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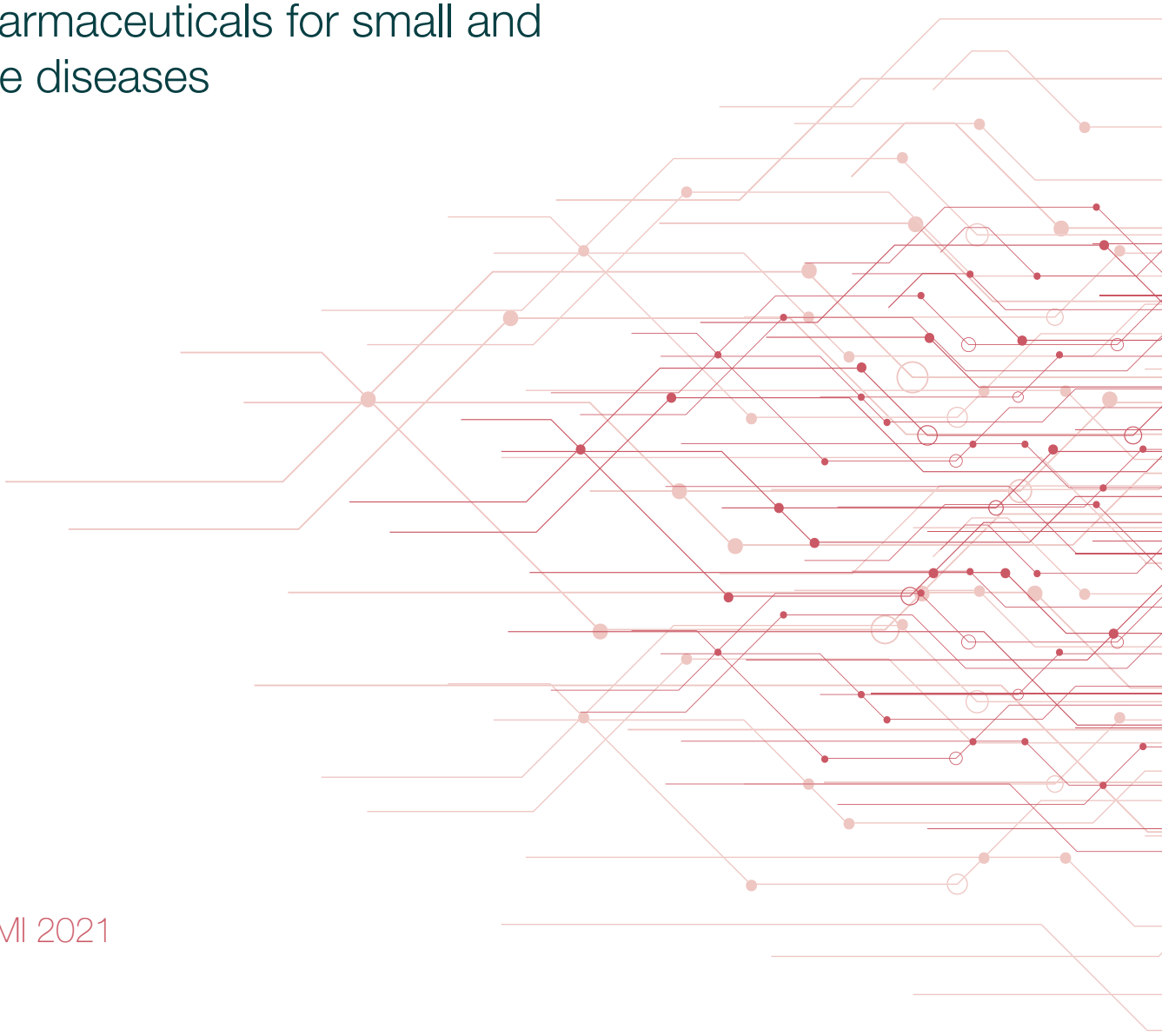
WHITEPAPER

MULTI-CRITERIA DECISION ANALYSIS

A framework for assessing pharmaceuticals for small and rare diseases



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INTRODUCTION

The aim of this whitepaper is to describe some of the main challenges regarding the assessment of pharmaceuticals for small and rare diseases in Denmark. We will provide specific but non-exhaustive examples of obstacles in the assessment of pharmaceuticals for small and rare diseases. Thus, it should be noted that there are more nuances in the matter than included in this paper. Furthermore, we will highlight one possible option for assessing pharmaceuticals for small and rare diseases, as we look to the multi-criteria decision analysis (MCDA) assessment framework.

Assessing pharmaceuticals for small and rare diseases is seldom straightforward. In recent years, the standard assessment method has been criticized for being unfit to assess pharmaceuticals for small and rare diseases. The critique is mainly focused on two aspects of the assessment process: the pharmaceutical's inability to meet cost-utility requirements and the construct of the system itself (12). Applying novel ways of evaluation in the decision-making process, in addition to cost-utility, could amend the assessment challenges (6).

What is a rare disease?

According to the European Medicines Agency (EMA), any disease affecting fewer than five out of 10,000 people in the EU is considered rare (2). Most of these patients suffer from even rarer diseases affecting one in 100,000 people or more. Approximately 5,000–8,000 distinct rare diseases affect 6–8% of the EU population, i.e., between 27 and 36 million people (3). A rare disease is often non-curable; however, with relevant efforts, the consequences of the disease can perhaps be prevented, limited, or treated (4).

Complexity in the decision-making process is inevitable, and limited resources make it difficult to reconcile all competing interests. MCDA has gained increasing attention during the last couple of years, as it can provide insight into the rationale behind value assessment (1, 13). MCDA is a framework for supporting decision-making where multiple criteria, in addition to cost and efficacy, can be arranged and evaluated (6). MCDA has gained attention in the assessment of orphan drugs and at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). In addition, various researchers have looked to its potential in health care decisions (6, 7, 9, 13).

CHALLENGES IN THE ASSESSMENT PROCESS

The assessment of pharmaceuticals for small and rare diseases is a complicated decision-making process, and access to the market continues to be challenging (1). Looking at orphan drug applications received by the Danish Medicines Council (DMC) between 2018–2020, 39.3% of the orphan drug applications were recommended for standard use, while 17.9% were partly recommended. For all other pharmaceuticals, 59.3% were recommended for standard use, and 13.6% were partly recommended. This means that 20 percentage points fewer orphan drugs were recommended for standard use compared to all other pharmaceuticals between 2018 and 2020 (23).

> *Access to market-approved orphan therapies remains an issue (1)."*

Pharmaceuticals for small and rare diseases often struggle to meet the DMCs' assessment requirements because of their inability to collect sufficient clinical evidence. The current assessment process follows principles of rational pharmacotherapy. Evaluating health care interventions mostly based on cost-utility can be considered a form of health care optimization, as it guides the allocation of health care resources to achieve the greatest possible health benefit under a given budget constraint.

To comply with the DMC's assessment process, pharmaceutical companies must provide substantial evidence for the pharmaceutical's efficacy and demonstrate value in a health economic analysis. The quality of evidence is assessed according to The Grading of Recommendations Assessment, Development and Evaluation (GRADE), and the health economic analysis is a cost-utility analysis (10).

The inherent challenge of evidence for small and rare diseases

It is recognized that in the clinical study of pharmaceuticals for small and rare diseases, data will inevitably be sparse (8). Data are usually collected from clinical studies, with randomized clinical trials as the gold standard, and then statistically analysed to determine efficacy. However, the small population size makes the recruitment and execution of randomized clinical trials difficult within the field of small and rare diseases.

> *The small population size makes it difficult to gather adequate quality evidence."*
>
> *Janne Petersen, Associate Professor, PhD, Head of Copenhagen Phase IV Unit*

Various analytical challenges arise in the process, including insufficient statistical power. Due to the small sample size, researchers must be aware of whether data have an appropriate amount of power to inform decision-makers and provide a sound basis for their conclusions (21).

Therefore, the limited number of patients decreases the possibility of gathering adequate evidence with an acceptable degree of uncertainty and thereby complying with the health technology assessment body's (HTA) data requirements, as illustrated in Figure 1.

Figure 1: Evidence challenges for small and rare diseases

Challenges of applying a health economic analysis focus

The DMC applies a cost-utility analysis[1]. One of the advantages of a cost-utility analysis is that it provides an incremental cost-effectiveness ratio (ICER) that allows for outcome comparisons of different technologies across different diseases (7). We argue that the analysis can be considered partly insufficient and nontransparent for the assessment of pharmaceuticals for small and rare diseases. Even though the analysis includes quality-adjusted life years (QALYs), cost data, and disease-specific model assumptions (10), there are some limitations in such measures in relation to small and rare diseases.

[1] This paper was written before the DMC published the first results of applying the new assessment methodology, which was implemented on January 1st 2021.

By definition, QALYs look to length and quality of life. Treatments for rare diseases are naturally approved based on clinical trials with fewer patients and predicting the longevity of patients in these trials is challenging. Therefore, it can be difficult to demonstrate the pharmaceutical's cost-effectiveness, but the inability to demonstrate cost-effectiveness does not necessarily mean that the treatment is ineffective.

The health economic analysis considers treatments for small and large patient populations in the same way. However, the focus on cost-effectiveness disregards the impact of disease rarity on data uncertainty, which influences the accurate estimation of a pharmaceutical's health benefit in terms of QALYs (22).

We find that the drug cost of treatment per patient is often higher for small and rare diseases than for more common diseases. This means that small patient populations will appear more costly to payers in the health care system when measured as cost per QALY. In addition to the difficulties of demonstrating robust efficiency in small populations, the price point means that pharmaceuticals for small and rare diseases will not be considered cost-effective in a cost-utility analysis.

Placing too much focus on cost-effectiveness will potentially limit decision-making, as this process does not consider rarity and equity. It can be argued that a focus on cost-effectiveness jeopardizes patients' equity in access to treatment. Hence, a lack of proven cost-effectiveness may not be a sufficient reason to reject access to treatments in the case of small and rare diseases (24).

Construct of the DMC's method

The DMC assesses the application of new hospital pharmaceuticals and recommends which pharmaceuticals are to be standard treatments in the Danish hospital system. A recommendation by the DMC is based on the assessment of whether the pharmaceutical's safety and effect have a reasonable proportionate relationship to the cost of bringing the pharmaceutical into use (10). The DMC works within the political framework of the Danish Parliament's seven principles for prioritization of hospital medicine and the two principles of caution and severity (10). On January 1st, 2021, the DMC changed the methodological approach to QALYs.

In 2019, before the change in the DMC's assessment method, Oxford Research evaluated the DMC (5) and found that the DMC applied a rigorous methodological approach to assess pharmaceuticals. The report mentioned that documentation was treated systematically and uniformly, as there were stringent methods for collecting and assessing documentation. However, the DMC's rigorous method and data requirements were criticized by pharmaceutical companies and patient organizations for hindering pragmatic reflections that consider the characteristics of small and rare diseases. Oxford Research described that the DMC struggled to adhere to the Danish Parliament's seventh principle: access to treatment. The predicament about this principle seems to particularly apply to small and rare diseases and to therapeutic areas without existing treatments (5). Within these areas, an increasing number of new pharmaceuticals are unable to document sufficient treatment effects while simultaneously being associated with high costs (6).

Thus, pharmaceuticals for small and rare diseases may struggle to meet the DMC's requirements, as data are often too sparse to demonstrate efficacy. In these situations, the DMC evaluates data on effect, safety, and cost without a cost-utility analysis. This can be a helping hand to pharmaceutical companies, as data will be evaluated "as is". However, currently, there is no description of or guideline for how this process proceeds. The DMC's assessment does not include an explicit description of what a "reasonable proportionate relationship between cost and effect" entails. Without such a description, it is basically unclear whether the willingness to pay for a treatment to one patient group is, for example, higher than for other comparable patient groups and treatments. Hence, this raises the question of how the DMC's decision is made and on which parameters the decision is based.

The criticism of the construct of the system and the challenges in meeting cost-utility requirements suggest the possibility of including a supplementary methodology in the assessment process. This could enable decision-makers to assess pharmaceuticals holistically while still ensuring quality and clarity in the assessment (11, 12).

MULTI-CRITERIA DECISION ANALYSIS (MCDA)

MCDA is a framework that enables the exploration of stakeholders' preferences and allows for an explicit organization of multiple factors in the decision-making process (1, 9). The framework allows multiple criteria to be arranged and assessed, and it helps bring forth the relevance and the weighted importance of each criterion.

The MCDA framework supports decision-making when various criteria, aside from cost and efficacy, can be considered in the assessment (7, 12). In MCDA, multiple criteria that influence the decision are identified. Several criteria are selected, and each criterion is weighted for its relative importance to the overall score. The weight of each criterion is defined by including stakeholders' and experts' opinions (13). Subsequently, alternatives (i.e., treatments) are scored against each criterion and weighted to provide a summary score. The overall score is used to compare the alternatives to each other. By combining multiple criteria into one overall assessment, MCDA helps to make the decision-making process more transparent. This may improve accountability and consistency in decision-making (14) and provide nuanced insights into the evaluation and assessment of pharmaceuticals.

> *"MCDA is a domain of operational research that is beginning to be used in health care decision-making." (14)*

ISPOR has suggested MCDA as a supportive framework for a standard assessment methodology (13). MCDA has shown to be valuable for assessing decision problems outside the health care sector (15). According to the literature, MCDA has been applied in banking and finance (16) and in environmental policy issues for many years (17). MCDA has previously been applied in health care studies, and the literature shows that more researchers and practitioners have become aware of its application (18, 19).

As an example, MCDA has been applied in two pilot projects by the German Institute for Quality and Efficiency in Health Care (IQWiG), in health care decisions in Lombardia, Italy, and in health technology assessment (HTA) decisions in Thailand (13, 20, 24). IQWiG initiated two pilot projects to explore the use of MCDA as a way of incorporating patient involvement into its HTA process. The projects applied two MCDA techniques (analytical hierarchy process and discrete choice experiment) to investigate whether the methods could be applied in health economic evaluations in Germany in the identification, weighting and prioritization of multiple patient-relevant outcomes. Both projects concluded that MCDA techniques can be used to support the HTA process. Both projects also pointed out methodological challenges that need to be clarified before full-scale implementation (20, 24). For instance, outcomes and treatment goals can correlate or overlap. When it comes to interviewing stakeholders, one question that should be considered in both MCDA and in the process of recording QALYs is: Which persons should be interviewed and how transferable are the results to the entire patient population (20, 24)?

It should be emphasized that there is a wide range of MCDA approaches available in the literature (13). As such, selecting a suitable MCDA approach is not easily done.

DISCUSSION & CONCLUSION

In the beginning of 2021, the Danish Medicines Council introduced a new assessment method with the application of QALYs. The advantage of the new method is the possibility of comparing outcomes from different technologies across different diseases. Despite this, we argue that the assessment process will continue to be challenging for pharmaceuticals for small and rare diseases.

We recognize that there is no simple or straightforward solution to the problems pointed out in this paper regarding the inability to meet requirements and the construct of the assessment system. Applying a supporting framework in the assessment process does not take away the challenges, and it can be argued that limitations will occur in most assessment methods. In assessment scenarios where it is impossible to perform a cost-utility analysis, it can be argued that it would be valuable for pharmaceutical companies to have a description of how data will be evaluated and what criteria will be highlighted in the assessment process. As such, a supportive framework for pharmaceuticals seeking to treat small and rare diseases can provide transparency in the decision-making process.

We believe that small patient populations will become more common in the future as an increasing proportion of new pharmaceuticals target specific mutations or genotypes. Because small populations yield small datasets, limitations and uncertainty will also occur in the future. This means that a growing number of new pharmaceuticals will have to be evaluated based on a very limited amount of evidence. For this reason, developing a tailored decision framework, such as MCDA, and initiating early dialogue between small and rare disease stakeholders could increase patients' access to treatment.

The strength of MCDA is its ability to capture factors beyond cost and efficacy. It allows for stakeholders' preferences, and it provides a structured and transparent approach to identifying preferred alternatives by combining calculations of the criteria's relative importance and the performance of alternatives on various criteria.

The construct and application of MCDA has limitations and requires careful consideration of some methodological issues, e.g., how to select and weigh decision criteria and how to handle evidence uncertainty.

The initial definition of criteria is essential to ensure that overlap between criteria is avoided. In addition, criteria should not be selected in a way that favours a certain outcome. Weighting criteria can be complicated and dependent on the perspective of the assessment.

The subject of this paper was not to solve these limitations but to highlight one possible option for assessing pharmaceuticals for small and rare diseases. Further research on model structure, framework design, criteria selection and weighting, as well as practical functioning, is necessary to bring about the application of MCDA in the assessment of pharmaceuticals for small and rare diseases in Denmark.

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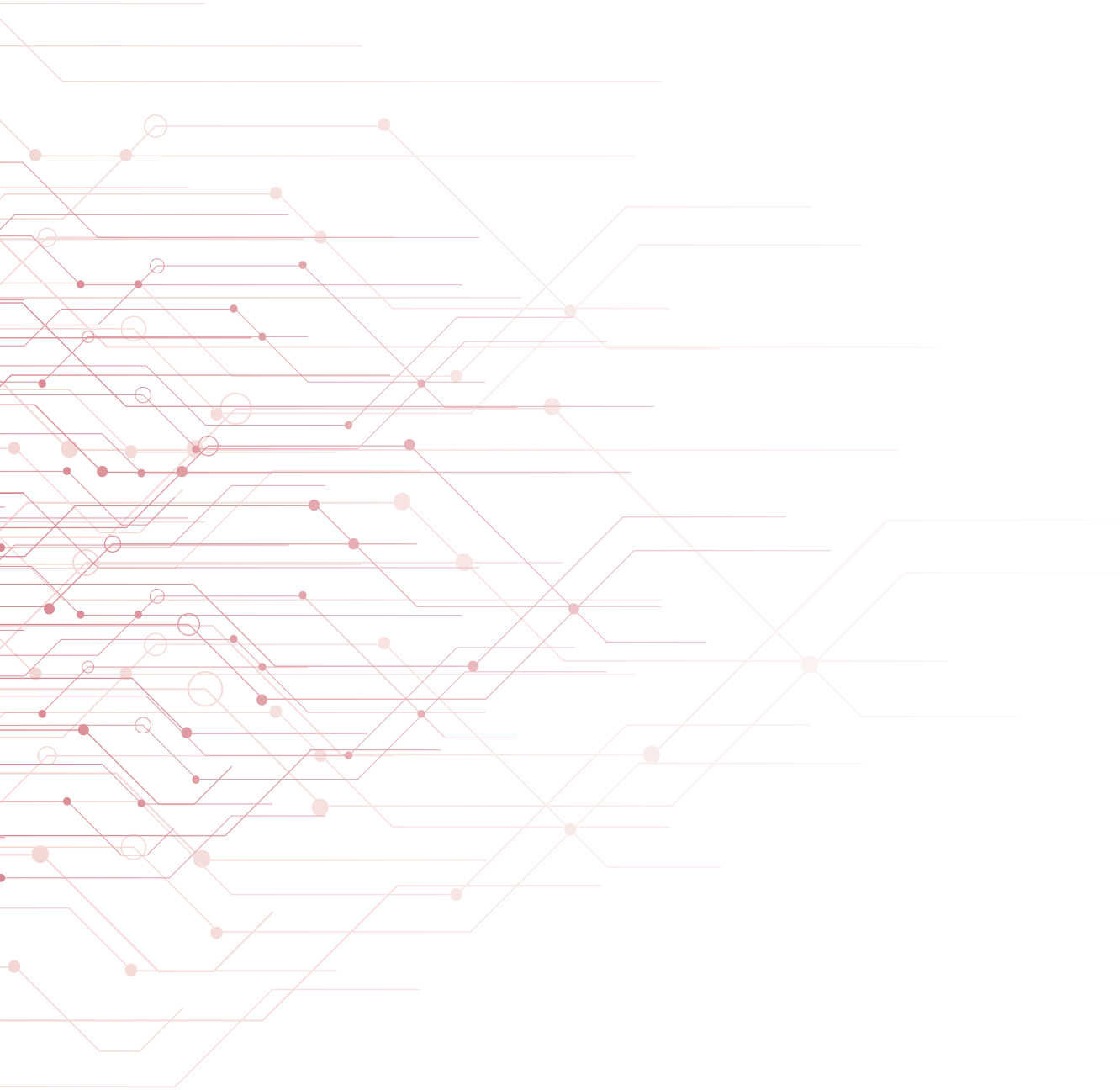

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