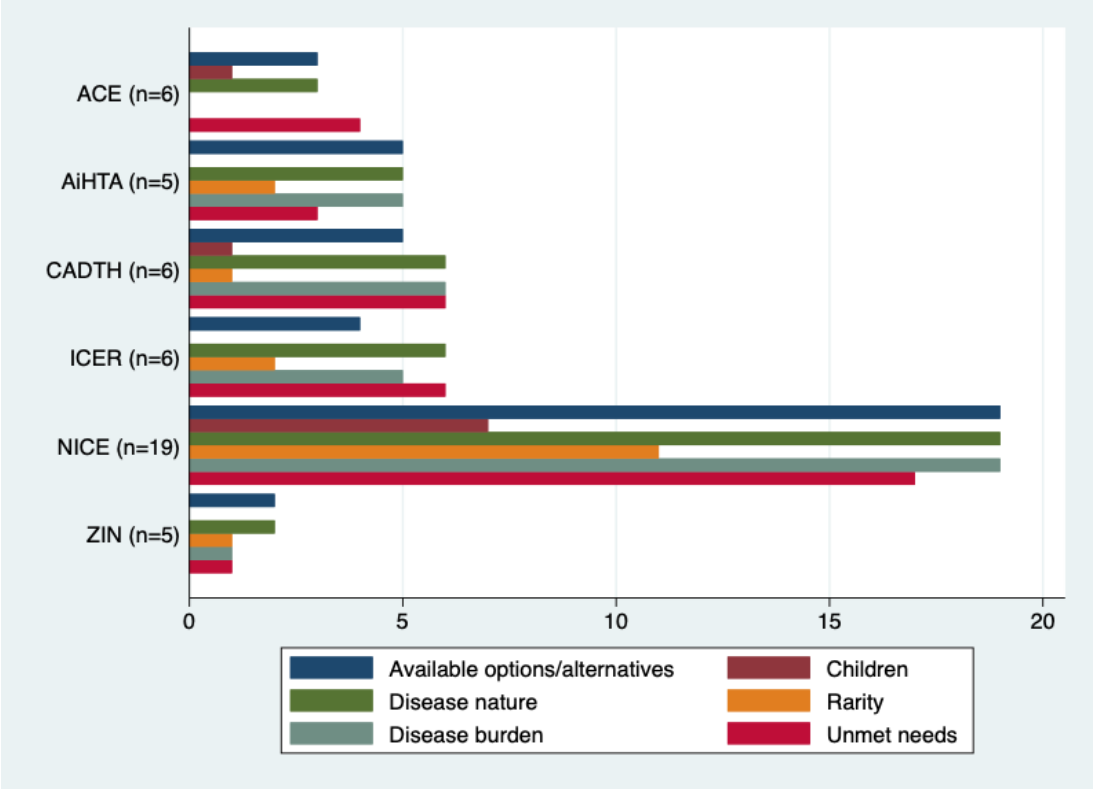


(c) Disease-related considerations (Table 6c)

Only CADTH and NICE reported all six factors in their evaluation of disease-related considerations, as shown in Figure 6. Dossiers from all HTA agencies reported 'rarity' and 'disease burden' except ACE. 'Unmet needs', 'available options/alternatives' and 'disease nature'

were reported by all HTA agencies. In terms of the proportion of dossiers reporting these factors, 'available options/alternatives' was reported in all dossiers from AiHTA and NICE, 'disease nature' in all dossiers from AiHTA, CADTH, ICER and NICE, 'disease burden' in all dossiers from AiHTA, CADTH and NICE, 'unmet needs' in all dossiers from CADTH and ICER. Both 'available options/alternatives' and 'disease nature' were the most frequently reported factors in dossiers from ZIN and ACE along with 'unmet needs' for the latter agency. 'Children' was least commonly reported in this sample. Fisher Exact Test showed that, four out of six factors, 'available options/alternatives', 'disease nature', 'disease burden' and 'unmet needs' were statistically significantly different across HTA agencies and financing systems. All aforementioned factors were strongly associated with HTA agencies but moderately associated with financing systems except for 'disease burden', which was found to be strongly associated with both HTA agencies and financing systems. Reporting frequencies for 'children' and 'rarity' were shown to be statistically significantly different across financing systems but not HTA agencies. With regards to disease-related considerations, these two factors were moderately associated with financing systems.

Figure 6. Number of dossiers reporting factors under 'disease-related considerations' across HTA agencies



(d) Treatment-related considerations (Table 6d)

Figure 7 summarises factors reported under treatment considerations. Only NICE reported all nine factors in its evaluation of treatment-related considerations. 'Cost of treatment' was reported by all HTA agencies. 'Treatment duration' was reported by all agencies except ACE, and it is the only factor reported in every agency-specific dossier (from AiHTA). 'Innovation' was considered by all HTA agencies except AiHTA and along with 'indirect benefits', was most frequently reported amongst ICER's and NICE's dossiers and across HTA agencies. 'Managed entry agreement' was considered by all HTA agencies except ACE. Comparatively, 'patient access schemes' was most frequently reported amongst ACE's dossiers, 'treatment duration' amongst AiHTA's and ZIN's dossiers and 'cost of treatment' amongst CADTH's dossiers, and ' and when compared across HTA agencies.

Figure 7. Number dossiers reporting factors under 'treatment-related considerations' across HTA agencies

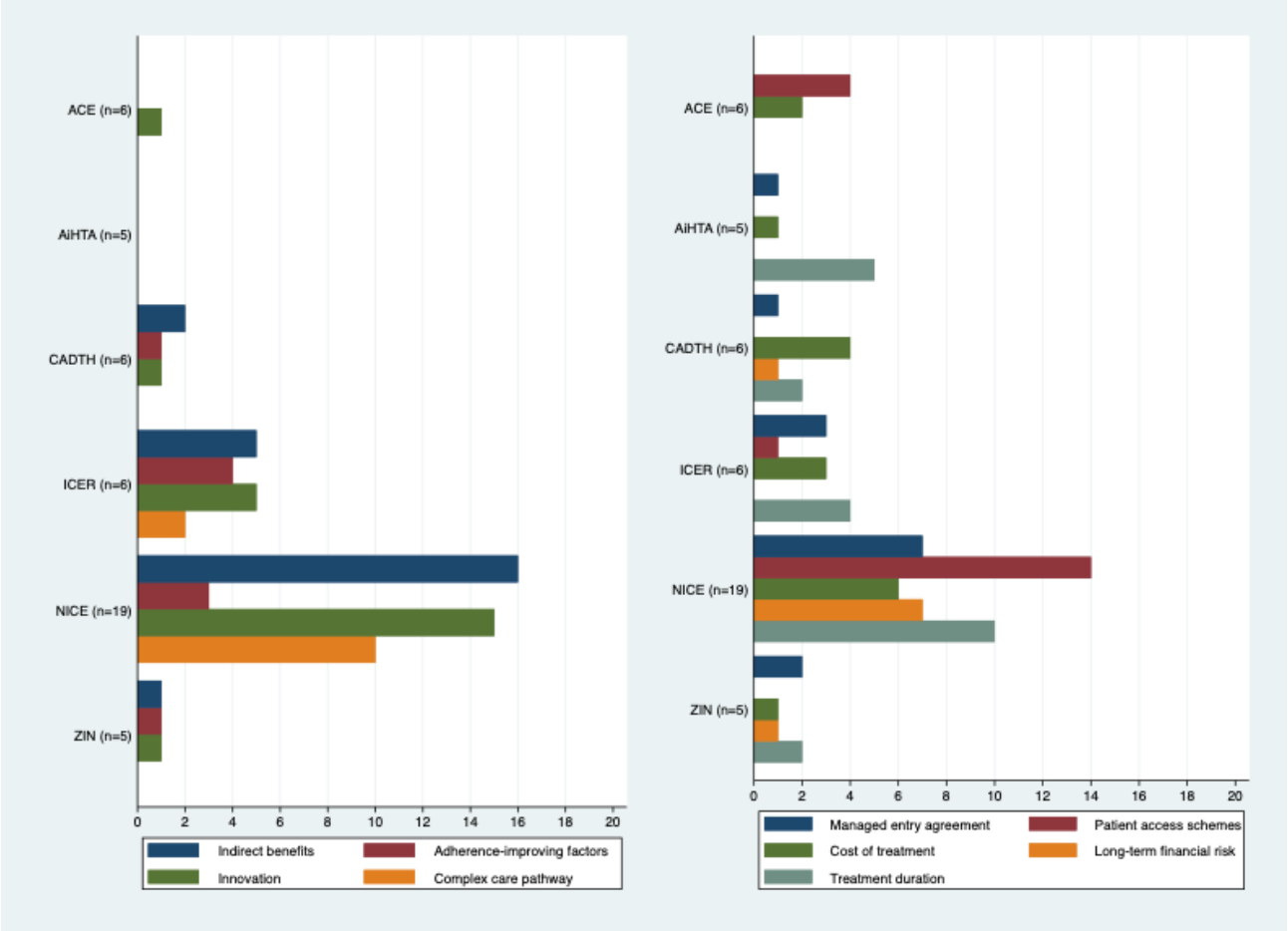


Table 6c. HTA factors reported across HTA agencies and financing system for disease-related considerations (*statistically significant i.e. p < 0.05)

Test of Association	**Factors under evaluation of disease-related considerations across *HTA agencies* (d.f = 5)**					
	Available options/alternatives	Children	Disease nature	Rarity	Disease burden	Unmet needs
$\chi 2$ (Cramér's V)	15.57 (0.58)	7.68 (0.40)	22.76 (0.67)	9.60 (0.45)	37.89 (0.90)	16.42 (0.59)
Fisher Exact (p value)	0.003*	0.28	0.001*	0.09	<0.001*	0.01*
	Factors under evaluation of disease considerations across *financing systems* (d.f = 1)					
$\chi 2$ (Cramér's V)	7.92 (-0.41)	5.70 (-0.35)	7.82 (-0.41)	4.63 (-0.31)	16.32 (-0.59)	5.62 (-0.35)
Fisher Exact (p value)	0.01*	0.03*	0.01*	0.03*	<0.001*	0.03*

Table 6d. HTA factors reported across HTA agencies and financing system for treatment-related considerations

Test of Association	**Factors under evaluation of treatment-related considerations across *HTA agencies***								
	Indirect benefits	Adherence-improving factors	Innovation	Complex care pathway	Managed Entry Agreement or equivalent	Patient Access schemes or equivalent	Cost of treatment	Long-term financial risk	Treatment duration
$\chi 2$ (Cramér's V)	25.02 (0.73)	11.52 (0.50)	21.16 (0.67)	15.07 (0.57)	5.14 (0.33)	22.71 (0.70)	4.24 (0.30)	7.89 (0.41)	12.57 (0.52)
Fisher Exact (p value)	<0.001*	0.06	<0.001*	0.01*	0.42	<0.001*	0.57	0.22	0.02*
	Factors under evaluation of treatment considerations across *financing systems*								
$\chi 2$ (Cramér's V)	9.37 (-0.45)	0.342 (0.09)	4.85 (-0.32)	5.88 (-0.35)	0.13 (-0.05)	5.38 (-0.34)	0.34 (-0.09)	5.70 (-0.35)	0.02 (0.02)
Fisher Exact (p value)	0.003*	0.72	0.04*	0.02*	0.76	0.04*	0.76	0.03	1.00

Overall, 'treatment duration', 'indirect benefits', 'managed entry agreements' and 'cost of treatment' were, broadly, more frequently reported, despite differences across HTA agencies. In terms of treatment considerations, reporting frequencies for 'indirect benefits', 'innovation', 'complex care pathway', 'patient access schemes' were statistically significantly different across HTA agencies and financing systems. All four factors were strongly associated with HTA agencies but moderately associated with financing systems. Reporting frequencies of 'treatment duration' were found to be statistically significantly different across HTA agencies but not financing systems, and were strongly associated with HTA agencies. Five of out nine factors regarding considerations of the new intervention of treatment were found to be statistically significantly associated with HTA agencies.

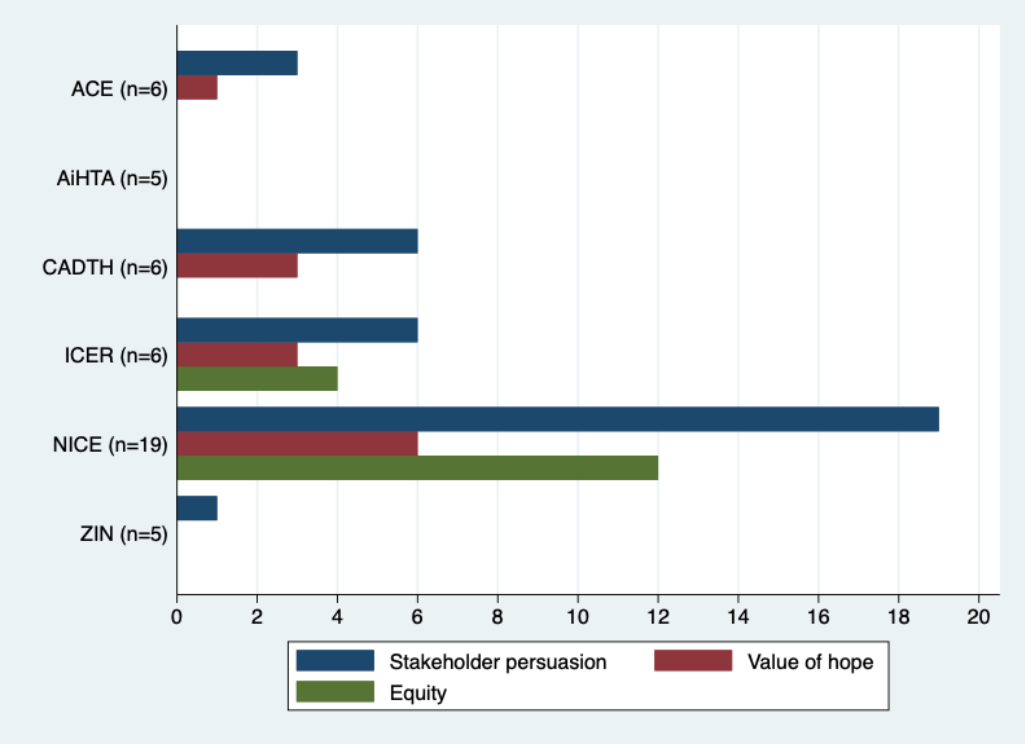
(e) Other considerations (Table 6e)

Table 6e. HTA factors reported across HTA agencies and financing system by categories

Test of Association	**Factors under evaluation of other considerations across *HTA agencies***		
	Stakeholder persuasion	Value of hope	Equity
$\chi 2$ (Cramér's V)	34.90 (0.86)	7.33 (0.40)	21.37 (0.67)
Fisher Exact (p value)	<0.001*	0.22	<0.001*
	Factors under evaluation of other considerations across *financing systems*		
$\chi 2$ (Cramér's V)	18.31 (-0.62)	1.86 (-0.20)	4.63 (-0.31)
Fisher Exact (p value)	<0.001*	0.21	0.06

As shown in Figure 8, out of the six agencies representing respective countries, only NICE and the ICER reported all three factors under 'other considerations'. 'Stakeholder persuasion' was reported in all dossiers from CADTH, ICER and NICE and considered by all HTA agencies except AiHTA. It was the most frequently reported factor amongst dossiers from ACE, CADTH, ICER and NICE. 'Value of hope' was most frequently reported by ICER and NICE, which were also the only two agencies that considered 'equity' in their evaluation. AiHTA did not report any of these factors and ZIN reported only 'stakeholder persuasion' out of the three.

Figure 8. Number of dossiers reporting factors under 'treatment considerations' across HTA agencies



'Stakeholder persuasion' was more frequently reported than the other two factors in terms of other considerations constituting value judgment in HTA evaluation processes. Fisher Exact Test showed statistically significant differences in reporting frequencies for 'stakeholder persuasion' and 'equity'. While 'stakeholder persuasion' was strongly associated with both HTA agencies and financing systems, 'equity' was found to be strongly associated with the former and moderately associated with the latter.

To sum, statistically significant differences in reporting frequencies were found for 22 out of 32 factors (68.8%) across HTA agencies - four out of five pertains to economic evidence, seven out of nine to clinical evidence, four out of six to disease considerations, six out of nine to treatment considerations, and two out of three to other considerations. None of the categories of factors was particularly emphasised more than the other based on reporting data. 18 of the 22 factors were more strongly associated with HTA agencies than financing systems of the countries studied here. 'Rarity' and 'children' were associated with only financing systems and 'survival' and 'safety' only with HTA agencies. To further understand the associations between reporting frequencies of HTA evaluation factors and HTA agencies, reference was also made to the output of the correspondence analysis from Minitab 18 in the next section.

Correspondence analysis (CA)

Since the Fisher Exact Test concluded statistically significant differences in the reporting frequencies of 22 HTA evaluation factors (out of 32) which were found to be strongly associated with HTA agencies, a CA was conducted to explore relationships between these variables and plotted, as shown in Figure 9. Narrowing down to these factors served to focus the analysis on factors that varied significantly in being reported by the HTA agencies in this study and refine the interpretations. Based on their relative distances from the origin, it can be broadly deduced that ACE and AiHTA are highly differentiated than CADTH, ICER, NICE and ZIN i.e. the latter four agencies are probably less distinct in terms of their reporting frequencies of various HTA factors, in that they are not differentiated by the data collected in this study. On the same note, it can also be seen that 'unmet needs', 'clinical benefits', 'disease nature', 'disease burden', 'quality of life', 'safety', 'available options/alternatives' and 'stakeholder persuasion' are factors closest to the origin (within the first quadrants from the origin). These nine factors were more commonly reported in the assessment of RDTs than others across dossiers in this dataset although statistically significant differences were found in the reporting frequencies of these factors across the HTA agencies.

The statistical outputs of CA from Minitab 18 showed that the two dimensions explain a total of 67.9% of the inertia, and inclusion of dimension 3 increased the inertia to 86.3%. 'Cost-effectiveness', 'additional/other evidence' and 'patient access schemes' contributed most to dimension 1, 'survival', 'indirect benefits' and 'innovation' to dimension 2, and lastly, 'budget impact analysis' and 'complex care pathway' to dimension 3. These eight factors were amongst the most salient factors contributing to variability in the data set based on the statistical outputs of the CA, based on their *contr* and *corr* values (Appendix A, Table 4). Figure 10 shows a moon plot that also displays associations with distinct factors (indicated by larger font sizes i.e. they were also the furthest away from the origin in the CA plot). ACE was shown to be more associated with 'additional/other evidence', NICE with 'long-term effectiveness' ', ICER with 'complex care pathway'- and with relatively less distinct factors - ZIN with 'clinical benefits', CADTH with 'disease burden', and AiHTA with 'available options/alternatives'.

Figure 9. Correspondence plot (principal normalization) evaluation factors (column) that were found to be associated with HTA agencies (row)

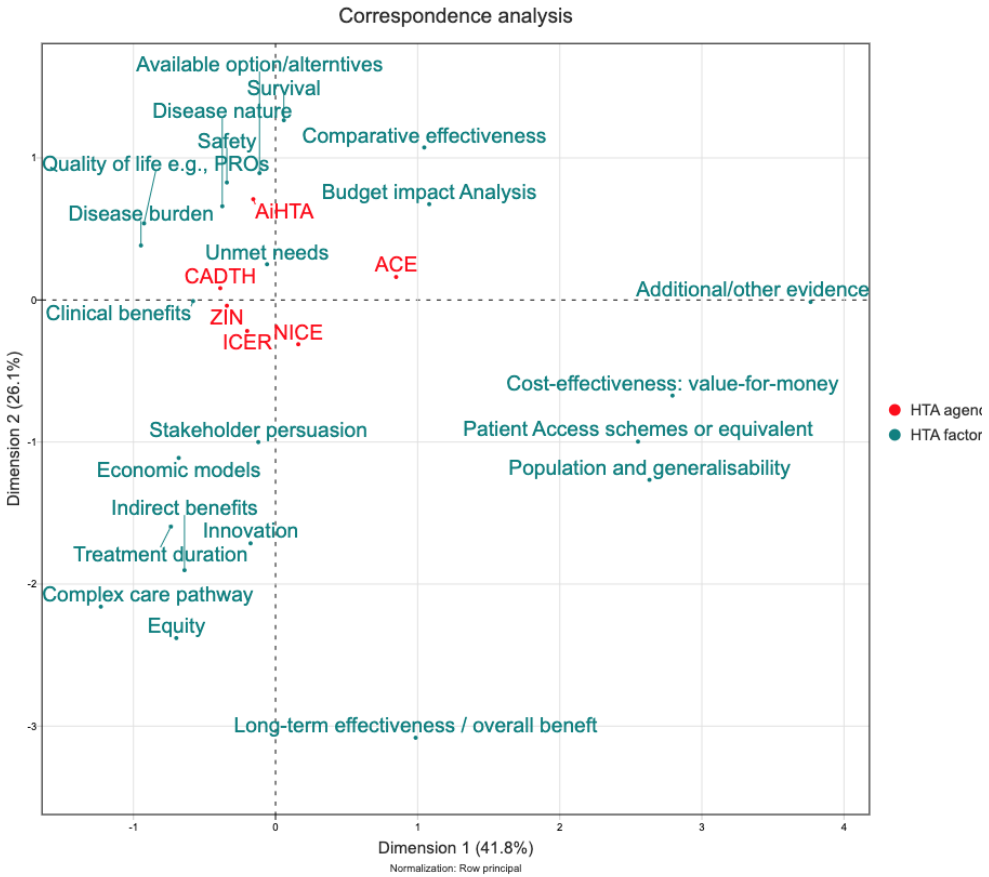
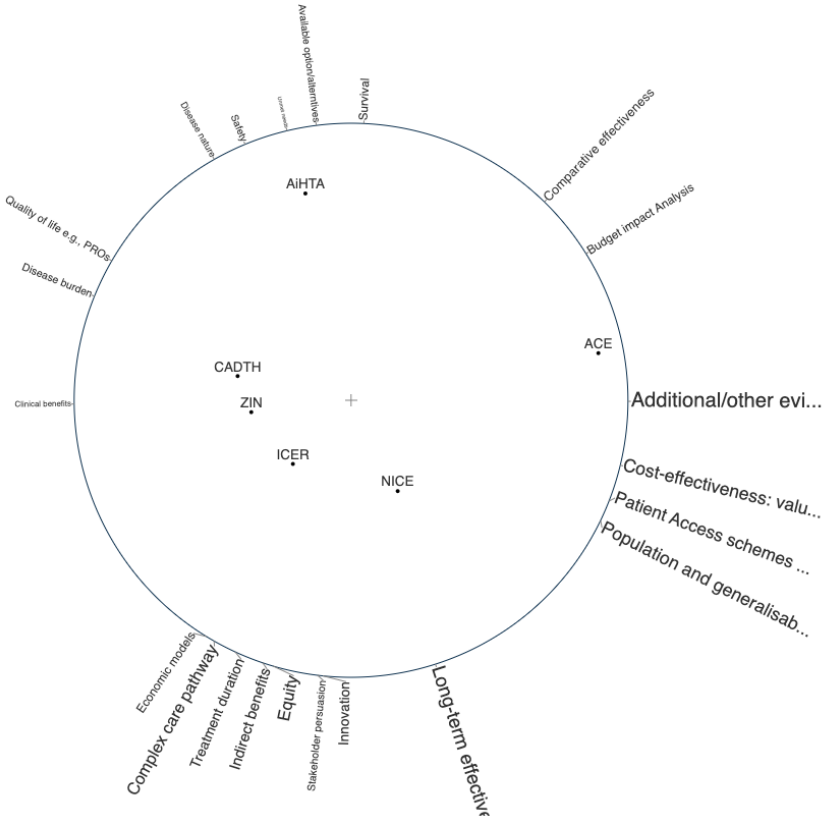


Figure 10. Moon plot showing association between HTA agencies and factors with statistically significant reporting frequencies



5.4 Recommendation decisions and HTA evaluation factors

Table 7. Factors showing statistically significant association with recommendation decisions

Test of Association	**Reporting frequencies of HTA evaluation factors across *recommendation decisions* (d.f = 1)**							
	Economic modelling	Clinical benefits	Safety	Long-term effectiveness	Available options/ alternatives	Disease burden	Indirect benefits	Stakeholder persuasion
$\chi 2$ (Cramér's V)	6.75 (0.38)	19.05 (0.64)	15.7 (0.58)	6.03 (0.36)	6.03 (0.36)	10.00 (0.46)	5.84 (0.35)	8.73 (0.43)
Fisher Exact (p value)	0.02	<0.001*	<0.001*	0.04	0.04	0.01	0.02	0.01

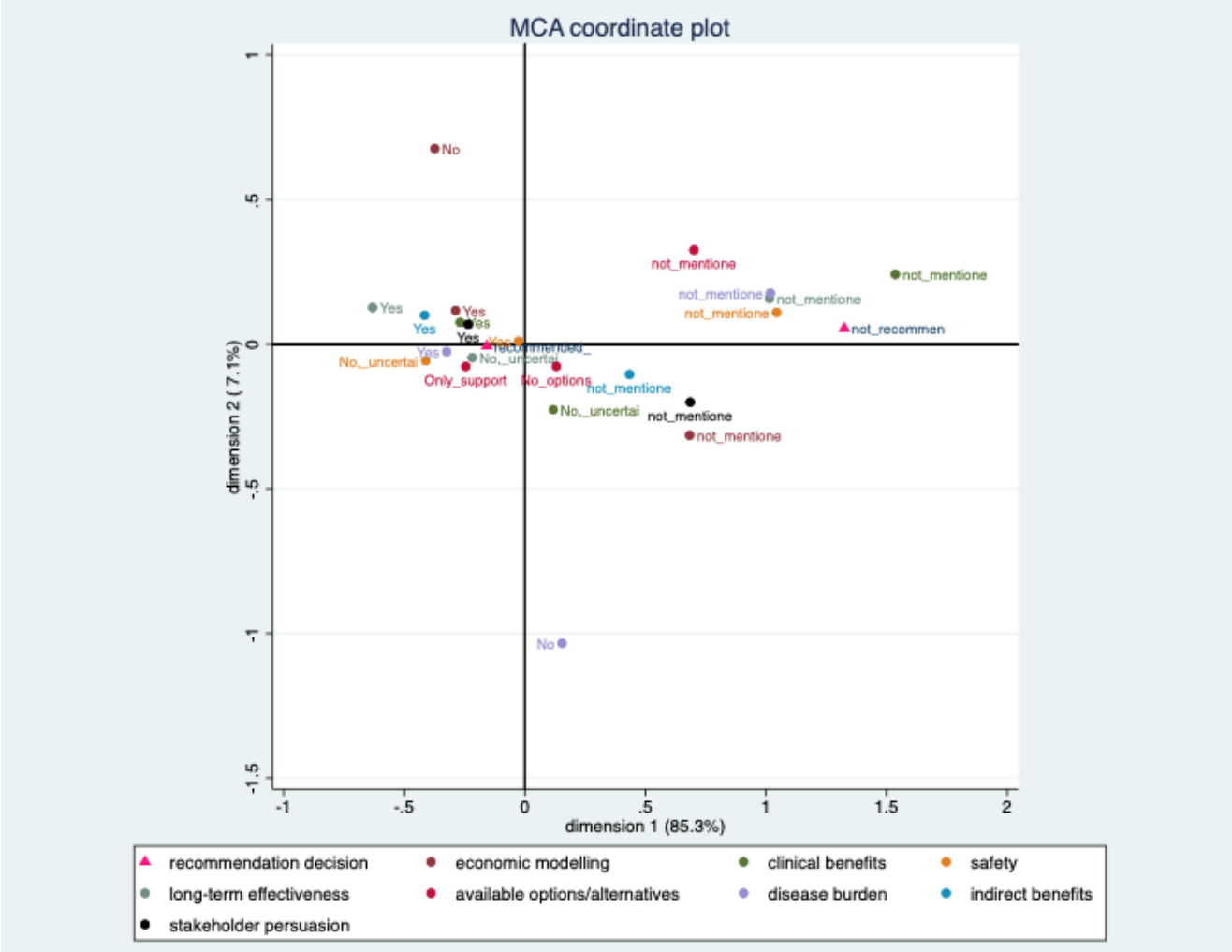
An investigation of how reporting frequencies of HTA factors are associated with recommendation decision for each dossier (Appendix A, Table 5) revealed statistically significant results for eight factors i.e. 'economic modelling', 'clinical benefits', 'safety', 'long-term effectiveness', 'available options/alternatives', 'disease burden', 'indirect benefits' and 'stakeholder persuasion'. Only 'clinical benefits' and 'safety' were found to be strongly associated (Cramer's V > 0.50 for d.f = 1) with recommendation decisions. To understand how the outcomes of assessment of these factors (besides their reporting frequencies) are associated with recommendation decisions , a multiple correspondence analysis (MCA) was conducted between recommendation decisions and the outcomes of assessment (Appendix C) of eight HTA factors in Table 7.

Multiple correspondence analysis (MCA)

Statistical outputs of MCA (Appendix A, Table 6) showed that 92.42% of the inertia (variability) was explained by the first two dimensions, 85.32% and 7.10% respectively. Statistical outputs were interpreted for the factors' *contr* and *corr* values, just as for CA. The MCA plot in Figure 11 displays the association between outcomes of factor assessment in the HTA evaluations and recommendation decisions. Dimension 1 contrasts between 'recommended' and 'not recommended' as well as outcomes of assessment of the eight HTA factors (Table 7) since they are on opposite sides of the origin. For instance, 'not mentioned' for all of the factors are on the opposite side of the origin from the other outcomes of evaluation such as 'yes', 'no' or 'uncertain'. Specifically, inertia in dimension 1 was explained mostly by 'recommendation decision' i.e. *not recommended*, 'economic modelling' i.e. *yes* and *not mentioned*, 'clinical benefits' i.e. *.yes* and *not mentioned*, 'safety' i.e. *no, uncertain* and *not mentioned*, 'long-term effectiveness' i.e. *no* and *not mentioned*, 'available options/alternatives' i.e. *only supportive care* and *not mentioned*, 'disease burden' i.e. *yes* and *not mentioned*, 'indirect benefits' i.e. *yes* and *not mentioned* and

'stakeholder persuasion' i.e. *yes* and n*ot mentioned*. Inertia of dimension 2 was mostly contributed by 'disease burden' i.e. *no* and 'clinical benefits' i.e. *no, uncertain*. For instance, dimension 2 contrasts between *no* from other outcomes or categories i.e. *yes* and *not mentioned* for 'disease burden' and between *yes* and *no* for 'clinical benefits'. '*Not recommended*' and the outcome '*not mentioned*' i.e. outcome of evaluation of the respective factors are not mentioned, contributing most to the variability in the dataset. Although 'clinical benefits' was statistically significantly and strongly associated with recommendation decisions (Table 7), the association between a **particular** recommendation decision and the outcome of assessment may not be confidently concluded, just as for 'disease burden' since they are not distinguished by dimension 1 (which, as mentioned, contrasts recommendation decisions) based on the data collected in this study.

Figure 11. MCA plot showing association between HTA recommendation decisions and outcomes of the eight evaluation of HTA factors



5.5 Case analysis: Evidence evaluation for Zolgensma®

With growing attention on patient access to rare neuromuscular disease treatments, a case study was conducted to explore the way in which scientific and clinical evidence was used by the different HTA agencies in evaluating Zolgensma® (onasemnogene abeparvovec), a gene therapy for treating children less than two years old with spinal muscular atrophy. Spinal muscular atrophy is a rare neuromuscular disease that is most severe when it affects infants and young children. The most common cause of this disease is the homozygous deletion or deletion and mutation of the alleles of the survival motor neuron 1 (SMN1) gene[142]. It works by replacing the function of the missing or nonworking SMN1 gene with a new working copy of a human SMN gene[143].

The aim of this case analysis is to illuminate any variations in approaches and conclusions made on the same body or sources of evidence and if so, attempt to explain the differences in the outcomes of assessment made by the three HTA agencies with reference to the type of healthcare financing system and possibly country-specific elements such as HTA as a tool for local purposes as well as HTA capacities in the country. To meet the aim of this part of the research, dossiers evaluating Zolgensma® for reimbursement eligibility from CADTH, NICE and ICER were used as samples for this case study because the three agencies evaluated evidence from the same clinical trials (Appendix D, Table 1) and used Nusinersen as the comparator (current) current best supportive care). Content analysis of the supporting information from the HTA dossiers that was quoted to substantiate the outcomes of assessment for each factor was subsequently conducted (Appendix D, Table 2). Based on dossier information, differences in the outcomes of assessments for evaluation factors (indicated by the value labels i.e. 0, 1 or 2) were found for the following:

(a) Comparative effectiveness

*'Several major **limitations** could not be addressed, most importantly the lack of information on the **long-term** comparative clinical effectiveness…adding to the **uncertainty**. Considering the lack of proper anchoring for the indirect comparisons and the inability to control for the considerable heterogeneity in the included studies, the basic assumptions behind the ITCs (indirect treatment comparisons) are unlikely to have been met.' - CADTH*	*'The committee concluded that, compared with best supportive care, there are **substantial** clinical benefits…(although) the expected **long-term** outcomes remain **uncertain**.' - NICE*	*'Despite the **limitations** of the single-arm, open-label design…we have high certainty that Zolgensma provides a **substantial** net health benefit, and rate the evidence base as "superior" to standard care (A). - ICER*

The foreground of either 'benefits' or 'concerns' showed differences in the way evidence of comparative effectiveness was weighed against decisions to be made. NICE and ICER foregrounded the substantial

benefits from Zolgensma® compared to the best supportive care (Nusinersen) against the uncertainties with long-term outcomes. On the other hand, CADTH weighed the evidence against an overriding aspect of its HTA processes - ITCs (Indirect Treatment Comparisons) - where direct comparisons are not available, limited or insufficient. It foregrounded the limitations of comparative evidence according to the assumptions in the ITC framework, which place an emphasis on synthesising evidence from example, randomised controlled trials, and hence the importance of meta-analyses.

(b) Study design

'(Although the) assessed outcomes in both studies (are considered) to be clinically meaningful, the lack of a concurrent control group precludes a precise estimation of the magnitude of benefit…leading to a potential ***overestimate*** *of treatment effect. The use of a natural history cohort in the STR1VE-US and the SPR1NT studies did not allow for unbiased estimates of treatment effect…' - CADTH*	*'The ERG also explained that all the studies had strengths and weaknesses, but that it preferred NeuroNext because of its relatively mature outcome data and prospective design. The committee considered that the natural history studies all had limitations, including a high proportion of people who have a tracheostomy unlike best supportive care in the NHS.'* *- NICE*	*'For Zolgensma, an additional concern is the single-arm design and the small sample size. Comparisons with historical controls can* ***exaggerate*** *perceived treatment effects, particularly when standards of care improve over time or when there is a variable natural history…" - ICER*

Both CADTH and ICER placed similar emphasis on the limitations of the study design in terms of whether appropriate comparisons can be established. All three agencies acknowledged the concerns regarding the use of natural history cohorts but only NICE made explicit reference to the local context, comparing it with patients in the NHS. Because of the way the same issue was highlighted or framed by all three agencies, it was challenging to distinguish between an 'issue' (clinical factors defined as being problematic) and 'uncertainty' (unclear or insufficient clinical evidence hindering solid judgment). In the use of '*did not allow for unbiased estimates*' versus '*perceived treatment effect*' by CADTH and ICER respectively, the latter suggests room for interpretation that can be shaped or influenced by a particular context while the former was a judgment that clearly implied the 'problem' with the estimates used.

(c) Clinical benefits

*'The magnitude of the observed **benefits** is clinically meaningful compared with outcomes from a historical cohort of patients who received standard of care treatment' - CADTH*	*'The committee concluded that onasemnogene abeparvovec is likely to have long-term health benefits, but the long-term effectiveness data were limited, and the exact amount of **benefit** was uncertain' - NICE*	*'Overall, where data were available, Spinraza and Zolgensma demonstrated improvements in motor function, survival, and need for permanent ventilatory support…Results of the interim analysis showed a statistically-significant **benefit** on HFMSE score favoring Spinraza…and caregivers consider a 1-point increase to be meaningful.' - ICER*

The description of the 'size' of the benefits between the three HTA agencies appeared vague, especially between 'magnitude' and 'exact amount' (how much) and between 'long-term' and 'observed' (what) when comparing CADTH and NICE respectively. ICER was more specific in that it considered benefits that are measured on scales that allowed statistical significance and the perspective (caregiver) to be included or considered for interpretation. However, given what was reported, it could be inferred directly that NICE, CADTH and ICER agreed on the treatment efficacy, but NICE particularly emphasised the need for long-term data for them to be 'certain' about the said clinical benefits.

(d) Safety

'Given these safety concerns and the limited duration of the study treatment periods, the long-term balance of safety and efficacy for onasemnogene abeparvovec is unknown' - CADTH	*'The company stated that all **treatment- related adverse events** were resolved during the studies.' - NICE*	*'Two infants also experienced asymptomatic elevations in serum aminotransferase levels which were deemed non-serious, **treatment-related AEs (adverse events)**…In terms of safety, liver toxicity was mitigated by amending the protocol to include an administration of prednisolone before and after Zolgensma infusion.' - ICER*

While CADTH perceived the reported adverse events as safety concerns for long-term consideration, thereby classifying it as 'unknown', when referring to these treatment-related events, NICE and ICER perceived or accepted the resolution of these events (as reported by Novartis) as a result of them being non-serious or addressed by protocols. Here, perception of how 'dangerous' the treatment and the time horizon within which to situate these adverse events seemed to differ.

(e) Population generalisability

'The generalizability of the results from the STR1VE-US and the SPR1NT studies to other patients with SMA (including different functional capabilities, ages, and SMN2 copy numbers), and patients who were previously treated with medications for SMA, such as nusinersen, was also noted as an important limitation' - CADTH	*'The clinical experts considered that the evidence from START and STR1VE-US was generalisable to NHS clinical practice. It concluded that the evidence presented was not generalisable to types 2 or 3 SMA with up to 3 copies of the SMN2 gene. and was unable to make a recommendation about them' - NICE*	*'...the narrow eligibility criteria of trials and the limited sample size raises concerns about generalizability of results to the wider population of patients with SMA.' - ICER*

CADTH and NICE specified clearly on the 'scope' of generalisability they were considering, unlike the vagueness of 'wider' population that was considered by ICER with respect to what it deemed as 'narrow eligibility criteria'. Only NICE specifically referred to generalisability to the local context i.e. the NHS clinical practice and indicated the boundaries of their recommendation rather than defining inapplicability as a limitation.

All in all, applying content analysis in this case analysis has highlighted, albeit briefly, explicit differences ranging from utilisation of evidence or data to evidence perceptions and acceptance across HTA evaluations from the three agencies, based on data collected in this study.

6 Discussion

In juxtaposing the evaluations of orphan drugs with the current HTA landscape, many researchers have unanimously concluded that appropriate value assessment frameworks (VAFs), HTA methodologies and capacities, as well the use of evidence across countries in the world are crucial for the alignment of payer and societal perspectives of 'value' with the actual 'dollar-value' in rare diseases. Assessing healthcare technologies for their 'value-for-money', particularly the novel ones, has also received enormous attention from researchers, policy-makers and many relevant industries[14]. The recent hype about value-based healthcare approaches and models have fueled research efforts to identify enhancers and key drivers of reimbursement decisions in several therapy areas, especially oncology and rare diseases, as well as a diversity of fit-for-value VAFs to strengthen the link between value and patient access. Many of these efforts comprise studies that illuminate understanding of diverging recommendations for reimbursement and variations in evaluation methodologies compared across HTA agencies internationally.

6.1 HTA evaluation factors as an indication of preference and/or priority

This study explored the dynamics of commonly assessed or used evaluation factors in HTA processes as well as factors that were recently proposed for inclusion in order to capture additional and unconventional elements of value across different settings. Out of these, *equity*, *disease severity* and *value of hope* were included in the checklist used for the study's research objectives. Here, while *disease severity* was shown to be relatively consistently considered, the other two were found to be less commonly reported. Overall, NICE was the only HTA agency that reported all 32 factors in the aforementioned evaluation factor checklist. The least number of factors were reported by ACE and AiHTA. The factors prioritised in the evaluation of economic evidence appeared to be 'comparative effectiveness', cost-effectiveness' and 'budget impact analysis'. Findings of this study also showed that 'comparative effectiveness' distinguished between HTA agencies more than financing systems in terms of methodological approaches to evaluating economic evidence. Agency-specific preferences seemed to exist in the evaluation of factors particularly those under clinical evidence, disease- and treatment-related considerations. 'Clinical' benefits', 'quality of life', 'long-term effectiveness' and 'safety' took precedence over other factors in the evaluation of clinical evidence. Interestingly, all five factors under disease considerations appeared to be relatively more highly prioritised than 'children'. 'Stakeholder persuasion' was shown to be most commonly reported out of the three factors under 'other considerations', and formed a valuable observation in the context of rare diseases because of the emphasis on its importance across literature in value assessment frameworks and methodologies.

Exploration of the associations between reporting frequencies of HTA factors across (a) *HTA agencies* (b) *financing systems* and (c) *recommendation decisions* revealed statistically significant differences for 68.8% (22), 56.3% (18) and 25% (8) of the 32 factors included in this analysis, despite the small sample size. Since stronger relationships with reporting frequencies of these factors were ascertained for *HTA agencies* than *financing systems* and *recommendation decisions* based on Cramér's V, it formed the focus of subsequent correspondence analysis. Variations in the reporting frequencies of these factors across dossiers in this study, on top of other research findings, reflect discrepancies in the concepts of both scientific and social value judgment that may be associated with underpinning principles of distributive justice upon which the healthcare financing systems of the countries are built. Correspondence analysis between the 22 HTA factors and the six HTA agencies showed that distinctively discerning variations exist in the reporting frequencies of eight of factors ('cost-effectiveness', 'additional/other evidence', 'patient access schemes', 'survival', 'indirect benefits', 'innovation', 'budget impact analysis', 'complex care pathway') for HTA evaluations of rare disease treatments (RDTs). This concluded that they may be more associated with agency-specific preferences than the other nine factors ('unmet needs', 'clinical

benefits', 'disease nature', 'disease burden', 'quality of life', 'safety', 'available options/alternatives' and 'stakeholder persuasion') which were probably more commonly reported by HTA agencies in RDT evaluations although their reporting frequencies differ significantly across agencies as well. The aforementioned eight factors were concluded to be amongst the chief HTA factors contributing to variability in the dataset, and were hence, deemed to be more associated with *HTA agencies* than the other factors i.e. these factors distinguish between the six HTA agencies more than the other HTA factors.

A study[144] to investigate the HTA landscape in Asia found that all countries surveyed have quality assurance processes in place to strengthen the methodological rigour and ensure consistency across HTA evaluations. This includes practices like seeking clinical stakeholder inputs to ensure that the evidence available and base case analysis conducted are aligned with local practices. In countries like Singapore and Thailand, in-house evaluations are sent to independent reviewers for validation of scientific rigour before being used to inform funding decisions. Results of this study also prompted ample opportunities to discuss the future of HTA in Singapore. Analysis of the limited published HTA dossiers highlighted the prioritisation of technology cost in ACE's decision-making for subsidy listing, along with cost-effectiveness and budget impact[145]. Analysis of HTA dossiers from ACE provided preliminary insights that showed its association with factors that mapped closely with the aim of the agency's technical evaluations to inform subsidy decisions based on four core criteria 1. Clinical needs and nature of the condition 2. Clinical effectiveness and safety 3. Cost-effectiveness 4. Estimated annual technology cost and number of patients who will benefit[146]. Although ACE evaluates data from international references like the UK and USA for decision-making, especially where local data is not available, emphasis on the importance and 'fit' of international decisions and conclusions for the local context is explicitly evident in most dossiers. In addition, ACE does not publish HTA evaluations and decisions that are as comprehensive as the other agencies. Notwithstanding this, it cannot be assumed or inferred that factors that are not reported in full details or not at all, are unimportant to ACE because they might have been considered but just not published. This is further supplemented with ACE's disclaimer that HTA reports are not published because of confidential considerations. Similar observations were also noted in ZIN's HTA dossiers, which are letters of advice or recommendation regarding inclusion of the assessed technology in the basic insured package i.e. the GVS list. Although ACE has developed standardised HTA methods and processes in line with international best practices to ensure consistency and robustness in methodologies, there is still currently a lack of clarity in whether or how orphan drugs are assessed. It is thus valuable to draw references from common international practices and derive some comparisons of approaches to such decision-making in Asia, especially those in the process of implementing or revising (universal) healthcare schemes and explore areas of improvement to better account for rare diseases.

'Stakeholder persuasion' was also found to be associated with *HTA agencies*, *financing systems* and *recommendation decisions* in this study. This not only illustrated the increasing prominence of stakeholder inputs in HTA evaluations of RDTs, but also the importance of this factor for studies that aim to investigate drivers of diverging HTA reimbursement decisions in this field. Although single-payer healthcare financing models of the UK and Canada are based on utilitarian approaches, it can be seen that their HTA approaches are egalitarian as much as they are utilitarian. This demonstrates a growing awareness of the need to provide coverage that not only maximise overall utility but also improve health outcomes rated by risks to reduce health inequalities, in both single- and multi-payer systems. Health is also a context where egalitarianism and altruism play an important role in individuals' preferences. On this note, including stakeholder inputs in decision-making frameworks require transparency as it demands more thorough deliberations on the constitution of the 'stakeholders' involved since their inputs are increasingly and more formally considered in HTA evaluations. Most HTA agencies in this study included inputs from scientific and clinical experts, as well as patients and patient experts, in their evaluations. In attempt to provide recommendations for addressing challenges in the health economic evaluations of gene therapies, such as valuation of health outcomes, assessment of clinical effectiveness and incorporation of broader elements of value, a study[147] confirmed the value of expert opinions where there is limited data, and recommended for these opinions to be obtained using structured elicitation techniques. For instance, analysis of ICER's dossiers in this study concluded that the agency publishes the list of stakeholders, including a 'voting' panel comprising the patient population, who were involved in the development of key policy indications through round table discussions. The names, titles and affiliations of the participants were published along with public comments in all the dossiers from ICER. In the opinion of this study, although this has significantly increased transparency in HTA reimbursement decision-making and allowed cross-contextual references and decisions to be made, it is noteworthy that inclusion of stakeholder inputs should be done as strategically and meticulously as possible to address or account for ethical controversies associated with distributive justice. Abásolo et al.[148] concluded a statistically significant empirical relationship between egalitarianism and altruism and that people who are politically left wing have a high propensity to be egalitarian and are likely to be altruistic individuals. It would seem that, although HTA is a utilitarian approach in its basis, decisions for rare diseases may also be influenced by egalitarian approaches. The dynamics between these two objectives may manifest as recurring questions about where exactly the line should be drawn in terms of validity of 'special' judgments, what constitutes a 'valuable' **value** statement from the public or other stakeholders including policymakers, and where and under what circumstances these judgments fit into existing or new decision-making frameworks, and so on.

6.2 HTA factors and recommendation decisions for reimbursement

Investigation of the associations between recommendation decisions and assessment outcomes of the evaluation factors revealed varying levels of importance some of them have in decision-making, and hence, useful in understanding the mechanisms behind HTA judgments and recommendation decisions. These have been shown by many studies in this subject area to be confounded by country- or HTA agency-specific preferences, HTA capacities and methodological variations. On this note, there is general agreement that variations in HTA practices between international jurisdictions have substantial impact on recommendation decisions by HTA agencies[11]. It is thus intriguing to observe that although most of the factors selected for inclusion in the HTA criteria list in this study are used in conventional HTA evaluation processes, statistically significant differences in reporting frequencies were found for the highest number of factors across HTA agencies (22 out of 32). In addition, stronger associations were found between HTA factors and *HTA agencies* than *financing systems* or *recommendation decisions.* Therefore, within the scope of this study, statistically significant differences in reporting frequencies of these factors can be more confidently explained by HTA-agency specificities than how healthcare is currently financed based on payer-systems in the respective countries. This further supported the existence and influence of agency-specific preferences in evaluating RDTs or orphan drugs. The inclusion of healthcare financing models in this study served to develop insights on the role of underpinning principles of distributive justice (or rationing criteria) in HTA methodologies across the countries included in the dataset. 'Long-term effectiveness', 'disease burden' and 'stakeholder persuasion' were the only three factors found to be strongly associated with *HTA agencies*, *financing systems* and *recommendation decisions*. To add, 'rarity' and 'children' were also the only factors that were strongly associated with healthcare financing models. Thus, these five factors may be useful in distinguishing financing model-related preferences more than the other factors in the evaluation factor checklist applied in this study since they were moderately associated with *financing systems*. To build upon this finding, it is noteworthy to reiterate that resources are undoubtedly finite and it necessitates priority-setting principles that segment patients in terms of risk to ensure that the resource allocation is maximised for the target population-level objectives[141]. As mentioned, the two most common objectives are egalitarianism and utilitarianism. Many publicly funded health systems across the world are egalitarian, in that they prioritise the reduction of socioeconomic health inequalities. Possible links between HTA evaluation factor preferences and health financing models could be drawn or substantiated by the results from the correspondence analysis conducted in this study, which showed that NICE was more associated with 'long-term effectiveness' and CADTH with 'disease burden'. Thus, these two factors may be more commonly reported or preferred by single-payer healthcare financing systems than the other factors for RDTs or orphan drug evaluations. From a utilitarian perspective, governmental interventions in health

coverage serves to maximise total utility or welfare of everyone in the society[149]. This forms the basis of single-payer systems defined in this study, and examples include the Beveridge model of the UK and the national health insurance system of Canada. Health services, in this approach, are produced and allocated in accordance to equity. However, equity principles based on disease prevalence and unavailability of alternative options may increase the price premium of orphan drugs, and hence stir up controversies with regards to their reimbursement in cases where public funding resources are more restricted[150]. While evaluating 'long-term effectiveness' may stem from a utilitarian approach, consideration of 'rarity' and 'children' in HTA evaluations might be a suitable example to quote for an egalitarian approach although this was not evidently shown in this study. This is partly because the two factors were 'rarely' reported (17 and 9 out of 47 dossiers respectively), where the highest proportion of dossiers reporting 'rarity' (57.9%) and 'children' (36.8.4%) was found from NICE, and the next highest proportion of dossiers reporting 'rarity' (40.0%) was found from AiHTA. Overall, the two factors were proportionally more frequently reported by single-payers than multi-payers in terms of *financing systems*. If they represent a more egalitarian approach to HTAs but are found more frequently reported by single-payer systems which are based largely on utilitarian principles of resource allocation, this indicates that there might be other drivers (beyond healthcare financing systems) influencing prioritisation of evaluation criteria or factors for the assessment of RDTs. To substantiate this, Zimmerman et al.[94] suggested a multidisciplinary perspective to resolve discrepancies in reimbursement of orphan medicines because there is no clear-cut solution for the ethical challenges in granting this group of technologies a 'special status'. They pointed out that scientific debates should focus more on the variability within this class of treatments in terms of e.g., target population and mechanism of action, rather than on the prevalence of the target indication or disease itself, and explore how these could be appropriately and meaningfully accounted for in the implementation of HTA. Interestingly, on this note, a similar study in the UK[151] revealed that the general public does not value rarity as a sufficient reason for justifying the special status of RDTs or orphan drugs to be considered for additional NHS funding. In fact, preference for funding to be allocated to treating more common diseases over rare diseases was indicated. Because HTA decision makers often make comparisons with benchmarks to justify a standard or higher cost-effectiveness threshold (CET), researchers have been conscientiously looking to develop broader frameworks of value, including the additional elements of value proposed by ISPOR, to justify a higher threshold for new RDTs or emerging gene therapies. This has important implications on the appropriateness of modified assessment frameworks which operate on higher CETs for this class of treatments and their rare disease indications although there is a general recognition that ultra-rare, health-catastrophic conditions should be assessed against a higher CET[152]. Application of a higher CET or a factor to inflate the QALYs constitute broader elements of value beyond direct health gains related to a treatment[147]. ICER and NICE have discussed a

range of up to $500,000 per QALY gained and a variable threshold of up £300,000 per QALY depending on the magnitude of benefits for ultra-rare diseases respectively[152]. Out of all the six HTA agencies, only ICER and NICE applied agency-specific value assessment frameworks specially adjusted or modified for rare or ultra-rare diseases where the conventional CEA is augmented to include higher CETs and weight-adjusted measures on quality of life to account for rarity of the drug indications of the new treatment. In light of this, Nicod and Kanavos[22] pointed out that 'other considerations' which capture the broader aspects of a treatment's value and the impact of the condition on the patient in HTA methods using clinical and economic evidence may influence HTA processes in different settings. These social value judgments (aka 'other considerations') were found to be the main reasons behind decisions pertinent to the acceptance of a higher incremental cost-effectiveness ratio or uncertain evidence, and yet they were non-quantified or non-nelicited according to the assessor's judgments. Their study highlighted the advantages of systematic approaches to identifying areas of value judgment as they enhance understanding of the dimensions of value. This has undoubtedly fueled the prerogative to improve transparency and consistency in the use of social value judgments across decisions and settings.

Indeed, the incorporation of social value judgements has been increasingly advocated by many studies in the field of rare diseases to capture value beyond standard clinical benefit assessments[72]. A research[153] conducted to understand different reimbursement decisions for RDTs or orphan drugs concluded that the most common social value judgments are related to *innovation*, *disease severity* and *unmet need* and differences were found in the way these concepts were defined and accounted for across different countries. In this study, these three factors were found to be distinct according to the results of the correspondence analysis and were statistically significantly different in their reporting frequencies across the six HTA agencies although they are 'common factors' related to social value judgments. If there are varying approaches to the use of HTA factors that capture social value judgments, the question would be about the real impact or even, repercussions of these variations on recommendation decisions, especially for the same RDT or within the same class of therapies for rare diseases. In a study of the assessment approach of NICE, Rawlins et al.[121] reported that decision drivers of NICE's recommendations are influenced by both scientific and social value judgments. Dakin et al.[154] found that cost-effectiveness analyses, where "correctly done", predicted 82% of NICE's recommendations. This also demonstrated clearly that affordability or financial feasibility for the 'expected return' on investment (i.e. the predicted benefits) dominate underpinning principles of decision-making by HTA agencies even though these organisations may have different priorities or preferences for factors of consideration to capture other elements of value. While scientific judgments consider clinical and economic evidence, social value judgments consider the severity of the disease in question, end-of-life treatments, stakeholder persuasion,

significant innovation, disadvantaged populations and children. It is clear that social values are multifaceted and subject to individual preferences and belief systems or principles. This has implications on the use of HTA to make resource allocation decisions because capturing social value judgments is challenging since it is influenced by the myriad of ethical principles, preferences, cultures and aspirations across or even within societies[155]. Although the key is to strike a "balance", it appears easier said (reported) than done (to put to practice). Other elements that may also contribute to variability in reporting frequencies of these factors include the type and prevalence of the target rare diseases within the local context, as well as the type of intervention the assessed treatment is classified under e.g., gene therapy. Further research is needed to ascertain the relevance, influence and significance of variations in assessments of HTA factors that are associated with social value judgments for RDTs or orphan drugs in HTA evaluations. Besides social value, clinical and scientific value of an intervention, in recognition of challenges facing RDTs in the evaluation of their value, research paving the way for innovative approaches in considering other aspects or concepts of 'value' and valuation have ensued. These include the aforementioned additional elements of value proposed by ISPOR. Out of the three selected factors (*'equity'*, '*disease nature/severity*' and '*value of hope*') that are considered novel considerations for economic evaluations according to ISPOR, only *'equity'* and '*disease nature*' (i.e. disease severity) were found to be strongly associated with *HTA agencies*, suggesting differential preferences in the value judgment of 'other considerations' for RDTs although they may not be associated with *recommendation decisions* i.e. differences in reporting frequencies of the two factors were not statistically significant across *recommendation decisions*. Another element of value considered in conventional VAFs according to ISPOR, '*adherence-improving factors*', was rarely reported (9 out of 47 dossiers), but was found to be proportionally more frequently reported across ICER's dossiers (66.7%). This implied that the interest in adoption of some of these novel considerations of value as part of a 'standardised approach' in HTA evaluations of RDTs across international jurisdictions may still be lower than what is ideal. In view of this discussion, it is beneficial to also highlight how patient preferences were deemed to have added value in HTA in some cases[156]. Some HTA agencies were found to value patient preference studies to investigate attributes related to benefits, risks and administration, and are willing to incorporate patient preferences as supportive evidence in HTA evaluations[157]. It would be very much worthwhile to address this gap and establish the existence of patient preferences to address or surface possibly 'missed' elements of value from their perspectives (besides that of society in general). Other similar efforts to include patient involvement in HTA have also gained traction recently in the field of RDTs. Specifically, there is growing interest in involving patients in HTAs to influence the scope and preparation of HTA reports for subsequent consideration by decision-makers[158]. For instance, The European Network for Health Technology Assessment (EUnetHTA) explored several approaches to patient involvement in 2019.

Elvsaas et al.[158] analysed the experience gained by EUnetHTA and found that the approaches to patient involvement included the use of patient input templates, group discussions, scope meetings and one-to-one conversations with patients. While the benefits in understanding the needs of the target population were largely acknowledged, challenges with timely patient involvement were also highlighted. More research efforts were recommended to develop implementation guidelines and assessment frameworks to enhance the visibility of patient inputs in HTAs. Hailey[159] also recommended the retrieval of patient perspectives from reviews of published studies and that primary research approaches can be utilised if good quality, published evidence is not available. However, the challenges in achieving effective patient involvement pertain to identifying suitable sources of patient organisations and HTA agencies-specific requirements or criteria. The importance of deciding when patient inputs are appropriate was also reiterated, such as which questions or aspects of the assessed technology require these inputs the most in ways that are transparent and valuable[159].

Due to disease prevalence and varying health and clinical outcomes, most RDTs or orphan drugs are challenged with uncertainty in many aspects of value assessment that are key to HTA decision-making frameworks and methodologies, mainly clinical and economic evidence. Nicod[120] compared factors and elements driving orphan drug HTA recommendation decisions and concluded that heterogeneity in appraised evidence and in the interpretation of the same evidence as well as different ways in handling the same uncertainty constitute some reasons behind cross-country differences in HTA recommendations for reimbursement. More importantly, it was also highlighted that other considerations like disease nature or severity and decision modulators such as patient access schemes and lower discount rates were found to render greater acceptability of uncertainties and cost-effectiveness estimates[120]. In this study, '*disease nature*' and '*patient access schemes*' were found to be more strongly associated with *HTA agencies* than *financing systems,* with statistically significant differences in their reporting frequencies, but were **not** statistically significantly associated with *recommendation decisions*. Here, '*patient access schemes*' was proportionally more frequently reported in dossiers from NICE (14 out of 19 i.e. 73.7%) and ACE (4 out of 6 i.e. 66.7%). On the topic of access schemes and their value for consideration in this context, Lucas[160] and Carlson et al.[161] suggested that products with simple methods for measuring treatment effects and clearly defined outcomes are likely suitable candidates. According to Carlson et al.[161], the uncertainty in modelled long-term outcomes has also become increasingly significant due to accelerated market approvals and growing acceptance of surrogate endpoints by market authorisation authorities. These uncertainties impact the payer's decision-making metrics, namely, a product's clinical effectiveness, budget impact and cost-effectiveness, where the goal is to attenuate health and financial impact risks associated with these uncertainties[161]. It is beneficial here to illuminate further understanding in how

including '*patient access schemes*' in HTA evaluations increases the acceptability threshold for uncertainties using the UK as an example, where there is an NHS commercial framework for new medicines[162]. The NHS England and NHS Improvement play a crucial role in supporting patient access to clinically and cost-effective medicines through appropriate and feasible commercial arrangements, with inputs from partners like NICE. The appraisal committee considers the effect(s) of a patient access scheme proposal on the clinical and cost-effectiveness of the technology and clarifies relevant points with the manufacturers[163]. The Evidence Review Group (ERG) assesses the impacts of the proposed scheme on clinical and cost-effectiveness. Most orphan medicines are assessed by NICE through the Single Technology Appraisal (STA) process and a few qualify for assessment under Highly Specialised Technology evaluation (HST). In this dataset, out of 19 dossiers from NICE, 16 were assessed under HST and three under STA. To be assessed as HST, the assessed technologies must meet strict criteria, such as being licensed for a chronic and severely disabling conditions, targeting a small patient group, used within a highly specialised service concentrated in a few NHS centres, showing the potential for lifelong benefits and having high acquisition costs, thus the need for national commissioning[164]. Clarke et al.[165] conducted an analysis of STA appraisals of orphan medicines and found that they were **disadvantaged** by worse outcomes with respect to positive recommendations than orphan medicines that were assessed under HST evaluation, and this was postulated to be attributed to uncertainties inherent to orphan drug development. Given that the UK and Singapore have different structures and underpinning philosophies in healthcare financing, this showed that '*patient access schemes*' may be included for HTA evaluation based on context-specific HTA factor prioritisation principles or reasons. Nonetheless, it is generally presumed that payers may be more willing to engage in such schemes in areas with high unmet needs, high costs (i.e. high budget impacts or high volume), variable treatment duration and uncertain benefits, but manufacturers are likely to engage in these schemes if required for access or in competitive areas. In other words, while payers may prefer the existence of these schemes to tackle uncertainties, high costs and therapeutic gaps, manufacturers are more geared towards gaining competitive edge in the market[160,161]. This reiterates the importance of alignment between payers and manufacturers through orphan drug regulations and/or incentives because the desire to gain competitive edge may lead to monopolistic markets especially in the case of novel treatments, thereby impeding timely patient access. Such alignment may be also partly dependent on approaches to healthcare financing because of reimbursement decisions and/or insured packages. In fact, statistically significant association was also found between *financing systems* and *recommendation decisions* based on the scope of data collected for this study. A comparatively higher proportion (100%) of the dossiers from single-payer systems reported positive HTA recommendations than multi-payer systems (76.2%). To build on this, on the payer side, the monopsony power of single-payer systems like that of the UK in the health services market, favourably positions them

to influence technology allocation[166]. NICE, being a single public agency, compiles guidelines on the effective use of technologies[167]. Adherence to these guidelines can be adopted consistently throughout the entire NHS through the single, centrally set benefit package which applies to every citizen. The Ministry of Health allocates the annual capital budgets to regional Health Authorities. Here, another layer of centrality ensures proliferation and distribution or access of the health technologies[166]. Furthermore, the Commission for Health Improvement audits providers to ensure provider adherence to NICE guidelines. In the context of orphan drugs and rare diseases, the healthcare financing model may play a significant role in reimbursement decisions since the majority of direct healthcare costs are driven by drug costs followed by direct informal and formal healthcare costs[168]. Conclusions from a meta-analysis[168] of costs and QoL dimensions data deduced that Gross Domestic Product per capita, public health expenditure in the country of study and the body system affected by the rare disease were the **most** significant determinants in predicting economic impacts of rare diseases in Europe. Thus, positive HTA recommendations (for reimbursement) may very well be driven by specific factors related to *financing systems*, such as reimbursement policies and packages (e.g. co-payment, deductibles etc.) or other related factors. This is especially the case for countries that depend on funds collected through general taxation to finance its healthcare system. Although this consequently questions the ceiling of taxes that society is prepared to fork out for the benefit of the 'rare' others i.e. rare disease patients, Azar et al.[169] found that the effects of income on egalitarian values and attitudes towards healthcare policy is small and insignificant across 29 countries. However, a positive association was found between willing-to-pay taxes to improve healthcare and income in the same study. Citizens across socioeconomic groups are also generally willing to support state-funded healthcare and favour 'non-selfish' policies[169]. These findings are positively suggestive of possible opportunities for policymakers to increase healthcare spending for specific target groups or to instigate broader institutional changes. Other approaches that have been increasingly explored to handle uncertainties in the evaluation of RDTs and orphan drugs are health-outcomes based schemes such as Managed Entry Agreements (MEA). However, this factor was not found to be significantly associated with *HTA agencies*, *financing systems* or *recommendation decisions* in this study. However, it was proportionally more frequently evaluated across ICER's dossiers (3 out of 6 i.e. 50.0%) but only in 14 out of 47 dossiers (29.8%) across all agencies. MEAs encompass a diverse range of contracts between drug manufacturers and payers which aim to address payers' concerns about clinical performance and/or budgetary aspects by tying reimbursement to **future** performance measures of clinical or intermediate endpoints that are ultimately related to patient quality or quantity of life[160,161]. In this case, coverage and reimbursement of medical products is linked to the provision of additional evidence in measures of real-world health outcomes outside of highly controlled trials in performance-based health outcomes reimbursement schemes or performance-based MEAs[160,170].

Henceforth, these schemes promote patient access to novel and potentially valuable healthcare technologies in spite of pressures regarding uncertainties and costs. On this note, it is essential to note that a robust clinical and practical rationale is key in developing a performance-based MEA, taking into account, country-specific legal frameworks and payer preferences that will determine what MEAs are likely to be accepted[160]. Although contracts like MEAs may be more valuable in managing uncertainties and feasibility of funding than implementing a separate VAF for orphan drugs, their appropriateness is largely context-dependent. Ideally, payers and end-users should be constructively engaged in the development of the schemes, the approach is simple with a clear rationale, and the capturing of data should tap on existing systems or the data infrastructure supported by the pharmaceutical companies.

6.3 Assessment outcomes of HTA factors and recommendation decisions for reimbursement

Only eight out of 32 HTA factors investigated in this study were found to be statistically significantly associated with *recommendation decisions*. Multiple correspondence analysis of these HTA factors supplemented thought-provoking insights on the mechanisms behind a positive HTA recommendation. It appears that special considerations or exceptions seemed to apply where uncertainties and non-ideal circumstances were concluded in the assessment of specific HTA factors. It is highly likely that recommendation decisions documented by dossiers included in this study were not made based on the outcomes of assessment of individual factors interpreted in-silo. Rather, the decision-making matrix might be specially 'formulated' as a bundled or aggregated approach to evaluating RDTs against a preferred set of interlinked or interdependent criteria, which may be further complicated by the specificities of the drug indication in question. Nonetheless, it is valuable to highlight that the MCA plot showed how positive HTA recommendations seem to be associated with (i) the demonstration of ideal long-term effectiveness and indirect benefits (ii) the inclusion and consideration of stakeholder inputs (iii) situations where the current comparator is a supportive care, and ***despite*** (i) the lack of or uncertain safety evidence (ii) issues identified with submitted economic models. In a nutshell, with respect to the eight factors found to be associated with *recommendation decisions*, the MCA results suggested relatively greater influence of outcomes of assessment of '*long-term effectiveness*', '*indirect benefits*', '*stakeholder persuasion*', '*availability options/alternatives*', '*safety*' and '*economic modelling*' compared to '*disease burden*' and '*clinical benefits*' in contributing to positive HTA recommendations for reimbursement of orphan drugs across the six HTA agencies. It is worthy of mention that out of these, '*indirect benefits*' and '*stakeholder persuasion*' are two crucial factors forming the facets of 'value', not only to patients but also their families, especially in the context of rare diseases. However, where reimbursement was **not** recommended, information about 'available options/alternatives', 'disease burden', 'safety' and 'clinical benefits' were indicated '**not mentioned'** i.e. information regarding the HTA factor was not available for

interpretation. Reference to the raw data showed that most of these were contributed by the dossiers from ZIN and ACE, which were relatively much less comprehensive in terms of the information that was published. Concrete conclusions about whether missing or lack of information or evidence related to the specific factor led to a negative recommendation (not recommended for reimbursement) cannot be made. The nature of the dossiers analysed in this study constitutes a major limitation in terms of generalisation that may be made in this aspect. Nonetheless, it is beneficial to address this using insights gained from other studies. For instance, Nicod et al.[153] explored the role of evidentiary requirements and approaches to dealing with limited or imperfect evidence regarding trial designs and durations, study populations and subgroups, comparators and end-points to understand differences in reimbursement decisions in four European countries. They found that decisions regarding orphan drugs were often made in the context of lower quality evidence and were based on a varied threshold of acceptable uncertainty in different countries. There were inconsistencies in validation requirements and evidentiary standards, and where higher requirements were imposed for greater clinical claims, orphan drugs often face greater challenges in establishing their value to qualify for positive recommendations. To substantiate the significance of HTA practices on recommendation decisions due to the interplay between outcomes of assessments of the evaluation factors demonstrated in this study, it is worth mentioning that inclusion of societal perspectives may cause a new intervention to become a dominant strategy i.e. becoming cost-effective compared to just using a healthcare payer perspective. This reinforces the magnitude of the impact that other elements of value can have on economic evaluations. On the contrary, Aranda-Reneo et al.[171] found that inclusion of societal perspective did not result in significant changes in economic evaluation in the field of rare diseases due to the immensely high cost of the treatments and in some cases, low QALYs gained. However, it is indisputable that good clinical evidence is the key basis for cost-effectiveness analyses in HTA, especially in resource-constrained economies[172]. In a review of HTA recommendations for reimbursement in Australia, Canada, England and Scotland, case studies demonstrating examples of rejection were shown to be due to uncertainties surrounding a range of factors including cost-effectiveness, comparator choice, clinical benefit, safety, trial design and submission timing[173]. All in all, the decisions that HTA agencies make can have a sizable impact on the therapeutic market because HTA recommendations can impact patient access. These decisions also influence how pharmaceutical companies design and conduct clinical trials to collect essential evidence that is necessary for reimbursement of their products. Indeed, the ‘stars’ must align in order to make constructive and progressive steps towards achieving real value and impact in healthcare with regards to therapeutic areas for rare diseases.

6.4 HTA judgments and evidence-based policymaking

Finally, a case analysis of HTA evaluation of Zolgensma® illustrated some challenges associated with arbitrariness in the definition or evaluation of HTA factors as criteria by different HTA agencies. This was further complicated by some level of ambiguity in the way judgment of the same body of clinical evidence was communicated in dossiers by the agencies. Although the same evidence was evaluated by the three HTA agencies (CADTH, NICE and ICER) and the same factors were reported across the dossiers (implying similar agency priorities and preferences for HTA evaluation of the treatment), variations in clinical and scientific HTA judgments exist with regards to some evidence-based or -related factors, namely '*comparative effectiveness*', '*study design*', '*clinical benefits*', '*safety*' and '*population generalisability*', based on the data collected in this study. The analysis focused on how the inferences made on the outcomes of assessment of the HTA factors by the researcher in this study may differ because of the way information was textually communicated or reported in dossiers from CADTH, NICE and ICER evaluating Zolgensma®. Content analysis of selected quotes of supporting information regarding factor outcomes of assessment illustrated possible existence of variations in evidentiary requirements and judgments which can be attributed to agency-specific standards of acceptability. Policy-making in health is largely driven by ideas, interests and institutions[174]. The case analysis provided an opportunity to further discuss the roles of ideas and ideologies in evidence-based health policy since HTA has been increasingly used to inform policy-making in healthcare. To begin, it is practically impossible to allocate resources based merely on clinical needs due to resource constraints and uncertainty of most new interventions in reality. The process of evidence-based policy making is complex in a world driven by existing policy, social and cultural ideologies[174]. With regards to resource allocation, it is oversimplifying to talk about prioritisation principles without considering the influence of political power in policy-making. Prinja[174] explained how prevailing ideas and ideologies shape evidence and that they are key in determining the success of evidence in making an impact on policies i.e evidence-based policy making, thereby bridging the gap between health researchers and policy-makers. Ideas and ideologies are major determinants in the consideration of evidence for policy-making because they may shape evidence and have been found to impact different stages of evidence generation and utilisation. Since ideas shape one's belief systems, a country's healthcare system reflects the ideology and philosophy behind the prevailing models. Ideas are concerned with how a given policy problem is perceived i.e. framing, which is related to the use of language in a way that evidence is in harmony with one's view[175]. It has been contended that only information that fits into the mental frame of a problem is likely to be accepted. So the issue is not limited to the use of language, rather, it is the idea communicated by language that matters[175]. Ideology affects the way evidence is received at the political level and the extent to which it is used for policy-making. They affect each step of research, from generation to final publication, and dissemination of evidence (Prinja[174],

Table 1). While political circles may use research to generate evidence in their favour, there is a general notion that some types of evidence are more superior than others. More importantly, even if evidence is produced against a technology, healthcare practice etc., nothing may be achieved at the policy-level due to the role of ideas in formulating, conducting and interpreting research. Factors found to hinder the use of evidence for policy-making include the lack of quality evidence, difficulty in applying evidence and organisational and resource constraints for evidence application. This highlights how existing political ideology may influence the likelihood of evidence acceptance rather than its mere scientific quality. In the case of Zolgensma®, despite the variations in the way outcomes of assessment of evidence by HTA agencies has been framed based on existing local requirements, contexts and prioritisation principles, all three dossiers documented positive recommendation decisions. Although this study did not directly explore the impact of different clinical or scientific judgments and types of evidence on recommendation decisions, some references can be drawn from Cohen et al.[176] who explained that all VAFs have inherent varying degrees of arbitrariness from the subjectively determined end-points and arbitrary methods of combining scores from multiple dimensions to arrive at a composite health outcome measure. As such, the degree to which different VAFs capture value accurately to arrive at the decisions made is unknown. A study[177] on preferences for criteria in the use of multi-criteria decision analysis for assessing orphan drugs showed differences in perspectives on the importance of the criteria used although there is general consensus that several disease- and drug-related criteria should be included in MCDA frameworks for the purpose. Nonetheless, the role of ideas and ideologies in the use of evidence might be a worthwhile consideration for future studies analysing HTA dossiers acrossing international jurisdictions.

6.5 Study limitations

Despite these relatively insightful takeaways, besides small sample size, several other limitations exist particularly in the nature of the data and the process of data collection. There were many instances where there was ambiguity or uncertainty in the inferences that could be made based on information collected from the dossiers. This was largely complicated by the use of different words, phrases and jargons (e.g., “sham procedure” in place of the conventional ‘control group/intervention’) that were specific to the key subject areas like clinical research. It is useful to acknowledge that the researcher’s limited competency, proficiency and experience in the relevant subject areas may possibly confound the interpretations of the HTA dossiers in this study despite dutiful efforts made to acquaint with necessary knowledge fields through literature reviews and other scientific references. This was addressed to the best ability of the researcher through thorough and repetitive review of the dossiers to understand terms that were preferred by different agencies as well as the elaborations of their judgments in order to make objective conclusions that reflect as closely as what was intended to be communicated through the reports as much as possible.

At the point of the study, the data was also interpreted based on a self-determined level of sufficiency in understanding of the key concepts that formed the background knowledge required for the earlier stated research objectives. Thus, the data collected may be subjective and limited in this aspect but addressed as best possible through defining the scope and depth of the research objectives in relation to the subject areas pertinent to this study. To streamline the definitions of the HTA factors for a more focused analysis, literature-relevant questions were self-developed to scope the factors included in the checklist (against which the dossiers were reviewed). Since this study was conducted by a single researcher, subject-related doubts were clarified through cross-checking with field experts who are not a direct contributor to this study. To ensure consistency despite varying methods of reporting evaluation information by different HTA agencies and evidence or information from the respective dossiers were quoted to substantiate the inferences made by the study regarding whether a factor was reported as well as the outcomes of assessment of each HTA factor as a form of self-monitored 'cross-checking' procedure built into the data collection. In terms of sufficiency of data, the dossiers retrieved from ICER and NICE were also the most comprehensive in terms of the scope and depth of details. This is followed by AiHTA's dossiers, which are Horizon Scanning reports and CADTH's summary reports. Dossiers which are most brief or 'conservative' in terms of information that was published were from ACE and ZIN. Because of the varying extent to which how comprehensive the dossiers are from each HTA agency, the depth and scope of information available for data collection and subsequent interpretation was not consistent across the different agencies. Although this constitutes a major limitation on generalisability of the findings derived here, it was addressed by targeted literature review to supplement gaps or inadequacy in the findings or conclusions made from this study. In addition, analyses of factor reporting frequencies of factors were also interpreted and presented according to categories under which the HTA factors fall i.e. *economic evidence*, *clinical evidence*, *disease and treatment-related considerations* and *other considerations*, where applicable, to develop insights of interest to this research.

Finally, although the sample size for each HTA agency renders it more challenging to make confident conclusions, the use of Fisher Exact test as a statistical tool and correspondence analyses yielded insights that appropriately and sufficiently answered the research questions. Despite the small sample size and inclusion of only high-income countries, this study has contributed in some ways to understanding the mechanisms behind these complex decisions and the possible reasons driving diverging HTA recommendation decisions, by exploring the extent to which common evaluation factors and elements beyond scientific, clinical and economic tools, that capture other aspects of value, are used and how they differ, and hence the significance of their role in influencing decision-making and priority-setting for orphan drugs evaluations.

7 Conclusion

Scientific and clinical judgments based on evidence of substantially proven quality or grade are still prominently crucial in HTA evaluations. There is increasing pressure for judgments made by HTA agencies to be two-fold i.e. agencies should go beyond the examination of the evidence base for clinical benefits and cost-effectiveness (as with conventional CEA frameworks) and include social value judgments informed by the general public since they have no legitimacy to impose their own social values[178]. Factors which are more uniquely relevant to RDTs and orphan drugs i.e. those that capture social value judgments, financial feasibility and other elements of value that are non-scientific or clinical, vary significantly in their reporting frequencies across *HTA agencies*, and can be inferred to be likely driven largely by differences in agency- or country-specific preferences and methodologies than the healthcare financing models in the countries. This is an insightful finding because it challenges the assumption in this study that approaches and perspectives forming the framework of HTA evaluations tend to be affiliated with principles of distributive justice underpinning a country's healthcare system, including how healthcare is financed. Correspondence analysis showed how the six HTA agencies were associated with different HTA factors, rather than specific categories like economic or clinical evidence. Interestingly, only eight out of the 32 HTA factors investigated were also shown to be statistically significantly but not strongly associated with recommendation decisions. Multiple correspondence analysis narrowed this down to six factors where their outcomes of assessment may drive recommendation decisions. Although no concrete conclusions can be made on this aspect due to the differences in how comprehensive the dossiers are since their reported information formed the data collected in this study, the MCA outputs analysed in this study has posited that outcomes of assessment of particular HTA factors, including stakeholder inputs, in orphan drug evaluations may potentially drive recommendation decisions. Future studies can explore this aspect, especially based on HTA dossiers that are most comprehensive in the information they report, such as those from NICE. This would further ascertain and illuminate payer and societal perspectives, considerations and expectations that are key to decision and policy-making for orphan drugs and rare diseases. This exploratory study has expanded insights on the existence and drivers of variations in HTA preferences and methodologies. In view of the earlier defined scopes, concrete conclusions about the statistical significance of varying recommendation decisions for a ***specific*** RDT and disease indication were not established. Nonetheless, it is evident all other HTA evaluation factors do play a fundamental role in VAFs and contribute in one way or another to HTA decision-making, whether they are underpinnings of utilitarian and/or egalitarian approaches to resource allocation. Content analysis of dossiers considered for the case analysis of Zolgensma® also demonstrated the value of qualitative approaches in understanding HTA judgments and evidentiary

requirements or standards. Further studies in this aspect could contribute to insights on *diverging* HTA judgments in positive HTA recommendation for reimbursement and how variations in the way the same body of evidence is evaluated, perceived or interpreted may exist across international jurisdictions.

Comparative analyses of national regulations for rare diseases and orphan drugs has shown that public authorities should regard rare diseases as a public health priority and take definite actions, including legislations[7]. These will serve to legitimately define and classify rare diseases, assemble accurate epidemiological data, promote incentives for research and development efforts for orphan drugs, develop appropriate support systems to ensure access to orphan drugs, and foster international collaborative efforts[7]. The impact of HTA on patient access in the case of rare diseases is particularly relevant because early cures may have substantial benefits at a young age and could produce significant gains in work productivity than treatments delivering marginal gains over many years[179]. It is apparent that understanding decision-making frameworks used by HTA agencies and the factors driving variations in HTA recommendations are instrumental in informing reimbursement or other related policies that can be developed to ensure appropriate and timely patient access. The way societal costs and perspectives, as well as patient and manufacturer inputs, are represented in a suitable VAF that is fit-for-value in HTAs, require more extensive research efforts to explore other factors that may influence recommendation decisions and continue supporting the evolving role of HTA in other therapeutic areas besides rare diseases. It is also vital to develop appropriate and relevant pricing and reimbursement models that will incentivise research and development investments while not jeopardising the sustainability of healthcare systems. The large single payment and the need for life-long clinical follow-up to understand the benefits and safety of treatments like gene therapies present uncovered grounds of scientific, financial, social and ethical challenges for the pharmaceutical industry, payers and society[180]. Given similar predicaments of neglected diseases in developing countries and orphan disease in developed countries in terms of challenges they face, novel policy tools are needed for orphan drugs reimbursement since the special status of 'rarity' does not stand up to critical assessments[181]. Although research has demonstrated the value of identifying and discussing possible ethical and/or social features of VAFs for RDTs or orphan drugs, as well as social value judgments to better improve transparency and consistency in the use of the dimensions of value across decisions and settings, payers or budget holders stringently scrutinise the quality of medical data that proves a drug's efficacy even before considering reimbursement. Because of limited efficacy data and uncertainty in long-term durability of outcomes that are more frequently faced by orphan drugs, payers and manufacturers must acknowledge each other's constraints by developing innovative approaches to ensure timely treatment access[88]. McCabe[181] proposed policies such as Public Private Partnerships and Advanced Market Commitments in the area of orphan drugs while others like

Kerpel-Fronius et al.[180] have raised the ethical necessity of closer cooperation between the pharmaceutical industry and society to endorse the fair sharing of benefits and risks in the development of treatments like orphan gene therapies where the two parties can agree on a fair locally-affordable drug price with installment payments. These are indeed noteworthy, considering that the late outcomes of the treatment for most rare diseases are often unknown (due to the need for long-term follow-up) and assuming society's rather unquestionable role in collecting real-world evidence for better drug evaluation and improved accessibility. Nonetheless, Further research is needed to propel the development of optimal approaches to measure and include the additional elements of value in decision-making, especially in the context of therapeutic pathways in oncology and rare diseases[30]. Enhanced understanding of the challenges in orphan drug development as well as clearer guidelines or frameworks for decision-makers to navigate uncertainty in the HTA processes may both promote equity in terms of access to RDTs[165]. There are undoubtedly substantial differences in HTA practices and methodologies that may be confounded by other drivers such as the existing ideologies behind the design of a healthcare system and the 'position' of HTA within a country's healthcare landscape, a country's healthcare expenditure (and resource constraints) and its technical capacities in HTA, the scope of HTA (the purpose HTA is adopted for e.g., funding decisions or clinical practice decisions etc.) and even elements regarding decision-making authority e.g., single or multiple, centralised or decentralised. Although there is similarity in the use of HTA to inform funding or reimbursement decisions, it is still crucial to understand and investigate context-relevant drivers of diverging recommendation decisions. These can explicate potential opportunities for alignment of HTA methodologies that may be vital in improving HTA capacities that will spur efforts in ensuring appropriate care and accessibility[44].

To conclude, a one-size-fits-all or fool-proof approach to building HTA may not be valuable and efforts to do so should be attuned to the existing HTA landscape of the healthcare system in question, in relation to types of coverage, reimbursement and pricing policies[53]. This would, in the best-case scenario, lead to adequate compensation in the healthcare area it was meant to reimburse, and hence ensure access and equity in the area of rare diseases. To achieve this as best as possible, payers can explore how they can communicate more clearly what they value to the potential suppliers or manufacturers through their reimbursement practices and policies. Transparent evaluation and decision-making processes that are relevant to the local context can be put in place to review the acceptability of submissions from manufacturers. Engagement with these manufacturers should aim to critique and support them in their submission processes and provide a direction for e.g., evidence generation. Lastly, findings from this study has illustrated how learning and reflecting on current HTA practices in the ever-evolving HTA landscape is paramount to address gaps in HTA capacities and explore solutions to challenges in

implementing a transparent, 'harmonised', and aligned HTA system especially within the same region, such as the case of Europe. Future studies should include more countries with well-established HTA systems and provide directions for countries in the budding stages of implementing HTA in their healthcare systems. Reimbursement and HTA methodologies are indeed critically important and yet challenging and multifaceted topics that require rigorous deliberation, international cooperation and collaboration to address and leverage on subject-matter expertise in some countries to efforts to address contextual variations and constraints. Future research can certainly encourage more 'conservative' HTA agencies to consider alternative approaches to their current HTA evaluation processes and analytical approaches. This can potentially provide an avenue for constructive deliberations or dialogues regarding the goals, emphases and directions of policy-making in the area of rare diseases. Although some variations in HTA processes are inherent in the so-called 'in-house approaches', it is still crucial to expand current and explore new approaches to the use of HTAs in informing funding decisions for RDTs and evaluate the feasibility of their implementation in existing local HTA decision analysis frameworks. There is definitely a value-of-hope in the hope for **value** for the future of RDTs.

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Appendix A

Table 1. Summary of criteria stated by relevant regulatory agencies with respect to the orphan drug legislation in each country/region

Criterion / Authority	**FDA (USA)**	**EMA (EU)**	**MHRA (UK)**	**Health Science Authority (Singapore)**
Orphan drug legislation / regulation	The Orphan Drug Act (1983)	The Orphan Medicinal Product legislation (2000)	Human Medicines Regulation (2012)	Therapeutic Products Guidance
Indication: definition of rare disease	Prevent, diagnose or treat a rare disease or condition	Treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating	Treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating	life-threatening and severely debilitating illness
Prevalence of condition	Affects less than 200,000 people in the United States	prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development	prevalence of the condition in Great Britain must not be more than 5 in 10,000, or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development	Affecting less than 20,000 persons
Others e.g., existing alternatives	There is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recover from sales of such drugs. Determinations under the preceding sentence shall be made on the basis of the facts and circumstances as of the date the request for designation of the drug is made.	No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.	No *satisfactory method of diagnosis, prevention or treatment of the condition concerned exists in Great Britain, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition. **authorised medicinal products, medical devices, prevention or treatment which are used in Great Britain*	None that is of knowledge at the point of this study

Table 2. Recommendations across HTA agencies and financing system

Recommendation decision	Dossiers indicating recommendation decision / n (%)							
	(i) by HTA agencies						(ii) by financing system	
	ACE (n = 6)	AiHTA (n = 5)	CADTH (n = 6)	ICER (n = 6)	NICE (n = 19)	ZIN (n = 5)	Single-payer (n = 25)	Multi-payer (n =22)
(i) Recommended	5 (83.33)	5 (100.00)	6 (100.0)	6 (100.00)	19 (100.00)	1 (20.00)	25 (100.00)	17 (77.27)
(ii) Not recommended	1 (16.67)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (80.00)	0 (0.00)	5 (22.73)

Table 3. Dossiers reporting HTA evaluation factors across HTA agencies and financing systems

HTA evaluation factors (criteria)	Dossiers reporting each factor / n (%)							
	(i) by HTA agency						(ii) by financing system	
	ACE (n = 6)	AiHTA (n = 5)	CADTH (n = 6)	ICER (n = 6)	NICE (n = 19)	ZIN (n = 5)	Single-payer (n = 25)	Multi-payer (n =22)
ICER assessment framework for rare conditions	0 (0.00)	0 (0.00)	0 (0.00)	5 (83.33)	17 (89.47)	0 (0.00)	17 (68.00)	5 (22.73)
Cost-effectiveness: value-for-money	5 (83.33)	0 (0.00)	6 (100.00)	6 (100.00)	19 (100.00)	2 (40.00)	25 (100.00)	13 (59.09)
Budget impact Analysis	5 (83.33)	5 (100.00)	0 (0.00)	6 (100.00)	7 (36.84)	3 (60.00)	7 (28.00)	19 (86.36)
Comparative effectiveness	4 (66.67)	5 (100.00)	6 (100.00)	4 (66.67)	10 (52.63)	1 (20.00)	16 (64.00)	14 (63.64)
Economic models	1 (16.67)	0 (0.00)	6 (100.00)	5 (83.33)	19 (100.00)	2 (40.00)	25 (100.00)	8 (36.36)
Study design	0 (0.00)	4 (80.00)	4 (66.67)	2 (33.33)	10 (52.63)	2 (40.00)	14 (56.00)	8 (36.36)

Sample size	0 (0.00)	2 (40.00)	2 (33.33)	3 (50.00)	3 (15.79)	1 (20.00)	5 (20.00)	6 (27.27)
Additional/other evidence	3 (50.00)	0 (0.00)	4 (66.67)	0 (0.00)	7 (36.84)	0 (0.00)	11 (44.00)	3 (13.64)
Clinical benefits	5 (83.33)	5 (100.00)	6 (100.00)	6 (100.00)	19 (100.00)	2 (40.00)	25 (100.00)	18 (81.82)
Safety	3 (50.00)	5 (100.00)	6 (100.00)	6 (100.00)	17 (89.47)	2 (40.00)	23 (92.00)	16 (72.73)
Population generalisability	1 (16.67)	5 (100.00)	5 (83.33)	5 (83.33)	17 (89.47)	2 (40.00)	22 (88.00)	13 (59.09)
Survival	5 (83.33)	5 (100.00)	6 (100.00)	6 (100.00)	18 (94.74)	2 (40.00)	24 (96.00)	18 (81.82)
Long-term effectiveness / overall benefit	0 (0.00)	5 (100.00)	6 (100.00)	5 (83.33)	19 (100.00)	3 (60.00)	25 (100.00)	13 (59.09)
Quality of life e.g., PROs	2 (33.33)	5 (100.00)	6 (100.00)	6 (100.00)	19 (100.00)	4 (80.00)	25 (100.00)	17 (77.27)
Available options/alternatives	3 (50.00)	5 (100.00)	5 (83.33)	4 (66.67)	19 (100.00)	2 (40.00)	24 (96.00)	14 (63.64)
Children	1 (16.67)	0 (0.00)	1 (16.67)	0 (0.00)	7 (36.84)	0 (0.00)	8 (32.00)	1 (4.55)
Disease nature	3 (50.00)	5 (100.00)	6 (100.00)	6 (100.00)	19 (100.00)	2 (40.00)	25 (100.00)	16 (72.73)
Rarity	0 (0.00)	2 (40.00)	1 (16.67)	2 (33.33)	11 (57.89)	1 (20.00)	12 (48.00)	5 (22.73)
Disease burden	0 (0.00)	5 (100.00)	6 (100.00)	5 (83.33)	19 (100.00)	1 (20.00)	25 (100.00)	11 (50.00)
Unmet needs	4 (66.67)	3 (60.00)	6 (100.00)	6 (100.00)	17 (89.47)	1 (20.00)	23 (92.00)	14 (63.64)
Indirect benefits	0 (0.00)	0 (0.00)	2 (33.33)	5 (83.33)	16 (84.21)	1 (20.00)	18 (72.00)	6 (27.27)
Adherence-improving factors	0 (0.00)	0 (0.00)	1 (16.67)	4 (66.67)	3 (15.79)	1 (20.00)	4 (16.00)	5 (22.73)
Innovation	1 (16.67)	0 (0.00)	1 (16.67)	5 (83.33)	15 (78.95)	1 (20.00)	16 (64.00)	7 (31.82)
Complex care pathway	0 (0.00)	0 (0.00)	0 (0.00)	2 (33.33)	10 (52.63)	0 (0.00)	10 (40.00)	2 (9.09)
Managed Entry Agreement or equivalent	0 (0.00)	1 (20.00)	1 (16.67)	3 (50.00)	7 (36.84)	2 (40.00)	8 (32.00)	6 (27.27)
Patient Access schemes or equivalent	4 (66.67)	0 (0.00)	0 (0.00)	1 (16.67)	14 (73.68)	0 (0.00)	14 (56.00)	5 (22.73)
Cost of treatment	2 (33.33)	1 (20.00)	4 (66.67)	3 (50.00)	6 (31.58)	1 (20.00)	10 (40.00)	7 (31.82)
Long-term financial risk	0 (0.00)	0 (0.00)	1 (16.67)	0 (0.00)	7 (36.84)	1 (20.00)	8 (32.00)	1 (4.55)

Treatment duration	0 (0.00)	5 (100.00)	2 (33.33)	4 (66.67)	10 (52.63)	2 (40.00)	12 (48.00)	11 (50.00)
Stakeholder persuasion	3 (50.00)	0 (0.00)	6 (100.00)	6 (100.00)	19 (100.00)	1 (20.00)	25 (100.00)	10 (45.45)
Value of hope	1 (16.67)	0 (0.00)	3 (50.00)	3 (50.00)	6 (31.58)	0 (0.00)	9 (36.00)	4 (18.18)
Equity	0 (0.00)	0 (0.00)	0 (0.00)	4 (66.67)	12 (63.16)	0 (0.00)	12 (48.00)	4 (18.18)

Table 4. Correspondence Analysis between HTA factors and HTA agencies (statistical outputs)

				Component 1			Component 2			Component 3		
Name	Qual	Mass	Inert	Coord	Corr	Contr	Coord	Corr	Contr	Coord	Corr	Contr
Cost-effectiveness	0.997	0.027	0.092	1.125	0.960	0.210	0.214	0.035	0.012	-0.048	0.002	0.001
Budget impact analysis	0.988	0.042	0.072	0.436	0.283	0.049	-0.214	0.069	0.019	0.653	0.636	0.250
Comparative effectiveness	0.835	0.041	0.039	0.422	0.484	0.045	-0.341	0.317	0.048	0.111	0.033	0.007
Economic modelling	0.888	0.064	0.055	-0.275	0.227	0.030	0.354	0.376	0.079	-0.308	0.286	0.085
Additional/other evidence	0.972	0.015	0.093	1.517	0.961	0.214	0.005	0.000	0.000	-0.163	0.011	0.006
Clinical benefits	0.635	0.071	0.016	-0.234	0.624	0.024	0.003	0.000	0.000	0.030	0.010	0.001
Safety	0.716	0.063	0.043	-0.138	0.071	0.007	-0.263	0.257	0.043	0.323	0.388	0.092
Population generalisability	0.941	0.009	0.035	1.060	0.699	0.059	0.403	0.101	0.014	-0.476	0.141	0.027
Survival	0.955	0.089	0.043	0.024	0.003	0.000	-0.402	0.852	0.142	-0.137	0.099	0.023
Long-term effectiveness	0.608	0.002	0.017	0.397	0.048	0.002	0.980	0.295	0.020	-0.930	0.265	0.025
Quality of life	0.558	0.034	0.031	-0.373	0.401	0.029	-0.171	0.085	0.010	-0.159	0.073	0.012
Available options/alternatives	0.399	0.063	0.041	-0.045	0.008	0.001	-0.284	0.324	0.051	-0.129	0.066	0.015
Disease nature	0.846	0.097	0.020	-0.151	0.285	0.014	-0.210	0.550	0.042	-0.030	0.011	0.001
Disease burden	0.731	0.076	0.047	-0.382	0.603	0.068	-0.122	0.062	0.011	-0.126	0.066	0.017
Unmet needs	0.349	0.086	0.004	-0.024	0.029	0.000	-0.080	0.320	0.005	-0.002	0.000	0.000
Indirect benefits	0.933	0.044	0.053	-0.258	0.143	0.018	0.605	0.784	0.158	0.052	0.006	0.002
Innovation	0.921	0.040	0.041	-0.071	0.013	0.001	0.545	0.745	0.116	0.255	0.164	0.036
Complex care pathway	0.986	0.007	0.056	-0.495	0.075	0.010	0.686	0.144	0.031	1.581	0.766	0.231
Patient access schemes	0.989	0.031	0.096	1.028	0.882	0.203	0.317	0.084	0.031	-0.166	0.023	0.012

Treatment duration	0.635	0.018	0.035	-0.297	0.115	0.010	0.507	0.337	0.045	-0.374	0.183	0.035
Stakeholder persuasion	0.646	0.073	0.032	-0.049	0.014	0.001	0.318	0.596	0.073	-0.079	0.037	0.006
Equity	0.942	0.009	0.038	-0.281	0.046	0.004	0.757	0.335	0.049	0.979	0.561	0.117

Table 5. Association between HTA factors and recommendation decisions

(a) Economic evidence

Association	Factors under evaluation of economic evidence (d.f = 2) across recommendation decisions				
	ICER assessment framework for rare conditions	Cost-effectiveness: value-for-money	Budget impact Analysis	Comparative effectiveness	Economic modelling
$\chi 2$ (p value; Cramér's V)	3.797 (0.150; 0.284)	3.196 (0.202; 0.261)	5.015 (0.081; 0.327)	2.603 (0.272; 0.235)	6.755 (0.034; 0.379)
Fisher Exact (p value)	0.201	0.146	0.102	0.350	0.030

(b) Clinical evidence

Association	Factors under evaluation of clinical evidence (d.f = 2) across recommendation decisions								
	Study design	Sample size	Additional/ other evidence	Clinical benefits	Safety	Population generalisability	Survival	Long-term effectiveness	Quality of life
$\chi 2$ (p value; Cramér's V)	1.698 (0.428; 0.190)	0.036 (0.849; -0.028)	2.374 (0.305; 0.2247)	21.078 (0.000; 0.670)	15.969 (0.000; 0.583)	3.745 (0.154; 0.282)	5.525 (0.063; 0.343)	6.093 (0.048; 0.360)	2.119 (0.347; 0212)
Fisher Exact (p value)	0.585	0.668	0.456	0.000	0.002	0.210	0.140	0.080	0.266

(c) Disease considerations

Association	Factors under evaluation of disease considerations (d.f = 2) across recommendation decisions					
	Available options/alternatives	Children	Disease nature	Rarity	Disease burden	Unmet needs
$\chi 2$ (p value; Cramér's V)	10.183 (0.006'; 0.466)	1.325 (0.516; 0.168)	3.727 (0.054; -0.282)	0.672 (0.714; 0.120)	10.006 (0.007; 0.461)	5.009 (0.025; -0.327)
Fisher Exact (p value)	0.005	1.000	0.115	0.682	0.012	0.057

(d) Treatment considerations

Association	Factors under evaluation of treatment considerations (d.f = 2) across recommendation decisions								
	Indirect benefits	Adherence-improving factors	Innovation	Complex care pathway	Managed Entry Agreement	Patient Access schemes or equivalent	Cost of treatment	Long-term financial risk	Treatment duration
$\chi 2$ (p value; Cramér's V)	5.839 (0.016; -0.353)	0.938 (0.626; 0.141)	1.943 (0.378; 0.203)	1.918 (0.383; 0.202)	0.256 (0.613; -0.074)	0.969 (0.325; -0.144)	0.634 (0.426; -0.116)	0.148 (0.928; 0.056)	2.469 (0.291; 0.229)
Fisher Exact (p value)	0.022	0.673	0.544	0.659	1.000	0.635	0.640	1.000	0.390

(e) Other considerations

	Factors under evaluation of other considerations (d.f = 2) across recommendation decisions		
	Stakeholder persuasion	Value of hope	Equity
$\chi 2$ (p value; Cramér's V)	8.731 (0.003; -0.431)	2.139 (0.144; -0.213)	2.888 (0.236; 0.248)
Fisher Exact (p value)	0.012	0.303	0.420

Table 6. Multiple correspondence analysis of eight HTA factors and recommendation decisions (statistical output from STATA MP 17)

```
Multiple/joint correspondence analysis         Number of obs     =         47
                                               Total inertia     =  .25519558
    Method: Joint (JCA)                        Number of axes    =          2

                |   Principal              Cumul.
      Dimension |     inertia   Percent    percent
    ------------+--------------------------------
          Dim 1 |    .2177374     85.32      85.32
          Dim 2 |    .0181214      7.10      92.42
    ------------+--------------------------------
          Total |    .2551956    100.00

Statistics for column categories in principal normalization

                |          Overall          |        Dimension_1        |        Dimension_2
      Categories |    Mass  Quality   %inert |   Coord   Sqcorr  Contrib |   Coord   Sqcorr  Contrib
    ------------+---------------------------+---------------------------+---------------------------
    rec         |                           |                           |
    not recomm~d |   0.012    0.940    0.087 |   1.325    0.938    0.095 |   0.055    0.002    0.002
    recommende~) |   0.099    0.940    0.010 |  -0.158    0.938    0.011 |  -0.007    0.002    0.000
    ------------+---------------------------+---------------------------+---------------------------
    econ_mod    |                           |                           |
             No |   0.002    0.519    0.011 |  -0.373    0.121    0.002 |   0.676    0.398    0.060
            Yes |   0.076    0.976    0.029 |  -0.287    0.838    0.029 |   0.117    0.138    0.057
    not mentio~d |   0.033    0.985    0.075 |   0.683    0.812    0.071 |  -0.315    0.173    0.181
    ------------+---------------------------+---------------------------+---------------------------
    clin_bf     |                           |                           |
    No, uncert~d |   0.033    0.748    0.011 |   0.117    0.159    0.002 |  -0.226    0.589    0.093
            Yes |   0.069    0.871    0.024 |  -0.269    0.807    0.023 |   0.076    0.064    0.022
    not mentio~d |   0.009    0.944    0.095 |   1.536    0.921    0.102 |   0.241    0.023    0.030
    ------------+---------------------------+---------------------------+---------------------------
```

safety								
No, uncert~d	0.045	0.906	0.034	-0.412	0.888	0.035	-0.057	0.017	0.008
Yes	0.047	0.019	0.008	-0.027	0.016	0.000	0.010	0.002	0.000
not mentio~d	0.019	0.941	0.087	1.044	0.930	0.095	0.110	0.010	0.013
lt_eff								
No, uncert~d	0.085	0.921	0.018	-0.219	0.881	0.019	-0.047	0.040	0.010
Yes	0.005	0.708	0.011	-0.631	0.681	0.009	0.127	0.027	0.004
not mentio~d	0.021	0.942	0.093	1.014	0.920	0.101	0.158	0.022	0.029
avai_op								
No options	0.019	0.260	0.007	0.131	0.193	0.001	-0.077	0.067	0.006
Only suppo~s	0.071	0.873	0.021	-0.245	0.794	0.020	-0.077	0.079	0.023
not mentio~d	0.021	0.925	0.054	0.701	0.760	0.048	0.326	0.164	0.125
di_burden								
No	0.002	0.772	0.013	0.154	0.017	0.000	-1.034	0.755	0.140
Yes	0.083	0.972	0.035	-0.324	0.966	0.040	-0.026	0.006	0.003
not mentio~d	0.026	0.971	0.112	1.018	0.943	0.124	0.177	0.028	0.045
indir_bf								
Yes	0.057	0.977	0.042	-0.416	0.923	0.045	0.100	0.054	0.031
not mentio~d	0.054	0.977	0.043	0.434	0.923	0.047	-0.104	0.054	0.033
stake_per								
Yes	0.083	0.941	0.021	-0.235	0.867	0.021	0.069	0.074	0.022
not mentio~d	0.028	0.941	0.060	0.685	0.867	0.061	-0.200	0.074	0.063

Appendix B

Table 1. *Reporting frequencies of HTA factors across 47 dossiers*

Country	HTA agency	Financing system	Recommendation outcome	ICER assessment framework for rare diseases	Cost-effectiveness	Budget impact Analysis	Comparative effectiveness	Economic modelling	Study design	Sample size	Additional/other evidence	Clinical benefits	Safety	Population generalisability	Survival	Long-term effectiveness	Quality of life	Available options/ alternatives	Children	Disease nature	Rarity	Disease burden	Unmet needs	Indirect benefits	Adherence-improving factors	Innovation	Complex care pathway	Managed Entry Agreement or equivalent	Patient Access schemes or equivalent	Cost of treatment	Long-term financial risk	Treatment duration	Stakeholder persuasion	Value of hope	Equity	Numer of factors reported / dossier
CADTH	1	0	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	0	0	1	0	1	0	1	1	1	0	23
CADTH	1	0	1	1	1	0	1	1	1	0	0	1	1	0	1	1	1	0	0	1	0	1	1	0	1	0	0	0	0	0	0	1	1	1	0	17
CADTH	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	0	0	0	0	0	0	1	0	0	1	0	0	19
CADTH	1	0	1	1	1	0	1	1	1	0	0	1	1	1	1	1	1	1	0	1	0	1	1	0	0	0	0	0	0	1	0	0	1	0	0	17
CADTH	1	0	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	0	1	0	0	0	0	0	0	1	0	0	19
CADTH	1	0	1	1	1	0	1	1	0	0	1	1	1	1	1	1	1	1	0	1	0	1	1	1	0	0	0	0	0	1	1	0	1	1	0	20
ZIN	2	1	0	1	1	0	0	0	0	0	0	0	0	1	0	1	1	1	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	8
ZIN	2	1	0	1	1	1	0	1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	8
ZIN	2	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	3
ZIN	2	1	1	1	0	1	0	1	0	0	0	1	1	0	0	1	1	0	0	0	0	0	0	1	0	0	0	1	0	1	0	1	0	0	0	11
ZIN	2	1	0	1	0	1	1	0	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	0	1	0	0	0	0	0	0	1	0	0	0	18
ACE	3	1	1	1	1	1	1	0	0	0	1	1	1	0	1	0	0	1	1	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	13
ACE	3	1	1	1	1	1	1	0	0	0	1	1	1	0	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	11
ACE	3	1	1	1	1	1	1	0	0	0	1	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	10
ACE	3	1	0	1	0	1	1	0	0	0	0	1	0	0	1	0	1	0	0	1	0	0	1	0	0	0	0	0	1	1	0	0	0	0	0	10
ACE	3	1	1	1	1	0	0	1	0	0	0	1	1	1	1	0	1	0	0	1	0	0	1	0	0	1	0	0	1	1	0	0	0	1	0	14
ACE	3	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	3
AiHTA	4	1	1	1	0	1	1	0	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	0	0	0	0	1	0	0	0	1	0	0	0	17
AiHTA	4	1	1	1	0	1	1	0	1	1	0	1	1	1	1	1	1	1	0	1	0	1	1	0	0	0	0	0	0	0	0	1	0	0	0	16
AiHTA	4	1	1	1	0	1	1	0	1	0	0	1	1	1	1	1	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	14
AiHTA	4	1	1	1	0	1	1	0	1	1	0	1	1	1	1	1	1	1	0	1	0	1	1	0	0	0	0	0	0	0	0	1	0	0	0	16
AiHTA	4	1	1	1	0	1	1	0	0	0	0	1	1	1	1	1	1	1	0	1	0	1	0	0	0	0	0	0	0	1	0	1	0	0	0	14
NICE	5	0	1	0	1	0	0	1	0	0	0	1	1	1	1	1	1	1	0	1	0	1	1	0	0	1	0	0	1	0	0	0	1	0	0	15
NICE	5	0	1	0	1	0	0	1	0	0	0	1	1	1	1	1	1	1	0	1	0	1	1	0	0	1	0	0	1	0	0	0	1	0	0	15
NICE	5	0	1	1	1	0	0	1	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	0	0	1	0	1	0	1	1	0	1	0	0	20
NICE	5	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0	1	1	0	0	23
NICE	5	0	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	0	0	26
NICE	5	0	1	1	1	0	1	1	0	0	0	1	1	1	1	1	1	1	0	1	0	1	1	1	0	1	0	0	1	0	0	1	1	0	1	20
NICE	5	0	1	1	1	0	1	1	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	0	1	1	0	1	0	26
NICE	5	0	1	1	1	0	1	1	0	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	0	1	0	0	1	1	0	1	22
NICE	5	0	1	1	1	0	0	1	0	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	0	0	1	0	0	0	1	1	1	21

NICE	5	0	1	1	1	0	0	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	0	1	0	1	1	0	1	1	1	23
NICE	5	0	1	1	1	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	0	0	0	1	1	1	23
NICE	5	0	1	1	1	0	0	1	0	0	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	0	1	0	0	0	1	1	0	20
NICE	5	0	1	1	1	0	0	1	0	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	0	0	1	0	0	0	1	1	1	21
NICE	5	0	1	1	1	0	1	1	1	0	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	0	1	25
NICE	5	0	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	0	1	0	1	1	0	0	1	1	1	1	1	1	1	26
NICE	5	0	1	1	1	1	1	1	1	0	0	1	1	0	1	1	1	1	0	1	0	1	1	1	0	1	1	1	1	0	1	1	1	0	0	23
NICE	5	0	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	0	1	0	1	1	1	1	0	0	0	1	0	1	1	1	0	1	23
NICE	5	0	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	0	1	0	1	0	1	24
NICE	5	0	1	1	1	1	0	1	1	0	0	1	1	1	1	1	1	1	0	1	0	1	1	1	0	1	1	0	0	0	1	1	1	0	1	22
ICER	6	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	0	0	1	0	1	1	1	1	1	0	0	0	1	0	1	1	0	1	22
ICER	6	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	0	0	0	0	0	1	1	1	1	20
ICER	6	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	0	0	1	0	1	1	1	0	1	1	0	0	1	0	1	1	0	0	21
ICER	6	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	0	0	1	1	0	1	25
ICER	6	1	1	1	1	1	0	1	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	26
ICER	6	1	1	1	1	1	1	1	0	0	0	1	1	0	1	0	1	1	0	1	0	0	1	0	0	0	0	1	0	0	0	0	1	1	0	15

Appendix C

Table 1. *Evaluation outcomes of HTA factors across 47 dossiers*

HTA Agency	Dossier	Recommendation outcome What is the recommendation decision?	ICER assessment framework for rare diseases Does a modified cost effectiveness analysis apply for assessment?	Cost-effectiveness Is ICER considered cost-effective ie. within WTP or cost-effectiveness threshold at current price level?	Budget impact Analysis Is treatment affordable for the healthcare system?	Comparative effectiveness Could comparative effectiveness be assessed/concluded?	Economic modelling Were there issues identified with the inputs and assumptions that question the validity of the models?	Study design What were the concerns raised regarding the studies?	Sample size What were the concerns raised regarding the sample size?	Additional/other evidence Where these evidence are considered, are they deemed valid for decision making?	Clinical benefits Is efficacy deemed overall clinically meaningful based on measured outcomes (if applicable, for all relevant subgroups/indications)?	Safety Is the treatment deemed safe for patients (overall safety profile)?	Population generalisability Are results generalisable to most patients in routine or general clinical practice?	Survival Was survival highlighted as an important clinical outcome or required for consideration ?	Long-term effectiveness Does treatment improve long-term outcomes for patients?	Quality of life Does treatment lead to significant improvement to the quality of life?	Available options/alternatives Is current treatment/alternatives unavailable, limited, time-consuming, burdensome for patients and carers, not well tolerated, resulting in complications which impact QOL and mental well-being?	Children Are special considerations for children/pediatrics included in decision-making (with exceptions)?	Disease nature Does disease rank high in terms of severity in its worst form?	Rarity Is special consideration given to the rarity of the disease?	Disease burden Is disease determined to have a significant burden?	Unmet needs Does treatment address a therapeutic gap or unmet needs?	Indirect benefits Does treatment render indirect benefits to patients, family, caregivers etc.?	Adherence-improving factors Does treatment improve adherence, thereby health outcomes?	Innovation Is the treatment a new innovation of important benefits?	Complex care pathway What is the impact of the treatment on the delivery of specialised health services?	Managed Entry Agreement or equivalent Are MEAs or equivalent considered for decision-making?	Patient Access schemes or equivalent Are patient access schemes considered for decision making?	Cost of treatment Is the cost of treatment deemed costly ?	Long-term financial risk Does treatment present potential financial risks to public payers?	Treatment duration Is treatment lifelong?	Stakeholder persuasion Are stakeholder inputs, where considered, valid for decision making?	Value of hope Does treatment offer a value of hope?	Equity Does recommendation/accessibility to treatment impact equity?
CADTH	Onasemnogene Abeparvovec for Spinal muscular atrophy	1	0	0	2	0	1	1	2	0	1	0	0	1	0	0	1	1	1	2	1	1	1	2	2	2	2	1	2	1	2	0	1	1	2
CADTH	Nitisinone (Orfadin) for adult and pediatric hereditary tyrosinemia type-I	1	0	0	2	0	1	0	2	2	1	0	2	1	0	0	2	2	1	2	1	1	2	2	2	2	2	2	2	1	1	1	2
CADTH	Patisiran for polyneuropathy in adult patients with hATTR amyloidosis	1	0	0	2	0	1	1	1	0	1	1	0	1	0	1	2	1	2	1	1	2	2	2	2	2	2	1	2	2	1	2	2
CADTH	Inotersen for polyneuropathy in adults with hATTR	1	0	0	2	0	1	1	2	2	1	1	0	1	0	1	1	2	1	2	1	1	2	2	2	2	2	1	2	2	1	2	2
CADTH	Lanadelumab (Takhzyro) for prevention of attacks of hereditary angioedema (HAE) in adolescents and adults	1	0	0	2	0	1	2	1	0	1	0	0	1	0	1	1	2	1	1	1	1	2	2	1	2	2	2	2	2	2	1	2	2
CADTH	Tafamidis Meglumine (Vyndaqel) for the treatment of adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary	1	0	0	2	1	1	2	2	0	1	1	0	1	0	1	0	2	1	2	1	1	1	2	2	2	2	2	1	1	2	1	1	2
ZIN	Nusinersen (Spinraza) for treatment of 5q SMA	0	0	0	2	2	2	2	2	2	2	2	0	2	0	0	0	2	1	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2
ZIN	Tafamidis (Vyndaqel) for the treatment of wild-type or hereditary transthyretin amyloidosis	0	0	0	0	2	1	2	2	2	2	2	2	1	2	0	2	2	2	2	2	2	2	2	2	1	2	2	2	2	1	2	2	2	2
ZIN	Ibrutinib (Imbruvica) in combination with rituximab for the treatment of Waldenstrom's disease	0	0	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2
ZIN	Voretigene neparvovec (Luxturna) for the treatment of vision loss due to inherited retinal dystrophy with bi-allelic RPE65 mutations	1	0	2	0	2	1	2	2	2	1	1	2	2	0	1	2	2	2	2	2	2	2	1	2	2	2	1	2	1	2	0	2	2	2
ZIN	Metreleptin for the treatment of congenital, generalized lipodystrophy or acquired generalized lipodystrophy	0	0	2	0	1	2	1	1	2	0	1	0	1	0	0	0	2	1	1	1	1	2	0	2	2	2	2	2	2	1	2	2	2	2
ACE	Ursodeoxycholic acid for treating primary biliary cirrhosis	1	0	1	1	1	2	2	2	1	1	1	2	1	2	2	0	1	2	2	2	1	2	2	2	2	2	1	2	2	2	1	2	2	2
ACE	Temozolomide for the treatment of malignant glioma	1	0	1	1	1	2	2	2	1	0	1	2	1	2	2	1	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2
ACE	Rituximab for treating non-Hodgkin's lymphoma and chronic lymphocytic leukaemia	1	0	1	1	1	2	2	2	1	0	2	2	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	2	2
ACE	Nintedanib and pirfenidone for treating idiopathic pulmonary fibrosis	0	0	0	0	1	2	2	2	2	0	2	2	1	2	0	2	2	1	2	2	1	2	2	2	2	2	2	1	1	2	2	2	2	2
ACE	Blinatumomab for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia	1	0	1	2	2	1	2	2	2	1	1	1	1	2	1	2	2	1	2	2	1	2	2	2	1	2	2	1	1	2	2	2	1	2
ACE	Imatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia	1	0	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2
AiHTA	Defibrotide for the treatment and prophylaxis of hepatic veno-occlusive disease	1	0	2	0	0	2	1	2	2	0	0	0	1	0	0	1	2	1	1	1	1	2	2	2	2	1	2	2	2	0	2	2	2	2
AiHTA	Ibrutinib (Imbruvica) in combination with rituximab for the treatment of Waldenström's macroglobulinemia	1	0	2	1	1	2	1	1	2	1	1	0	1	0	1	0	2	1	2	1	1	2	2	2	2	2	2	2	2	0	2	2	2	2
AiHTA	Rituximab (MabThera) after autologous stem-cell transplantation (ASCT) in mantle cell lymphoma (MCL)	1	0	2	0	1	2	1	2	2	1	1	0	1	0	0	1	2	1	0	1	2	2	2	2	2	2	2	2	2	0	2	2	2	2
AiHTA	Venetoclax (VenclextaTM) for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) with chromosome 17p deletion	1	0	2	0	0	2	0	1	2	0	0	0	1	0	0	1	2	1	2	0	1	2	2	2	2	2	2	2	2	0	2	2	2	2
AiHTA	Obinutuzumab (Gazyvaro) in combination with bendamustine for the treatment of relapsed/ refractory follicular lymphoma (FL)	1	0	2	1	0	2	2	2	2	0	1	0	1	0	0	1	2	1	2	1	2	2	2	2	2	2	2	1	2	0	2	2	2	2
NICE	Cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome	1	2	0	2	2	1	2	2	2	1	0	0	1	0	0	1	2	1	2	1	1	2	2	0	2	2	1	2	2	2	1	2	2	2
NICE	Cannabidiol with clobazam for treating seizures associated with Dravet syndrome	1	2	0	2	2	1	2	2	2	1	0	0	1	0	0	1	2	1	2	1	1	2	2	0	2	2	1	2	2	2	1	2	2	2
NICE	Nusinersen for treating spinal muscular atrophy	1	0	0	2	2	1	2	2	1	0	2	0	1	0	0	1	1	1	1	1	1	2	2	0	2	1	2	1	1	2	1	1	2	2
NICE	Eliglustat for treating type 1 Gaucher disease (2017)	1	1	1	1	0	1	1	1	2	1	0	0	0	0	0	1	2	1	1	1	1	1	1	2	2	0	2	1	2	2	1	1	2	2
NICE	Elosulfase alfa for treating mucopolysaccharidosis type IVa (2015)	1	1	0	0	1	1	1	2	2	0	0	0	1	0	0	0	1	1	1	1	2	1	0	1	0	1	1	1	2	1	1	2	2	2
NICE	Givosiran for treating acute hepatic porphyria	1	1	1	2	1	1	2	2	2	1	0	1	1	1	0	1	2	1	2	1	1	1	2	1	2	2	1	2	2	1	1	2	2	0

NICE	Onasemnogene abeparvovec for treating spinal muscular atrophy	1	1	1	2	1	1	0	2	2	0	1	1	1	0	0	1	0	1	1	1	1	1	1	2	1	0	1	1	1	2	0	1	2	1
NICE	Metreleptin for treating lipodystrophy	1	0	1	2	1	1	2	2	1	1	0	0	1	0	0	0	2	1	1	1	1	1	2	2	0	2	1	2	2	1	1	2	0	
NICE	Volanesorsen for treating familial chylomicronaemia syndrome	1	0	1	2	2	1	2	2	0	1	1	0	0	0	0	1	2	1	1	1	1	1	2	1	2	2	1	2	2	2	1	1	0	
NICE	Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2	1	1	0	2	2	1	0	2	0	0	0	0	0	0	0	1	2	1	1	1	1	1	2	2	2	1	2	1	1	2	1	1	0	
NICE	Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations	1	1	1	2	2	1	0	2	1	1	0	1	1	1	0	1	1	1	1	1	1	1	2	1	2	2	1	2	2	2	1	1	0	
NICE	Patisiran for treating hereditary transthyretin amyloidosis	1	0	0	2	2	1	2	2	2	1	0	0	1	0	1	1	2	1	1	1	1	1	2	1	0	2	1	2	2	2	1	1	2	
NICE	Inotersen for treating hereditary transthyretin amyloidosis	1	0	1	2	2	1	2	2	1	1	0	0	1	0	1	1	2	1	1	1	1	1	2	1	2	2	1	2	2	2	1	1	0	
NICE	Burosumab for treating X-linked hypophosphataemia in children and young people	1	1	1	2	0	1	0	2	1	0	0	1	2	0	0	1	0	1	2	1	1	1	1	1	0	1	1	2	2	0	1	2	0	
NICE	Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency	1	1	1	1	1	1	0	1	2	0	2	0	1	0	0	1	0	1	1	1	2	1	2	1	0	2	2	1	1	0	1	1	1	
NICE	Asfotase alfa for treating paediatric-onset hypophosphatasia (2017)	1	1	1	1	0	1	0	2	2	1	1	2	1	0	0	1	2	1	2	1	1	1	2	1	0	1	2	1	0	1	1	2	2	
NICE	Migalastat for treating Fabry disease	1	1	0	1	0	1	1	1	2	0	0	2	0	0	0	1	2	1	2	1	1	1	0	2	2	2	1	2	1	1	1	2	0	
NICE	Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene	1	1	0	0	1	1	2	2	2	1	0	1	1	0	0	1	1	1	2	1	1	1	2	1	0	1	1	2	1	2	1	2	0	
NICE	Eculizumab for treating atypical haemolytic uraemic syndrome	1	1	0	0	2	1	1	2	2	1	0	0	1	0	1	1	2	1	2	1	1	1	2	1	0	2	2	2	1	1	1	2	0	
ICER	Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value	1	1	0	1	0	1	2	1	2	1	1	0	1	0	0	2	2	1	2	1	1	1	1	1	2	2	2	1	2	0	1	2	1	
ICER	Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value	1	1	0	1	2	2	2	2	2	1	1	0	0	0	1	1	2	1	2	1	1	1	1	1	2	2	2	2	2	0	1	1	1	
ICER	Modulator Treatments for Cystic Fibrosis: Effectiveness and Value	1	0	0	0	1	0	2	1	2	1	1	0	0	0	1	2	2	1	2	1	1	1	2	1	1	2	2	1	2	1	1	2	2	
ICER	Spinraza and Zolgensma for Spinal Muscular Atrophy: Effectiveness and Value	1	1	0	1	1	1	0	1	2	1	1	0	1	0	0	1	2	1	1	1	1	1	1	1	2	1	2	2	2	0	1	2	0	
ICER	Voretigene Neparvovec for Biallelic RPE65 Mediated Retinal Disease: Effectiveness and Value	1	1	1	1	2	1	0	2	2	1	1	0	0	0	0	0	2	1	1	1	1	1	0	1	1	1	1	1	2	2	1	1	0	
ICER	Obeticholic Acid for the Treatment of Primary Biliary Cholangitis: Comparative Clinical Effectiveness, Value, and Value-Based Price Benchmarks	1	2	0	1	0	1	2	2	2	1	1	2	1	2	0	1	2	1	2	2	1	2	2	2	2	1	2	2	2	2	1	1	2	

Appendix D

Table 1. Summary of evidence used by HTA agencies and the year HTA of Zolgensma was conducted

HTA agency	Year of assessment	Key sources of evidence used for HTA
CADTH	2020	• Two completed open-label single-arm studies: START, STR1VE-US • STR1VE-EU: open-label single-arm phase 3 study (type 1 SMA) • SPR1NT: open-label single-arm phase 3 study (diagnosis of SMA without symptoms) • Natural history studies 1. Neuronext 2. PCNR (Pediatric Neuromuscular Clinical Research Network) 3. ENDEAR 4. SHINE: long-term extension study of ENDEAR **Note: Only ICER considered a Phase I dose comparison trial (STRONG) of intrathecal administration of Zolgensma in patients with Type II SMA*
NICE	2021	
ICER	2019	

Table 2. Summary of data collected from CADTH, NICE and ICER on the evaluation of Zolgensma

		CADTH	NICE	ICER
ICER assessment framework for (ultra-)rare conditions	Does a modified cost effectiveness analysis apply for assessment?	X	✓	✓
Cost-effectiveness: value-for-money	Is ICER considered cost-effective ie. within WTP or CE threshold at current price level?	X (uncertainty)	✓	X
Budget impact Analysis	Is treatment affordable for the healthcare system?	-	-	✓
Comparative effectiveness	Could comparative effectiveness be assessed/concluded?	X (uncertainty)	✓	✓

Economic models	Were there issues/uncertainties identified with the inputs and assumptions that question the validity of the models?	✓	✓	✓
Study design	What were the concerns raised regarding the studies?	✓ (issue)	X (uncertainty)	X (uncertainty)
Sample size	What were the concerns raised regarding the sample size?	-	-	✓ (issue)
Additional/other evidence	Where these evidence are considered, are they deemed valid for decision making?	X (limitations)	-	-
Clinical benefits	Is efficacy deemed overall clinically meaningful based on measured primary outcomes (if applicable, for all relevant subgroups/indications)?	✓	X (uncertainty, limited)	✓
Safety	Is the treatment deemed safe for patients (overall safety profile)?	X (unknown)	✓	✓
Population and generalisability	Are results generalisable to most patients in routine or general clinical practice?	X (uncertainty)	✓	X (uncertainty)
Survival	Was survival highlighted as an important clinical outcome or required for modelling?	✓	✓	✓
Long-term effectiveness / overall beneft	Does treatment improve long-term outcomes for patients?	X (uncertainty)	X (uncertainty)	X (uncertainty)
Quality of life e.g., PROs	Does treatment lead to significant improvement quality of life?	X (no evidence)	X (no evidence)	X (no evidence)

Current/main treatment alternative(s)	Is current treatment / alternatives unavailable, limited, time-consuming, burdensome for patients and carers, not well tolerated, result in complications which impact QOL and mental well-being?	✓ (limited)	✓ (limited)	✓ (limited)
Children	Are special considerations for children/pediatrics included in decision-making (with exceptions)?	✓	x	-
Disease nature	Does disease rank high in terms of severity in its worst form?	✓	✓	✓
Rarity	Is special consideration given to the rarity of the disease?	-	✓	✓
Disease burden	Is disease determined to have a significant burden?	✓	✓	✓
Unmet needs	Does treatment address a therapeutic gap or unmet needs?	✓	✓	✓
Indirect benefits	Does treatment render indirect benefits to patients, family, caregivers etc.?	✓	✓	✓
Adherence-improving factors	Does treatment improve adherence, thereby health outcomes?	-	-	✓
Innovation	Is the treatment a new innovation of important benefits?	-	✓	✓
Complex care pathway	What is the impact of the treatment on the delivery of specialised health services?	-	X (additional training and education for staff at specialised centre)	-

Managed Entry Agreement or equivalent	Are MEAs or equivalent considered for decision-making?	✓	✓	✓
Patient Access schemes or equivalent	Are patient access schemes considered for decision making?	-	✓	-
Cost of treatment	Is the cost of treatment deemed costly ?	✓	✓	-
Long-term financial risk	Does treatment present potential financial risks to public payers?	-	-	-
Treatment duration	Is treatment lifelong?	X	X	X
Stakeholder persuasion	Are stakeholder inputs, where considered, valid for decision making?	✓	✓	✓
Value of hope	Does treatment offer a value of hope?	✓	-	-
Equity	Does recommendation/accessibility to treatment impact equity?	-	✓ (disadvantaged groups)	X (no impact identified)

'X' indicates 'No' and '✓' indicates 'Yes' to the question in second column unless specified otherwise