Health technology assessment decisions in Sweden and Denmark: a comparative study in understanding the challenges of approval for single-arm trials

Zamfir, Alexa and Dibbern, Therese[1]
Correspondence: alexa.zamfir@nordicmarketaccess.com, therese.dibbern@nordicmarketaccess.com
[1]Nordic Market Access, 113 59 Stockholm, Sweden

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Background

Submissions of Health technology assessments (HTA) with single armed registration trials for the intervention risk rejection by HTA agencies due to uncertainty of relative effect compared to current standard of care. The objective of this study was to identify and compare relevant parameters for Sweden and Denmark respectively that influence the decisions' outcome.

Methods

Decisions and recommendations for products with single arm trials were retrieved from the public databases of the respective authorities - the Danish Medicines Council (DMC)[1], the Swedish Dental and Pharmaceutical Benefits Agency (TLV)[2] and the Swedish New Therapies (NT) Council[3], between January 2017 and April 2022. Parameters of relevance were identified, examples being disease area, severity, prevalence, clinical value, and cost per quality adjusted life years. The decisions were categorized by the recommendation outcome and parameters were quantitatively assessed through a logistic regression.

Results

17 individual drugs across one or more indications in Sweden and Denmark were identified in the following disease categories, 60% in oncology, 10% in genetic disorders, 15% in neurological disorders and 15% categorized as others. In Sweden, the received outcomes were, 47% positive, 37% negative and 16% still pending. In Denmark, the outcomes were, 37% positive, 37% negative, 10% still pending, 11% not yet submitted and 1 (5%) withdrawn. Comparing Sweden and Denmark, there were cases where an assessment was not made in Denmark following an earlier negative recommendation for the same assessed indication in Sweden.

Variables have been sequentially removed for the final model specification by both interpreting the numerical results (i.e., deviance, p-values, presence of singularities) as well as the practical relevance of the variables. For Sweden, Table 1, these were Severity (Sev), Prevalence (Prev), Possibility of cure (Cure) and cost per QALY (QALY), while for Denmark, Table 2, Prevalence (Prev) and treatment cost difference (Cost).

Table 1: Statistical output Sweden

Coefficients:

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-0.3655	1.7201	-0.212	0.8318
SSevvery high	**2.6206**	**1.4379**	**1.823**	**0.0684**
SPrevrare	-1.6952	1.6878	-1.004	0.3152
SCuremoderate	-1.4310	1.5502	-0.923	0.3560
SQALYlow	1.6525	1.5618	1.058	0.2900

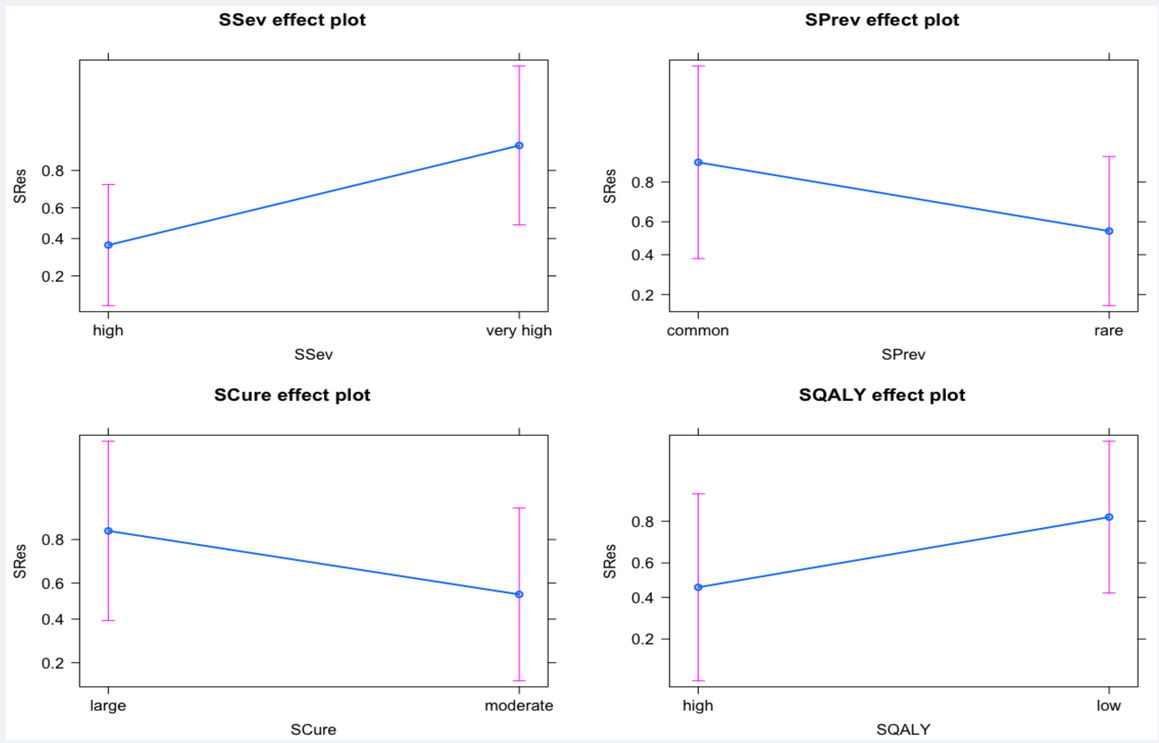
Table 2: Statistical output Denmark

Coefficients:

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	0.6219	0.9405	0.661	0.508
DPrevrare	-0.7589	1.1746	-0.646	0.518
DCostlow	-0.7040	1.1214	-0.628	0.530

The results of the logistic regressions showed that the disease severity and indications within the oncology category were most likely to lead to a positive recommendation in both Sweden and Denmark. The probability plot for Sweden (Figure 1) shows that products with indications with very high disease severity, a higher prevalence, a large clinical effect, and a low incremental cost effectiveness ratio have a higher likelihood for a positive outcome, while for Denmark (Figure 2) similarly indications with a higher prevalence and low estimated cost difference have a higher probability.

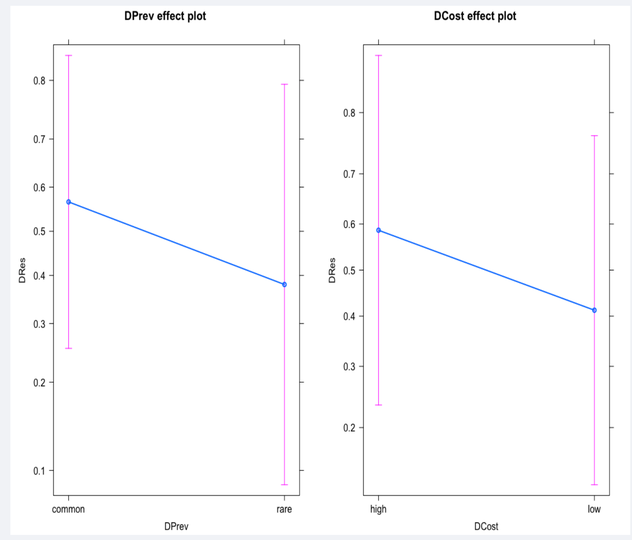
Figure 1: Probability plot Sweden



The results from the logistic regressions did not provide statistically significant results at the 5% significance level, the closest occurring at **p=0.0684** for effect size of disease severity for Sweden as seen in Table 1.

The severity grade and oncology indications would be the most likely to lead to a positive recommendation in both Sweden and Denmark.

Figure 2: Probability plot Denmark



Discussion

The previous DMC process (valid from 2017 to the end of 2020) presented a seven level-scale for the assessment of a product's added value from large to negative added value for the indication relevant to the submission. Most evaluations in this current study were granted a "non-documented added value" status due to lack of comparative evidence for clinical effectiveness. The switch to cost per QALY or cost-utility analysis as a decision tool may allow the DMC to consider indirect comparisons for relative effect and increase the rate of positive recommendations.

Existence of price-agreements between the MAH and the health agencies could be further investigated as an outcome itself, alongside insight into stakeholders' dialogues, which is currently lacking in the publicly available assessment reports. An example of this could be The National Institute for Health and Care Excellence (NICE)'s public records on correspondence and minutes from the dialogue meetings.

Numerous inconsistences in the documentation of the publicly available HTA reports have proved to be a barrier in establishing a measurable outcome. Both countries present thorough guidelines, ranks and scores that are used for the HTA, however, many of these scores were either missing in the available documentation or were used/presented inconsistently. This leads to less transparency of the decision-making process.

Conclusions

Both Sweden and Denmark exhibited unpredictability in estimating the outcome of the HTA processes, with Denmark presenting a more apparent conservative approach, with more negative recommendations. Quantitative results of the parametrizations are inconclusive with the current sample size.

References

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3. NT-rådet, S.K.o.R. *NT-rådet (nya terapier)*. 2022