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ANALYSIS OF REIMBURSEMENT DECISIONS AND IMPROVING THE APPRAISAL METHODS OF INNOVATIVE MEDICINAL PRODUCTS

Ph.D. thesis

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADT	Androgen Deprivation Therapy
BC	Base Case
CAB	Clinical Added Benefit
CAV	Clinical Added Value
CASP	Critical Appraisal Skills Programme
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
eBC	Early Breast Cancer
ERG	Evidence Review Group
ESMO-MCBS	European Society for Medical Oncology - Magnitude of Clinical Benefit Score
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
IFR	Individual Funding Request
ITT	Intention-to-treat
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LoE	Level of Evidence
MAH	Marketing Authorisation Holder
MAIC	Matching-Adjusted Indirect Comparison
MPM	Malignant Pleural Mesothelioma
NHIFM	National Health Insurance Fund Manager
NICE	National Institute for Health and Care Excellence
NIPN	National Institute of Pharmacy and Nutrition
NSCLC	Non-Small Cell Lung Cancer
OR	Odds Ratio
PICO	Patients, Intervention, Comparison, Outcome
RCT	Randomised, Controlled Trial
RoB	Risk of Bias
RSA	Risk Sharing Agreement
ScA	Scenario Analysis
SLR	Systematic Literature Review
SOP	Standard Operating Procedure
STC	Simulated Treatment Comparison
VoI	Value of Information

1 INTRODUCTION

Health systems all over the world struggle how to provide better quality and more accessible health services to the whole population within the limits of available resources. Long term trends, such as ageing and the rise of non-communicable diseases and short term external shocks, such as the COVID-19 pandemic all aggravates this tension, in the alleviation of which efficiency improving social innovations play a key role (1).

Innovative pharmaceutical products are essential in enhancing the ability of health systems to tackle previously incurable diseases, but they usually come at a high cost, which puts further pressure on the budget of publicly financed healthcare. How the public benefit package is expanded, therefore, has a fundamental impact on the quality, accessibility and efficiency of health service. Studying the impact of various factors influencing the inclusion decisions is important to achieve these health policy objectives, so that the benefit package contains those technologies, which maximize health gains within the constraints of the available funding. These factors may simply be categorised as external and internal, depending on whether we are talking about intrinsic features of the product, such as its efficacy, effectiveness or cost (internal factors), or factors that are related to the context of reimbursement decisions, such as certain financing agreements between the marketing authorisation holder (MAH) and the payer (external factors). Optimally, internal factors should play the most important role in the decision of including an innovative pharmaceutical among reimbursed technologies, but how internal and external factors influence the outcome of the decision making process has been largely unexplored so far in Hungary.

The reimbursement decision on innovative pharmaceutical products may depend on certain parameters concerning the direct financial environment of each submission. Confidential risk-sharing agreements (RSAs) between the MAH and the payer, or the uptake of the technology preceding its reimbursement in routine practice through individual funding requests (IFRs) are factors that create information asymmetry and can possibly influence the outcome of the reimbursement decision. However, scientific evidence is lacking on the association between the outcome of the decision and the impact of IFR volume, or the interaction on RSAs with IFRs. The impact of RSAs has already been evaluated by researchers with specific focus on Central and Eastern European countries. Some emphasized their importance in broadening access to innovative therapies in settings with budgetary pressures (2). Others endorsed the use of both financial- and outcome-based agreements in Hungary as a confidential way to manage price, to

mitigate budget impact, and also to address uncertainty about the clinical value of a pharmaceutical product while expressing criticism on the lack of monitoring and evaluation, as well as their sustainability as a financial mechanism (3). The role of IFR volume in reimbursement decision-making has not been evaluated so far with similar details. These financial and procedural mechanisms that are enabling access to innovative pharmaceuticals can impact some reimbursement decisions as well. We may assume that if an agreement is in place for indication „A", it is expected that the payer is more likely to engage in further negotiations, and to decide on reimbursement for new indication „B" of the same product. This may occur as there is already an established net price to start negotiations with, as well as data is available on the uptake of the product. Some agreements are reported to cover pharmaceuticals, which are not routinely reimbursed, but available via IFRs. Handling these applications on a case-by-case basis might be burdensome due to administrative capacity constraints of the financing agent.

Independently from the aforementioned mechanisms, reimbursement decisions should ideally consider the information generated by health technology assessment (HTA) which is an evidence-based scientific method used to assess the added value, and ultimately, facilitate the reimbursement of efficient and affordable health technologies (4). HTA covers, among others, clinical and economic domains that are addressed as part of the local reimbursement procedures in a number of countries or regions in Europe. As for the scope of HTA, the procedure itself can be described as "proactive" or "reactive", depending on whether a governmental body acting as a purchaser selects the technologies for assessment; or the MAH is the entity who initiates the procedure by submitting a reimbursement dossier that eventually requires a formal assessment and critical appraisal (5). From this aspect, the legal framework of HTA in Hungary can be characterised as "reactive", as the public administration itself does not conduct full assessments, but critically appraises manufacturer submissions (6), contrary to the proactive HTA systems of Germany or the United Kingdom. In order to assess the clinical and economic aspects of a pharmaceutical product, national law requires the MAHs to submit a reimbursement dossier for the local payer to obtain financing. In addition to administrative information, the local submission dossier includes a summary of the available clinical data, a cost-effectiveness analysis of the technology and a budget impact analysis as well. An economic model must also be submitted, if it was used to conduct the cost-effectiveness analysis. The legal obligation to submit these documents and analyses is set out in a ministerial decree (7), whereas the local recommendations for conducting health economic evaluations are set out in a methodological

guideline (8). The MAH prepares the analyses alongside the recommendations of this methodological guidance; the local HTA body (the Department of Health Technology Assessment, operating at the National Institute of Pharmacy and Nutrition (NIPN)) is expected to validate the submitted clinical data and the economic analysis to the same recommendations through the assessment procedure.

The local HTA body produces a non-binding assessment report for each submission dossier, serving as a basis for the critical appraisal of the submitted clinical and economic evidence. The critical appraisal of reimbursement dossiers has been a core component of the local assessment procedure in Hungary since the institutionalisation of HTA in 2004. The assessment reports are issued for each pharmaceutical product, medical aid or medical device submitted for reimbursement under the appropriate administrative procedure, covering internal factors, more precisely, clinical (health problem and current use of technology; clinical effectiveness; relative efficacy) and economic (costs and fiscal aspects, including budget impact) domains, although other (most frequently, organisational) aspects can be presented occasionally. The report has a section on conclusions, yet it does not provide an explicit proposal on whether or not to reimburse a particular product, but rather a general description on the expected benefit of the technology, incremental costs, outcomes and consequently, cost-effectiveness and budget impact. It is possible that the criticism over the potential of the assessment reports for supporting evidence-based decision-making not being fully realised (9) is partially rooted in the lack of a well-established methodological approach for preparing the assessment report.

There is a personal motivation to carrying out this research to improve the local assessment procedure methodology. First of all, one may doubt the added value of formal assessment considering the frequently echoed capacity constraints to the entire critical appraisal procedure. Moreover, with limited control over the contents of the MAH's submission dossier and confidential price discounts embedded in RSAs managed by the payer, one might also question what benefit does improving the local HTA methodology hold. However, we can also conclude that assessors working at the HTA body are considered highly qualified professionals with a drive of pursuing scientific excellence in their field, and therefore external circumstances in themselves should not discourage the development of an assessment procedure that helps evidence-based decision making in healthcare. Second, the assessors' supervisor has the responsibility of coming up with methods facilitating the efficient production and streamlined quality assurance of assessment reports. In other words, assessors are only able to deliver if they are aware of the expectations prior to their contribution and possess the necessary tools to

fulfil these. It is the interpretation of the author that improvements to the critical appraisal procedure initiated by the HTA body are essential both due to internal motivation and from an organisational viewpoint as well.

1.1 Potential determinants of the reimbursement decision

It is unknown if the critical appraisal conclusion has already been formally studied as a determinant of the reimbursement decisions in Hungary, or whether any efforts have been made to operationalise these as potential factors considered in the assessment procedure. Therefore, as an initial step, the current body of evidence needs to be reviewed.

For this purpose, a literature review was conducted. A systematic review implies the development of a unique and often complex strategy, covering the aims of the current research. In order to retrieve the most relevant publications on the local critical appraisal methodology and determinants of the reimbursement decision, a literature search was conducted using the MEDLINE and EMBASE databases. The search was carried out on the 28th of September 2022, with the aim of identifying publications that examine the relationship between the HTA, critical appraisal and reimbursement of pharmaceutical products in Hungary. The search term and flow diagram of the literature review is presented in Appendix 1. Due to the nature of this research, neither the description of the risk of bias and nor carrying out a quantitative analysis of results were feasible. After identification, screening, and review, only two publications were found to be relevant to this study and included in the qualitative summary and presented in this thesis. As part of the literature review, differences among the legal frameworks of HTA were not addressed, as these are set out by legal acts rather than publications.

Vončina and colleagues (10) reviewed the existing literature and conducted interviews on the pricing and reimbursement systems of South-Eastern European countries, as well as Hungary, with an emphasis on the assessment and appraisal process among other features of the systems. When discussing the results of their research from Romania, Bulgaria and Hungary, the authors take note of the availability of the formal criteria set out for the appraisal of submission dossiers. However, they also claim that prioritisation of submissions between competing products is arbitrary in the absence of practical guidelines or criteria, and there is some chance that this results in over-relying on budget impact aspects. As a conclusion, the authors call for defining simple, transparent and robust decision-making frameworks to strengthen pricing and reimbursement systems that increase access to innovative pharmaceutical products while also ensuring affordability.

The article of Inotai and colleagues (11) reported the development of a checklist to address the most common problems in the economic evaluations and budget impact analyses submitted as part of reimbursement dossiers in Hungary. The authors created a panel of experts (of academics and assessors from the predecessor of the Department of Health Technology Assessment) who reviewed a number of past reimbursement submissions and developed a locally tailored checklist on the basis of the Critical Appraisal Skills Programme (CASP) checklist. It is highlighted that the newly developed checklist has a high level of internal validity for the Hungarian procedure, as it considers the local specificities of reimbursement, such as therapeutic guidelines and financing protocols. Nevertheless, it is also noted by the authors that there are no weights assigned to each of the questions. Therefore, it is not possible to construct a hierarchy of the checklist items that would enable to summarise the quality of economic evaluations in a comparable manner, or even to make a distinction between the issues identified within the same evaluation, based on their significance to the decision problem.

1.2 Role and procedural steps of health technology assessment

Descriptively reporting the problems of economic evaluations is a good basis for creating an assessment report, but this method does not meet expectations of using assessment reports for decisions on prioritisation. In order to help local decision-making, some national or regional HTA bodies provide a conclusion on the clinical added benefit (CAB) of health technologies in their assessments (12). The exact procedure of formulating a conclusion on CAB are usually set out by legal act, and unique to each setting, as policy goals, implications on pricing, methodological guidelines, capacities and other technical circumstances may differ (4). European HTA bodies, such as the ones operating in Germany (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* – IQWiG) (13) or France (*Haute Autorité de Santé* – HAS) (14) have developed their own classification systems to assess CAB, with the outcome of the classification linked to the pricing of the product via law. The local assessment procedure in Hungary has not been providing a conclusion on CAB so far; the reason for this delay might be related to the legal framework and resource constraints of HTA in the Central and Eastern European region, which has already been discussed by other researchers (15; 16). Frameworks already exist for making recommendations in clinical practice (for example, Grading of Recommendations, Assessment, Development and Evaluation – GRADE) or in reimbursement decision-making (the ones used by HAS or IQWiG), but their modification is not recommended (17). Adopting other agencies' classification is also not trivial as according to Boucaud-Maitre and colleagues (18), there were not more than 50% concordance in ratings between HAS and

IQWiG, discrepancies potentially caused by differences in choosing the locally appropriate comparators and target populations. This raises the need for the development of a new, tailored framework, which could facilitate evidence-based reimbursement, in accordance with the tasks, timelines, the local legal environment and resource constraints in the daily routine of Hungarian HTA.

While some HTA bodies focus only on clinical domains, other HTA bodies assess economic aspects as well before the decision on pricing and reimbursement. In terms of the critical appraisal of economic evaluations, the scientific approach to evaluate the sources of uncertainty incorporates a number of already available tools. Several, widely used checklists (for example, Consolidated Health Economic Evaluation Reporting Standards – CHEERS (19) and CASP (20)) are available for providing a conclusion on the quality of economic analyses, as well as to explore the structural assumptions in the economic analysis. These checklists may not always fit the needs of local HTA bodies and payers, as they do not attempt to conclude on the quantifiability or the significance of an identified methodological issue, but optimised for providing a detailed scientific conclusion on the overall quality of a cost-effectiveness analysis. Therefore, a more practical, flexible and scalable framework is needed to complement the tools of the local HTA body in formulating the conclusion on the submitted economic assessments. The comprehensive and consistent analysis of methods and sources of uncertainties can have a potentially high added value both for the payer and the policy maker, as this can reflect the risks that need to be managed during the reimbursement procedure. As noted earlier, an adapted methodological checklist for economic assessments for this purpose is available particularly for local use in Hungary (11). This checklist helps to get a qualitative picture on uncertainty, but does not provide an insight into the comparable impact of each contributing source to the overall uncertainty in the economic evaluation. Another possible approach is to harness the local "reactive" reimbursement procedure, and expect the MAHs to present the sources of uncertainty in their submissions. As part of the economic assessment, MAHs may make assumptions for their analysis or pick input values for model parameters that support the cost-effectiveness of a new treatment at the expense of introducing additional uncertainty. These assumptions and input values rarely make an analysis irrelevant or unrealistic as a whole, but their appropriateness depends heavily on the context and the availability of evidence. In theory, sensitivity analyses carried out by the author of the submitted economic assessment should be sufficient to describe uncertainty. In practice, the detail and interpretation of these sensitivity analyses can be heterogeneous: if the choice of input variables and their respective input values

is selective in order to support cost-effectiveness arguments, the validity of such sensitivity analyses may be compromised as well.

Distinguished authors discussing the local reimbursement procedure echoed the capacity constraints of smaller-size and lower-income countries for preparing full HTA reports (21). Although it is possible to ask the applicants (most of the time, MAHs) for handing over analyses of clinical data, one may rightfully question whether the submitted information is processed in its full details due to the limited analytical capacity of the public administrative bodies and the annual number of pharmaceutical products' submissions exceeding 100. Capacity constraints can limit the added value of assessment reports and the budget-based approach to reimbursement can overshadow their usability (22), portraying a vicious circle which marginalises the role of HTA in healthcare decision-making, while shifting the focus of decision-making to fiscal aspects that are not directly related to the core assessment procedure.

1.3 Quality assurance in assessment procedures

The quality and consistency of assessment reports is inseparable from their uptake by decision-makers and consequently, their impact. This issue was addressed in the efforts to set up the joint European HTA system to enhance evidence-based decision making. Luhnen and colleagues (23) reported on the quality management in EUnetHTA, covering a series of interventions, such as the development of templates, standard operating procedures (SOPs), methodological guidelines, other guidance documents as well as how these are expected to contribute to capacity building through training and knowledge sharing. A core component of the quality management system is the web-based Companion Guide, a platform incorporating all outputs of the collaboration and with restricted access especially for EUnetHTA member organisations. The quality management system of EUnetHTA is anticipated to increase uptake and trust in joint work.

1.4 Current state of play

Due to the lack of a holistic value framework covering both clinical and economic aspects in the assessment procedure, as well as the confidentiality of risk-sharing agreements (RSAs) between the payer and the MAH, evidence is extremely sparse and indirect on the outcome of reimbursement decisions and the interaction between the outcome of the critical appraisal procedure, IFRs, RSAs. However, even a high number of IFRs in itself, or RSAs combined with an increasing number of IFRs may incentivise the public administrative bodies to support

a positive reimbursement decision on a product to ease their administrative workload on their stretched capacities at the cost of compromising the conclusion of the critical appraisal procedure.

Considering everything, only anecdotal evidence is available on how the assessment reports, their quality, or other financial and procedural circumstances outside of the core assessment procedure influence the outcome of decision-making on the reimbursement submissions of innovative pharmaceutical products in Hungary. It seems that the assessment reports do not have the desired impact on reimbursement decisions, potentially due to the lack of solid methodological foundations. To some extent, the lack of relevant research may be as well due to the difficulty of operationalising the added value of assessment reports alongside a reliable methodology and the confidentiality barriers to accessing assessment reports in full detail. In this setting, any attempt to improve the methods should also test and demonstrate their feasibility, as currently, there are no documented appraisal methods that are used consistently: assessment reports are compiled in an ad hoc fashion. It is also not feasible to adapt an already existing and used set of appraisal methods, as the resources, the legal framework, or even organisational culture are highly specific to the local setting.

Therefore, the overarching aim of this research is to explore the impact of external factors on the reimbursement decisions to position the role of intrinsic factors in the reimbursement process, as well as to design, implement and evaluate some improvements to the local critical appraisal methodology. The methodological improvements are supported by an organisational intervention and seeking synergies with the broader legal framework of HTA in order to increase the quality, and consequently, the impact of assessment reports on reimbursement decisions.

2 OBJECTIVES

This research covers the external and internal factors influencing the reimbursement decisions of innovative pharmaceuticals in Hungary to promote an evidence-based process through which the performance of the health system could be improved.

The first objective of this research is to analyse the association of exogenous factors (such as the presence of risk-sharing agreements at the time of submission, expenses on individual funding requests for the particular compound, overall aim of the submission, the need for a legal act for a positive decision) on the reimbursement decisions on innovative medicinal products in the social health insurance system of Hungary. The research question related to this objective is which, if not all of the evaluated exogenous factors are associated with reimbursement decisions, and how can their relationship be characterised. The hypothesis related to this objective is that all of the evaluated exogenous factors have a statistically significant association with the outcome of the decision on reimbursement.

The second objective is to develop a methodological approach to conclude on the clinical added benefit of an innovative medicinal product, and also the implementation of a framework to identify, quantify and interpret the sources of uncertainty in economic evaluations as part of the assessment report. The research question related to this objective is to find out if viable methodological improvements are possible to design in alignment with the current assessment procedure of the submitted clinical and economic evidence. The expectation is that a methodological improvements created by an iterative development process need to acknowledge and if possible, take full advantage of specificities arising from the broader legal framework of health technology assessment, as well as resource constrains.

The third objective is to test the implementation of these methods on actual reimbursement submissions and produce more coherent assessment reports where the appraisal methodology was improved. The research question related to this objective is whether the novel methods can be scaled up and implemented to the day-to-day routine of critical appraisal, and if so, to see if any organisational improvements can help the implementation process.

3 METHODS

This chapter describes how exogenous factors were assessed, what the methodological approach to concluding on the clinical added benefit (CAB) is and how the assessment of sources of uncertainty in economic evaluations is carried out to operationalise intrinsic factors of reimbursement. It is also described what data sources and analytic methods are used to describe the reimbursement submissions based on the aforementioned parameters on clinical added benefit, sources of uncertainty in economic assessments. The methods for presenting a series of cases are also introduced, covering both endogenous and exogenous factors to the value framework.

3.1 Impact of exogenous factors on reimbursement decisions (Objective 1)

The role of external factors is first explored to quantify their link with reimbursement decisions on pharmaceutical products in the frame of the Hungarian social health insurance system. In order to analyse the potential association between the outcome of the reimbursement procedure and the anecdotal contributing factors exogenous to the clinical or economic assessment of the health technology, the latter were operationalised as independent variables in a multivariate logistic regression framework. This analysis is reported elsewhere in full details (24), however, the essentials are outlined below. Univariate- and multivariate models were used to estimate odds ratios (ORs), quantifying the association between each factor and the outcome of the decision procedure. Basic administrative information (name of the product, date of the submission) is publicly available on each reimbursement submission (25), maintained by the National Health Insurance Fund Manager (NHIFM).

Having an risk-sharing agreement (RSA) in place on the submitted product at the time of submission means that the NHIFM and the market authorisation holder (MAH) already engaged in price negotiations before the actual submission for a different indication of the identical pharmaceutical product. This is mostly relevant for submissions with purposes other than introducing an entirely new compound to the healthcare system, and an effective RSA is expected to increase the likelihood of a positive decision on reimbursement. Although the contents of RSAs are confidential, there are public semi-annual reports on products that are reimbursed with RSAs in place (26). Combined with the administrative information on the date of the start of the reimbursement procedure, this information can be used to identify submissions which were involved in an RSA at the time of their submission.

Expenditure on individual funding requests (IFRs) may also have an impact on the reimbursement decisions, as the financing agent may not be fully capable of engaging in price negotiations, and the administrative burden of handling these requests is also demanding. Therefore, a high level of expenditure on IFRs would presumably develop an interest in the financing agent to facilitate the inclusion of the product on the list of reimbursed medicines, i.e. increasing the chance of a positive decision while reducing the administrative burden of enabling access to the product. Moreover, a high level of expenditure on IFRs would also imply a lower net budget impact of introducing the particular product into routine reimbursement. We used publicly available financial reports on expenditures reimbursed through IFRs of pharmaceutical products to further expand our dataset (27).

A number of other explanatory variables need to be considered when studying the impact of RSAs and expenditure via IFRs on the outcome of reimbursement decisions. Apart from the name of the product, date of the submission and further administrative details, the data source maintained by the NHIFM (25) also contains the outcome of the procedure and information on whether a positive decision on the submission would imply the amendment of the current legislation. The need for the amendment of the current legislation occurs, if a new compound is submitted for reimbursement, aiming at a novel, authorised, but non-reimbursed indication which is not yet recognised in reimbursement legal acts. For pharmaceutical products intended for outpatient use, the reimbursed indication is described by a ministerial decree. Given the availability of a reimbursed indication, NHIFM decides on whether or not to reimburse such pharmaceutical products. For innovative pharmaceuticals intended for inpatient use (available under a special, so-called itemised reimbursement technique), both the indication and the international non-proprietary name is specified in the legislative act, as well as the designated healthcare facilities that can provide the treatment. This essentially means that for the reimbursement of novel product-indication pairs, the State Secretary for Health is directly involved on behalf of the legislator (the Ministry of Interior), which is a new entity in the decision-making procedure. This variable is expected to decrease the chance of a positive decision on reimbursement.

The purpose of the submission may also impact the outcome of the decision-making procedure and therefore should be assessed. The reimbursement submission of an entirely new compound, or an attempt to introduce a novel indication of an already reimbursed compound would possibly invoke different levels of interest, as these may address an unmet need in the population or offer a new therapeutic option for patients and clinicians. A reimbursement

submission may also have other purposes, such as introducing a new pharmaceutical form, or a new indication of an already reimbursed compound, or increasing the price of an already reimbursed compound.

The archives of the Department of Health Technology Assessment at the NIPN were used to review the submitted documentation to identify the overall purpose of the submission, namely, whether it aimed for the reimbursement of an entirely new compound, or had other purposes, such as extending the current reimbursement of a compound to a new indication.

As the current legislative framework of pharmaceutical reimbursement submissions was issued in late 2017 (28), reimbursement submissions between 1st of January 2018 and 7th of June 2021 were considered for this analysis. First, dossiers not submitted for the full procedure and procedures which did not conclude during the observation period were both omitted from the analysis. Second, procedures related to submissions aiming to increase the price of an already reimbursed product were also excluded, as these are not relevant to providing information on access to innovative pharmaceutical products.

Apart from descriptive analyses, the association between the outcome of the decision-making procedure as the dependent variable and having an RSA in place at the time of submission, expenditure on IFRs, overall purpose of the submission and the need of a legal act as independent variables was studied in univariate and multivariate logistic regression framework. A quasi case-control study design was adapted where the outcome of the decision-making procedure was coded as a binary variable with the value „1" marking a positive decision, and „0" if any other outcome was reached (negative decisions or no decision reached within mandatory deadlines of the procedure). The presence of an RSA at the time of submission (yes=1, no=0), the need of a legal act for decision-making (yes=1, no=0), overall purpose of the dossier (new compound or a new combination containing a new compound=1, any other purpose, but not a price increase=0) were also included as dichotomous variables. Expenditures via IFRs were collected for the actual and preceding year of submission for each procedure. However, to help interpretation, this variable was recoded by using units of 200 million HUFs for the biennial expenditures on IFRs to tackle the potential seasonality and fluctuation of expenditures on IFRs. As the current analysis covers a broader time period, the effect of the year of submission was included in a supplementary logistic regression analysis to explore the effect of adjusting to the date of submission. Data analysis was conducted in R version 4.1.2 (29). The threshold for statistical significance was 0.05. Missing data points were omitted from the analyses, no data imputation techniques were considered.

3.2 Conclusion on clinical added benefit (Objective 2)

Following the analysis of exogenous factors, a complex methodological development of the critical appraisal procedure is designed and implemented. Methodological improvements directly related to the clinical domains of HTA are addressed first as part of this research. The designing of the framework on CAB can be divided into the steps of drafting, testing, feedback assessment from stakeholders and implementation. The design and development process is described elsewhere in full details (30), but the framework is briefly introduced here. The proposed framework aims to link the added benefit of a technology to its pricing. Therefore, it could serve as a pillar for the characterization of the relationship between the CAB and the incremental health gain quantified in the cost-effectiveness analysis. In order to do so, the framework should have a dual aim of

(a) enabling the formal comparability of interventions in terms of their CAB and
(b) serving as a basis for validating the type of health economic evaluation against the existing scientific evidence on incremental health gains.

The framework of concluding on clinical added benefit was tested in the field of oncology. The reimbursement submissions of antineoplastic drug (that is, compounds having with a first-level anatomical therapeutic chemical classification equal to “L”) were included in the scope of this methodological improvement to formulate a conclusion on CAB, as the majority of reimbursement submissions intended for the reimbursement of a new compound or a combination that includes a new compound, or a new therapeutic indication of an already reimbursed compound are submissions antineoplastic agents. In the calendar year of 2022, the proportion of reimbursement submissions aiming to reimburse an antineoplastic agent was 58% (57 out of 98 submissions, excluding those that aim price increases). Selecting antineoplastic agents in the scope is intended to efficiently use the resources available for methodological improvements and therefore to maximise its impact on the uptake of assessment reports.

To conclude on the extend of CAB, we used the scoring of ESMO-MCBS as a starting point. Scores A and 5 were considered as “Major added benefit”, scores B, 4 and 3 as “Important”, and scores C and 2-1 were categorized as “Minor added benefit”. In cases where statistically significant difference on a relevant endpoint in the PICO of the reimbursement submission was not observed (e.g. because a single-arm trial does not have the comparator determined by PICO), we assigned the categories “No proof of benefit” or the category “Not quantifiable” in cases where methodological issues emerged as well.

A draft framework was proposed, and then further elaborated in two rounds of internal discussions within the Department of Health Technology Assessment, with emphasis on the feasibility of the proposed procedure.

The retrospective testing and the implementation of the framework was done in four consecutive rounds. First, two previously uninvolved assessors piloted the matured draft version of the procedure, and their feedback was also discussed and incorporated into the documentation. They evaluated two current reimbursement dossiers using ESMO-MCBS and compared them to the published score available at the ESMO website (round #1). In this pilot round, the results were consistent with the scores published on the ESMO website. Additional rounds (#2-#4) of retrospectively evaluating assessments involved all available medical assessors (n=7 or 9) to identify any divergence between them on the components of the conclusion on CAB assessed jointly by all assessors according to the guidance and to build consensus on handling such cases. These rounds of exercises were used to provide concordance estimates as a reflection to the assessor team. The three consecutive rounds of exercises each contained three different submission dossiers in each round, with the complexity of submissions increasing from round to round.

Each round was followed by detailed discussions, and the internal guidance was consensually revised to cover the questions raised during assessments. These questions concerned incomplete data regarding toxicities; evaluation of RoB and decisions on endpoint relevance. The experts of ESMO have been consulted via email on certain issues related to subgroup analyses, evaluation of PFS plateaus and indirect comparisons. For clarifying questions regarding toxicity-related downgrading, the Department of Pharmacovigilance at NIPN was contacted.

A call for open consultation and a working paper on CAB was posted on the website of NIPN on the 15th of June 2021, with a deadline for feedback on the 17th of September 2021. Dissemination materials briefly described the procedure of formulating the conclusion on the CAB in general, and its potential impact on the reimbursement procedure. There was no restriction on who could reply to the call, but twenty-four entities (patient organisations, medical societies, academic centres, public bodies, industry associations and consultancy firms) were invited to comment on the working paper. A self-administered questionnaire was provided for stakeholders in which respondents could express their response on a four-level Likert scale to a pre-defined set of questions on four different domains (see Appendix 2 for the questionnaire). Their feedback was also gathered as comments without restrictions via a standardised commenting form which included the lines number of the before mentioned

dissemination materials and the category of the comment (major/minor/linguistic) for each comment. After closing this consultation period, the working group developed consolidated answers for each comment. The working paper and the framework itself was amended if deemed necessary. Finally, ten stakeholders responded to the call from which two responded only to the questionnaire and two responded only to the commenting form, while six participants provided feedback via both instruments. We received one response from academic centres and one from public bodies and two responses from each of the following entities: patient organisations, medical societies, industry associations and consultancy firms. A total of seventy-two comments were received from the eight participants filling out the standardised commenting form. Answers of the responders to the questionnaire were regrouped as concordant (fully agree, rather agree) and discordant (fully disagree, rather disagree) responses.

Broad internal discussions were performed to integrate the results of pilot (round #1) and retrospective testing (rounds #2-4) as well as the input from stakeholders. These discussions were used to elicit questions to be answered in order to reach alignment on procedural- and methodological details for the implementation of concluding on CAB (that is, integration into the Department's assessment procedure). The final version the working paper was shared with the stakeholders and the roll-out date of 1st of January 2022 was agreed upon internally; a set of common phrases for the assessment template were drafted to ease reporting. A sequential escalation procedure was designed to support the medical assessors, should uncertainty in formulating the conclusion on CAB arise. The Department's internal knowledge repository was used to capture all relevant findings and to facilitate dissemination among assessors. Eventually, a summary of the framework was also anticipated for publication to inform stakeholders.

3.3 Assessing the sources of uncertainty (Objective 2)

Proceeding with presenting the methodological improvements, the procedure to critically appraise economic evaluations follows. This improvement relies on identifying, quantifying and interpreting the sources of uncertainty in economic evaluations, and preceded by the assessment of model face validity via an internally used checklist. Therefore, at the time of applying this critical appraisal methodology, the economic model and the presented base case is assumed to be assessed for credibility, and deemed generally suitable for supporting the economic evaluation of the technology. The procedure is illustrated in Figure 1.

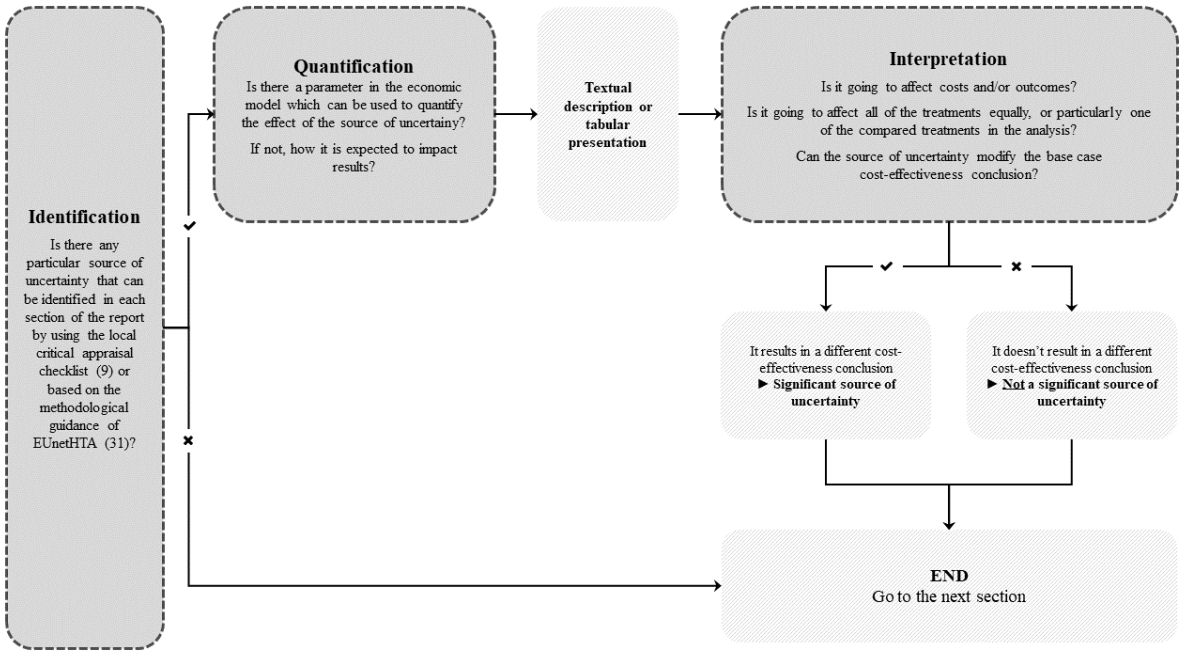

Figure 1.: The graphical illustration of the procedural framework to assess the sources of uncertainty (31).

The development of the framework was initiated by reviewing the local checklist and methodological guidance mentioned earlier; this was followed by several internal discussions and pilot applications within the Department of Health Technology Assessment at NIPN, as well as the presentation of case studies. Feedback on the pilot applications of the framework was collected via personal discussions with the colleagues of NHIFM. The first pilot application of the framework is presented as part of the results.

Within this framework, the potential sources of uncertainty are examined according to the structure (i.e. the sections on economic domains) of the assessment report. These sections are the following: type of economic analysis; evaluation of the economic model and its core assumptions, evaluation of economic model inputs (particularly transition probabilities, health utilities, resource use and unit costs), results and the sensitivity analyses. The tools for identifying the sources of uncertainty are the appropriate European Network for Health Technology Assessment guidance (32) and the checklist developed by Inotai et al (11): the sections of the guidance and the topics of checklist broadly correspond to the structure of the assessment report structure. Although to some extent, identification also relies on expertise accumulated via the Department's internal knowledge repository. Depending on the actual submission, there might be multiple sources of uncertainty identified for each section, as well as none.

After identifying the potential sources of uncertainty, the analysis of quantifiability follows. An identified source of uncertainty is considered quantifiable, if there is a relevant (and modifiable) parameter to depict its impact in the submitted health economic model. For each source of uncertainty, the alternative input value for the relevant model parameter is chosen based on its availability (i.e. the alternative value had already been included in the model by the applicant, but was not part of the submitted base case). It is also evaluated if all possible or relevant scenarios are considered for the particular parameter. If a more plausible input value is identified during critical appraisal, the analyst may include it instead of the ones already available in the model. If there is no appropriate parameter in the model to quantify the impact of a source of uncertainty, and it is not feasible to implement one, it is not possible to quantify the impact of the given uncertainty. In such cases, it can be considered whether formally reaching out to the analyst preparing the economic evaluation is reasonable, while the analyst may have access to information that can be used to quantify the impact of the given uncertainty.

The interpretation of all identified (both quantifiable and not quantifiable) sources of uncertainty should cover whether each of these affect

1. Costs and/or outcomes;
2. All of the treatments equally, or particularly one of the compared treatments in the analysis.

As a final step of interpretation, the significance of the impact on cost-effectiveness results is determined. In case of a quantifiable source of uncertainty, the impact is deemed ‘significant’ if the scenario analysis with the alternative set of inputs results in the change of the conclusion on cost-effectiveness, compared to the base case. If the scenario analysis with the alternative set of inputs yields the same conclusion on cost effectiveness as in the base case, the impact of the given source of uncertainty is deemed ‘not significant’. If the source of limitation cannot be quantified within the economic model, the exact significance cannot be determined neither, so the expectations of the assessor (‘probably significant’ / ‘probably not significant’) preparing the assessment report can be presented as an indicative impact when interpreting the results.

In case of having a number of mutually exclusive quantifiable sources of uncertainty identified in the economic assessment, the assessor critically appraising the submission may wish to combine some, if not all of those into an alternative base case in addition to analysing them separately. This is hoped to enhance the uptake of cost-effectiveness arguments by the payer

even if the impact of individual sources of uncertainty is entirely characterised as non-significant to the base case cost-effectiveness results.

3.4 Case series: implementation to routine practice (Objective 3)

To assess its applicability in the routine practice of producing assessment reports, the new methodology is tested and findings are presented using case studies of new oncology medicines.

Apart from analysing exogenous factors as potential determinants of reimbursement decisions and presenting the experience gathered through piloting the methodological developments on selected cases of reimbursement submissions, the current research investigates the pharmaceuticals submitted for reimbursement since the formal start of using the aforementioned methodological improvements in the assessment procedure, that is, since the 1st of January 2022. Submissions with a completed assessment report as of the 16th of July 2022 are included in this research. Narrative synthesis was used to rationalise and present the relevant data on each dossier.

The archives of the Department of Health Technology Assessment at the NIPN were used to review the submitted documentation to identify the overall purpose of the submission, namely, whether it aimed for the reimbursement of an entirely new compound, or had other purposes, such as extending the current reimbursement of a compound to a new indication. The archives were used to review the accompanying clinical summaries to conclude on the CAB and also to identify, quantify and interpret the sources of uncertainty in the submitted economic assessments. The extent of CAB is expected to have a positive association with the likelihood of the reimbursement of the product, as well as the lack of a significant source of uncertainty in the economic evaluation. Non-significant sources of uncertainty in economic evaluations are not assumed to impact decisions.

For each case, the conclusion on CAB, level of evidence (LoE), risk of bias (RoB), as well as the identified sources of uncertainty were extracted from the assessment reports and presented as part of a narrative synthesis of the quantitative and qualitative results. This information is enriched with expenditure data on IFRs and presence of RSAs, if available, and qualitative information on the aim of the submission, the need for a legal act to the reimbursement.

4 RESULTS

4.1 Impact of exogenous factors on reimbursement decisions (Objective 1)

The total number of reimbursement submissions between 1st of January 2018 and 7th of June 2021 was 1,390. Among these, 486 were submitted in the full procedure, of which 162 did not conclude at the time of analysis. Of the remaining 324 submissions, 92 was aiming for a price increase, or was already reimbursed and proposed changing the reimbursement technique, therefore could be considered irrelevant to the current research.

The primary analysis dataset for the exogenous factors consisted of information on 232 submissions, enriched with data on risk-sharing agreements (RSAs) in place at the time of submission, compound-level biennial expenditure on individual funding requests (IFRs) (expressed HUFs), the need for a legal act to decide on reimbursement, and overall aim of the submission.

Table 1 summarises the descriptive data on submissions according to the outcome of reimbursement decision-making and the independent variables considered in the analysis. Chi-square and independent samples T-tests were performed to test the association between the outcome of the decision-making procedure and the respective independent variables.

Table 1: Description of the submissions according to independent variables. *The association between the outcome of the reimbursement decision and having an RSA in place, the overall aim of the submission and the positive decision needing a legal act were descriptively assessed by a Chi-square test. The association between the outcome of the reimbursement decision and the average biennial expenditure on compound through IFRs was assessed via independent samples T-test.

	Positive	Any other outcome	All procedures	p-value*
RSA was in effect at the time of submission				
Yes	32 (31.07%)	18 (13.96%)	50 (21.55%)	p=0.002
No	71 (68.93%)	111(86.04%)	182 (78.44%)	
Average biennial expenditure on compound, based on IFRs (HUF, mean (SD))	194,934,323 (531,420,827)	164,388,885 (463,476,416)	181,050,033 (499,868,965)	p=0.5617
Overall aim of the submission				
Introducing a new compound or a combination with a new compound	13 (12.62%)	53 (41.09%)	66 (28.21%)	p<0.001
Introducing a new indication for an already reimbursed compound	48 (46.60%)	70 (54.26%)	118 (50.43%)	
Other, but not a price increase	42 (40.78%)	6 (4.65%)	50 (21.37%)	
A legal act is needed for the positive decision				
Yes	30 (29.13%)	112 (86.82%)	142 (61.21%)	p<0.001
No	73 (70.87%)	17 (13.18%)	90 (38.79%)	

Whereas the number of submissions where the compound was not covered by an RSA was higher for the subgroup of cases with other-than-positive decisions, the proportion of submissions where the compound itself was covered by an RSA at the time of submission were significantly more frequent in case of procedures with positive outcomes (31.07% of submissions with positive outcomes covered in an RSA, whereas only 13.96% of those with a different-than-positive outcome). In comparison, the distribution of submissions of compounds that have not had an RSA at the time of their submission were more balanced in the subgroups created according to the outcome of the procedure (68.93% versus 86.04% for positive and any other outcomes, respectively). The average biennial expenditure on the compound, based on

IFRs tended to be numerically higher in the case of procedures which finally concluded in a positive decision, yet the difference was not statistically significant. Among reimbursement procedures with a non-positive outcome, submissions proposing to introduce a new compound (or a combination with a new compound) to the healthcare system were also more frequently occurring than for positive reimbursement decisions, although this difference was not statistically significant. It can also be observed that the number of all submissions aiming to introduce a new compound is roughly half of those that aim to introduce a new indication of an already reimbursed compound (66 versus 181, respectively), with the distribution of positive decisions skewed towards submissions aiming to introduce a new indication of an already reimbursed compound. More than two thirds of reimbursement submissions with a positive decision did not need a legal act, whereas 86.82% of reimbursement submissions with non-positive outcomes would have needed a modification of the current legislation on reimbursement, yielding a statistically significant difference in this comparison.

The results of the univariate and multivariate logistic regression models (Table 2) showed that having an RSA in place at the time of submission was consistently positively associated in both univariate and multivariate models with a statistically significant higher chance of a positive decision (adjusted OR=3.49, 95% CI: 1.56–7.82, p=0.003). However, the average biennial expenditure exceeding 200 million HUFs did not show statistical significance, although it was positively associated with the decision outcome being supportive (adjusted OR=1.04, 95% CI: 0.92–1.19, p=0.54) in both univariate and multivariate models. Neither did the overall aim of the submission show statistically significant association with the outcome of the decision procedure (adjusted OR=1.32, 95% CI: 0.65–2.69, p=0.45); moreover, the direction of the association was not consistent between univariate and multivariate models. A consistent and significant negative association can be observed between needing a legal act for the positive decision and the odds of the procedure arriving at a positive decision (adjusted OR=0.05, 95% CI: 0.02 – 0.11, p<0.001).

The univariate model containing the need for a legal act for a positive reimbursement decision showed similar diagnostic parameters of AIC and R^2 as the multivariate model containing all assessed exogenous factors, although the likelihood ratio test yielded a statistically significant difference in model goodness-of-fit characteristics between the two (D=11.519, p=0.009).

Table 2. Results of the logistic regression analyses with the outcome of the decision being positive as the dependent variable

	The decision procedure is positive					
	OR (95% CI) Univariate Model			OR (95% CI) Multivariate Model		
RSA was in place at the time of submission	2.78 (1.45–5.32)	p=0.002	AIC: 312.78 R^2=0.03	3.49 (1.56–7.82)	p=0.003	AIC: 232.15 R^2=0.30
Average biennial expenditure on the basis of IFRs exceeds 200 million HUFs	1.02 (0.92–1.13)	p=0.710	AIC: 322.56 R^2<0.01	1.04 (0.92–1.19)	p=0.540	
Introducing a new compound or a combination with a new compound	0.74 (0.44–1.24)	p=0.250	AIC: 321.35 R^2<0.01	1.32 (0.65–2.69)	p=0.450	
A legal act is needed for the positive decision	0.06 (0.03–0.12)	p<0.001	AIC: 237.67 R^2=0.27	0.05 (0.02–0.11)	p<0.001	

In a separate analysis, the role of the date of submitting the dossier was explored (see Appendix 2. for detailed results). Having the reimbursement dossier submitted in the year 2019 was associated with a statistically significant higher likelihood of a positive decision (adjusted OR=3.24, 95% CI: 1.36–7.72, p= 0.008). Therefore, the date of submission can be interpreted as an effect modifier, yet results on other independent variables were consistent both in terms of the direction of association and statistical significance with the primary multivariate analysis. The goodness-of-fit characteristic was somewhat improved for the multivariate model including the year of submission, in line with our previous expectations (AIC: 229.11).

4.2 Results regarding the conclusion on clinical added benefit (Objective 2)

The procedure of concluding on the clinical added benefit (CAB) facilitates the standardised description of endpoint relevance, level of scientific evidence and accompanying RoB, as well as determining the existence and extent of CAB (see Figure 2.).

Two technical steps precede concluding on the CAB: the first is defining the assessment scope, that is, the PICO (patient population, intervention, comparators and health outcomes) structure of the submitted dossier (1. on Figure 2.) and a targeted literature review as a second step to decide whether higher quality scientific evidence is available (2. on Figure 2.) than what was submitted by the MAH in the dossier. Using the proposed set of parameters in the assessment

scope helps the consistent assessment of the clinical evidence submitted, while only expecting the essential information to conclude on CAB.

To align the current practices with the formulation of the conclusion on the CAB, the four domains in the developed framework are considered as equal contributors to the conclusion (as appearing on Figure 2):

(3/a) information on the relevance of the considered clinical endpoints;

(3/b) the existence/extent of the added benefit, and

(3/c) the quality of evidence supporting it; which has two subdomains: LoE and RoB associated with it in the cases of clinical trials.

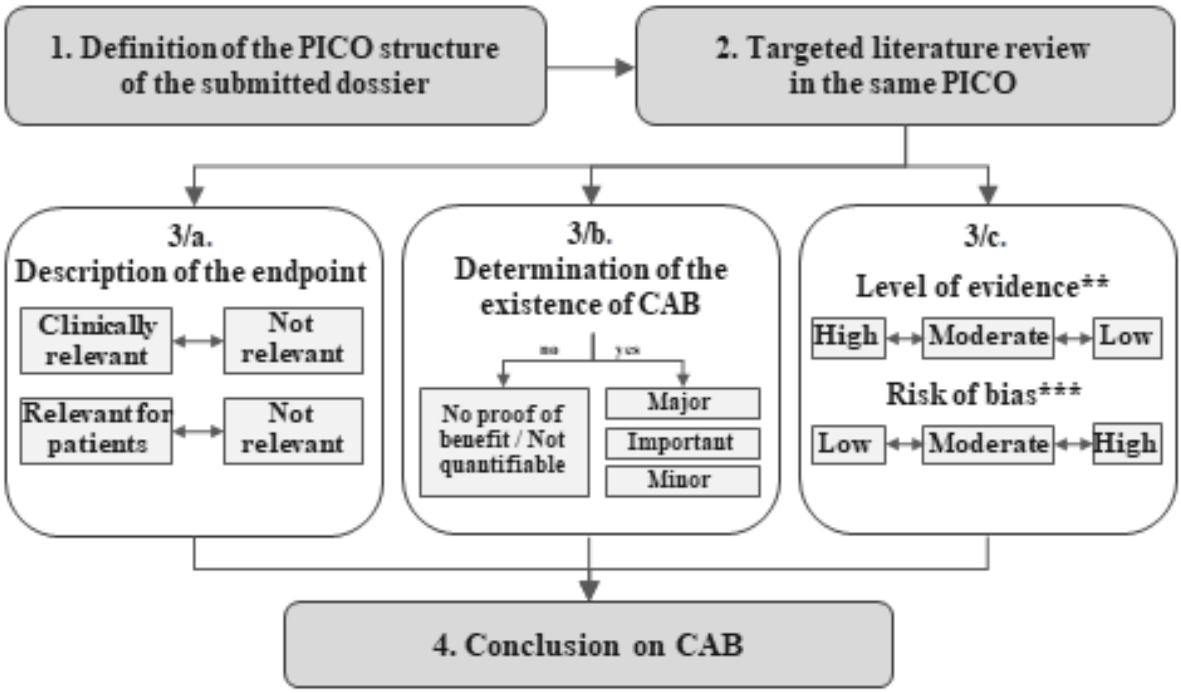

Figure 2: Schematic presentation of the process of formulating conclusion on CAB (30).

To evaluate the relevance of an endpoint we rely on the local guidelines for conducting health economic evaluations' (8) recommendations (in specific, number 11; 12 and 13): In case of a life-threatening disease, mortality as an endpoint or survival endpoints are the most relevant and morbidity and / or quality of life are secondary. In case of non-life-threatening diseases, morbidity and quality of life endpoints are preferred. Endpoints were considered relevant for patients if they are associated with either improved overall survival or improved/sustained quality of life.

We decided to use the ESMO-MCBS for scoring the extent (magnitude) of clinical benefit of antineoplastic drugs. Using this instrument is reasonable due to the society's geographical

coverage and the local medical oncologists' society reliance on ESMO's guidelines. However, ESMO also issues scorecards that can be used as a reference when developing the local framework of CAB. We assigned categories for determining the extent of benefit from the ESMO-MCBS scores (Table 3).

Table 3: Mapping the ESMO-MCBS scores to the extent of CAB categories. *Scores A, B, 5 and 4 are considered as substantial benefit according to ESMO.

Extent of CAB (categories)	ESMO-MCBS Curative setting scores	ESMO-MCBS Non-curative setting scores
Major	A*	5*
Important	B*	4*, 3
Minor	C	2, 1
No proof of benefit / Not quantifiable	No statistically significant difference on a relevant endpoint in the PICO of the reimbursement submission	

In the case of indirect comparisons, where the dual-rule of the ESMO-MCBS cannot be used (only relative efficacy can be derived, direct comparison is not available), we are not able to determine the extent of CAB. However, the conclusion on the existence of CAB always preludes the conclusion on its extent. In layman's terms, it has to be made sure that either there is sufficient information to say that one treatment delivers better or the same health gains compared to another, or we can't say for sure according to what we know. In more professional terms, first, our conclusion includes information on the existence of the CAB: 1) the existence of the CAB is possible; 2) it is not proven (= No proof of benefit) or 3) it cannot be determined based on the presented evidence (= Not quantifiable). If the existence of CAB is possible - in the cases of direct comparisons - we can extend the conclusion with determining its extent. In case of using indirect comparisons to conclude on CAB, we can still formulate a conclusion on the existence (but not the extent) of CAB and make sure that this proposed framework is flexible to use while maintaining its integrity.

Classification of the level of evidence was adapted from one of the published SOPs of ESMO (33). Different levels of evidence were merged into a simplified rating scale with the categories of high, moderate, or low levels of evidence (Table 4).

- High: large, good quality randomized controlled trials (RCT) and meta-analyses of these without considerable heterogeneity.
- Moderate: small RCTs or large RCTs with susceptible bias and meta-analyses of these or meta-analyses with considerable heterogeneity or indirect comparison.

- Low: cohort studies, case reports and indirect comparisons (34) where the methodology is not clearly presented in the submitted application for reimbursement or if the indirect comparison carries serious methodological flaws.

Due to capacity constraints, the conclusion refers to an external source of RoB assessment (e.g. from IQWiG or future joint clinical assessment reports, Cochrane or other published sources) for the time being. The argument for this rather conservative approach is that in practice, the submitted clinical evidence on innovative medicinal products for pricing and reimbursement in the member states of the European Union can be described as homogenous. In other words, the results coming from the same (usually, the pivotal) clinical study is used to inform the relative benefit assessment of a particular product. Therefore, there is a potential for efficiency gains by relying on the RoB assessment of other member states with less capacity constraints, given that the scope of the assessment report from the other member state is identical to the local one.

Table 4: Levels of evidence

* Categories based on a use of an internationally accepted tool (e.g. GRADE, Cochrane RoB2 or reference from a peer-reviewed paper or a publicly available HTA report (e.g. IQWiG)

**e.g. GRADE, Cochrane RoB2

RoB: Risk of Bias; SLR: systematic literature review; MAIC: Matching-Adjusted Indirect Comparison; PICO: Population-Intervention-Comparator-Outcome;
STC: Simulated Treatment Comparison.

Evidence level	Evidence level by ESMO	Direct comparative trial(s) are available		Indirect comparison (lack of direct comparative clinical trial)
		One comparative clinical trial	Meta-analysis of several direct comparative trials	
High	I	Evidence from at least one large randomized, controlled phase 3 trial of good methodological quality (low potential for bias)*	Meta-analyses of well-conducted randomized trials (low potential for bias), without significant inconsistency and without significant differences within the PICO, supported by an SLR and grading of evidence or RoB assessment**.	
Moderate	II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality)*.	Meta-analyses of trials representing moderate level of evidence, or meta-analysis of trials with significant differences within the PICO frame / inconsistency with its appropriate correction. Meta-analyses not supported by an SLR or without grading of evidence or RoB assessment.	Indirect comparisons and network meta-analyses of randomized, controlled trials of good methodological quality, adjusted for differences in PICO if there are (with MAIC, STC or other suitable method) supported by an SLR and grading of evidence or RoB assessment**

Evidence level	Evidence level by ESMO	Direct comparative trial(s) are available		Indirect comparison (lack of direct comparative clinical trial)
		One comparative clinical trial	Meta-analysis of several direct comparative trials	
Low	III	Prospective cohort studies	Meta-analyses of low evidence level trials or meta-analysis of such moderate or high evidence level trials with significant differences within the PICO frame.	Naïve indirect comparisons. Indirect comparisons with significant differences within the PICO frame / network meta-analyses with inconsistency without corrections or where the methodology is not well-documented in the reimbursement dossier. Indirect comparisons not supported by an SLR or without grading of evidence or RoB assessment.
	IV	Retrospective cohort studies or case-control studies		
	V	Studies without control group, case reports, expert opinions		

Average results had more than seventy-five percent concordance between assessors on each element of the conclusion in all rounds, except for two categories ('RoB' (51.7% in round #2) and the category 'endpoint relevance (61.9% in round #4)). The highest concordance rates between assessors were observed regarding the levels of evidence and the baseline ESMO-MCBS scores (Table 5).

Table 5: Concordance between assessors during the three rounds of retrospective assessments. n: number of participating medical assessors.

Pilot test round no.	Endpoint relevance	Extent of CAB			Level of evidence	Risk of Bias
		Category	Baseline score with ESMO-MCBS	Adjusted score with ESMO-MCBS		
Round #2 n=7	85.7%	83.3%	100.0%	76.2%	85.7%	57.1%
Round #3 n=9	77.8%	76.9%	100.0%	77.8%	88.9%	85.2%
Round #4 n=7	61.9%	90.5%	76.2%	76.2%	90.5%	90.5%
Average (SD)	75.1% (15.1)	83.5% (6.2)	92.1% (11.9)	76.7% (13.8)	88.4% (2.7)	77.6% (13.6)

The causes of the discordance, in the cases of adjusted ESMO-MCBS scores, were due to the different evaluation of toxicity, or in cases of dossiers requiring adjustments based on progression-free survival (PFS) plateaus. As for the categories representing the extent of benefit, the concordance between assessors were high in most cases. The low concordance initially observed regarding the RoB was caused by the differences on the whole study level versus the RoB associated with the relevant endpoints. The lowest concordance was found regarding the endpoint relevance.

In general, the initiative to develop a new procedure to assess CAB was welcome by all stakeholders and it was also agreed that the proposed framework would greatly contribute to an increase in the quality of assessment reports in Hungary. Most of the responses were concerned with the following topics: i) concepts used in the framework; ii) aspects considered during the formulation of the conclusion on CAB and iii) methodology to decide on the extent of CAB. Patient organisations and medical associations shared their opinion mainly about relevant outcomes, emphasizing that patients' perspective is

important to be included. Industry associations, consultancy firms and academic centers provided in-depth feedback concerning methodological issues, including the assessment of available evidence, the relevance of endpoints and the classification of CAB in the final conclusion. After careful consideration, their suggestions were implemented and the framework was refined accordingly.

According to the data gathered via the stakeholder questionnaire, the system describing the quality of clinical evidence was welcome. Opinions were also generally supportive about the scale used to score the extent of CAB and all of the respondents had a positive attitude towards the implementation of the ESMO-MCBS and shared the opinion that the proposed framework might improve the quality of HTA reports.

As a widely used measure to evaluate concordance, Kendall's Coefficient of Concordance (Kendall's W) was calculated to assess the concordance of responses between stakeholders. This measure is understood similarly to Spearman's correlation coefficient for normally distributed values (i.e. values closer to 1 indicate close correlation between two variables). The coefficient was found to show some, yet statistically significant unanimity between stakeholders (W=0.367, p=0.002) that can be interpreted as a fair agreement in this context.

4.3 Results on assessing the sources of uncertainty (Objective 2)

The pilot exercise that had been carried out for assessing the sources of uncertainty was conducted for the reimbursement submission of darolutamide for treating non-metastatic castration-resistant prostate cancer (see Table 6 for the identified sources of uncertainty). For context, the submitted base case cost-effectiveness results indicated darolutamide generating an incremental health gain of 1.31 QALYs alongside incremental costs over ADT; the calculated ICER is marginally below to the local cost-effectiveness threshold. For incremental costs, effectiveness and cost-effectiveness ratio, cell percentages show the deviation from the base case when the alternative input was applied in the economic model. For non-quantifiable parameters, the expected direction of deviation is included in the cell.

According to the local guideline, the time horizon of cost-effectiveness analyses should be lifelong; the base case value in the current analysis was 27 years, with the average age

at baseline being 73.6 years in the ARAMIS trial. However, as the life expectancy in the local male population is 10.10 years, it was concluded that a shorter time horizon would be reasonable for the analysis. The alternative input of 10 years was selected for the model parameter to quantify the potential impact of this source of uncertainty, affecting the costs (incremental costs decreased by 2% in the scenario analysis compared to the base case) and outcomes (incremental QALYs decreased by 32% in the scenario analysis compared to the base case) of both treatments compared in the analysis. This yielded a different conclusion on cost-effectiveness than in the base case therefore its impact was considered as significant (the ICER increased by 45% in the scenario analysis compared to the base case).

In the base case of the cost-effectiveness analysis, efficacy inputs were estimated based on a modified intention-to-treat sample of study subjects. That is, patients who developed metastasis at baseline, after randomization, but before receiving the first dose of treatment were censored. To quantify the impact of this source of uncertainty, the already built-in model settings were adjusted to use the estimates on the intention-to-treat population. Using the alternative input implied the change in estimates of costs (incremental costs increased by 13% in the scenario analysis compared to the base case) and outcomes (incremental QALYs increased by 8% in the scenario analysis compared to the base case) for both treatments. This also resulted in a different conclusion on cost-effectiveness than in the base case so its impact was interpreted as significant (the ICER increased by 4% in the scenario analysis compared to the base case).

Although the latest results on overall survival included in the economic model from the ARAMIS trial showed a statistically significant benefit for darolutamide (hazard ratio for death, 0.69; 95% CI: 0.53 – 0.88; p=0.003), although the data might not be fully relevant to draw conclusions on mortality risk reduction versus ADT, as the different distribution of subsequent treatments may impact survival prognosis to an uncertain extent. In order to quantify the impact of this uncertainty on cost-effectiveness estimates, an already built-in model parameter was used to assume the same mortality risk for all treatment arms in the model after 10 years as an alternative input, instead of assuming an effect during the entire time horizon. Quantifying the source of uncertainty affected the effectiveness estimates for darolutamide (incremental QALYs decreased by 5% in the scenario analysis compared to the base case) and marginally, cost estimates as well (incremental costs

increased by less, than 1% in the scenario analysis compared to the base case); as the conclusion on cost-effectiveness also changed with the ICER exceeding the threshold, the impact of considering the uncertainty can be also interpreted as significant (the ICER increased by 6% in the scenario analysis compared to the base case).

The comparator for darolutamide + ADT in the cost-effectiveness analysis was ADT alone; however, the distribution of compounds included in ADT was based on an undisclosed expert opinion. By base case, an equal distribution (20% for each) of compounds was applied; this was changed to reflect a higher share for degarelix, goserelin and leuprorelin (30% for each) and a lower share for triptorelin and buserelin (5-5%). Applying the alternative input for the already available model parameter affected the cost estimates for both treatments compared in the analysis (incremental costs increased by less, than 1% in the scenario analysis compared to the base case), yet the cost-effectiveness conclusion remained the same, and so its impact can be interpreted as not significant (the ICER increased by less, than 1% in the scenario analysis compared to the base case).

The targeted database review during the assessment procedure identified several risk-sharing agreements and successful procurement notices that may impact the net prices of compounds used throughout the treatment sequence. As the impact of these agreements on prices were originally not explored in the cost-effectiveness analysis, as an alternative input for quantification, 30% price reduction was assumed for the list prices of enzalutamide, abiraterone and degarelix. Adding the parameter for price discount was a minor modification to the model. The cost estimates changed for both treatments (incremental costs increased by 7% in the scenario analysis compared to the base case), and the resulting ICERs also yielded a change compared to the base case cost-effectiveness conclusion, so the impact of this source of uncertainty was determined significant (the ICER increased by 7% in the scenario analysis compared to the base case).

The utility values applied in the economic model were derived based on the EQ-5D data collected in the ARAMIS clinical trial (and from some secondary sources), and UK tariffs were used to estimate the weights. However, a local tariff set, suitable to provide more relevant estimates of utility had already been published when the economic evaluation was carried out. This source of uncertainty is impossible to quantify without accessing

the patient-level data from the clinical trial, yet it could alter the effectiveness estimates for both treatments. Nevertheless, without the ability to quantify its impact or describe its direction, the effect of the uncertainty was described as „not quantifiable”.

Table 6: Summary of the identified sources of uncertainty in the economic analysis of darolutamid. *The quantifiable or expected impact on base case results of each source of uncertainty. **If considering the impact of the source of uncertainty changes the base case cost-effectiveness conclusion, it is deemed significant. For non-quantifiable sources of uncertainty, „?↕" marks the uncertain direction of impact. „?↓" marks that a lower value is expected compared to the base case. For each source of uncertainty, parentheses hold the parameter input for base case (BC) and the scenario analysis (ScA), respectively; brackets hold the name of the relevant section of the assessment report.

	Quantifiable?	Scenario available in the model?	Incremental costs (HUF)*	Incremental effectiveness (QALY)*	ICER (HUF/QALY)*	Impact on cost-effectiveness conclusion**
Base case (darolutamide is cost-effective to ADT)	Reference					
Time horizon of the analysis (BC: time horizon is 27 years; ScA: time horizon is 10 years) [Type of economic analysis]	Yes	Yes	-2%	-32%	45%	Significant
Restriction of the efficacy analysis population to mITT (BC: censor patients who develop metastasis before starting treatment; ScA: patients who develop metastasis before starting treatment count as events) [Evaluation of the economic model - transition probabilities]	Yes	Yes	13%	8%	4%	Significant
Long-term effectiveness of darolutamide on overall survival (BC: assume benefit in mortality over the entire analysis time horizon; ScA: do not assume benefit in mortality after 10 years) [Evaluation of the economic model - transition probabilities]	Yes	Yes	<1%	-5%	6%	Significant
Resource use patterns (comparator and subsequent therapies) (BC: assume equal distribution of degarelix, goserelin, leuprorelin, triptorelin and buserelin as part of ADT;	Yes	Yes	<1%	-	<1%	Not significant

	Quantifiable?	Scenario available in the model?	Incremental costs (HUF)*	Incremental effectiveness (QALY)*	ICER (HUF/QALY)*	Impact on cost-effectiveness conclusion**
ScA: differentiate the distribution of compounds used as part of ADT: higher share for degarelix, goserelin and leuprorelin, lower for triptorelin and buserelin) [Evaluation of the economic model – cost inputs]						
Price discount on subsequent treatments (BC: use the public list prices of abiraterone-acetate, enzalutamide, degarelix; ScA: assume 30% discount on abiraterone-acetate, enzalutamide, degarelix list prices) [Evaluation of the economic model – cost inputs]	Yes	No	7%	-	7%	Significant
EQ-5D value set used to estimate utilities (BC: use the UK value set when estimating utilities; ScA: use the Hungarian value set for estimating utilities) [Evaluation of the economic model – utility inputs]	No	No	-	?↕	?↕	Not quantifiable

4.4 Implementation to routine practice (Objective 3)

4.4.1 Case series analysis

Between the 1st of January and the 16th of July 2022, a total number of 66 reimbursement submissions for 42 product-indication pairs were assessed, of which 33 were evaluating treatments of other diseases than solid tumours. Of the remaining 9 product-indication pairs, 3 were re-submissions of earlier dossiers (as the previous procedure ended without a legally binding decision), and there was one submission requesting a price increase. Therefore, a total number of 5 product-indication pairs fell within the scope of the current analysis. The product-indication pairs are described in Table 7.

Table 7: Product-indication pairs

Product (as per SmPC section 1.)	**Active Substance**	**Indication (as per SmPC section 4.1)**
OPDIVO 10 mg/mL concentrate for solution for infusion.	Nivolumab	OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.
OPDIVO 10 mg/mL concentrate for solution for infusion.	Nivolumab	OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.
TAGRISSO 40 mg film-coated tablets TAGRISSO 80 mg film-coated tablets	Osimertinib	TAGRISSO as monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA nonsmall cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations (see section 5.1).
Mekinist 0.5 mg film-coated tablets Mekinist 2 mg film-coated tablets Tafinlar 50 mg hard capsules Tafinlar 75 mg hard capsules	Trametinib, dabrafenib	Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation. Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.

Product (as per SmPC section 1.)	Active Substance	Indication (as per SmPC section 4.1)
Verzenios 50 mg film-coated tablets Verzenios 100 mg film-coated tablets Verzenios 150 mg film-coated tablets	Abemaciclib	Verzenios in combination with endocrine therapy is indicated for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence. In pre- or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

The conclusions on CAB, LoE and RoB and the identified sources of uncertainty in the economic evaluations are summarised at the end of this chapter in Table 8, Table 9, and Table 10, respectively.

In two cases out of five, the assessment included an alternative base case that combined multiple quantifiable sources of uncertainty. Both alternative base-cases yielded less favourable cost-effectiveness results for the technology assessed. It is difficult to make an inference based on this very limited set of data, yet the feasibility of proposing an alternative base case could have depended on the quantifiability of sources of uncertainties identified, as well as operational factors (i.e. the economic assessor's experience). Although proposing an alternative set of base case cost-effectiveness results did not occur for three assessments, it is difficult to determine whether doing so could have delivered added value for these reports.

4.4.1.1 Nivolumab for the treatment of NSCLC

The reimbursement submission of nivolumab aimed to introduce a novel indication for the first-line treatment of adults with metastatic non-small cell lung cancer (without sensitising EGFR mutation or ALK translocation), combined with ipilimumab and 2 cycles of chemotherapy. Nivolumab is already reimbursed for some other indications to treat neoplastic diseases, but the decision still requires a legal act. According to publicly available reports, no RSA was in place at the time of the submission, and the therapy was not funded for individual patients through IFRs.

The clinical added benefit of nivolumab combined with ipilimumab and 2 cycles of chemotherapy was described as important over the comparator (4 cycles of platinum-

based chemotherapy) in terms of overall survival. This conclusion is supported by high-level evidence with low study-level RoB based on the CheckMate 9LA study (35).

The applicant presented scenario analyses with pembrolizumab monotherapy and pembrolizumab combined with platinum-based chemotherapy as alternative comparators. However, there is no data available from direct comparisons to inform these comparisons, and the respective relative effectiveness data was sourced from an unpublished indirect comparison. The source of uncertainty was described as significant, yet non-quantifiable, affecting estimates on both costs and outcomes (section *Type of health economic evaluation*).

A further, significant source of uncertainty was identified: as both pembrolizumab and nivolumab have undergone public procurement and have been purchased by NHIFM, achieving an undisclosed price discount (section *Costs*). Certain high cost pharmaceutical products, such as nivolumab and pembrolizumab, are available through a special ("itemised") reimbursement technique, only accessible at designated healthcare providers, i.e. specific university clinics and large hospitals. Instead of these individual healthcare providers buying the products themselves and billing the payer (NHIFM), the payer arranges a centralised public procurement procedure. This procedure facilitates significant, yet confidential rebates on prices. This source of uncertainty impacts the cost estimates significantly in the economic evaluation, also having implications on the expected savings in the budget impact analysis, which partially depends on the market share of the new technology.

4.4.1.2 Nivolumab for the treatment of MPM

This submission of nivolumab aimed to introduce a novel indication of an already reimbursed compound for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma, in combination with ipilimumab. According to publicly available reports, no RSA was in place at the time of the submission, and the therapy was not funded for individual patients through IFRs. The decision on this reimbursement submission also needs a legal act.

The clinical added benefit of nivolumab combined with ipilimumab was described as important over pemetrexed combined with platinum-based chemotherapy in terms of overall survival. The endpoint was considered both clinically- and patient-relevant. This

conclusion is supported by moderate-level evidence with high RoB on study level (i.e. open-label design of the CheckMate 743 study (36)), although the endpoint-level RoB was not high.

The methodological approach to the long-term (2-6 years) survival was identified as a quantifiable and significant source of uncertainty, as the applicant used data from a clinical study that might not be relevant to the current PICO (section *The economic model used for the assessment and its key assumptions*) based on the pivotal trial. There were a number of differences between the pivotal CheckMate 743 study and the MAPS trial, in terms of baseline characteristics, prognosis and subsequent therapies. No attempts to adjust for these differences were made when fitting distributions to the survival curves. Apart from the base case using the MAPS data, the assessment report contained a scenario prepared by the Department of Health Technology Assessment which used overall survival data from the CheckMate 743 study, showing a different, less favourable conclusion on cost-effectiveness than for the submitted base case.

The following non-significant sources of uncertainty were identified:

- inconsistent calculations regarding the unit costs of pemetrexed: there was double counting for the comparator arm and as subsequent treatment for both arms, as the acquisition cost of pemetrexed was accounted for both as a standalone cost while it is also included in a DRG used to value direct health costs. This source of uncertainty affected cost estimates in the economic evaluation (section *The economic model used for the assessment and its key assumptions*).
- only grade 3 or higher adverse events affecting at least 2% of the study population were captured in the economic evaluation, and the assessment assumed that adverse events only occur once over the entire treatment period, affecting estimates on costs and outcomes in the economic assessment (section *Health outcomes*).
- the impact of subsequent therapies on quality of life and overall survival is overlooked (subsequent therapies are only assumed to impact costs), as well as having inconsistency in the distribution of therapies between the economic model, the expert opinion and the CheckMate 743 study. This source of uncertainty affects estimates on outcomes (section *Health outcomes*).

- An additional source of uncertainty related to subsequent treatments is their inconsistency in terms of assumed duration. The study referenced by the applicant reports the duration of 2L+ therapies to be 1.6 months. However, in the economic assessment, it is estimated that treatment with a subsequent line of therapy will last 2.54 months. This estimate appears as 11 weeks in the cost-effectiveness model and 10.16 weeks in the budget impact model. This effects treatment cost estimates (section *Costs*).
- By base case, the relative dose intensity for nivolumab and ipilimumab was 100%, whereas the observed values in the Checkmate 743 study were 69% and 83,6%, respectively. Moreover, the economic assessment does not consider vial sharing, despite that the dosage of ipilimumab is dependent on body weight and the dose of pemetrexed combined with cisplatin is conditional upon body surface area. This source of uncertainty affects treatment costs, and was found to be quantifiable (section *Costs*).
- The base case time horizon of 20 years in the analysis may be excessive in light of the relatively short duration of follow-up in the clinical trial (43.1 months), the methods used for the extrapolation beyond trial data, and given that the average life expectancy at the age of 68 is 14.32 years. The source of uncertainty was quantifiable in the analysis, affecting both costs and outcomes (section *Input parameters for the economic evaluation*).

A further source of uncertainty was that despite the explicit recommendation of the local guidelines for economic evaluation, the results of the budget impact analysis were only presented for three years, yet this does not affect cost-effectiveness results.

4.4.1.3 Osimertinib for the treatment of NSCLC

Osimertinib was submitted for reimbursement in a novel indication as an adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer, whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. Osimertinib was already reimbursed for the treating for some patients with locally advanced or metastatic EGFR T790M+ patients with NSCLC, yet decision on this reimbursement submission also implies a need for a legal act. According to publicly available reports, no RSA was in place at the time of the submission, and the therapy was not funded for individual patients through IFRs.

Osimertinib was deemed to deliver a major clinical added benefit over routine surveillance (placebo) in terms disease-free survival, described as a clinically relevant endpoint in NSCLC. This is supported by a clinical study with high level of evidence with low RoB in ADAURA (37). It is important to note (as ESMO highlighted as well) that DFS was a secondary endpoint in the trial.

The incremental cost-effectiveness ratio was favourable according to the base case analysis; the time horizon (37 years) of the analysis was identified as a major source of uncertainty (section *Type of health economic evaluation*). It has been noted that on a time horizon shorter than 20 years, osimertinib is not cost-effective (given its current list price). Choosing the appropriate time horizon for the economic assessment can be difficult, as the local guideline advises it to be long enough to enable all relevant outcomes and costs to occur which can be related to the disease to be treated. MAHs usually assume that it is not reasonable for a person to live beyond the age of 100, so they estimate the time horizon if the economic assessment as the time until the age patient cohort (usually defined as the mean age at baseline in the pivotal trial) reaches the age of 100. This may be exaggerative for a disease with poor prognosis, such as NSCLC (especially that in this particular case, where the median follow-up was only available for disease-free survival: 22.1 months in the osimertinib group and 14.9 months in the placebo group). Moreover, choosing a long time horizon increases the impact of assumptions and extrapolations of treatment effect on estimates on outcomes. Therefore, the average residual life expectancy at the baseline age of the cohort may provide a more conservative estimate of the time horizon under the assumption that the relevant time horizon for a group of patient suffering from a life-threatening disease may not exceed the time horizon that would have been relevant for the general population.

The following sources of uncertainty were also present, affecting estimates on both costs and outcomes:

- a non-quantifiable source of uncertainty was that the transition probabilities and utility values for patients with distant metastasis were sourced from the FLAURA study, which compared first-line treatment with osimertinib against either erlotinib and gefitinib in patients with EGFR+ NSCLC (section *Input parameters for the economic evaluation*);

- a quantifiable source of uncertainty was that the gender- and age-specific mortality rates were from 2019, but at the time of the analysis, more recent data were available on these parameter from 2020 (section *Input parameters for the economic evaluation*).

The applicant did not consider the recommendation of the guidelines on health economic evaluations for providing estimates on budget impact for 4 years, although this source of uncertainty does not impact the conclusion on cost-effectiveness.

4.4.1.4 Dabrafenib and trametinib for the treatment of NSCLC

The reimbursement submissions of dabrafenib and trametinib aimed to introduce a new indication (non-small cell lung cancer) of an already reimbursed compound, originally for the treatment of melanoma. There was no RSA in place for dabrafenib and trametinib; some patients gained access to the treatment via IFRs (40 packs of Mekinist in 2021, totalling at 45.29 million HUFs). The decision on the reimbursement of dabrafenib and trametinib also requires a legal act.

Based on the phase II single arm pivotal study BRF113928 (38), the clinical added benefit for both first- and second line use can be described as minor in terms of objective response rate, which was deemed a clinically (but not patient-) relevant endpoint. This is supported by low-level evidence coming from studies with high RoB. The applicant also presented an indirect comparison of PFS and OS with pembrolizumab+platinum+pemetrexed and immunotherapy. Although the endpoints can be characterized both clinically and patient-relevant, the indirect comparison showed no proof of benefit for dabrafenib and trametinib over the comparator, supported by low-level evidence coming from an indirect comparison.

The most important source of uncertainty is the effectiveness of the comparator (concerning both the sources of clinical data and curve fitting methods used for the extrapolation) due to the lack of comparative data. Given that a clinical trial directly comparing the technology with its locally relevant comparator is available, MAHs often rely on indirect comparisons to present data on effectiveness. However, these may be quite heterogeneous in terms of their methodology, e.g. whether or not a systematic literature review was conducted or if any adjustments were attempted to correct for potential bias. The results of indirect comparisons can be explicitly used in health

economic models to feed the extrapolations beyond the actually available data. Moreover, the choice of methods to produce these extrapolations should be well documented as in economic assessments, it is crucial to determine the extent which the estimated incremental effectiveness relies on scientific evidence, rather than assumptions.

This source of uncertainty is quantifiable to some extent, affecting both cost and outcomes estimates for the comparator arm, with a significant effect on the cost-effectiveness conclusions (section Input parameters for the economic evaluation). Further sources of uncertainty were:

- the use of utility decrement values from an unclear source for depicting the effect of adverse events, affecting the estimates on outcomes on both treatment arms in the economic evaluation (non-significant, section *Health outcomes*);
- the unit costs of pembrolizumab, nintedanib, nivolumab, atezolizumab, bevacizumab as there has been a public procurement procedure for these affecting the cost estimates on both treatment arms in the economic evaluation (significant, section *Costs*).

Applying the price levels reached by the procurement procedures yielded the change of the cost-effectiveness conclusion, and implying a price reduction to the offered list price of dabrafenib or trametinib. As expected, the price reduction needed to maintain cost-effectiveness was higher for the first-line treatment than for the second-line treatment.

4.4.1.5 Abemaciclib for the treatment of eBC

The reimbursement submissions of abemaciclib aimed to introduce a new indication for the treatment of early breast cancer. Abemaciclib is already reimbursed, the submission aimed to introduce a new indication. The reimbursement decision did not necessitated a legal act; there was also a biennial RSA (more precisely, a price-volume agreement) in place for the products. The volume on IFRs in the last available calendar year (2021) was 20 packages, totalling at 7.66 million HUFs on gross retail price.

Abemaciclib was determined as delivering a major clinical added benefit on a clinically and patient-relevant endpoint (invasive disease-free survival; distant metastasis-free survival). The level of evidence can be described as high based one the monarchE study (39), however, the RoB on study level could not be determined as the IQWiG report was not available at the time of the analysis. However, as there was no masking in the trial

and there were a number of protocol modifications affecting the primary endpoint and patient reported outcomes following the start of patient enrolment. The uncertainty arising from the immature overall survival data was identified as a major source of clinical uncertainty. Although there is evidence on the risk reduction in disease recurrence following the completion of the 2-year treatment period, it is not known whether the treatment affects the incidence of late recurrence.

The most important, also quantifiable and significant source of uncertainty in the health economic evaluation was the unit costs of pharmaceuticals in the analysis. This is due to that RSAs were in place for abemaciclib, ribociclib, palbociclib, denosumab and rivaroxaban, resulting in presumably lower net prices for these compounds. The cost-effectiveness results are dominantly affected by the price of CDK4/6 inhibitors (abemaciclib, ribociclib and palbociclib), although the association of their prices with the results is somewhat complex:

- Apart from abemaciclib being offered in eBC, all CDK4/6 inhibitors can be offered in the later stages of the disease, but only once for the treatment pathway of each patient. Once patients experience disease recurrence while being treated with abemaciclib, it is not reasonable to re-challenge the treatment of the disease with another CDK4/6 inhibitor. This essentially means that early treatment with abemaciclib will result in avoiding the costs of using CDK4/6 inhibitors later in the treatment trajectory.
- As no major differences were observed between the efficacy of CDK4/6 inhibitors in the advanced or metastatic setting of breast cancer, it is not reasonable to assume that any difference in their net prices are supported by the judgement of their therapeutic value. Therefore, the price of each CDK4/6 inhibitor is not independent from the price of the other compounds: if one of the three MAHs is not willing to offer at least the same discount as the others, that MAH will have to face a challenge in the competition.
- The local pharmaceutical reimbursement system in Hungary does not formally allow different prices for the same compound used in different indications. This means that the price of a compound used in a particular indication is not independent from the value of the compound in a different indication.

Therefore, if a set of similarly effective compounds can be used once, but either earlier or later in the disease trajectory, and differential pricing based on the specific indication is not reasonable to assume, the discounts on one of the compounds will not simply improve its cost-effectiveness, but will also impact the avoided costs as well.

Moreover, a biosimilar intravenous formulation of trastuzumab is available, also yielding a lower price for this treatment (although it is unclear why this compound is used in this assessment as trastuzumab is not authorized to treat HER2 negative breast cancer). Finally, the decision on the price increase of tamoxifen was pending at the time of the assessment, and the dosage of tamoxifen in the economic assessment was different to the one described in the summary of product characteristics. This source of uncertainty concerned the *Costs* section of the assessment report.

Further, yet non-significant sources of uncertainty affecting both costs and outcomes were the following:

- assumptions concerning the long-term relative effectiveness of abemaciclib on iDFS (section *Health outcomes*);
- waning of the treatment effect of abemaciclib after discontinuation (section *The economic model used for the assessment and its key assumptions*);
- time horizon of the analysis (section *Type of health economic evaluation*);
- inconsistency between the monarchE ITT population and the proposed wording for the reimbursed indication (section *Type of health economic evaluation*);
- inconsistency between the life-year payoffs in this analysis and the estimates in earlier submissions (section *Input parameters for the economic evaluation*);
- inconsistency between the assumptions concerning overall survival with abemaciclib and the observations related to overall survival in the monarchE trial (section *Health outcomes*);
- inconsistency between the distribution of subsequent therapies in this submission and the assumptions in earlier submissions (section *Input parameters for the economic evaluation*).

A more recent publication on breast cancer incidence estimates was identified from the same data source, affecting budget impact estimates, but having no impact on cost-effectiveness estimates.

Finally, an alternative base case was proposed that captured the quantifiable sources of uncertainty, yielding a higher price discount than in base case to reach the relevant cost-effectiveness threshold.

4.4.1.6 Qualitative Synthesis

Regarding the exogenous factors to the medicinal products covered in this analysis, all compounds were already reimbursed for a different indication at the time of submissions. Rather unsurprisingly, a legal act was needed for all but one submission (as these medicinal products aimed to treat a group of patients without a targeted therapy), whereas having an RSA in place was reported for only one medicinal product. Expenditures on IFRs were either not reported at all, or were relatively low, making it difficult to interpret the association of this factor with the outcome of the reimbursement decision.

Table 8: Exogenous factors to reimbursement submissions

Product	Indication	Reimbursed in a different indication?	Legal act needed?	RSA in place?	Expenditure on IFRs
Nivolumab	NSCLC	Yes	Yes	Not reported	Not reported
Nivolumab	MPM	Yes	Yes	Not reported	Not reported
Osimertinib	NSCLC	Yes	Yes	Not reported	Not reported
Dabrafenib / Trametinib	NSCLC	Yes	Yes	Not reported	45.29 mn HUFs
Abemaciclib	eBC	Yes	No	Yes	7.66 mn HUFs

Contrary to the observations made on the exogenous factors, the conclusions on CAB, LoE and RoB were quite heterogeneous among submissions, however, this seems to be reasonable in light of different assessment scopes and maturity of clinical data. In one case, the risk of bias could not be determined due to the lack of assessment report from IQWiG.

Table 9: Conclusions on clinical added benefit, level of evidence and risk of bias

Product	Indication	Comparator	Clinical added benefit	Level of evidence	Risk of bias
Nivolumab	NSCLC	Platinum-based chemotherapy	Important	High	Low
Nivolumab	MPM	Platinum-based chemotherapy	Important	Moderate	High
Osimertinib	NSCLC	Routine surveillance	Major	High	Low
Dabrafenib / Trametinib	NSCLC	Pembrolizumab, platinum and pemetrexed	No proof of benefit	Low	High
Abemaciclib	eBC	Placebo (endocrine therapy)	Major	High	N/A

As for the critical appraisal of economic evaluations, the highest number of major sources of uncertainty was identified for the section *Input parameters for the economic evaluation* and *Costs*, whereas no sources of uncertainty were identified for *Results of the economic evaluation* and *Sensitivity analyses* sections. While the latter are rather technical sections of the assessment reports, the high number of sources of uncertainty in the former section highlight the focus of the appraisal methods on the external validation of model inputs.

In two cases out of five, the assessment included an alternative base case that combined multiple quantifiable sources of uncertainty. Both alternative base-cases yielded less favourable cost-effectiveness results for the technology assessed. It is difficult to make an inference based on this very limited set of data, yet the feasibility of proposing an alternative base case could have depended on the quantifiability of sources of uncertainties identified, as well as operational factors (i.e. the economic assessor's experience). Although proposing an alternative set of base case cost-effectiveness results did not occur for three assessments, it is difficult to determine whether doing so could have delivered added value for these reports.

Table 10: Sources of uncertainty in the economic evaluations. Numbers indicate the number of identified sources of uncertainty per section as [significant/non-significant].

Product	Indication	Type of health economic evaluation	The economic model used for the assessment and its key assumptions	Input parameters for the economic evaluation	Health outcomes	Costs	Results of the economic evaluation	Sensitivity analyses	Alternative base case proposed?
Nivolumab	NSCLC	1/0	0/0	0/0	0/0	1/0	0/0	0/0	N
Nivolumab	MPM	0/0	1/0	1/1	0/2	0/2	0/0	0/0	N
Osimertinib	NSCLC	1/0	0/0	1/1	0/0	0/0	0/0	0/0	N
Dabrafenib / Trametinib	NSCLC	0/0	0/0	1/0	0/1	1/0	0/0	0/0	Y
Abemaciclib	eBC	0/2	0/1	0/2	0/2	1/0	0/0	0/0	Y

4.4.2 Practical application of the research findings: knowledge repository

These methodological improvements assume essential core professional competencies to the assessment procedure in the public administration, complemented by awareness of legal acts, instructions or databases. These can be considered publicly available information that might be subject to change and updated from time to time. Good practices and experience may have a formal (i.e. via an SOP) and informal component (for example, a verbal discussion on a meeting of the assessors). These heterogeneous pieces of information can be described as organisational knowledge which has the potential to be turned into a formalised know-how that can be handed over to newcomers in the organisation. The imbalance of expectations in terms of quality and consistency towards the deliverables of public administration processes as well as respective resource constraints to meet these expectations implied the need for novel tools for knowledge management and supportive approach to quality assurance. The attempts to standardise the assessment methods and the report structure were complemented with setting up an internal knowledge repository that enables capturing formal and informal knowledge on

compiling assessment reports (40). In terms of its contents, apart from formalised knowledge (by summarising and referencing book chapters, journal articles or other rather formal sources of knowledge), good practices, experience gained through past assessments and even conclusions from internal meeting memos may be viewed as informal knowledge that can be stored in a knowledge repository. The repository is also a platform for smart capacity building, by efficiently distributing organisational knowledge between assessors, as well as identifying the lack of competencies for capacity building. Sustainability is key aspect to such services: although setting up a similar service can be demanding, maintenance can be carried out by relying on resources that is already available within the organisation. The knowledge repository is described through its functional-, content- and technical specification.

4.4.2.1 Functional specification

The basic functionality of the knowledge repository is to serve as a single-direction communications channel to deliver professional content for the colleagues of the Department of Health Technology Assessment. The information is available in structured (according to the sections of the Department's deliverables) and searchable format. At the same time, the content is modifiable with the appropriate authorisation level, and editing can be carried out with a fundamental knowledge of text editing and system administration skills. Accessing the repository should not imply other authorisation than having access to NIPN's virtual private network, although editing the repository requires administrator (i.e. content steward) access. The appropriate authorisation level ensures quality control over the content and that the information in the repository is curated.

4.4.2.2 Content specification

The contents of the repository consist of formalised, publicly available information that is only available in a fragmented way, and to some extent informal, but also well-established good practices. The core component of the knowledge repository is set up to correspond to the structure of the assessment report (clinical assessment; cost-effectiveness analysis; budget impact analysis; international outlook and corresponding subsections), complemented by the documentation of good practices (case studies), a collection of ad-hoc literature reviews, and few other, miscellaneous sites. Processing and even recycling already available, fragmented training materials has been essential during content production. The add-on functions of the knowledge repository (searchability,

structure, uniform design) imply that the content is not available as separate files to download, but as part of a content management software.

4.4.2.3 Technical specification

The technical solution used for the knowledge repository as a service should be scalable while at the same time, content management should be intuitive. In order to have the best possible user experience, the service should be platform-independent and attractive to the colleagues of the Department of Technology Assessment. The scarcity of resources in the public administration imply that the service should be provided without paying any licensing fees, as well as maintained without the purchase of external goods or services. Eventually, Grav was selected as the technical solution for the knowledge repository, as it matched these expectations. The services aiming to share knowledge within the public administration, such as NIPN's intranet, are related to a particular supportive department (i.e. Human Resources) more focused on distributing information related to the operations of the public administrative body itself (i.e. citing legislation, internal instructions) than elaborating on professional know-how.

4.4.3 Practical application of the research: organisational improvements

The effect of the aforementioned methodological improvements on the impact of assessment reports on reimbursement decisions were accompanied (and possibly enhanced) by organisational developments. First of all, the assessment report template was revised to create sections that represent mutually exclusive topics of the submission dossier, so the identified sources of uncertainty can be presented along the report structure. Second, a set of common phrases (and even templates for tables) were developed for the assessment report template that can be used to describe the contents of the reimbursement submission in the appropriate section, regardless of the technology or the disease to be treated. Third, as an attempt to have a direct impact on health policy, we published a handbook in Hungarian that laid down the expectations towards reimbursement submissions and presented the detailed methods used by the Department of Health Technology Assessment for creating assessment reports on the website of NIPN (41). Finally, the SOPs of the Department of Health Technology Assessment were updated to cover the implications of the updated methodology on the core assessment procedure.

Regardless of the complementary organisational changes that facilitate taking full advantage of improving the assessment procedure, some components of the presented methodological approaches were determined too ambitious for routine use. For example, as part of a demonstrative exercise to conduct a de novo network-meta analysis to evaluate the risk of urinary tract infections with gliflozins, the risk of bias for all included studies have been assessed (42). This can be interpreted as a feasibility study, noting that although there is capacity to provide an evidence synthesis and to assess of risk of bias, it is not yet sensible to scale this process up with the current resources to the level of all assessment reports of pharmaceutical products.

Ideally, a methodological improvement should not only be accompanied by organisational changes, but it should also seek synergies with, rather profoundly, the legal framework of health technology assessment (HTA). First, regarding the economic aspects of HTA, following the revision of the local guidelines on economic evaluations in healthcare (8), cost-effectiveness analyses are expected to explicitly present their key assumptions. This recommendation serves as a basis for identifying, quantifying and interpreting their impact on the cost-effectiveness conclusion in the assessment report. Second, in terms of the clinical domains of HTA, the EU legislation on joint clinical assessments for health technologies created an environment where sufficient information is expected to enable the competent authorities of member states to conclude on the added benefit, as well as on the level of evidence and risk of bias (43).

5 DISCUSSION

5.1 Potential impact on reimbursement decisions

The current research reports on the analysis of exogenous factors as potential determinants to reimbursement decisions, the development of novel methodological improvements to the assessment procedure, and five cases of reimbursement submissions when these novel methods have been applied in preparing the assessment reports.

The analysis of factors exogenous to reimbursement procedures suggests that risk-sharing agreements (RSAs) and the need for a legal act to reimburse are effective tools in managing the entry of innovative medicinal products to the Hungarian public healthcare system. Although it can be observed that a positive decision on reimbursement was more likely for a submission that aimed to introduce a novel indication of an already reimbursed compound (which is often the case for targeted cancer treatments), in case of the overall purpose of the submission and the expenditure on individual funding requests (IFRs), results were not conclusive. It seems that the local healthcare system is less likely to provide broader access to entirely new compounds, but, on the other hand, more likely to reimburse treatments for additional groups of patients once the compound itself is reimbursed. As the expenditure on IFRs did not seem to explain this, one possible explanation to this phenomenon is that, to some extent, decision on a reimbursement submission that proposes the introduction of a completely new pharmaceutical product, or new indication of an already reimbursed product may also be affected by other, endogenous factors to the actual submission, such as judgement on the relative effectiveness or cost effectiveness. These concepts are captured among the domains of HTA and should be addressed by the local assessment reports, though they have not been evaluated consistently until so far.

Using frameworks similar to the one presented in this research to characterise the clinical added benefit (CAB) as part of the value assessment of health technologies is not unique. Recent research shows that such value frameworks are being tailored to geographic regions and types of health technologies (44). Although many elements of this framework are already in use and assessed in the critical appraisal procedure, a standardised and transparent system was lacking. Using existing frameworks, like ESMO-MCBS, in a national setting is not unique either. In Korea, the American Society of Clinical Oncology

and the ESMO-MCBS were adapted to produce a reliable framework (45). In Canada, multi-criteria decision analysis methods were applied to the development of a value assessment framework for antineoplastic drugs. In addition, researchers validated the framework by assessing the correlation of the resulting scores and ESMO-MCBS thresholds for meaningful benefit (46). In Slovenia, the overall time to access novel antineoplastic pharmaceuticals and its correlation with ESMO-MCBS scores were assessed. Researchers found that time to access is similar for drugs with or without substantial CAB. According to their conclusion, integrating the ESMO-MCBS into reimbursement deliberations could improve access to drugs with substantial clinical benefit (47).

Good practices on approaching uncertainty in economic assessments have been distilled in recent years. The report of Fenwick and colleagues (48) demonstrates value of information (VoI) analysis assessing the extent to which the information generated through research on a particular parameter would improve the expected payoffs associated with a decision by reducing the uncertainty surrounding it. Nevertheless, the concept of VoI focusses on interpreting parameter uncertainty, whereas this framework enables the explicit evaluation structural uncertainty, prompting potential synergy for the complex evaluation of quantifiable and significant sources of uncertainty. In order to aid decision-making and ensure the relevance of their reports, national HTA bodies use different approaches in their processes to evaluate the sources of uncertainty in economic assessments. The framework presented hereby can be seen as similar to the one applied by the National Institute for Health and Care Excellence (NICE). An Evidence Review Group (ERG) is commissioned by NICE to carry out complimentary economic analyses (or even to set up a de novo cost-effectiveness assessment) to identify the potential sources of uncertainty; a research suggests that the analyses of the ERG are highly influential on the outcome of the decision-making process (49). Applying the exact same procedure as in England and Wales would be quite challenging due to resource constraints, as the local HTA body with a headcount of 8 medical and 8 economic assessors in Hungary has 50 days to deliver the assessment reports. Moreover, the number of pharmaceutical submissions per annum exceeded 130 in the last three calendar years.

A strength of the current research is attempting to explore the association between the outcome of the reimbursement procedure and certain independent variables, generated

from the legal and financial environment of each submission in a quantitative way. So far, only limited, descriptive research has been available on the reimbursement decisions in Hungary (50). Studying the impact of exogenous factors on reimbursement decisions contributes to identifying the unmet need for methodological developments to the local critical appraisal procedure. The strength of the methodological developments is their contribution to standardising local assessment reports, while also considering the legal and organisational circumstances of health technology assessment (HTA) in Hungary. The framework to determine the CAB pinpoints the direction of future developments to extending the scope of this procedure: expanding the procedure to other diseases is desirable. A very recent and also positive externality for this future expansion is the publication of ESMO-Magnitude of Clinical Benefit Scale for Haematological Malignancies (51) that may serve as a basis for concluding on the extent of CAB in case of haematological diseases. Future developments should also enable the efficient uptake of deliverables (such as guidelines) coming from joint efforts to improve HTA methodology in Europe, as the organisational bedrock of producing joint work is currently being set up by member state delegates and the European Commission. As part of a future research, the framework to describe CAB could serve as a pillar for the characterisation of the relationship between the CAB and the incremental health gain quantified in the cost-effectiveness analysis, as observed in the case of HAS (52). The structured approach to assessing the sources of uncertainty in economic evaluations also can be viewed as a strength, as these can be used to facilitate price negotiations between the MAH and the payer. Eventually, appropriately described clinical added benefit, alongside with the sources of uncertainty can also help in allocating the right amount of capacity to analysing dossiers throughout decision-making. The case series analysis and organisational improvements contribute to the implementation of findings and may also help formulating approaches for the further improvement of assessment methods. There is further research potential regarding the economic evaluation of health technologies on how (and when) to set up an alternative base case scenario to the one submitted by the MAH, as these have been proposed heuristically.

A potential limitation of studying the determinants of reimbursement decisions as part of the current study is that we did not consider the time necessary for arriving at a decision for each procedure like other studies did (53). Although time is certainly an important

factor, we argue that the time required for decision-making may be biased in the Hungarian setting. Positive decisions may accumulate over time, because some reimbursement procedures (such as the ones needing legislative changes or re-allocation of funds between government functions) apply a sequential, interactive approach and involve stakeholders who are other governmental entities (Ministry of Finance, Ministry of Interior) than the payer and the MAH. Therefore, a clear political mandate to reimburse may also be needed for such decisions that might affect the semi-annual convention of the committee responsible for the prioritisation of product-indication pairs; a lack of mandate essentially means that committee meetings are delayed, creating a backlog in formal decision-making. In the context of this research, this essentially means that the effect of exogenous factors may be prone to time-dependence, limiting the generalisability of findings.

The methods applied to the series of cases yielded comparable results in terms of CAB and sources of uncertainty that can be compared between reimbursement submissions. In themselves, the exogenous factors would not have been suitable to make a distinction between reimbursement submissions, and consequently, should not be used when setting healthcare system priorities. The extent of CAB does not seem to correlate with conclusions on LoE and RoB, but it should be noted that LoE and study-level RoB may be negatively associated, as it can be observed among the cases. It is difficult to identify a clear pattern of association between conclusions on clinical and economic aspects in the case of these reimbursement dossiers. Despite the low number of cases, this phenomenon highlights the importance of consistently applying the methods developed in this research. Although the application of both novel frameworks were straightforward, there are some limitations to evaluating the impact of assessment reports using the methodological improvements as well. First of all, there was no control group of assessment reports that may serve as a reference in evaluating the net impact of the difference in the applied methods, not to mention adjusting to the effect of exogenous factors to the reimbursement procedure. To address this limitation, it must be noted that the partial implementation of the frameworks would have implied a compromise on the quality and consistency of assessment reports that would undermine the reputation of the Department. A historical comparison of assessment reports could have been reasonable, but the operationalisation of the contents of earlier documents would have been difficult due to the lack of an

alternative approach for concluding on clinical benefit or identifying sources of uncertainty in economic assessments. A second limitation would be that there was no formal hypothesis testing carried out in a similar way as for exogenous factors to quantify the association between the contents of the assessment report (CAB, sources of uncertainty) and the outcome of the reimbursement decision. A potential response to this critique may be that to date, the presented frameworks have only been used to prepare five assessment reports. Although this figure is certainly expected to increase, the low number of cases limits the possibility of hypothesis testing, especially for multivariate methods to adjust for any potential confounding. Moreover, at the time of writing the thesis, the formal reimbursement decisions are still to be made for reimbursement submissions presented in the case series. This would also enable evaluating if a difference in formal decisions on medicinal products with identical conclusions on CAB, LoE, RoB or sources of uncertainty can be attributable to a determinant influencing the outcomes of reimbursement procedures that is not yet identified, or not operationalised until so far.

Evidence from other settings on the added value of assessment reports is promising. Kaltenthaler and colleagues (54) conducted a research with the aim of understanding how ERG's exploratory analyses are conducted and used by the NICE Appraisal Committee. The authors reported that for single-technology appraisals where an ERG exploratory analysis was carried out (n=76), the appraisal consultation document was clearly influenced by the analysis in the majority of the cases (n=55). Appraisal consultation documents frequently requested additional work from the company, while referring to the exploratory analysis conducted by the ERG.

It also seems that the evidence-based conclusion on clinical added benefit (CAB), together with implications on pricing help formal decision-making bodies throughout the negotiations (potentially by motivating market authorisation holders - MAHs - to offer guarantees on outcomes) to achieve their goals. A research carried out in Germany (55) covered the consistence on IQWiG's and G-BA's conclusions on additional benefit. The researchers found that G-BA decisions were generally more positive than the IQWiG recommendations: for the cases evaluated, G-BA concluded on an added benefit in two thirds of the cases, whereas IQWiG rated only half of the submissions as "delivering added benefit" over the appropriate comparator. It is suggested that the closed hearing by

G-BA between issuing the IQWiG recommendation and the final decision may explain the divergence of G-BA's position from IQWiG's recommendation.

5.2 Implications for future research

At the moment, the impact of methodological improvements to assessment procedures and their association with reimbursement decisions can be somewhat difficult to evaluate through quantitative methods, especially statistical hypothesis testing. In light of the relatively low number of assessment reports until so far and the recent introduction of the new methods to the local value assessment framework, we can reasonably expect the impact of any improvement to be assessed on a longer time horizon. Moreover, complementary tools like redesigned assessment report templates, introducing submission templates for MAHs and common set of phrases in assessments can amplify the impact of such methodological improvements.

A possible subject of future research is to explore the difference in reimbursement decisions according to the existence and extent of clinical added benefit, as well as in light of the sources of uncertainty identified by using different statistical methods, such as hierarchical models. The impact of assessment reports on time needed to arrive at a legally binding NHIFM resolution from the dossier submission date can also be up for interest. Needless to say that these endeavours can only be moved forward under the assumption of having a sufficient number of completed reimbursement procedures that used assessment reports with the improved methodology.

It might be up for interest to introduce different taxonomies to categorise the identified sources of uncertainty in economic evaluations. One of these taxonomies, possibly most relevant to economists preparing the economic evaluations is defining the type (56) of uncertainty as variability (or stochastic uncertainty), heterogeneity, parameter uncertainty and model (structural and methodological) uncertainty. Another possible taxonomy that might better serve the interest of reimbursement decision-makers is using the assessment scope to link each source of uncertainty to the respective component of the PICO. To seek better accountability in reimbursement procedures, it might be reasonable to make a distinction between sources of uncertainty that are related to the core economic evaluation (developed centrally by the MAH) and those that come from the local adaptation (supervised by the local subsidiary and frequently carried out by consultancies). On top

of describing the sources uncertainties with more sophisticated approach, it would be rational to describe the validity of economic models in details by addressing the face-, internal-, cross-, external-, predictive validity in assessment reports. While this is certainly desirable to enhance the credibility of an HTA body's deliverables, it should come with sufficient guidance for assessors to help them understand these concepts and make sure that these improvements scale up well. Moreover, the relevance of including these aspects needs to be clear to all stakeholders involved in reimbursement decision-making, implying external knowledge management efforts from the HTA body to avoid counterproductive effect on the uptake of assessment reports.

6 CONCLUSIONS

The analysis of exogenous factors showed that there is an association between having an RSA on the medicinal product at the time of submission and the reimbursement procedure concluding to a positive decision for the same compound. However, if a legal act is needed for the reimbursement of a medicinal product, the odds are is significantly less favourable for a positive decision for reimbursement. There is no evidence of a statistically significant association between the reimbursement decision and expenditure on individual funding requests, nor between the reimbursement decision and the overall aim of the submission (objective 1).

The assessment of clinical added benefit, accompanied with a framework for identifying, quantifying and interpreting the sources of uncertainty are methodological improvements that were possible to design in alignment with the current assessment procedure of the submitted clinical and economic evidence. These improvement take advantage of local specificities arising from the broader legal framework of health technology assessment, even in light of resource constrains (objective 2).

After testing the implementation of methods in the day-to-day routine of critical appraisal, it is believed to be shown that the proposed methods can be scaled up for routine use in the local decision-making on innovative medicinal products, and in particular for treatments of solid tumours. The methodological improvements are accompanied with the introduction of knowledge management tools and process developments, revised document templates, better quality assurance which can be characterised as organisational improvements (objective 3).

The described frameworks are methodological developments for the local assessment procedure, easy-to-use, facilitate efficiency in an environment with resource constraints and complement the already existing tools for critically assessing the submitted reimbursement dossiers. This assessment procedure with solid methodological foundations is also expected to facilitate access to innovative medicinal products that deliver tangible benefits for patients in exchange for reasonable societal costs. The uptake and consistent application of these methods by assessors and institutions are ensured by organisational developments, as well as by seeking synergies with the broader legal

framework of health technology assessment in Hungary and in the European Union as well.

Potential future developments include, but not limited to broadening the scope in terms of treatments for diseases covered by the assessment of the clinical added benefit; further formalising the identification of sources of uncertainty in economic evaluations. In general, increasing the transparency of documents used during critical appraisal is desirable to facilitate external quality control. Developing a template for clinical and economic assessments accompanying reimbursement submissions would also benefit the strive for consistent and high quality assessment reports.

Using both of the presented frameworks in the daily routine of the assessment procedure is expected to increase the efficiency of decision-making and also to amplify the impact of assessment reports on the outcome of decisions. The efforts on methodological developments and their implementation contribute to taking the local critical appraisal process to the next level; they also facilitate realising the vision of an active, responsible and responsive health technology assessment body in Hungary.

7 SUMMARY

The critical appraisal of reimbursement dossiers has been a core component of the local health technology assessment procedure in Hungary since its institutionalisation, although the methods to compile the assessment report have not been specified in details. The added value of assessment reports was unclear due to the lack of description of the potential association between the outcome of the formal reimbursement decision with exogenous factors to the submissions. This research analyses some of these factors (for example, the presence of risk-sharing agreements), and presents two methodological approaches to better describe clinical and economic domains in the local assessment reports. The feasibility of the methodological developments is demonstrated on a case series of five reimbursement submissions.

One of the methodological approaches aims to describe the clinical added benefit of antineoplastic pharmaceutical products, alongside the corresponding level of evidence and study-level risk of bias. The other methodological approach operationalises the critical appraisal of the submitted economic evaluations by identifying, quantifying and interpreting the sources of uncertainty in cost-effectiveness analyses. For the case series analysis, additional data were collected on administrative features, risk-sharing agreements, individual funding requests concerning the submissions.

The improved methods consider past efforts and are accompanied with organisational developments. The methods are also deemed to be pragmatic, as they take into account the local specificities, and most importantly, resource constraints of reimbursement decision making. They take advantage of the synergies with both the national and Union-level legal environment. As a result, the impact of assessment reports on reimbursement decisions is expected to increase in the near future.

Nevertheless, the current research falls short of quantifying the impact of the assessment methods in the presence of exogenous factors to the reimbursement procedure. Therefore, future research should attempt to quantify the impact of assessment reports on the outcome of reimbursement decision making, as well as to carry out a formal hypothesis testing via multivariate analysis techniques.

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Table 11 is intended to provide an overview of the candidate's contributions to the publications directly related to the thesis.

Table 11: Summary of the candidate's contributions to the publications

Contribution / Publication	Merész et al., 2020	Merész, 2021	Merész et al., 2021	Merész et al., 2022	Dóczy et al., 2022	Merész & Gaál, 2023
Conceived the ideas or design of the study	L	L	L	L	P	L
Performed data collection	P	L	L	L	P	L
Data analysis and interpretation	L	L	L	L	P	L
Primary author (wrote most of the paper or drafted the paper)	L	L	L	L	P	L
Provided revision to scientific content of the manuscript	P	L	P	P	L	P
Provided stylistic/grammatical revisions to manuscript	P	L	P	P	L	P
Provided access to crucial research components (data)	L	L	L	L	L	L

P: The candidate actively participated in carrying out these tasks.

L: The candidate lead the task, or carried out the task on his, or mostly on his own.

9.2 Publications not related to the thesis

9.2.1 Journal articles

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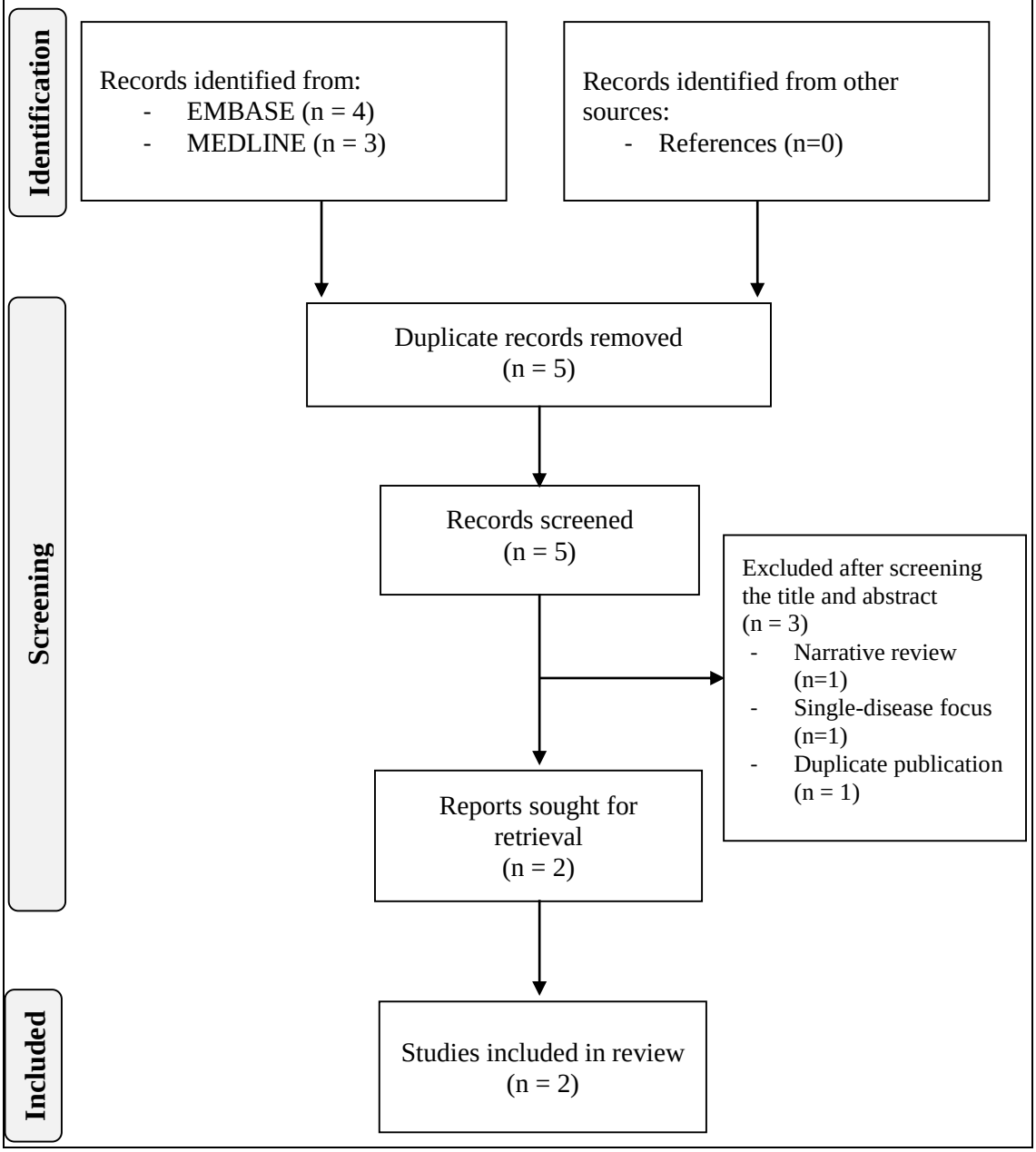
11 APPENDICES

Appendix 1. Search term and flow diagram of the literature review

Search term

((((health technology assessment) AND (critical appraisal)) AND (reimbursement)) AND (pharmaceuticals)) AND (Hungary)

Flow diagram



Appendix 2. Stakeholder questionnaire

A	REGARDING THE PROCEDURE OF DRAWING CONCLUSION ON THE CLINICAL ADDED BENEFIT, IT…	Answers*
A1	Might improve transparency during the reimbursement process	Choose an item.
A2	Specifies and simplifies the content of the dossiers submitted for critical appraisal	Choose an item.
A3	Might improve the quality of the submitted dossiers	Choose an item
A4	Might improve the quality of HTA reports	Choose an item
A5	Might validate and standardize the critical appraisal process	Choose an item
A6	Might make the HTA reports more ready-to-use	Choose an item
A7	Might support the reimbursement process and price negotiations	Choose an item
A8	Serves as a feasible alternative (taking into account the human resource capacities and legal frameworks) for drawing conclusion on the clinical added benefit	Choose an item
A9	Might facilitate the learning process of new clinical assessors of the HTA department of NIPN	Choose an item
A10	Might facilitate the learning process of new employees of companies preparing dossiers for reimbursement	Choose an item
A11	Might validate the rightness of the method chosen for health economic analyses (mostly the type of the analysis)	Choose an item
	Comments on questions A1-A11:	
B	**REGARDING THE SCORING SYSTEM USED IN THE PROCEDURE FOR DESCRIBING THE QUALITY OF CLINICAL EVIDENCE, IT…**	
B1	Might lead to a more uniform way of presenting scientific evidences in HTA reports	Choose an item
B2	Separation of the level of evidence from the risk of bias might facilitate identification of new limitations	Choose an item
B3	Its inclusion in HTA reports might further elucidate the generalizability of the presented results	Choose an item
B4	In a situation where the extent of clinical added benefit appears to be the same, it might serve as guide to choose that therapeutic option which is supported by higher quality of evidences, therefore in general might be more useful for patients	Choose an item
	Comments on questions B1-B4:	

C	**REGARDING THE SCALE USED FOR SCORING THE EXTENT OF CLINICAL ADDED BENEFIT, IT…**	
C1	In local circumstances a 3+1 grade scale should be enough to differentiate between therapies (extent categories: major, important, minor and no proof of benefit/not quantifiable)	Choose an item
C2	The ESMO MCBS is a broadly accepted measure for oncological therapies	Choose an item
C3	The ESMO MCBS considers several aspects which are meaningful for patients besides survival gain (e.g. adverse events, quality of life, patient-relevant endpoints)	Choose an item
	Comments on questions C1-C3:	
D	**REGARDING THE FIELD CHOSEN FOR INTRODUCTION (ONCOLOGY), IT…**	
D1	It is an appropriate starting point for further development of the procedure.	Choose an item
D2	The implementation of an internationally accepted scale (ESMO MCBS) into the local reimbursement process is acceptable.	Choose an item
	Comments on questions D1-D2:	

All subjects could choose from the following answer options: I fully disagree / I rather disagree / I rather agree / I fully agree with the proposed statement.

Appendix 3. Multivariate logistic regression analysis with the calendar year of the submission included as independent variable and the outcome of the decision being positive as the dependent variable

	The decision procedure is positive		
	OR (95% CI) Multivariate Model		
RSA was in place at the time of submission	3.23 (1.40–7.44)	p=0.006	AIC: 229.11 R^2=0.33
Average biennial expenditure on the basis of IFRs exceeds 200 million HUFs	1.03 (0.90–1.18)	p=0.621	
Introducing a new compound or a combination with a new compound	1.41 (0.68–2.90)	p=0.357	
A legal act is needed for the positive decision	0.04 (0.02–0.10)	p<0.001	
Calendar year of submission	2018: 1.0 2019: 3.24 (1.36–7.72) 2020: 1.94 (0.65–5.74) 2021: $3.54x10^6$ (0-Inf.)	(reference) p = 0.008 p = 0.233 p = 0.988	