Cost-effectiveness analysis of invasive EEG monitoring techniques as a preoperative diagnostic procedure in the planning of resective epilepsy surgery in drug-resistant epilepsy patients

PhD Thesis

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I INTRODUCTION

In the past five decades, technological improvements in healthcare have brought about significant breakthroughs across various domains. Technological areas, such as targeted cancer therapy, personalized medicine, advanced imaging diagnostics, different types of joint replacement surgeries, and modern pain management are merely the tip of the iceberg. The proliferation of health-related technologies and the associated rising healthcare costs have catalyzed the rise of a new science-based method, health technology assessment.

Health technology assessment (HTA) is the systematic evaluation of the effectiveness, efficiency, cost-effectiveness, and other attributes of a technology related to healthcare, which addresses the direct and intentional effects, as well as the indirect and unintentional consequences of the technology (Goodman, 2014). The main purpose of technology assessment is to inform health policy makers about the characteristics of a new technology compared to the current standard of care.

Over the last 30 years, the ever-increasing cost of healthcare and the societal expectation to maintain and improve access to high quality health services have stimulated the development of an analytical framework appropriate to health technologies and their application on the policy making level. New technologies increase healthcare costs in a wide variety of ways, often to critical levels, and given the limited budgets available for healthcare spending even in the richest countries, the HTA framework and its application has significantly improved the overall quality of resource allocation decisions in healthcare (Angelis et al., 2018; Drummond et al., 2008). HTA has become the basis for pricing and reimbursement decisions for new drugs and high-cost medical devices. Although, it would be equally important to assess the cost-effectiveness of medical interventions in the clinical setting, the use of HTA methodology in this area is still rare.

Epilepsy is one of the most common neurological disorders (Elger & Schmidt, 2008),with an estimated 50 million people diagnosed worldwide (WHO, 2017). The standardized incidence of epilepsy in Europe ranges from 24 to 82 per 100 000 inhabitants per year (Behr et al., 2016). In Europe, the prevalence of epilepsy varies between countries and demographies, ranging from 3.3 to 7.8 per 1000 people in the general population and 3.4 to 5.8 per 1000 people in pediatric studies (Behr et al., 2016).

Immediate antiepileptic drug (AED) treatment is not required after the first episode of epileptic seizure, it is usually initiated after two or more unprovoked seizures, and with the appropriate medication, 63% of patients remain seizure-free (Kwan & Brodie, 2000). Despite the emergence of new AEDs in the last 15-20 years, approximately 30% of patients with epilepsy experience recurrent seizures and many suffer from adverse side effects. Although, there remain unmet medical needs in the treatment of epilepsy with AEDs alone, and epilepsy surgery can bring about significant seizure reduction or complete seizure control for patients with refractory epilepsy (Kelly & Chung, 2011), surgery for the treatment of epilepsy remains the most underutilized therapeutic intervention (J. Engel, 2016). Although, surgical resection of the affected brain region provides long-term seizure relief, a comprehensive preoperative evaluation is essential prior to surgery, often including functional or metabolic imaging and long-term intracranial electroencephalogram (EEG) monitoring (Jeha, Najm, Bingaman, Dinner, Widdess-Walsh, et al., 2007; Lüders et al., 2006; Spencer & Huh, 2008).

When noninvasive workup fails and routine scalp EEG recording is not sufficient, EEG recording from proximity of the seizure focus is necessary, which can be achieved by placing electrodes on the surface or within the substance of the brain. This procedure requires significant resources on the part of the healthcare provider and the cost of the electrodes used is high, which cannot be covered by the DRG cost of conventional non-invasive monitoring. If the benefits of invasive EEG monitoring to the patient are proportionate to the costs, it ought to be reimbursed from public funds, a decision which must be supported by a health technology assessment. In Hungary, there is no evaluation of health technologies other than medicines, thus the lack of evaluation of a complex medical procedure (preliminary diagnostic examination followed by surgical intervention) limits the availability of scientific evidence for informed decision making in healthcare finance.

II OBJECTIVES OF THE STUDY

The aim of this study is to evaluate the cost-effectiveness of funding invasive EEG monitoring technologies in Hungary, for the purpose of preoperative planning of epilepsy surgery in patients with drug-resistant, MRI-negative, refractory focal epilepsy. Furthermore, this paper aims to support a reimbursement decision by determining whether health gain can be achieved by the use of invasive EEG monitoring interventions, and if so, at what additional cost, compared to the cost of currently used drug treatment, and thus which treatment alternative should be funded to achieve higher societal gains.

For the successful completion of a comprehensive health economic analysis of invasive EEG monitoring, the following research objectives were formulated:

Assessment of the effectiveness of invasive EEG monitoring procedures and potential complications:

- Comparison of the efficacy of invasive EEG monitoring interventions with that of currently used drug treatment by examining the likelihood of seizure-free outcome in MRI-negative, drug-resistant epilepsy patients.
- Comparison of the complication profile of invasive EEG monitoring interventions and currently applied drug treatment.

Assessment of the cost of invasive EEG monitoring procedures:

- Determining the cost of invasive EEG monitoring procedures based on healthcare provider data.

Assessment of the cost-effectiveness of invasive EEG monitoring procedures from the perspective healthcare payer:

- Determination of the health gain (QLAY) and cost of the invasive EEG monitoring alternatives and the standard of care.
- Calculation of the incremental cost-effectiveness ratio of invasive EEG monitoring procedures in comparison to the policy relevant comparator.
- Invenstigation of the impact of uncertain parameters on decision making using a deterministic and probabilistic sensitivity analysis.
- Determination of the aggregate budgetary impact of invasive EEG monitoring procedures.

Summary of changes in the technology assessment framework and their impact on the cost-effectiveness outcome of invasive EEG monitoring procedures:

- Between the technology assessment submission and the finalization of this thesis, the technology assessment framework has undergone significant changes, mainly regarding the cost-effectiveness threshold, and therefore my aim is to present these changes and their impact on the cost-effectiveness outcome.

III THE FRAMEWORK OF HEALTH ECONOMIC ANALYSIS

To optimize the utilization of scarce health resources, the uptake and reimbursement of health-related technologies must be linked to evidence of their efficacy, clinical effectiveness and cost-effectiveness (Rosen & Gabbay, 1999). Different healthcare services are generating different demands in the healthcare system and thus different preferences for these technologies. However, since resources are limited, and supply does not always match demand, new technologies and procedures are always emerging. In 1992, Newhouse showed that technological development is the largest contributor to the increase in health care expenditure (Newhouse, 1992). However, this inevitably leads to a prioritization between different health care technologies (Kristensen & Sigmund, 2007).

In health technology assessment (HTA) the allocation of resources between alternatives in the health sector is a central issue. Therefore, the primary inquiry of HTA concerns the degree to which different technologies generate health improvements and how these gains should be allocated across the society. In this sense, the role of health economic analysis in HTA is to prepare the necessary information on the resource use of different technologies and to compare the health gains they generate. The primary objective of HTA is also to determine whether or not a technology is attractive from social perspective (Kristensen & Sigmund, 2007).

In various countries, the social attractiveness of a technology is made visible through the development of different decision support frameworks. In most European countries, the basis for this decision support framework is provided by guidelines for health economic analysis. In some countries, these guidelines include a so-called cost-effectiveness threshold (CET), which quantifies the acceptable additional cost per unit of health gain. The nominal value of the threshold may vary from country to country and is subject to periodic review, however, for theoretical and practical reasons, its value should reflect the economic performance of the country and the wider economic context in which the country is making its decision to adopt a technology.

IV SCIENTIFIC BACKGROUND

IV.1 DEFINITION, EPIDEMIOLOGY AND THERAPEUTIC MODALITIES OF EPILEPSY

Epilepsy is one of the most common neurological conditions (Behr et al., 2016; Elger & Schmidt, 2008), a chronic central nervous system disorder whose main clinical feature is recurrent, shorter or longer seizure-like events (epileptic seizures) that usually occur spontaneously and resolve spontaneously. The development of epilepsy is the result of pathological processes that cause a persistent and abnormal increase in neuronal excitability. Epilepsy is considered to be a disease if the epileptic seizures occur recurrently without a recognizable provoking condition. However, the diagnosis of epilepsy can be made on the basis of a single unprovoked seizure if there is a high probability of seizure recurrence (Az Egészségügyi Minisztérium szakmai irányelv, 2008).

The manifestation of an epileptic seizure is determined by the anatomical localization and pathophysiological mechanism of the epileptogenic zone (EZ). The severity of epilepsy is mainly but not exclusively determined by seizure frequency and partly by seizure form (Magyar Epilepszia Liga, 2008).

The age-specific incidence of epilepsy is between 0.4-1.0‰, shows a bimodal distribution with the highest peak in childhood and then decreasing until adolescence, followed by a late peak after the age of sixty (Behr et al., 2016; Kotsopoulos et al., 2002). As epilepsy often lasts for decades, the cumulative incidence towards the end of life reaches 3-5.0%. The point prevalence of epilepsy in the Hungarian population is between 0.5-1.0% on average (Magyar Epilepszia Liga, 2008). Epilepsy affects 0.3-0.6% of the population in developed industrial countries, thus it is assumed that there are 50-60 thousand epileptic patients in Hungary (Péntek et al., 2013).

In general, patients with epilepsy disorder are treated with medication, called antiepileptic treatment. Drug-resistant epilepsy, also named intractable epilepsy or refractory epilepsy, is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom (French, 2007; Kwan et al., 2010, 2011). In these patients, although it does not provide complete seizure freedom, drug therapy should be sustained, as the drug discontinuation can cause life-threatening state of status epilepticus. Third and subsequent courses of adjunctive antiepileptic therapy provide seizure remission in 3-4% of patients (Choi

et al., 2008, 2011).The proportion of drug-resistant cases is 23-30% (Banerjee et al., 2009; Marson et al., 2005; Mula & Cock, 2015; Remy & Beck, 2006a), which represents at least 7,000-18,000 patients in Hungary.

Of drug-resistant epilepsy cases, 17-34% are MR-negative, and in these cases, no specific epileptogenic lesion can be confirmed by cranial MRI scan performed according to the epilepsy protocol (Alarcón et al., 2006; Chapman et al., 2005; Jeha, Najm, Bingaman, Dinner, Widdess-walsh, et al., 2007; Lee et al., 2005; Lerner et al., 2009; Remy & Beck, 2006b). Based on the above ratio, there are at least 1,500-6,000 MR-negative drug-resistant epilepsy patients in Hungary.

There are several treatment options for patients with epilepsy, including medical treatment surgery and other procedures. The basic aim of treatment is to achieve seizure freedom and improve quality of life. Between 60 and 70% of epilepsy patients become seizure-free with appropriate antiepileptic drugs (Kwan & Brodie, 2000). However, there are epilepsy syndromes, in which surgical therapy outperforms pharmacotherapy. In case of surgery eligible epilepsy, the possibility of surgical treatment should be considered after the failure of the first two adequate trials of antiepileptic drug treatments (Magyar Epilepszia Liga, 2008).

In general, long-term seizure freedom is ensured by resection of the brain area, affected by the epileptic focus (Jeha, Najm, Bingaman, Dinner, Widdess-Walsh, et al., 2007; Lüders et al., 2006; Spencer & Huh, 2008). In cases where non-invasive techniques fail to localize the epileptogenic zone (MR-negative cases), an EEG recording from the proximity of the seizure focus is necessary, which can be achieved by placing electrodes on the surface or within the substance of the brain (Shah & Mittal, 2014).

IV.2 DESCRIPTION OF THE NEW PROCEDURE TO BE INTRODUCED INTO CLINICAL PRACTICE

Long-term video-EEG monitoring is a standard tool for determining the type of epileptic seizures and the diagnosis of epilepsy. Over the last 30 years, in addition to noninvasive scalp EEG studies, long-term invasive EEG monitoring procedures have been developed, which can be used even in cases of extratemporal localization of, and/or MR negative epileptic foci. The main reason for the application of this monitoring procedure is that surgical removal of the epileptic focus provides a better, long-term outcome than the comparator drug therapy (Téllez-Zenteno et al., 2010; Wiebe et al., 2001).

Patients with MR-negative and MR-positive drug-resistant epilepsy may become operable by a 2-step surgical procedure using stereotaxic EEG monitoring (SEEG) and/or invasive EEG monitoring with subdural strip/grid electrodes (SDG) complemented with electrocorticography (Serletis et al., 2014; Taussig et al., 2014; Yang et al., 2017). SEEG and SDG are invasive, exploratory diagnostic procedures that can be indicated based on electroclinical data, as well as the results of cranial MRI and FDG-PET studies conducted according to the epilepsy protocol.

V METHODS

V.1 DEVELOPMENT OF MODEL CONCEPT

Using Cost-effectiveness Analysis Registry[1] (CEAR), Scopus and the NHS Economic Evaluations Database[2], we come to the conclusion that no cost-effectiveness analysis has yet been conducted regarding the utilization of invasive EEG intervention, as a stand-alone localization modality in the planning of epilepsy surgery. However, we have been able to identify two publications that analyze the cost-effectiveness of localization strategies used to identify the epileptogenic focus. Our model concept was based on the decision support and cost-effectiveness analysis developed and published by Burch et al., 2012. In our approach, we focused on determining the cost-effectiveness of stereotaxic EEG monitoring and developed a more detailed model representing the complexity of the disease (Kovács et al., 2021).

V.2 EFFECTIVENESS, SAFETY AND HEALTH-RELATED UTILITY OF THE INVASIVE EEG INTERVENTION

In epilepsy, the efficacy of different therapies is measured by the ratio of seizure-free population resulted from the intervention (Engel Class I) and the duration of this state, measured with progression-free survival. The Engel classification was used to describe the seizure state after epilepsy surgery (J. J. Engel et al., 1993).

Literature data on the efficacy and safety of invasive EEG diagnostics in preoperative epilepsy screening were identified by a targeted and reference-based literature search using a PubMed database. Synonyms for the terms of invasive EEG procedure and effectiveness or safety were used in our search, and no further restrictions were applied to see the widest possible range of results.

[1] http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx
[2] NHS Economic Evaluations Database available from https://www.crd.york.ac.uk/CRDWeb/

Experts in neurology and neurosurgery from the University of Pécs (PTE) and the National Institute of Clinical Neuroscience (OKITI) were involved in the targeted literature search, as well as in the evaluation of the articles and the data validity.

V.3 VALIDATION OF THE DATA USED IN THE MODEL THROUGH PROPRIETARY META-ANALYSIS

Given the identified limitations and uncertainty in modelling the effectiveness of invasive EEG monitoring, we conducted our own meta-analysis to evaluate the effectiveness of interventions, which we used to independently validate the transition probability variables used in our model.

V.4 RESOURCE USE AND UNIT COSTS

The resource utilization data used in the model were collected during the intervention performed at the Neurology and Neurosurgery Clinics of the University of Pécs Clinical Centre. To better identify the de facto resource utilization, the whole process of the intervention was divided into sub-processes, and the resource use was monitored for each sub-process. The unit cost for each cost component was calculated based on the actual costs retrieved from the accounting system of the University of Pécs.

The total direct cost of the invasive-EEG interventions was calculated as a product of resource use and unit cost. Indirect department costs, overheads and common costs were allocated separately on a per diem bases.

V.5 SENSITIVITY ANALYSES

The deviation of results arising from the uncertainty of the model parameters were tested in a series of deterministic and probabilistic sensitivity tests. In the deterministic sensitivity analysis (DSA), we tested the effect of the variables on the incremental cost-effectiveness index by varying the variables of the model one by one.

In the probabilistic sensitivity analysis (PSA), we ran 1000 simulations in the Monte Carlo analysis to obtain the corresponding incremental cost and QALYs for each simulation. These simulations were also used to calculate the cost-effectiveness acceptability curve (CEAC) for the SEEG and SDG interventions, which show the probability of cost-effectiveness for each alternative at different values of the cost-effectiveness threshold.

VI RESULTS

VI.1 EFFECTIVNESS AND COMPLICATIONS

VI.1.1 EFFECTIVENESS (SEEG)

Despite the increasing utilization of invasive EEG monitoring to determine the epileptogenic zone prior to epilepsy surgery in MR-negative drug-resistant patients, the quality of clinical trials and the level of evidence has not followed this change. In our search, we found neither a randomized clinical trial of adequate quality nor a meta-analysis. However, by conducting a detailed review of the literature cited in these publications, we identified a large number of monocentric trials (Cohen-Gadol et al., 2006; Devaux et al., 2008; Elsharkawy et al., 2009; Gonzalez-Martinez et al., 2014) whose outcome data we were able to use to model the SEEG procedure.

In case of SEEG intervention, based on Cohen-Gadol's results, the probability of a seizure-free outcome after the 1st year of surgery is 0.800, decreasing to 0.760 by the end of 2nd year and 0.740 from 5th year onwards. For extratemporal localization, the probability of a seizure-free outcome after the 1st year of surgery is 0.420, which does not decrease at later time points.

VI.1.2 EFFECTIVENESS (SDG)

We were unable to identify any meta-analysis of subdural strip and grid EEG monitoring in the literature, therefore, we examined the results of individual studies and applied MacDougall's results (Bulacio et al., 2012; MacDougall et al., 2009; Mullin, Sexton, et al., 2016; Vadera et al., 2013). Based on MacDougall's results, the probability of seizure-free outcome one year after the operation for temporal localization is 0.5254, decreasing to 0.4653 at the end of 2nd year. For extratemporal localization, the probability of a seizure-free outcome after surgery at the 1st year is 0.4075, while at the end of the second year it is 0.3608. In our SDG model, we extrapolated these efficacy results under the assumption that the probability of a seizure-free state does not decrease further after the second year.

VI.1.3 VALIDATION OF THE EFFECTIVENESS DATA OF INVASIVE-EGG INTERVENTIONS

Using the results of 31 'single arm' observational studies, we also used our proprietary meta-analysis to estimate the rate of all resective surgery performed after iEEG monitoring and the rate of seizure-free outcome in follow-up cases (Toth et al., 2019). 19 articles containing 1025

SDG-interventions and 16 publications comprising 974 SEEG-monitors were selected for analysis. The rate of resective surgery deriving from SDG-monitoring hovered 88.8% (95% CI: 83.3%-92.6%), whereas in the SEEG group it was 79.0% (95% CI: 70.4%-85.7%).

In SDG-group, ratio of Engel I seizure-free outcome reached 55.9% (95%CI:50.9–60.8%) while using SEEG-monitor and seizure-freedom occurred in 64.7% (95%CI:59.2–69.8%). The difference in seizure-free outcome between SEEG and SDG groups was statistically significant (p=0.02). In the temporal subgroup, ratio of Engel I seizure-free outcome was found to be 56.7% (95%CI:51.5%–61.9%) in SDG group; while the SEEG-group reached 73.9% (95%CI:64.4%–81.6%). The difference between seizure-free outcomes was statistically significant (p=0.002) for temporal localization.

For extratemporal localization, the Engel I outcome rate was 46.7% (95% CI: 36.5%-57.2%) in the SDG group and 61.0% (95% CI:51.0%-70.2%) in the SEEG group. Although the difference in seizure-free outcomes for extratemporal EZ localization is borderline, no statistically significant difference was detected at α=0.05 level (p=0.053).

Since the data presented above were not yet published at the time of the reimbursement procedure of invasive EEG, we only included them as a separate extreme scenario in our model and used them in the procedure only to validate the model inputs we used.

VI.1.4 COMPLICATIONS (SEEG)

The probability of complications in SEEG intervention was taken from the previously mentioned analysis by Mullin et al. (2016), which identified 30 publications using a systematic literature search and synthesized the results using a meta-analysis method.

Based on this publication, the most common complications during SEEG intervention are bleeding complications (intracerebral haemorrhage [ICH], subdural haematoma [SDH], epidural haematoma [EDH]), with an overall prevalence of 1.0% (95% CI 0.6-1.4%) and the prevalence by type is 0. 7% (95% CI 0.3-1.0%) for ICH, 0.4% (95% CI 0.1-0.7%) for SDH, and 0.3% (95% CI 0.1-0.6%) for EDH. In addition to these complications, various infectious complications may occur, with an overall prevalence of 0.8% (95% CI 0.3-1.2%).

VI.1.5 COMPLICATIONS (SDG)

Based on the literature, it is evident that the complication rate of the SDG intervention is much higher than that of the SEEG intervention, but the type of complications is the same (Arya et al., 2013; Hedegärd et al., 2014; MacDougall et al., 2009; Yang et al., 2017). Based on

Hedegard and Arya's publication, the overall morbidity rate during SDG intervention is 13.6%. The most common complications are bleeding complications (subdural haematoma [SDH], epidural haematoma [EDH], intracerebral haemorrhage [ICH]), with an overall prevalence of 4.4%. The prevalence by type was 0.7% (95% CI 0.3-1.0%) for ICH, 0.4% (95% CI 0.1-0.7%) for SDH, 0.3% (95% CI 0.1-0.6%) for EDH. These complications were accompanied by various infectious complications, with an overall prevalence of 5.9%.

VI.2 DIRECT COSTS

The intervention can be divided into 5 homogeneous sub-processes in terms of costs, summarized in *Figure 1*. The resection surgery in the case of SEEG intervention is most likely to be performed during a third independent surgery, but without the surgery the clinical impact of the diagnostic intervention would not be validated, so the costs of this surgery are included in my analysis. Furthermore, in the SDG intervention, most often the removal of electrodes and cortectomy are performed in one surgery, as the strip and grid electrode insertion require a craniotomy. The cost of resective surgery was calculated from the DRG weight of "002A Major intracranial surgery over 18 years, non-trauma" and of the unit cost of DRG weight.

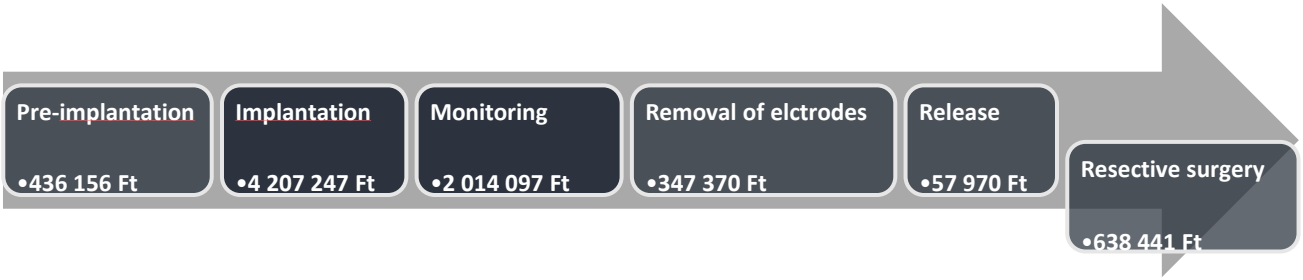

Figure 1: The costs of the relevant sub-processes of SEEG diagnostic process.

In addition to the cost of managing complications during the intervention and post-intervention period, the only additional direct cost that could be considered was the cost of medication use of patients in different Engel classes, for which data were provided by neurological and neurosurgical specialists at the National Clinical Neuroscience Institute (OKITI), in an anonymized form. Based on the data from the 53 patients available, the average monthly medication cost for patients before the intervention was HUF 25,671.3, while after the intervention this cost decreased to HUF 8,269.8 for patients with an Engel class I seizure-free outcome and to HUF 20,993.4 for patients with a worse outcome. The reduced drug costs were considered from the 13th month after the intervention.

VI.3 INCREMENTAL COST-EFFECTIVNESS RATIO (BASE CASE)

Our model's output data show that the net present value of invasive EEG intervention – using only deep electrodes – containing the consequent epilepsy surgery and drug utilization over the modelled period is 10,470,000 HUF, while the total cost of the comparator drug treatment arm, using the same discounting procedure, is 4,689,000 HUF. Accordingly, the incremental cost of the intervention is 5,781,000 HUF. However, on this incremental cost it provides an additional 3.978 quality-adjusted life years over the modelled 30-year time horizon, compared to the drug treatment. Thus, the ICER of the intervention is 1,453,000 HUF per QALY. According to the cost-effectiveness threshold in Hungary for 2017-2021, which was around 12.5 million HUF, invasive EEG monitoring is cost-effective (*Figure 2*).

Incremental Cost Effectiveness Ratio of iEEG interventions					
	Cost	**QALY**	**Incremental Cost**	**Incremental QALY**	**ICER**
Medical Management	4 688 718 HUF	8.304			
SEEG	10 469 954 HUF	12,282	5 781 237 HUF	3.931	1 453 000 HUF per QALY
SDG	8 064 197 HUF	11,558	3 375 480 HUF	3.444	1 038 000 HUF per QALY

Figure 2: Summary of ICER values for the iEEG intervention.

By running the model with SDG specific setup, using solely subdural strip and grid electrodes, the incremental cost of the intervention is 3,375,000 HUF, which translates into an additional 3.253 QALY gain. Thus, the ICER of the intervention is 1,038,000 HUF, and despite the lower QALY gain, due to the lower cost of the electrodes SDG intervention, is also cost-effective.

According to the new HTA guideline, which came into force in November 2021, in order to establish cost-effectiveness, the incremental relative QALY gains (IRQG) must first be calculated, where the numerator is the effect size (difference in QALY of new and comparator treatment), and the denominator is the expected QALY provided by the new treatment. The value of the IRQG indicator for both the SEEG and SDG interventions ranges from 0.25 to 0.60, so the cost-effectiveness of both interventions should be compared to twice the GDP per capita, as a cost-effectiveness threshold. Based on the currently available 2020 GDP per capita data, the threshold is ~8.3 million HUF. Thus, the interventions are cost-effective even at this threshold.

VI.4 SENSITIVITY ANALYSES

VI.4.1 DETERMINISTIC SENSITIVITY ANALYSIS

In the univariate deterministic sensitivity analysis, all input parameters were included, with the addition that in the case of complementary parameters, only one variable was changed, while the complementor was adjusted accordingly. We reduced and increased the values of the transition probabilities, the mortality and utility parameters by 10% and the values of the cost parameters by 25%, which provided the lower and upper bounds for the sensitivity test. To evaluate the effect of parameters' uncertainty on ICER, one-way deterministic sensitivity analyses (DSA) were performed, and the result was visualized on a Tornado diagram (*Figure 3*).

Out of 31 parameters, only 11 had noteworthy effect on the ICER, representing at least 50,000 HUF decrement or increment in ICER. For SEEG, the most influential parameters were utility in seizure-free state, cost of monitoring procedure, cost of disposable electrodes, followed by the probability of resective surgery given a successful EZ localization, successful localization of EZ and medication cost of patients in disabling seizure state. For SDG, the cost of monitoring procedure and the probability of patients remaining in DS state after surgery were the most significant parameters. However, these changes in parameters did not lead to a substantial change in the ICER. The parameter uncertainty therefore had no considerable influence on the evaluation of cost-effectiveness.

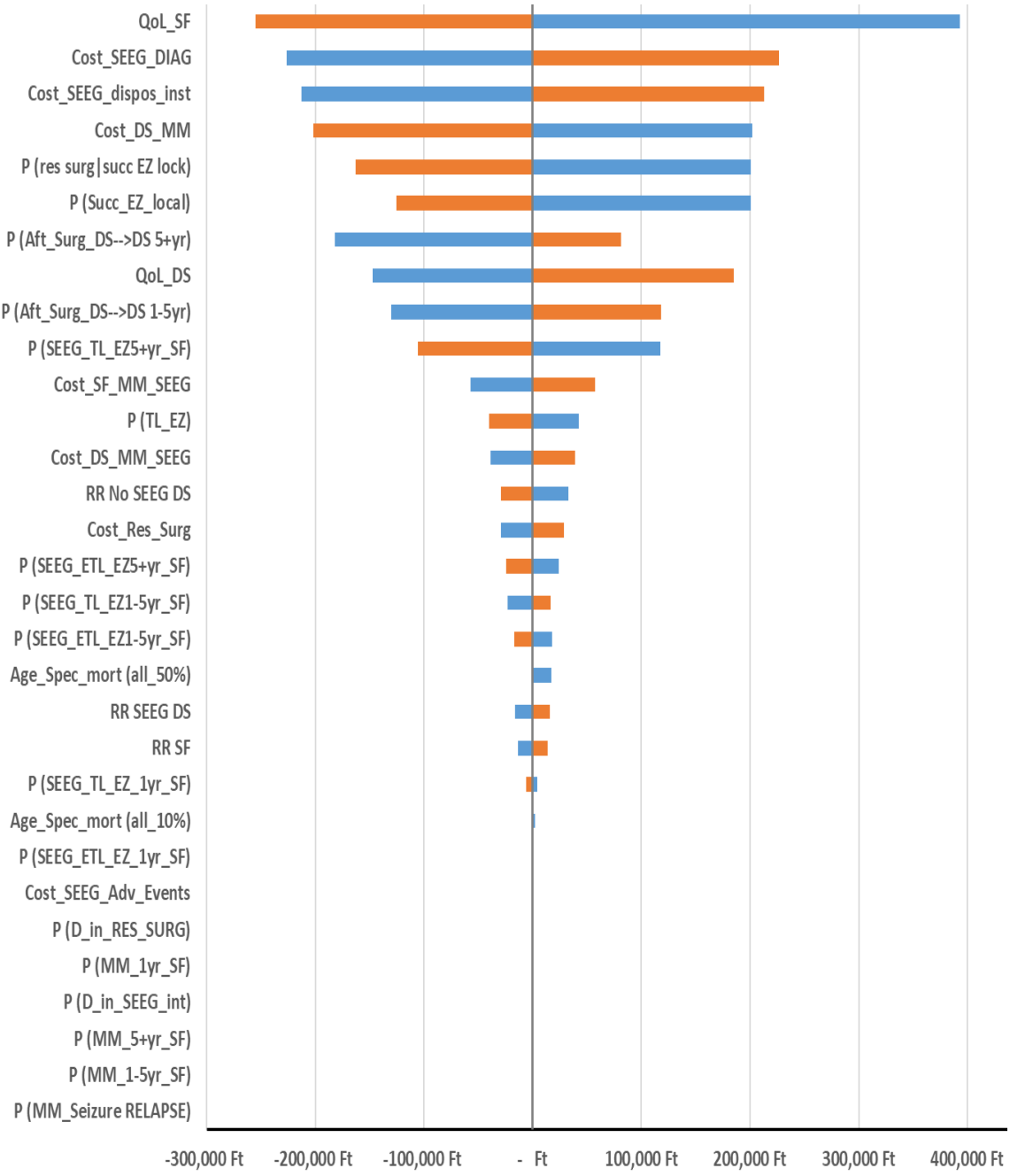

Figure 3: Tornado diagram of SEEG intervention

VI.4.2 PROBABILISTIC SENSITIVITY ANALYSIS

Based on the detailed probabilistic sensitivity analyses, 99,5% and 99,7% of simulation resulted in a cost-effective outcome for SEEG and SDG intervention respectively. The vast majority of the Monte Carlo simulations are below 41,000 € per QALY showed by scatter plot in the cost-effectiveness plane for both SEEG and SDG interventions separately (*Figure 4, A, B*).

The cost-effectiveness acceptability curves show that the inflection point of the function is around 1,200,000 HUF for SEEG and 800,000 HUF for SDG, which means that above these willingness-to-pay threshold limits, the corresponding intervention is cost-effective compared to medical management (*Figure 4, C, D*).

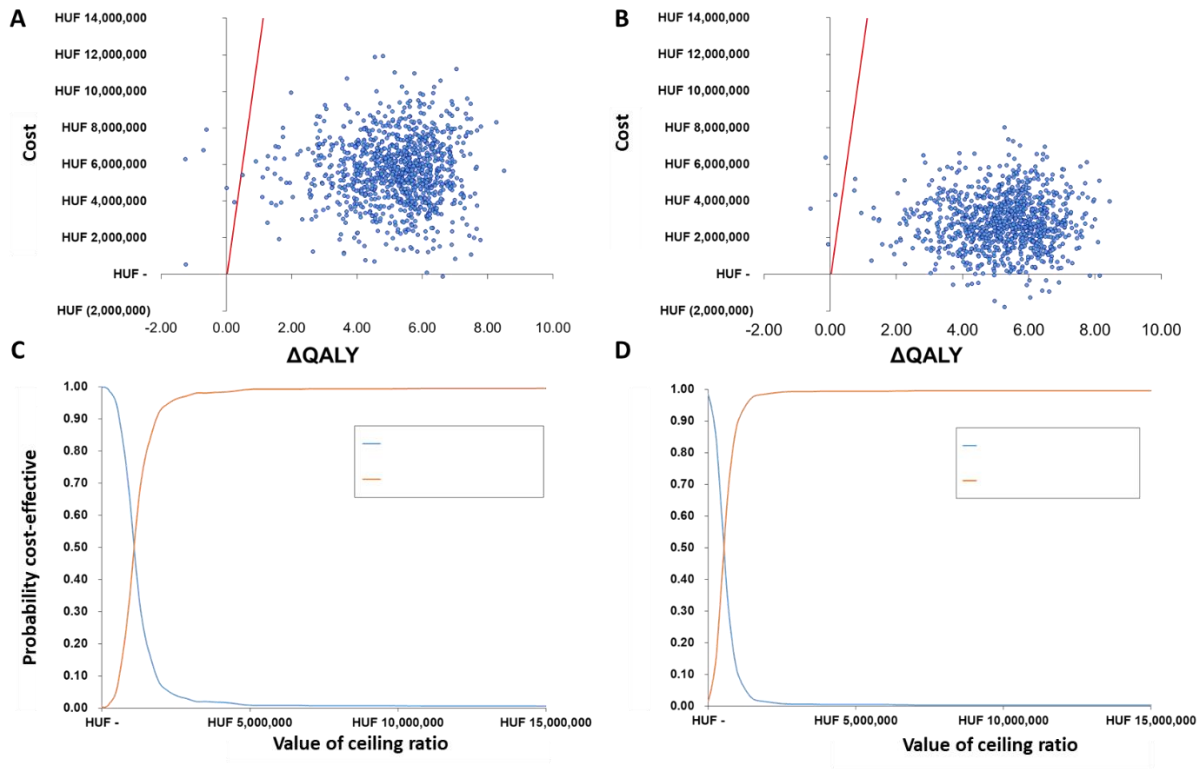

Figure 4: Probabilistic sensitivity analysis results of SEEG (A) and SDG (B) interventions. The line going through the origin represents the willingness-to-pay threshold/QALY; Cost-effectiveness acceptability curve of SEEG (C) and SDG (D) intervention. Y-axis: The probability of accepting the given intervention as a cost-effective technology for a given willingness-to-pay threshold; X-axis: The decision makers' willingness-to-pay threshold per QALY. In Hungary, the threshold was three times the GDP capita between 2017 and 2021 (12.5 Million HUF in 2020)

With the new threshold of 8.3 million HUF/QALY introduced in the new HTA guideline, which came into force in November 2021, 99.3% and 99.6% of the SEEG and SDG simulations are cost-effective. This means, that lowering the threshold by one-third did not significantly affect the cost-effectiveness of the interventions, as the ICER of the baseline model is still substantially lower than the new threshold.

VII DISCUSSION

The results of this analyses showed that in Hungary, the introduction of iEEG diagnostic interventions into the presurgical workflow of drug-resistant epilepsy is cost-effective compared to medical management. Furthermore, ICER of iEEG interventions remained well below the cost-effectiveness threshold in both sensitivity analyses and extreme scenarios, regardless of the electrode used in the intervention and the change in threshold in November 2021. For deep brain electrodes, the ICER is 370,000 HUF higher than for subdural electrodes, but still below 1.5 million HUF. This ICER value is one sixth of the cost-effectiveness threshold, indicating that despite the high costs, the intervention can provide significant health gains in the indicated patient population. The significant health gain provided by the intervention can be realized as the equivalent of an aggregated budgetary impact of 880,000,000 HUF over 4 years.

Based on these results, the intervention has the potential to increase the efficiency of the health care system, as it provides significantly higher health gains with higher resource utilization. Furthermore, the intervention aims to eliminate the disease or the cause of the complaints by the localization of EZ, rather alleviating the symptoms, as is the case with comparator drug treatment.

Based on our model and analysis, the National Healthcare Fund Administration has already recognized and confirmed the cost-effectiveness of iEEG intervention compared with medical therapy in MRI-negative, refractory focal epilepsy patients.

VII.1 LIMITATIONS OF OUR ANALYSIS

Besides its strengths, several limitations of our model should be considered. First of all, we have to emphasize that the available literature on the short- and long-term effectiveness of invasive epilepsy monitoring on the quality of life in epilepsy and the corresponding utility values, are highly fragmented, representing a lower level of evidence (Burns et al., 2011). However, considering the fact that the number of randomized clinical trials for surgical and invasive procedures is low due to the characteristics of the intervention, we can conclude that we were able to use good evidence to the extent possible.

We have included additional new data and treatment options to the model described by Burch et al. (2012), which serves as a predecessor to our work, making our model suitable for analyzing a broad spectrum of iEEG methods, as well as providing the opportunity to

incorporate additional testing modalities. However, it should be emphasized, that this extension also implied the introduction of restrictive conditions, which are limiting factors for the model results. The constraints we have applied are the following:

- All patients were assumed to comply with invasive procedures, with no associated uncertainty. Thus, the short model is based on a cohort, in which every patient is eligible for the SEEG intervention and there is no attrition due to noncompliance.
- The model is based on the work of Choi et al., 2008, and Burch et al., 2012, to which we have added new data for adaptation, hence all their limitations are considered valid for our own work. These limitations serve to ensure the fitness of the available data, complemented by a strict restriction on the patient population.
- The identified meta-analyses (Hotan et al., 2016; Mullin et al., 2016) were mainly used to develop the model structure, due to the identified discrepancies, while model input data were extracted from individual studies where the patient population, clinical outcome, number of elements and follow-up were appropriate.
- Mortality due to a respective surgery is assumed to be the same for temporal lobe and extratemporal lobe localization.
- In the cases of invasive monitoring and all surgical technologies, it is assumed that the technology is already in place, such that the cost considered is equal to the marginal cost.
- We further assumed that all of the relevant expertise exists as spare capacity, such that there is no ‘learning-curve’ associated with the implementation of SEEG intervention.
- In the long-term Markov model, iEEG patients who enter a seizure-free state after 1 year discontinue their antiepileptic drugs (AEDs) according to clinical protocols.
- Owing to limitations in the available data, it is assumed that patients who are taken off AEDs in our model have the same mortality and the same transition probabilities as those who are still on AEDs.
- The samples considered in the different source studies are assumed to be representative of the population investigated in our decision problem.

VIII NEW SCIENTIFIC RESULTS

The research presented in this dissertation sought to answer the questions detailed in the research objective. Based on the conclusions drawn from our investigations, the following new scientific findings have been made:

1. In Hungary, among drug-resistant, MRI-negative, refractory focal epilepsy patients, invasive EEG monitoring techniques are considered more effective than standard drug therapy in terms of seizure-free outcome and have a lower complication rate.
2. We determined the resource utilization and cost of iEEG intervention in an itemized data collection at the Neurology and Neurosurgery Clinics of the University of Pécs Clinical Centre.
3. We demonstrated that based on the Hungarian cost structure and therapeutic practice, iEEG intervention is cost-effective compared to standard drug therapy in an MRI-negative refractory focal epilepsy patient population.
4. This ICER of the intervention is one-sixth of the cost-effectiveness threshold, indicating that the intervention, despite its high costs, can provide significant health gains in the indicated patient population.
5. Furthermore, we have shown that the ICER of the iEEG intervention remains well below the cost-effectiveness threshold in both sensitivity tests and extreme scenarios.
6. In line with the recommendations of our research team, a new HTA guideline were introduced in 2021. Under this framework, the cost-effectiveness of a new health technology is assessed by calculating the incremental relative QALY gain (IRQG) indicator where the numerator is the effect size (difference in QALY of new and comparator treatment), and the denominator is the expected QALY provided by the new treatment.
7. Finally, we have shown that the iEEG intervention remains cost-effective under the new HTA guideline.

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X LIST OF PUBLICATIONS

X.1 ARTICLES RELATED TO THE THESIS:

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