EESTI RAKENDUSUURINGUTE KESKUS CENTAR

Assessment process and decision criteria of health technologies in Estonia

Final Report

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The study was completed on the order of the Association of Pharmaceutical Manufacturers in Estonia

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An important input for this study was interviews with representatives of the following organisations:

- Estonian Society of Hematologists
- Estonian Association of Oncotherapy
- Estonian Society for Rheumatology
- Estonian Patients Union
- Estonian Chamber of People with Disabilities
- Health Insurance Fund
- State Agency of Medicines
- University of Tartu
- Association of Pharmaceutical Manufacturers
- Roche
- Astra-Zeneca
- Johnson & Johnson

The following foreign experts responded to inquiries about the financing of health technologies in selected foreign countries:

- Iveta Palesova, AIFP Slovakia
- Leoš Fuksa, SÚKL (Czech Republic)
- Jurij Fürst, Health Insurance Institute of Slovenia

The authors of the study sincerely thank the experts who participated in the study. The responsibility for the conclusions reached in the study does not lie with the interviewed persons but with the authors of the study.

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1. Introduction

Medicinal products and other health technologies are advancing at a rapid pace, continuously opening up new possibilities for the treatment of various diseases and health problems. However, the resources available to society are inevitably limited, and therefore it is important that they are used in an optimal way, i.e., in such a way that the expenditure on health technology corresponds to the willingness and ability of society to pay and that no more reasonable alternative use is found for the expenditure. Health Technology Assessment (HTA) is a process that helps to ensure the optimal use of resources by bringing together information on the medical, economic, social, and ethical aspects of health technology use.

Health Technology Assessment includes several methodological options, which have been the subject of active discussion and development of applied practices in recent decades. This concerns, for example, the critical basic parameters of the economic assessment of health technologies (e.g., incremental cost-effectiveness ratio thresholds and their application in different situations, discount rates, and the basis of their formation), addressing the special challenges associated with new technologies in the assessment methodology, as well as the inclusion of patient assessments and the values of society members in general in the assessment process, etc. Therefore, it is important that the principles of health technology assessment implemented in the country and the criteria used in decisions keep up with the times and be in line with the development of society and the economy.

The objectives of the study are as follows:

- To provide an overview of the processes and practices implemented in selected leading HTA organisations, including:
    - Methods used for the economic assessment of health technologies and the principles for choosing between them
    - Cost-effectiveness thresholds used in different countries, the principles of their definition and change over time
    - Principles governing the selection of the time horizon used in analyses
    - The discount rate used in cost-effectiveness calculations, its variation from country to country
    - Taking uncertainty into account in analyses
    - Handling of aspects specific to new technologies in the assessment process
    - Application of risk-sharing (cost-based and performance-based) schemes when deciding benefits.
- To compare the HTA assessment process used in Estonia with modern practices of leading foreign countries, and to assess whether it is modern and in line with global developments, including:
    - Clarity and transparency of the process
    - Basic parameters of economic analysis
    - Decision criteria used
    - Involvement of various parties.
- To make recommendations for the modernization of the HTA process and to address possible bottlenecks.

In order to answer the research questions, a document analysis was performed based on the publicly available instructional materials of HTA institutions in foreign countries. The countries selected for the study were England, Sweden, and Ireland. The countries were selected keeping in mind that there should be sufficient variability in the methodologies used (e.g., different decision criteria in England and Sweden); so that both large and smaller countries and HTA institutions are represented (e.g., NICE in England and HIQA in Ireland, respectively).

The main parameters of the economic analysis (cost-effectiveness threshold, discount rate) were compared among a wider range of European countries, using previous studies, public data sources, and direct inquiries to experts from selected countries as data sources.

Document analysis (regulations and instructional materials) and interviews with various related or interested parties in the Estonian HTA process were used as a method for collecting information and assessments about the Estonian HTA process and mapping possible bottlenecks. Interviews were conducted with the following parties:

- Two medical professional associations
- Two patient-representative organisations (umbrella organisations represented in the Medicinal Products Committee)
- Two representatives of the Health Insurance Fund (member of the Medicinal Products Committee and member of the management board)
- Representative of the State Agency of Medicines (member of the Medicinal Products Committee)
- Representatives of pharmaceutical manufacturers (focus group interview)
- Representative of the Health Information Analysis Group of the Institute of Family Medicine and Public Health of the University of Tartu (written interview).

The results of the study are presented in the following chapters. In Chapter 2, a mapping of foreign practices is presented, followed by an overview of the Estonian health technology process, methodology, and the assessments of the interviewed parties in Chapter 3. Chapter 4 presents conclusions, and Chapter 5 presents suggestions and recommendations.

2. Health technology assessment in selected foreign countries

2.1. Health technology assessment process and steps

2.1.1. England

The main guidance material for health technology evaluations carried out by the National Health Service (hereinafter NHS) of England is a document called "NICE health technology evaluations: the manual, prepared by the National Institute for Health and Care Excellence (hereinafter NICE)[1]. It describes the process of health technology evaluation and provides guidance on which methodology to use in the evaluation. The information provided about England comes mainly from this guidance material.

The manual is used in the evaluation of the following programmes:

- Diagnostics Assessment Programme – in the framework of this programme, new and innovative diagnostic technologies, which are all types of measurements and tests used to assess a patient's condition, are assessed.[2]
- In the framework of the Medical Technologies Evaluation Programme, new medical devices (including diagnostic devices) are assessed; however, medicinal products are not assessed within the framework of this programme.[3]
- The Highly Specialised Technologies Evaluation Programme focuses on new, highly specialised technologies that deal with rare diseases (small number of patients, limited or no treatment options, challenges in conducting research, and gathering evidence).[4,5] In the assessment of such technologies, decision criteria differing from standard criteria are used.
- In the framework of the Technology Appraisal Programme, medicinal products, medical devices, diagnostic techniques, surgical procedures, and health promotion activities are assessed.[6]

[1] NICE. (2022) NICE health technology evaluations: the manual. Process and methods. 31 January 2022. [https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741]

[2] https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guideline/nice-diagnostics-guideline

[3] https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guideline/nice-medical-technologies-evaluation-programme

[4] https://www.nice.org.uk/process/pmg37/resources/nice-health-technology-evaluation-topic-selection-the-manual-pdf-72286780924357

[5] https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guideline/nice-highly-specialised-technologies-guideline

[6] https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guideline/nice-technology-appraisal-guideline

NICE assesses health technologies as part of the process of developing guidance. If the guidance concerns the introduction of a medicinal product or device, the guidance will, among other things, include a recommendation as to whether the NHS should fund it and, if so, under what conditions. The steps in the process of developing guidance are as follows (see Figure 1)[7]:

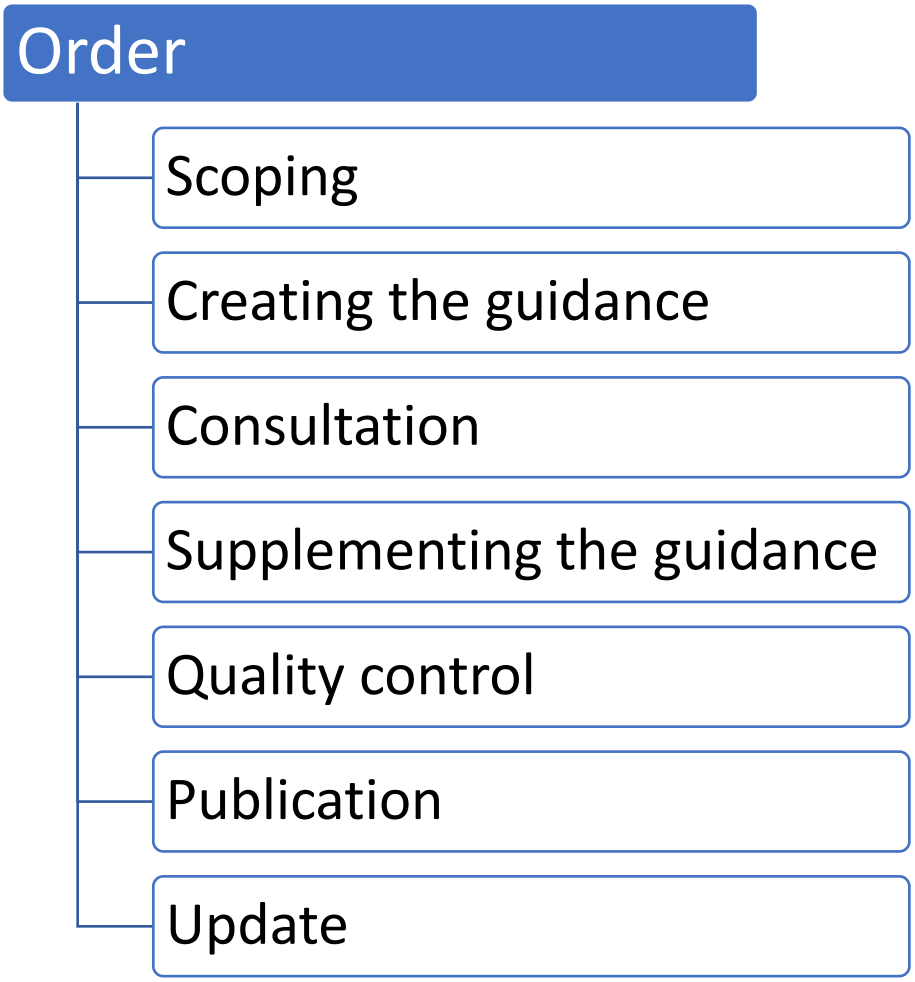
- **Order:** NICE is asked to assess a technology, or NICE itself decides to update its assessment of a technology
- **Scoping:** Limits are set on the assessment task by establishing what is and is not taken into account in the preparation of the guidance. Scoping includes, for example, decisions about which technology/medicinal product/procedure is evaluated, what it is compared to, which patient or societal groups are the focus of the guidance, which are the main questions to be answered, as well as which assumptions the economic analysis should be based upon.
- **Developing guidance:** At this stage, a draft version of the guidance will be developed. To this end, the final research questions are agreed upon, the literature is reviewed, additional input from stakeholders is requested, if necessary, analyses of treatment effectiveness are developed, and an economic analysis is conducted.
- **Consultation:** A draft version of the guidance is sent to stakeholders for comment.
- **Supplementing the guidance:** Based on stakeholder feedback, the guidance is (if necessary) amended and supplemented.
- **Quality control:** NICE staff will carry out quality control of the guidance in accordance with a procedure developed at NICE. Upon successful completion, the guidance executive appointed by NICE approves the guidance.
- **Publication** Two weeks before the official publication, the guidance will be circulated confidentially to all stakeholders, who agree to sign a non-disclosure agreement. This leaves stakeholders with the opportunity to draw the attention of NICE to potentially serious errors in the guidance. The official guidance will be published on the NICE website with possible additional materials.
  If the health technology assessment results in a recommendation by NICE for technology funding, the National Health Service (NHS) is required to do so. The NHS Constitution provides that patients are entitled to NICE-recommended medicinal products and treatments if their physician considers it clinically justified. Following a positive recommendation by NICE, the NHS must ensure that the technology is available to patients within three months of the publication of the recommendation.[8]
- **Update:** The guidance will be updated as necessary. This may mean the reviewing of the entire guidance, but the updating of the guidance may also take place in sections. NICE's HTA guidance material does not set a specific deadline for when each guidance must be updated (except in the case of fixed-term risk-sharing agreements, which involve the collection of additional data and review of new evidence). NICE monitors the receipt of new evidence or other important information and decides on an ongoing basis whether to initiate a surveillance review of the guidance. If it is initiated, relevant

[7] https://www.nice.org.uk/process/pmg20/chapter/introduction

[8] https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guideline/nice-technology-appraisal-guideline

information will be published on the website, and stakeholders will be contacted. During the monitoring, it will be assessed whether the added information (either in evidence, prices, regulatory status of the technology, etc.) affects the recommendation given in the previous guidance. If necessary, the decision will be taken to announce a public consultation, which will last 28 days.

Figure 1. The NICE Health Technology Assessment Process



Source: https://www.nice.org.uk/process/pmg20/chapter/introduction, adapted by the author.

2.1.2. Sweden

The regulatory framework for health technology assessment in Sweden is highly decentralized, with responsibility and tasks divided between three levels of government – national, county, and municipal. Regional levels are responsible for the provision of health care services, especially the county level, which, as a result of the Health Care Act (Riksdagen, 1982), must ensure the availability of medical services for its residents. The local government level is responsible for social and care services, as well as, for example, the school medicine service. Since the regional level finances the healthcare system from local-level taxes, it is also quite autonomous in its decisions and choices. The task of the national level is primarily the creation of uniform standards and their control.

A decision of the Swedish Parliament (Riksdagen, 1996) lays down the principles underlying health policy. According to it, there are three main principles that must be followed in the healthcare system: 1) the principle of the value of human life; 2) the principles of need and solidarity; 3) the principle of cost-effectiveness. The principles are arranged hierarchically, and the cost-effectiveness principle is the last consideration in this hierarchy. In addition, the principle of cost-effectiveness can only be applied to the treatment of the same health problem. The HTA institution must create a basis and opportunities for evaluating the evaluation process based on the basic principles of healthcare, but the final decision on the prioritisation of various aspects is not within the competence of the HTA institution (SBU, 2020).

In addition to the principle of cost-effectiveness, the need to consider ethical principles is also the reason why, for example, the thresholds of incremental cost-effectiveness are highly variable in assessments. In addition to cost-effectiveness, the severity of the disease, etc., must also be taken into account (SBU, 2020).

The Health Care Act (Riksdagen, 2017) stipulates, among other things, the requirement for the cost-effectiveness of health care services. Health technology assessments are carried out by various institutions in Sweden. At the national level, the assessments are mainly carried out by the Dental and Pharmaceutical Benefits Agency (*Tandvårds- och sälätkeförmånsverket*, TLV) and the Swedish Agency for Health Technology Assessment and Assessment of Social Service (*Statens beredning för medicik och social évaluation*, SBU). In addition, at the national level, there is the National Board of Health and Welfare (*Socialstyrelsen*), whose task is to supervise regional healthcare systems and institutions, manage healthcare statistics and registers, and prepare treatment guidance.

The task of the **SBU**[9] is to assess various health technologies from the widest possible perspective, including the medical, economic, ethical, and social aspects associated with them (Riksdagen, 2007a). In addition to health technologies, SBU has also been assessing social services, services for people with reduced working capacity, etc., since 2015.

[9] https://www.sbu.se/

1) Proposals for topics to be assessed come from various organisations, government agencies, politicians at different levels, or also from the SBU Research Council (*vetenskapliga rådet*), which gathers experts in the most important areas of healthcare.
2) The SBU council (*Nämnden för medicik och social överlängung*) decides which of the proposed topics will be assessed by the SBU. Top priority is given to topics that are ethically controversial or that would require significant changes in existing practices.
3) A project team is formed, which brings together external experts in addition to SBU employees.
4) The project team prepares an overview of the health technology to be assessed. SBU bases its reviews primarily on existing studies and literature reviews. The methodological guideline of the SBU (SBU, 2020) describes the stages of the process of preparing systematic reviews of health technologies to be compiled:
    a) Formulation of the research question – for intervention studies based on the PICO (*Population, Intervention, Control, Outcome*) format, for diagnostic tests or evaluations based on the PIRO (*Population, Index Test, Reference Test, Outcome*) format.
    b) Search of literature
    c) Assessing the relevance of studies
    d) Assessment of research quality – according to international and SBU checklists
    e) Data extraction
    f) Classification and synthesis of research results
    g) Quality assessment of pooled results – GRADE (*Grading of Recommendations Assessment Development and Evaluation*) for quantitative studies and GRADE-CERQual for qualitative studies.

    Together with the review, an economic assessment of the health technology is also carried out, and it is also assessed from an ethical perspective. In order to assess the quality of HTA studies and their suitability to the Swedish context, SBU has developed corresponding checklists. There are separate lists for empirical studies (SBU, 2017a) and model studies (SBU, 2017b). If the economic assessment cannot be derived from the available literature, the SBU will, if necessary, carry out the assessment itself (based on the existing literature).

5) The review is peer-reviewed by both the SBU Research Council and external experts before publication.

The SBU itself has no regulatory or legislative role but fulfils the orders of and makes recommendations to various other organisations, government agencies, political decision-makers, etc.

The main function of the **TLV**[10] is to assess medicinal products (as well as some medical procedures, such as dentistry) and decide which ones are included in the price protection (*högkostnadsskydd*) list, and set their selling price. Value-based pricing is used for medicinal products in Sweden, which means that the price of the medicinal product (only the prices of the

[10] https://www.tlv.se/

medicinal products that are included in the price protection list) for the patient is not related to the original product price but is determined by the effectiveness of the medicinal product for the patient's health. Price protection means that all medicinal product-related costs that exceed kr2,400 during a 12-month period are fully subsidized by the state. The TLV's decisions are mostly based on data and studies submitted by medicinal product manufacturers, based on which the TLV prepares a cost-effectiveness assessment. In addition, the TLV monitors new health technologies (including medical devices that are not part of the medicinal product price protection model), gives recommendations to the regions, and, if necessary, assesses their cost-effectiveness (at the request of health technology suppliers) (Riksdagen, 2007b).

Since the regions are relatively autonomous in their decisions regarding the health system, in addition to the national HTA institutions, there are several so-called regional HTA institutions at the regional level which deal with the assessment of health services at the county level. The fact that the regions are relatively autonomous in their decisions concerning the health care system, and the HTA assessments made at the national level are not mandatory for the regional level, means that it is difficult to ensure a unified health technology assessment framework based on the same standards and its implementation throughout the country (Shah et al., 2014). The SBU or TLV assessment reports are more advisory in nature, serving as inputs for decision-makers at the regional level rather than obliging the autonomous regions to follow these recommendations.

In 2020, the regional councils created a cooperation model for harmonizing the introduction of medical technologies and their prior evaluations (*Regionernas samverkansmodell för medicinteknik*) with the aim of ensuring a more equal, cost-effective and efficient use of medical devices (not medicinal products) across the country[11]. The cooperation model is coordinated and managed by the Swedish Association of Local Authorities and Regions (*Sveriges Kommuner och Regioner, SKR*). The Health Technology Council (*MTP-rådet,* MTP council) operates within the framework of the cooperation model, deciding which medical devices require cross-national cooperation, forwarding them to the TLV for assessment, and giving uniform recommendations to the regions for the introduction of new technologies. The TLV is an active partner of the Council, both in finding new technologies and assessing their cost-effectiveness.

The operation of the cooperation model is based on the following stages (TLV, 2022):

1) Identification of new technologies – the TLV and the SKR's health technology assessment group monitors various technologies that could contribute to the Swedish healthcare system.
2) Selection of technologies – the MTP Council decides which technologies will be further processed at the national level within the framework of the cooperation model. The decision is based on priority criteria[12].

[11] https://www.tlv.se/in-english/medical-devices/managed-introduction-of-medical-devices.html

[12] https://www.janusinfo.se/download/18.2f371950171ac3de412dabda/1589541051160/Priori

3) Economic assessment of technology – the TLV assesses health technologies. The assessment is based on the documentation and data provided by the pharmaceutical manufacturer.
4) Decision on recommending technology – the MTP Council makes a decision on the nationwide recommendation of technology based on the HTA's assessment, as well as taking into account other principles underlying healthcare policy.

Technology procurement – decision-making and procurement of recommended technologies occurs at the regional level. Regions are not obliged to follow the recommendations of the MTP Council.

The TLV considers the inclusion of the patients' perspective to be very important, and has thoroughly dealt with its regulation and the establishment of principles. In 2018, the TLV report on patient engagement practices in different countries was completed, the purpose of which was to map successful practices and, based on them, develop and enhance the TLV engagement process.

As a result of this and cooperation with local patient organisations, the TLV has developed a guideline regulating patient involvement (TLV, 2020), which states:

- The need to raise awareness regarding the impact of the TLV's decisions and assessments on patients.
- The TLV is engaged in an ongoing dialogue with patient representatives.
- Patient involvement occurs in the early stages of assessment projects.
- Patient organisations, patient networks, individual patients/representatives of patients, or relatives/representatives of relatives are involved (depending on the nature of the project).
- The inclusion takes into account possible mobility, communication, or other limitations of the patients. All patients must be guaranteed the opportunity to be involved.
- The TLV must ensure the availability of information about its work so that it reaches all relevant stakeholders, thereby creating opportunities for patient participation.
- The representative of the patients involved must be aware of a possible conflict of interest in relation to a particular case.
- If a patient representative is hired as an expert for the project, their work and travel expenses must be compensated. Travel expenses must also be reimbursed in the case of repeated invitations to meetings. Travel expenses shall not be reimbursed for individual meetings.

In addition, the TLV has developed a methodological framework for patient engagement[13], which describes five different forms of involvement (informing, asking for comments, holding a dialogue on general topics, holding a dialogue on specific topics, and partnership) and for each form the

13 hsttps://www.tlv.se/download/18.4df398f41705a23476643cd3/1582208221558/metodstod_patientmedverkan.pdf

activities of the TLV, the necessary competence of the TLV, and necessary competence of the patient.

Patient representatives are represented in the TLV's committees and project teams. Twice a year, Dialogue Forums are organised, in which, among others, patients also participate, and the topics of which are approved by the Program Council, in which patient representatives and the TLV participate.[14]

The SBU also considers the involvement of users of patient health technology to be important. Similar to the TLV, there are also plans to develop clear guidelines in order to regulate involvement practices.[15] Among other things, they must provide for the following:

- When preparing the project plan, the target groups of the assessed health technology and the stakeholders related to the topic must be mapped. They must be reflected in the project plan.
- At the beginning of the project, the target groups' view of the circumstances must be investigated.
- The creation of a monitoring group of patients/users who would monitor the progress of the project should be considered.
- Before the end of the project, a seminar should be held with patients/users to discuss the conclusions of the project and the potential application of the results.
- All SBU reports and assessments must be forwarded to relevant interest organisations (patient associations, etc.).
- Inviting a patient representative to the SBU council must be considered.

2.1.3. Ireland

In Ireland, Health Technology Assessments are carried out by different agencies in different contexts and scopes (HIQA 2016):

- The HTA is conducted by HIQA as an input to national-level policy decisions and national health system decisions;
- The cost-effectiveness of medicinal products within certain programmes is assessed by NCPE (*National Centre for Pharmacoeconomics*);
- The clinical effectiveness and cost-effectiveness of medical devices are assessed by the HSE (*Health Service Executive*);
- representatives of the pharmaceutical industry conduct the HTA as part of funding applications;
- academic institutions conduct the HTA for the healthcare industry and research.

The structure of the HTA process is shown in the figure below. After the European Commission has received a positive recommendation for the product from the Committee for Medicinal Products for Human Use of the European Medicines Agency and made an authorisation decision,

[14] https://www.tlv.se/om-oss/om-tlv/patientmedverkan.html

[15] https://www.sbu.se/sv/om-sbu/samverkan-och-natverk/brukarsamverkan/sbus-konferens-med-vardens-brukare/

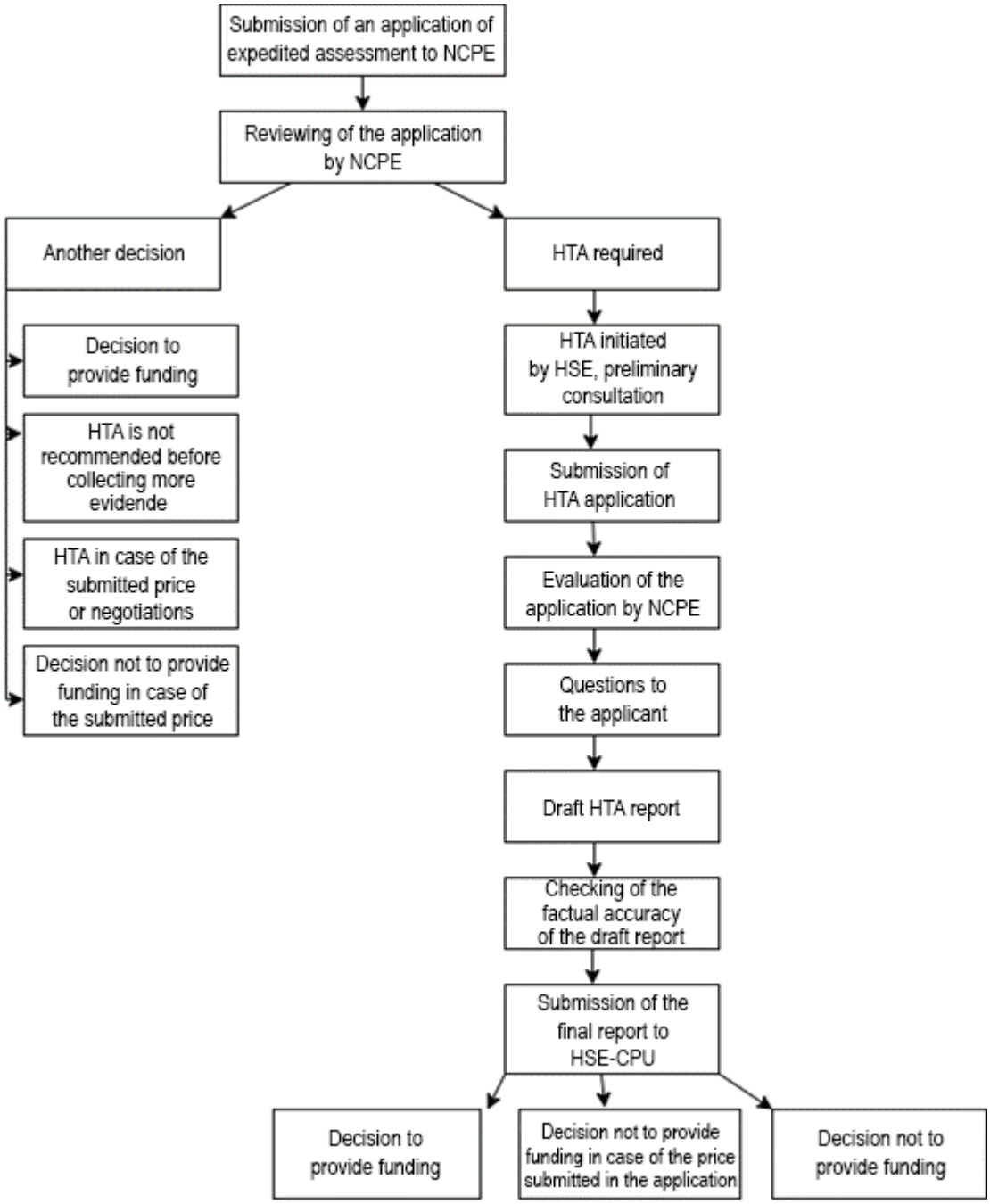
the HSE will inform the manufacturer of the requirement to submit an application for rapid assessment. The HTA process takes place in the following steps:

- The manufacturer submits a proper application to the NCPE for expedited evaluation.
- The NCPE will consider the application and the available evidence on efficacy and safety and will assess within four weeks whether the application can be processed through a fast-track assessment or whether a full-scale HTA is required.[16] The assessment takes into account the size of the patient population, the strength of the clinical evidence, the cost compared to the current regimen, and the budgetary impact.
- The NCPE informs the HSE-CPU about the need for the HTA and informs the applicant.
- If it is found necessary to carry out a full-scale HTA, it is formally initiated by the HSE-CPU.[17] Before submitting an HTA application, a preliminary consultation takes place between the NCPE and the applicant, during which the content of the application is specified.
- The applicant submits an HTA application.
- The NCPE invites patient stakeholders to submit their input using the provided form. The time to provide input is 90 days.
- The NCPE working group evaluates the submitted documentation and the models used for the economic assessment. An assessment of the product's cost-effectiveness, associated uncertainty, the validity of the data underlying the clinical effectiveness and cost-effectiveness estimates, and the budget impact is given.
- If necessary, the applicant will be asked for clarifications on any aspects of the application. The applicant has one month to answer the questions.
- The HTA process takes up to 90 days, which does not include the time spent by the applicant on preparing and correcting the application.
- The HTA assessment report is sent to the applicant for factual correctness checking, for which the applicant has five working days.
- A final HTA report will be drawn up, within which a positive funding recommendation will be given if cost-effectiveness has been demonstrated. If cost-effectiveness has not been achieved at the price level specified in the application, this will be pointed out. Where cost-effectiveness has not been demonstrated due to doubts about any aspect of the application, this will be pointed out in detail.
- The final evaluation report is forwarded to the HSE-CPU. The final report addresses three of the nine criteria set out in the Health Act: clinical effectiveness, cost-effectiveness, and budget impact.

[16] In the period 2012-2019, approximately half of the reviewed applications were referred to the full procedure of the HTA. The probability of referral to full procedure was statistically related to the high cost of the drug, cancer indication, and the novel unique mechanism of action. Varley, Á., Tilson, L., Fogarty, E. et al. The Utility of a Rapid Review Evaluation Process to a National HTA Agency. PharmacoEconomics 40, 203–214 (2022). https://doi.org/10.1007/s40273-021-01093-8

[17] An HTA may also be initiated in a context other than a request from a pharmaceutical manufacturer – for example, HIQA may be approached by a patient or physician representative organisation regarding the need for an HTA.

- The HSE will consider the assessment report in light of the additional criteria of public health needs, clinical need, clinical supervision necessary to ensure patient safety, product availability and suitability for supply and funding under existing schemes, costs, product benefits, and risks compared to therapeutically similar products; uncertainty about costs, benefits and risks; and resources available for HSE.
- As a rule, the product will be assessed by the HSE Medicines Group, which will make a funding recommendation to the HSE Board, which will make the final decision.



In the initial phase of the health technology assessment, the stakeholders related to the topic under consideration are identified. Stakeholder representative organisations are invited to nominate representatives to an advisory group that will directly participate in the HTA process. The selection of stakeholders is made in a transparent way. The aim is to involve all stakeholders

who have a legitimate interest in the subject under consideration or who are affected by the decision following the HTA, primarily patient representative organisations, who may not be well-versed in the decision-making process and may not have the opportunity to challenge the results. Representatives of health industry companies and insurance companies do not participate in the advisory group, but they may be called upon to provide relevant information for the HTA. Advisory group members and evaluation team members must identify potential conflicts of interest at the beginning of the HTA project. Persons identified as having a potential conflict of interest may be excluded from direct participation in the project.

The advisory group plays a critical role in the HTA, bringing clinical, organisational, and patient perspectives that are important to understanding and interpreting evidence, and formulating advice. Additional data or information about the organisation and provision of services in Ireland is often obtained from experts who are members of the advisory group, which helps to ensure that the HTA assessment is relevant to the Irish context. Information about the HTA is shared equally with all stakeholders, without favouring anyone (with the exception of sensitive business or confidential information). Stakeholders are provided with an explanation of what they can and cannot influence in the HTA process, and the example of previous HTAs is used to illustrate in which way the opinions of stakeholders have been taken into account in the past and when not. In communication with stakeholders, the use of complex technical terminology is avoided, which would exclude the active participation of some stakeholders. If necessary, participants will be trained on HTA methodology, so that they understand the process sufficiently to participate competently in the discussion.

Within the HTA, there are typically two meetings with the advisory board of experts (there may be additional meetings and communication with individual members of the advisory board on topics within their competence). The advisory group provides input into key decisions when conducting the HTA, e.g., defining which subject areas will be included in the HTA. The advisory group will also review and provide feedback on the draft HTA report. The feedback received from the members of the advisory group and the assessment team's responses to it is documented and shared with the entire advisory group.

In some cases, it is not possible to achieve representation of the relevant stakeholders, or it is not possible to define the relevant stakeholders. Also, the HTA result may affect the population as a whole or appear controversial. In such cases, a public consultation is conducted, which lasts 6-8 weeks. The consultation begins with media coverage to raise public awareness, and various organisations whose opinions are sought are also contacted directly. The draft HTA report will be made publicly available, and anyone can give feedback on it. At the end of the consultation period, the feedback is reviewed, it is decided which changes to the report need to be made based on it, and the response to each comment is documented. Together with the published report, the feedback received during the consultation, the HTA team's answers to that feedback, and a summary of the results of the consultation will also be published. The results are reported in the media.

2.2. Methods of economic assessment

2.2.1. England

The NICE (2022) provides two methods for the economic assessment of health technologies (NICE (2022), p. 63):

- Cost-utility analysis
- Cost comparison analysis

Cost-utility analysis is used to assess whether the expected changes in health associated with the use of technology justify the associated changes in expected costs. Health effects must be measured in terms of quality-adjusted life years (QALYs). (NICE 2022, p. 64)

Cost-utility analysis is used when a complete overview of both technology-related costs and health outcomes is needed. The goal of health technology assessment is to achieve maximum health outcomes under limited budget conditions, and quality-adjusted life years take into account both mortality and the impact of various health conditions on quality of life. Therefore, cost-utility analysis is well suited for this (NICE 2022, p. 64)

The analysis should include, among other things (NICE 2022, p. 64):

- The rate of incremental cost-effectiveness of the technology, which is found as the ratio of expected quality-adjusted life years to total incremental costs at low cost.
- It should be stated whether the technology has a dominant or extended dominant position compared to alternative technologies.

During the cost comparison analysis, the costs related to the use of the analysed technologies are compared, provided that the functionality of the technologies is the same or very similar. It is used when there is reason to believe that the technology will provide the same health outcomes as comparable technologies at a similar or lower cost. (NICE 2022, pp. 64-65)

A cost-effectiveness analysis is easier to carry out than a cost-utility analysis; however, it finds relatively little use in the NICE. In the conclusions of the analysis prepared at the NICE in 2019,[18] it is pointed out that in most cases, the cost minimisation analysis[19] is not suitable for health technology assessment in view of the NICE's goals (Wailoo *et al.* 2019, p 3). The above does not mean that the method should not be used at all, but its use requires a thorough evaluation of the clinical non-inferiority of the analysed solution (Wailoo *et al.* 2019, p. 4), and this is not a trivial task.

[18] In NICE analyses, the terms *cost-minimisation analysis* and *cost-comparison analysis* are treated as equivalent.

[19] Wailoo A., Dixon, S. (2019) The Use of Cost Minimisation Analysis for The Appraisal of Health Technologies. Report by the NICE decision support unit. NICE, 50 p.

2.2.2. Sweden

In Sweden, no general criteria or thresholds have been established based on which the economic evaluation of health technologies must take place. Swedish HTA institutions do not always carry out economic impact assessments themselves but rely on literature reviews (SBU) and materials and data provided by manufacturers (TLV). However, both the SBU and TLV have published guidelines that describe the methodological principles to be followed in economic evaluations. The SBU's methodological instructional materials (SBU, 2020) deal with the methodological aspects of assessment rather broadly and are of a pedagogical rather than a recommendatory or conditional nature. The TLV has developed more specific guidelines (TLV, 2017) for the economic assessment of medicinal product manufacturers who apply to add their medicinal products to the preferential list. However, these are not specific requirements but rather recommendations. In addition, the TLV has published a manual for describing the HTA assessment process of health technologies within the cooperation model of regions (TLV, 2022), which also describes the economic impact assessment process.

Due to the law regulating its activities, the SBU is obliged to assess health technologies from the widest possible perspective, including not only the medical and economic aspects but also the accompanying ethical and social aspects (Riksdagen, 2007a). Based on the TLV's recommendations (TLV, 2017), the TLV's HTA assessments should also be based on a **socio-economic** perspective, which means that all possible associated costs and benefits (for the state, municipalities, patients, and relatives) should be taken into account.

Based on the principles of health care policy, both the SBU (2020) and the TLV (2022) recommend presenting the results of the assessment process both with and without costs and benefits related to changes in productivity (the individual's tax revenues that remain uncollected due to their health problem or are collected to a greater extent due to treatment), since the assessment of a person based on their measurable productivity may not be consistent with the principle of the value of human life. Since the productivity of different social groups is different, groups with lower productivity end up in an unequal position.

The principle of need-based nature and solidarity requires that the analysis is evaluated based on the broader social context and that, in addition to the health sector, other sectors between which limited resources are distributed are taken into account (SBU, 2021).

Based on the TLV's recommendations (TLV, 2017), the most preferred method is the **cost-utility** analysis, where health outcomes are measured in **QALYs**. If treatment affects survival, both QALYs and added life years should be reported. In case it is not possible to use the QALY as a measure of health outcomes, studies of willingness to pay can be used as an alternative to assess health benefits. If the health effect of the assessed medicinal product is the same as that of the treatment alternative, a **cost**-**minimisation** analysis may also be sufficient.

The methodological guidance of the SBU (2020) also recommends being based primarily on the nature of the treatment and disease being assessed and the available data. If there are treatments with the same effect and similar side effects in the comparison, then one should limit the cost-minimisation method. If the comparable treatments primarily affect mortality, a cost-

effectiveness analysis may be sufficient, where health outcomes are measured in years of life. However, if it is, for example, chronic diseases that are not directly life threatening, the impact on the quality of life must also be taken into account, and a cost-utility analysis is necessary.

The most cost-effective, clinically relevant treatment alternative is used as the reference treatment. Treatment that is used in Swedish clinical practice and is in accordance with scientific results and proven experience is considered clinically relevant. The reference treatment can also be a non-pharmacological treatment, a treatment not included in reimbursable treatments, or, in special cases, a treatment with a different indication than the treatment being evaluated. In the absence of clinically relevant and cost-effective treatment, no treatment can be used as an alternative. In some cases, more than one comparator treatment may be used.

2.2.3. Ireland

In general (the so-called "reference case"), the preferred methodology is a cost-utility analysis. In exceptional cases, a cost-effectiveness analysis can be used, where health outcomes are expressed in life years (LYG) instead of QALY. In this case, a detailed empirical justification must be provided as to why a cost-utility analysis is an inappropriate choice. The cost minimisation method is used when the performance (efficacy and safety) of the benchmark technologies is found to be or are expected to be identical. The assumption of identity requires solid scientific proof. If it is not a generic medicinal product, it can be used in the comparison of drugs with the same mechanism of action, the results of which are not considered clinically different (so-called me-too drugs), but where the evidence of equivalence of effect provides sufficient statistical power to detect the sameness of clinical differences.

The analysis is carried out from the point of view of the public health and social care system in Ireland (in terms of costs); health outcomes are considered to be total health benefits to individuals. As an additional secondary analysis, if necessary, an analysis from the point of view of society as a whole is presented in cases where this would significantly affect the results. If necessary, the analysis can be done from a specific perspective (e.g., the healthcare system together with the education system), if it is necessary and clearly justified.

The reference treatment is the conventional treatment used in Ireland and the technology most commonly used in the target population under consideration. The reference treatment does not have to be one specific intervention but can also be an alternative sequence of interventions or an alternative set of rules for starting and ending treatment. If there is no active treatment alternative, no treatment can be used as a comparison.

2.3. Incremental cost-effectiveness thresholds

2.3.1. Introduction

The incremental cost-effectiveness threshold is the maximum amount one is willing to pay for an additional quality-adjusted life-year. If the threshold is adequately defined and the cost of some evaluated health technology exceeds it, the intervention under consideration is not considered cost-effective, and this is an argument against incurring the corresponding cost.

There is no internationally accepted practice for the adequate definition of the threshold level. The two main ways to define a threshold are as follows:

- **Demand-side method**, based on surveys of willingness to pay. The idea behind the method is to use a survey to determine the willingness by members of society to pay for health outcomes (so-called demand for health outcomes) and to derive from this the price that is appropriate to pay for one QALY. The main problem with this method is considered to be that the estimates of willingness to pay by respondents may fail to take into account the limited resources available to society or budgetary constraints. In other words, the threshold found as a result of the surveys may turn out to be so high that it may prove to be impossible to finance all of the interventions deemed to be cost-effective within a limited budget (although the counter-argument is that the budget limit of the healthcare system should instead be based on the preferences of society). It is also not always clear to what extent the willingness to pay expressed in surveys reflects preferences for financing the expenses for one's own health or the health of other members of society – it has been found that the respondent's own health is valued more highly.
- **The supply-side method** is based on the opportunity cost under conditions of limited resources. In the context of a limited budget, each expenditure on an intervention means giving up on an expenditure on another intervention, which in turn affects health outcomes. For example, in a hypothetical situation, if an intervention costing €40,000 is financed, another intervention should receive less financing in the equivalent amount, which would lead to a decrease in health in the amount of 1 QALY, with the cost-effectiveness threshold being €40,000 (we can pay such an amount for a new intervention if it wins us 1 QALY or more). The advantage of this method is that it takes into account actual resource constraints (unlike the demand-side method). However, the disadvantage is that the implementation of the method is complex and labour-intensive – it is not easy to assess which specific medicinal products or services should be given up in case of one or another funding decision, and what the health consequences would be.

In addition to the above, it is also possible to assess the additional cost-effectiveness threshold based on precedent, i.e., because if an intervention has ever received a positive funding decision, its additional cost-effectiveness has consequently remained within the threshold (Santos *et al.* 2018). However, such an approach does not guarantee a result that maximises health outcomes if previous decisions have been suboptimal for some reason.

The WHO assessment is also often cited, according to which treatment alternatives, the cost of which per DALY is less than three times GDP per person, should be considered cost-effective.[20] However, this rule of thumb is not based on any of the above methods and, according to the

[20] Hutubessy R, Chisholm D, Edejer TT. Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. Cost Eff Resour Alloc. 2003 Dec 19;1(1):8. doi: http://dx.doi.org/10.1186/1478-7547-1-8

subsequent clarification by the WHO, was not intended as a decision rule.[21] However, there are several countries where the cost-effectiveness threshold is linked to the level of GDP. The advantage of linking to GDP is that as society's wealth grows, the amount that it is willing to pay for a QALY gained is automatically renewed – otherwise, the threshold defined as a fixed amount becomes obsolete as the economy develops. However, this advantage only applies if the threshold is initially defined "correctly" in relation to GDP (i.e., optimally based on either a demand- or supply-side approach); otherwise, the threshold will remain permanently too high or low.

Cost-effectiveness threshold estimates obtained from the supply-side (opportunity cost-based) method are typically lower than those obtained from the demand-side (willingness-to-pay) method (Vallejo-Torres *et al.* 2016, Santos *et al.* 2018). There is no generally accepted solution for reconciling estimates obtained by different methods.

The practices of countries differ in terms of whether the cost-effectiveness threshold is explicitly established by normative documents (e.g., England and Thailand) or implicit, i.e., used in actual practice but not officially established. International comparative studies (e.g., Santos *et al.* 2018, Schwarzer *et al.* 2015) have found that there are more countries without an explicit threshold. There are arguments both for and against establishing an explicit threshold level. The pro-argument is the transparency of the decision-making process, and the counter-argument is the risk that health technology manufacturers may price products in such a way that the incremental cost-effectiveness is as close to the threshold as possible, thus making the product more expensive for society than it would have been otherwise.

The practice also differs regarding the role of the threshold as a decision criterion – in other words, whether exceeding the threshold automatically excludes a positive funding decision or not and whether staying below the threshold guarantees a positive funding decision. Ensuring a positive decision when falling below the threshold would be risky, e.g., if the budgetary impact associated with the decision turns out to be significant (e.g., it has been found in some countries that providing hepatitis C treatment, which is considered cost-effective, to all those in need would significantly increase the state's expenditure on medicinal products). The role of the rate of incremental cost-effectiveness exceeding the threshold in the formation of the decision also differs from country to country. For example, the Irish guideline material states directly that the threshold is not a strict restriction, and a positive decision is possible even if the threshold is exceeded.

In several countries, cost-effectiveness thresholds are differentiated, i.e., presented as thresholds or ranges applicable in different situations (see also below, subchapter 2.3.5). For example, in Lithuania, Norway, and the Netherlands, different levels are applied depending on the disease burden or the severity of the disease. In Sweden, England, and Slovakia, other factors are additionally taken into account (Kovacs et al., 2022).

[21] Bertram MY, Lauer JA, De Joncheere K, et al. Cost-effectiveness thresholds: pros and cons. Bulletin of the World Health Organisation. 2016 Dec 01;94(12):925-930. doi: 10.2471/BLT.15.164418.

2.3.2. England

The NICE is an example of an HTA institution that has formulated the cost-effectiveness threshold explicitly, i.e., as a published official value. This approach was introduced in 2013, before which specific threshold values were not referred to in the guidance materials (Schwarzer *et al.* 2015). The current NICE guidance calls for a corridor with a lower end of £20,000 (€23,100) as the value of added quality-adjusted life years for health technology assessment,[22] with an upper end of £30,000 (€34,700)[23] (NICE 2022, p. 159). The range is not dependent on GDP or any other renewal rule, and has remained unchanged since its inception. However, an additional, higher threshold has been added to this threshold range over time (since 2017) – the NICE guidance provides an exception for so-called highly specialised technologies, which are assessed using a threshold of £100,000 (€115,500)[24] (NICE 2022, p. 159). Highly specialised technologies are technologies that are characterised by

- a small number of patients (prevalence of the disease in the population is less than 1:50,000; no more than 300 patients per indication or 500 patients per indication in total qualify for the technology);
- lack of a satisfactory treatment alternative;
- the disease being treated significantly shortens life expectancy or severely impairs the quality of life.

Thresholds are important in making a decision, but they are not unequivocally binding. If the ICER is below the lower threshold, this does not mean that the Committee has to recommend the technology in any case. However, in the case of a decision not to support the use of the technology, it is usually necessary to explain in greater detail why this cannot be done (e.g., the insufficient plausibility of the assumptions used as input to the model, uncertainty regarding the ICER estimate, or the results of a sensitivity analysis indicating high uncertainty). For an ICER value of over £30,000, the situation is similar, but then the decision to support the adoption of the technology needs to be rather convincingly justified.

With thresholds, it should be taken into account that they apply in conjunction with decision modifiers (which are described below, in subchapter 2.4.1) dependent on relative health loss. For example, in a situation where the relative health loss is 0.95, QALYs are taken into account with a weight of 1.7. In essence, this is equivalent to a rule where a threshold range **of £34,000–51,000** would apply in such a situation. However, a modifier of 1.2 applied at 0.85 to 0.95 health loss would correspond to a threshold range of £24,000–36,000. For highly specialized technologies, QALY modifiers may be applied depending on the number of QALYs gained (maximum modifier value is 3, making the £100,000 threshold equivalent to the £300,000 threshold). Thus, different levels can be identified as thresholds used in England, depending on the specific situation.

[22] Eesti Pank exchange rate as at 14.06.2022 (€1 = £0.8658), rounded to the nearest hundred.

[23] Eesti Pank exchange rate as at 14.06.2022 (€1 = £0.8658), rounded to the nearest hundred.

[24] Eesti Pank exchange rate as at 14.06.2022 (€1 = £0.8658), rounded to the nearest hundred.

When comparing the threshold with other countries, it must be taken into account that **VAT is not taken into account** in the economic analysis. However, VAT is taken into account in the budget impact analysis.

2.3.3. Sweden

No single official or recommended threshold has been established in Sweden (SBU, 2020). Recommendations published by the Swedish National Board of Health and Welfare for evaluating the cost-effectiveness of diabetes treatment are often used as a reference in evaluations (Socialstyrelsen, 2018). According to this, cost-effectiveness is divided into four categories: a low price is considered to be up to kr100,000 (€9,414)[25] per QALY; the average price is kr100,000–499,999 (€9,414–47,072); a high price is kr500,000–1,000,000 (€47,072–94,144) and a very high price is in excess of kr1,000,000 (over €94,144). The limit of kr500,000 (€47,072) is mostly used as the threshold of acceptable cost-effectiveness based on these categories (for example, SBU, 2015). According to the SBU's methodological guideline, in addition to the principle of cost-effectiveness, the decision must be based on the principles of human dignity and solidarity, which is why the willingness to pay for one QALY is affected by various aspects, e.g., the severity of the disease (SBU 2020, p. 119). There is no exact rule on how the severity of the disease affects the willingness to pay.

Dahlstrand and Sandberg (2016) analysed incremental cost-effectiveness thresholds based on the TLV's 2008-2015 assessment decisions. They identified a total of 116 assessments based on the ICER estimate. Of these, 91 had a positive assessment and an average QALY unit cost of kr411,000 (€38,693).

Svensson, Nilsson, and Arnberg (2015) analysed the QALY unit prices and their association with positive decisions based on the decisions of the TLV's reimbursement applications evaluated from 2005-2011. The median QALY unit cost for positive decisions was kr351,000 (€33,044), varying from a negative unit cost to kr1,224,000 (€115,233). The negative decision with the lowest unit price was kr700,000 (€65,901). The unit price level, at which the probability of a positive and negative decision was equal, was calculated by the authors to be kr702,000 (€66,089) for milder diagnoses, and kr988,000 (€93,015) for more severe diagnoses. The authors concluded that the TLV's decisions are attempting to find a balance between cost-effectiveness and ethical principles emphasising need and solidarity, which is why the QALY unit prices of positive decisions are also highly variable. Henriksson *et al.* (2018) also arrived at the conclusion in their review of cost-effectiveness assessment practices in Sweden that, in addition to the lack of specific thresholds, there are not enough relevant studies to define the threshold in the Swedish context, and the thresholds found and recommended in the existing studies are highly variable and based on different methodologies.

[25] Eesti Pank exchange rate as at 14.06.2022 (€1 = kr10.622), rounded to the nearest hundred.

No VAT is applied to prescription medicinal products, hospital medicinal products, and healthcare services (except beauty services, aesthetic services, nutritional advice, etc.) in Sweden. On the other hand, over-the-counter medicinal products are subject to VAT at the rate of 25%.[26]

2.3.4. Ireland

The guidance material refers to the range of €20,000–45,000 as the cost-effectiveness threshold. Among the results of the analysis, the probability that the incremental cost-effectiveness rate will be below €20,000 and €45,000, respectively, must be presented. However, it is emphasised that the threshold range is used for historical reasons; it is used for pragmatic reasons and is not empirically validated. The threshold **is not used as the only decision criterion**: if the threshold is below the funding decision, the funding decision is not guaranteed, and positive decisions have also been given to technologies where the threshold has been exceeded. In addition to incremental cost-effectiveness, other considerations also influence the decision, and the conclusions of the cost-effectiveness analysis take into account the strength of the evidence (e.g., reliability of clinical effectiveness estimates, cost estimates, the plausibility of model inputs and assumptions, reliability of source data, the uncertainty of results and probability of error).

The turnover tax rate for health technologies varies from 0% to 23%. The VAT rate for oral medicinal products is 0%, but for non-oral medicinal products (including external and injectable medicinal products) the VAT rate is 23%. In the analysis of cost-effectiveness, **VAT is not taken into account,** but it is taken into account in the analysis of the budget impact.

2.3.5. Other countries

The incremental cost-effectiveness thresholds used in the countries discussed above and in other selected European countries are presented in the figure below.

It must be noted from the outset that comparing thresholds is difficult, first of all, because the role of the threshold in the decision-making process is different in different countries – for example, in some countries, it is not used as a rigid criterion, but as one criterion alongside others, and a positive decision can also be obtained according to the threshold criterion for technology with unfavourable cost-effectiveness (this is the case, for example, in Slovenia, Sweden, and Ireland – see below for more details).

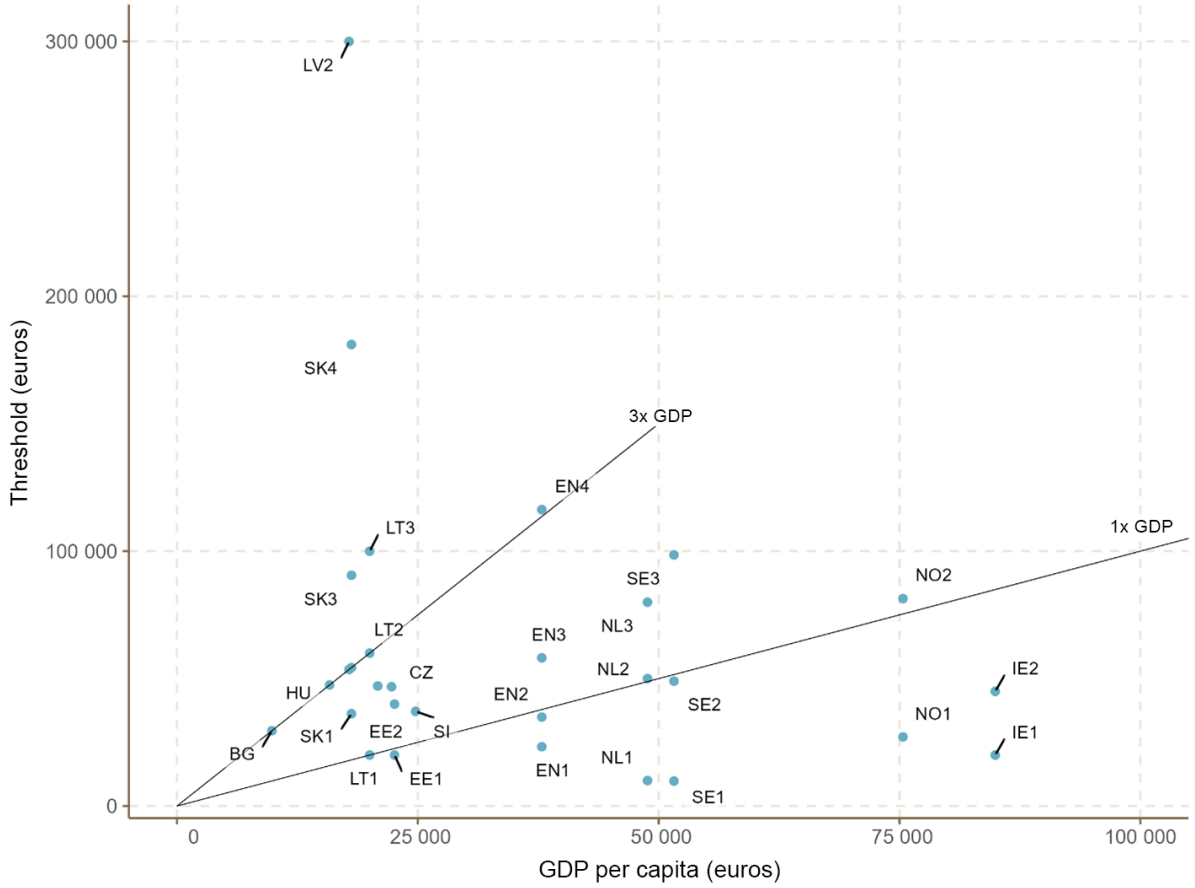
The comparison is also complicated by the fact that five countries use a single threshold level, while nine countries have two or more levels. In some countries (Sweden, Ireland, and England), the thresholds are presented as a range.

Most thresholds in use are between 1-3x GDP per capita. However, countries where the highest level of the threshold is very high, e.g., 5 or 10 times the level of GDP per capita, also stand out. As a rule, the highest threshold levels are special situations in terms of disease burden, availability of treatment alternatives, etc., and the application of the threshold requires a series

[26] Swedish Tax Agency (as of 05.11.2022): https://www.skatteverket.se/servicelankar/otherlanguages/inenglish/businessesandemployers/startingandrunningaswedishbusiness/declaringtaxesbusinesses/vat/vatratesongoodsandservices.html

of clearly defined conditions, which may differ from country to country. The absence of an extremely high level in other countries does not necessarily mean that treatment exceeding the usual thresholds in such situations will not be reimbursed in them – it is just that the decision-making process in such cases may be based on different criteria or not formalised.

Figure 2. Cost-effectiveness thresholds and GDP per capita (2021) in selected European countries



If several thresholds are used in the country, they are marked with a number after the country code from lowest to highest, e.g., EE1 is the lowest threshold used in Estonia and EE2 is the highest threshold.

Sources: Sweden: Socialstyrelsen (2018); Ireland: HIQA (2020); Norway: Ministry of Health and Welfare Services (2017); The Netherlands: ZIN (2015); England and Wales: NICE (2022); Estonia: interviews; Lithuania: Lasys (2022); Slovenia: Health Insurance Institute of Slovenia (inquiry); Slovakia: AIFP Slovakia (inquiry); Czech Republic: SÚKL (inquiry); Poland: Kamusheva et al. *(2021); Latvia:* Regulation No *899* of the Government of the Republic; *Hungary: Kovács* et al. *(2022); Bulgaria: Kamusheva* et al. *(2021). GDP per capita: Eurostat.*

The following aspects should be taken into account when comparing the cost-effectiveness thresholds used in different countries:

- National practices differ in terms of whether costs are taken into account with or without VAT in the cost-effectiveness analysis. For example, in Slovakia, and the Czech Republic, all costs are subject to VAT; in England, Ireland, and Slovenia, they are not. Although the lower threshold in Slovakia, and Slovenia, is similar in absolute terms, the different treatment of VAT, all else being equal, may lead to different cost-effectiveness

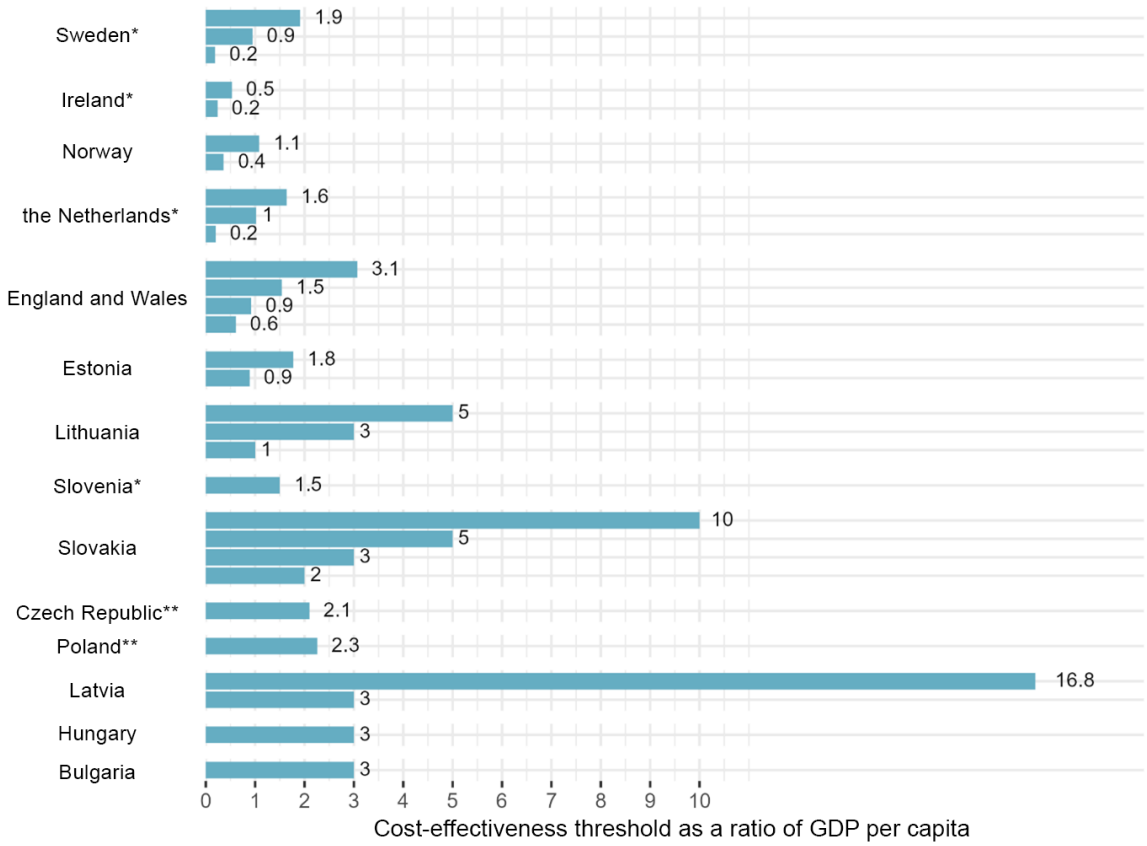
estimates in these countries. In addition, the VAT rate for medicinal products also varies from country to country: in the Czech Republic and Slovakia 10%, in Slovenia 9%, in Lithuania 5%, in Sweden, medicinal products, and healthcare services are exempt from VAT.

- A three-threshold system was recently introduced in Lithuania, where a lower level (1x GDP per capita) is used in situations where the burden of disease (measured on the basis of the proportional deficit method following the Dutch model) is 0.1-0.49 QALY; average level (3x GDP) at a disease burden of 0.5-0.74; and the highest level (5x GDP) at a disease burden of 0.75-1. The higher the threshold for use, the higher the requirements for proof of medical effectiveness (Lasys, 2022).
- In Slovakia, a lower level (2x GDP per capita) is applied to technologies with less than 0.33 QALYs gained; a higher level (3x GDP per capita) is applied when 0.33 QALYs or more are added. Three levels are used for orphan drugs and innovative drugs (cell and gene therapies): 3x GDP if < 0.33 QALYs are added; 5x GDP if 0.33 to 0.5 QALYs are added; and 10x GDP if more than 0.5 QALYs are added. Technologies whose additional cost-effectiveness exceeds 10x GDP per capita can be reimbursed only under special conditions (price agreement or managed entry agreement, high unmet need for treatment, lack of alternative treatment, does not threaten the stability of the budget).
- Ireland's thresholds (€20,000–€45,000 in absolute terms) are very low as a percentage of GDP per capita. This is due to an anomaly specific to Ireland in the measurement of GDP – Ireland's GDP is very high due to the fact that numerous large international companies have moved their operations there due to various tax incentives. Therefore, the relationship between GDP and living standards (and the solvency of society) in Ireland is not the same as in other countries.
- In the Netherlands, a lower threshold is applied for a disease burden of 0.1-0.4, an average threshold for a disease burden of 0.41-0.7, and a higher threshold for a disease burden between 0.71-1.0.
- The lower level used in Norway is meant to express the average opportunity cost in healthcare services, and the highest level is three times higher. Different levels are applied according to the severity of the medical conditions (six degrees of severity are distinguished).
- There is one threshold in use in Poland, and no exceptions are made within the framework of normal TTH for the treatment of rare diseases, the treatment of oncological diseases, etc. Reimbursement of expensive medicinal products, however, takes place within the framework of special programmes based on precisely defined criteria and careful monitoring of use.
- The threshold used in the Czech Republic is not applied in the following cases: especially innovative medicinal products that meet one of two criteria: a) at least a 30% improved outcome in terms of a clinically relevant result that affects the quality of life compared to a reference medicinal product subject to compensation; b) prolongation of median overall survival by at least 30%, a minimum of three months. In this case, temporary compensation will be applied for up to 5 years, after which the normal procedure and the normally required cost-effectiveness threshold will be applied.
- The cost-effectiveness threshold applied in Slovenia is explicit, but it represents only one of the applied criteria, which is why, in practice, numerous medicinal products that

do not meet the cost-effectiveness criterion are subject to compensation based on the threshold. The current threshold is not related to GDP and has been in use since 2013.

- In both Ireland and Sweden, the cost-effectiveness threshold is not rigid, and depending on the situation, technology whose incremental cost-effectiveness rate exceeds the threshold may receive funding.
- In Latvia, a higher threshold of €300,000 has recently been established, which is applied to the treatment of rare diseases.

Figure 3. Additional spending efficiency thresholds in selected European countries as a ratio of GDP per capita in 2021



Sources: See the previous figure

** The threshold is not rigid: the guidance allows for technology funding even in the case of unfavourable cost-effectiveness based on other criteria*

*** Threshold is not applied to advanced therapy medicinal products*

2.4. Assessment of health outcomes

2.4.1. England

Quality-adjusted life years link both life expectancy and quality of life. Assessments of quality of life are generally based on self-assessments, for which the EQ-D5 measuring instrument should be used[27,28].

The NICE guidance says that the committee can use decision modifiers where appropriate. Decision modifiers are factors that are not included in QALY estimates because they cannot be included there (factors that extend or complement it) (NICE 2022, p. 152). Modifiers can be both qualitative and quantitative (so-called QALY weighting).

If no decision modifiers are used, QALYs are weighted equally. One of the reasons for using weights can be the severity of the health condition. Severity is the future loss of health associated with living with the health condition under consideration and the usual care and treatment practices applied to it. A distinction is made between relative and absolute health loss. Absolute health loss is (taking into account current treatment practices) the future loss of years of life and quality of life resulting from a health condition measured in QALYs compared to people who do not have such a health condition. Relative health loss is the ratio of the loss of QALYs due to a health condition to the expected QALYs of people without that condition. Weights are determined according to the table below (see table); when choosing between relative and absolute health loss, the greater one is used.

Table 1 . Sizing QALY weights

QALY weight	Relative health loss	Absolute health loss in QALYs
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

Source: NICE 2022, p. 153

The use of health loss as the basis for a decision modifier is a relatively recent change made during the 2020 methodology update[29]. Before this, the criterion of end-of-life disease (life expectancy less than 24 months, treatment expected to extend life by at least three months) was used as the basis for a higher QALY modifier. During the methodology update, however, it was found that the use of the end-of-life criterion is arbitrary and non-evidence-based and that

[27] https://euroqol.org/

[28] If you are interested, you can get more information about this instrument here: Devlin, N., Roudijk, B., Ludwig, .K. (2022) Value Sets for EQ-5D-5L A Compendium, Comparative Review & User Guide. Springer. [https://link.springer.com/content/pdf/10.1007/978-3-030-89289-0.pdf]

[29] https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/nice-guideline/chte-methods-consultation/Modifiers-task-and-finish-group-report.docx

instead of extending the life expectancy at the end of life, the quality of life should be based on a broader perspective, one that is expressed by the criterion of health loss. It was also found that the use of the end-of-life criterion gives an advantage to the treatment of cancer compared to the treatment of other diseases. It was also pointed out that few HTA authorities in other countries use the end-of-life criterion as a decision modifier, but most use the severity of the disease as either an implicit or an explicit criterion (NICE 2020).

However, QALY weights based on relative and absolute health loss are not applied to the evaluation of all health technologies. They are not used (NICE 2022, p. 155):

- in the case of related diagnostic assessments
- in evaluating highly specialized technologies
- In the case of evaluations carried out as part of the *Medical Technologies Evaluation Programme*.

When evaluating highly specialized technologies, QALY weights can be applied based on the gains in quality-adjusted life years resulting from the technology. In making its decision, the Committee compares the incremental cost-effectiveness rate against a threshold of £100,000 for highly specialized technologies. If, because of the introduction of new technology, the expected quality-adjusted life years increase significantly, then the added QALYs can be given a weight between 1 and 3 (see details in Table 2).

Table 2. Sizing QALY weights in the assessment of highly specialized technologies

QALYs gained (per patient)	**Weight**
Less than 10	1
11 to 29	Between 1 and 3 (linear growth)
30 or more	3

Source: NICE 2022, p. 155

If the use of weights brings the incremental cost-effectiveness rate below the reference value, this supports the adoption of the technology.

2.4.2. Sweden

The methodological guidelines of the SBU (SBU, 2020) mention Standard Gamble, Time Trade-Off, and Visual Analogue Scale methods as direct methods and EQ-5D, SF-6D, and HUI-3 as indirect instruments when finding QALY weights.

The TLV guidelines (TLV, 2017) state that Standard Gamble or Time Trade-Off methods are the preferred methods for finding QALY weights, followed by Rating Scale methods. The EQ-5D classification system has also been mentioned as a possible method for finding indirect QALY weights.

QALYs are treated as equivalent; no modifiers similar to those in England are used.

2.4.3. Ireland

In general, health outcomes should be measured in QALYs, specifying the assumptions made and the methods used to estimate QALYs. The use of general preference-based instruments, such as EQ-5D or SF-6D, is recommended. Both the three-level version (EQ-5D-3L) and the five-level version (EQ5D-5L) can be used. The choice between them must be justified, and a sensitivity analysis must also be performed with the second choice, using the conversion function between the two versions. As an alternative, direct health-related quality-of-life assessment methods such as time trade-off or standard gamble can be used if they have been carried out in a suitable population.

No QALY modifiers are used; all QALYs are treated as equivalent. The use of modifiers by reweighting QALYs has been considered, but the methodological challenges in this regard are considered serious; however, if important considerations related to inequality are known (e.g., socio-economic status of the target groups, age, presence of dependents, etc.), they must be described in the analysis so that the decision-maker can be aware of them, e.g., by describing the unmet needs of disadvantaged social groups.

2.5. The time horizon used in the analyses

2.5.1. England

According to the NICE manual, the time horizon used in the analysis should be chosen in such a way that it is long enough to highlight differences in costs or output indicators between comparable technologies (NICE 2022, p. 65)

The impact of many technologies manifests itself over the patient's life span, in which case it is appropriate to use a lifetime time horizon.

The use of a shorter-than-lifetime time horizon is justified when there are no mortality differences in the output indicators of the compared technologies and the differences in costs and clinical outcomes persist for a relatively short period of time.

2.5.2. Sweden

According to the TLV guidelines (TLV, 2017), the time horizon must correspond to the period during which the main health effects and costs appear. If treatment affects survival, then a lifetime time horizon must be used in the evaluation. This means that the results of clinical trials must be extrapolated beyond their time frame. The fact that the time horizon is lifelong does not mean that lifelong treatment should be analysed. For chronic diseases, cost-effectiveness may vary by age. In this case, it is often reasonable to analyse treatment periods of one to five years so that the cost-effectiveness rate takes into account the cost-effectiveness at different ages.

The SBU guidelines (SBU, 2020) do not mention the time horizon.

2.5.3. Ireland

The time period must be clearly described and relevant to the disease in question and its treatment. The time horizon must be long enough to reveal meaningful differences in costs and health outcomes. The same time horizon must be used for costs and health outcomes and for all health technologies being compared.

As a rule, a lifetime time horizon is considered relevant, as most technologies have an impact on costs and health outcomes throughout the patient's lifetime, especially for chronic diseases. A shorter time horizon can be considered, for example, for acute health problems, where no difference in mortality is foreseen when using comparable health technologies. The use of a shorter time horizon must be justified, and the possible resulting bias in the results must be assessed.

In a situation where there is only short- or medium-term data on the intervention, and the results are extrapolated to a longer period, the assumptions used must be clearly stated and tested in a sensitivity analysis.

2.6. Discounting

2.6.1. Theoretical foundations of discounting

When making funding decisions about health technologies, it is important to compare the relevant costs and benefits (health outcomes). It is more complicated in situations where costs and health outcomes occur at different points in time. If a choice were to be made between two health technologies that provide the same desired health outcome, one today and the other a year from now, a rational decision-maker would prefer the earlier gain. The opposite is true with costs – a cost incurred later is preferable to an equally large cost incurred earlier. This is called time preference.

Discounting is used to systematically take time preferences into account. Discounting is an act in which a time value weight is applied to future costs and revenues that are smaller the further in the future the corresponding moment in time is. The corresponding weight is calculated as follows:

$$\frac{1}{(1+d)^t}$$

where t represents a period of time (typically a year), and d is a parameter called the discount rate. If, for example, the discount rate is 5%, the weight applied to the expense or income arising in the 10th year of the period under review is 0.61, while the weight applied in the 50th year is 0.09. If the discount rate is 3%, the 10 and 50-year weights are 0.74 and 0.23, respectively. As can be seen, the choice of the discount rate is a parameter that affects costs and revenues, and even more so, the further into the future the time periods are. Given that the time horizon for the assessment of health technologies is typically longer than a year and can reach quite far into the future, the discount rate must be considered an important parameter in the economic evaluation. Its selection affects health technology decisions: whether the incremental cost-effectiveness rate

falls below a prescribed threshold or not may depend on it. Also, the higher the discount rate, the less cost-effective the interventions are perceived to be, e.g., in which the costs are incurred at the beginning of the intervention, while the benefits are spread over a long period of time.

What should the choice of discount rate be based on? Speaking of which, we must return to the starting point of discounting – what is the reason to prefer a later cost to an earlier cost? One argument is based on the view of the so-called social opportunity cost, according to which the intervention made from public money takes place at the expense of investments made by the private sector, and therefore the intervention must be at least as profitable as an alternative private sector investment (and the discount rate should therefore be defined based on the average profitability of private investments).

According to the second approach, time preference is formed based on three explanations:

- The general increase in income means that one additional unit of consumption, e.g., 10 years from now, will most likely be less valuable to a person than today; therefore, it is more reasonable to consume it today;
- There is a risk of an existential disaster (e.g., death, war, natural disaster). At the individual level, this means that if there is a choice between consuming one unit today or, for example, 10 years from now, there is a probability that 10 years from now it may not be possible. At the societal level, the risk of a total disaster is, of course, significantly lower than at the individual level;
- Impatience – the person prefers today's consumption to tomorrow's because they do not want to wait. Whether this argument should also be used at the level of society is questionable.

Formalised, these three explanations are expressed as Ramsey's formula:

$$d = \mu g + L + \delta,$$

where d is the societal time preference rate (discount rate), μg is the so-called wealth growth effect (g is consumption growth, μ is a parameter expressing the utility of an additional consumption unit), L is the risk of catastrophe, and δ is pure time preference (so-called "impatience"). The discount rate should therefore be higher; the faster the growth of consumption, the higher the risk of catastrophe and the greater the desire of members of society to consume benefits now, rather than in the future. It should be noted that the estimation of the size of the components of the formula is rather complicated – the growth of consumption must be predicted *ex ante*, and the estimation of the catastrophe risk and impatience parameter is even more complicated. Conventionally, the risk catastrophe is estimated to be in the order of 1%, and the value of the time preference parameter δ is in the range of 0–1%.

When making decisions about health technologies, a series of specific questions arise:

- Is healthcare spending done from a fixed budget? In this case, they cannot be viewed (from the point of view of social opportunity cost) as expenditures that replace private sector investments; instead, each expenditure replaces some other healthcare expenditure within the budget limit. In this case, the discount rate cannot be derived from the profitability of private investments;

- Should health care spending and health outcomes be discounted at the same rate? There is no consensus on this. Gravelle and Smith (2001) justify the use of different rates by the fact that the value of health outcomes increases over time. Several health economists (e.g., Meltzer and Smith 2012, Claxton 2011) consider that health outcomes should be discounted at a lower rate than costs in the case where the health spending budget is fixed, but the incremental cost-effectiveness threshold is increasing over time. There are still a few countries where health outcomes and costs are discounted at different rates (e.g., the Netherlands, Belgium, and Poland), although the incremental cost-effectiveness threshold is increasing over time (due to linkage to GDP) in several countries;
- For long periods of time, should a lower discount rate be applied to income and expenses in the distant future? The question is motivated by the fact that when discounting with a uniform rate, the effects arising in the distant future (e.g., 30 or 50 years from now) are given such a low weight that they influence the decision very little, and the decision made is, therefore "short-sighted," i.e., too little considering the effects arising in the distant future.

In terms of discounting in general and in the treatment of specific aspects of the health field, the practices of the countries are not uniform, and the variability is quite large.

2.6.2. England

The results of the cost-effectiveness analysis must be presented as the present value of the costs and revenues arising during the period under review, i.e., discounted. According to the NICE guidance, both costs and benefits must be discounted at the same discount rate, which is 3.5% per annum. In addition, results calculated with a 1.5% discount rate can also be presented (NICE 2022, p. 75). The same discount rate is applied to health outputs and costs as the analyses are carried out to use the fixed NHS budget as efficiently as possible. If one technology receives money, it is not possible to give it to others. This means that health and money are interchangeable (if there is money, people can be treated, and their health is better, if not, then the reverse is true). Consequently, they should also be treated similarly in the economic analysis (NICE 2020, p. 31)

The 3.5% discount rate mentioned in the first paragraph is the solution preferred by NICE in the reference case. The Committee may also decide in favour of using a non-standard 1.5% discount rate if all the following conditions are met (NICE 2022, p. 75):

- The technology is aimed at people who would die without it or whose quality of life would be very low
- It is likely that their health can be fully or almost completely restored
- The beneficial effects of the treatment are permanent and last for a long time.

The size of the discount rates is discussed in greater detail in the NICE report completed in June 2020[30]. The 3.5% discount rate standard used by the NICE is based on the guidance given in the

[30] NICE (2020) CHTE methods review. Discounting. Task and finish group report, July 2020, 56 p.

HM Treasury Green Book for the assessment of public funded projects. According to this, the discount rate consists of three parts (NICE 2020, p. 11):

- **Time preference** (0.5%), representing the general preference of people to receive benefits today instead of in the future
- **Catastrophe risk premium** (1%), implying that catastrophic events may make the benefits promised for the future unattainable
- **Wealth effect** (2%), representing the fact that under the conditions of an increase in the standard of living, people attribute a lower value to the additional consumption of goods and services (the more I have, the less pleasure I get from the additional unit).

In a recent review of methods, it was decided at the NICE not to follow the guidance in *HM Treasury's Green Book* to apply a lower discount rate to revenues and costs arising in the more distant future (3% of the assessment period in years 31-75, 2% in years 76-125). The reason given was that the application of different discount rates complicates the process, although its effect on the analysis results was found to be small (NICE 2020, p. 35).

The possibility of discounting health outcomes with a lower discount rate than costs was also considered, as health economists (Claxton *et al.* 2011) have shown that the use of different discount rates is appropriate in the case of a time-increasing incremental cost-effectiveness rate threshold. However, it was decided not to introduce different discount rates, pointing to the fact that the threshold used by the NICE has not changed throughout the NICE's history. Since every expenditure within a fixed budget entails an opportunity cost in the form of not achieving another possible health outcome, expenditures and health outcomes are considered equivalent and, for this reason, are treated similarly in the economic analysis.

2.6.3. Sweden

According to the TLV guidelines (TLV, 2017), a discount rate of 3% must be used for both costs and health effects. Sensitivity analyses should additionally use 0% and 5% discount rates and a calculation where costs are discounted at a 3% rate and health effects at a 0% rate.

2.6.4. Ireland

All costs and health outcomes arising in a time frame longer than one year are discounted at a flat rate of 4%. The rate has been established by the Ministry of Finance for use in economic analyses (IGEES 2018). In the sensitivity analysis, the discount rate must be varied, with the recommended range for this being 0%–10%, and it is also recommended that the effect of a 1-percentage-point change in the discount rate in either direction be tested.

An example of distinctive practice: The Netherlands

The discounting practice used in the Netherlands differs from the practices other countries discussed here primarily in that costs and health outcomes are treated differently in discounting. Costs are discounted at a rate of 4%, health outcomes at a rate of 1.5%. Both rates are constant, i.e. no differentiated rates are applied for different time periods (e.g. the distant future) (ZIN 2015). The results of the economic analysis are presented in both discounted and non-discounted form.

Before 2006, a uniform discount rate was applied in the Netherlands. The previous application of a single discount rate was justified by the criticism presented in earlier literature, according to which the application of different discount rates can lead to paradoxical results. During the later debate, however, this criticism was found to be unfounded, referring to which the implementation of different discount rates began in 2006.

The selection of the 4% discount rate for costs was based on the estimates given in the literature and the yield indicators of the bonds. The choice of a 1.5% discount rate for health outcomes is based on the literature and the fact that life expectancy (in the form of healthy years lived) in the population continues to increase (College voor zorgverzekeringen, 2006).

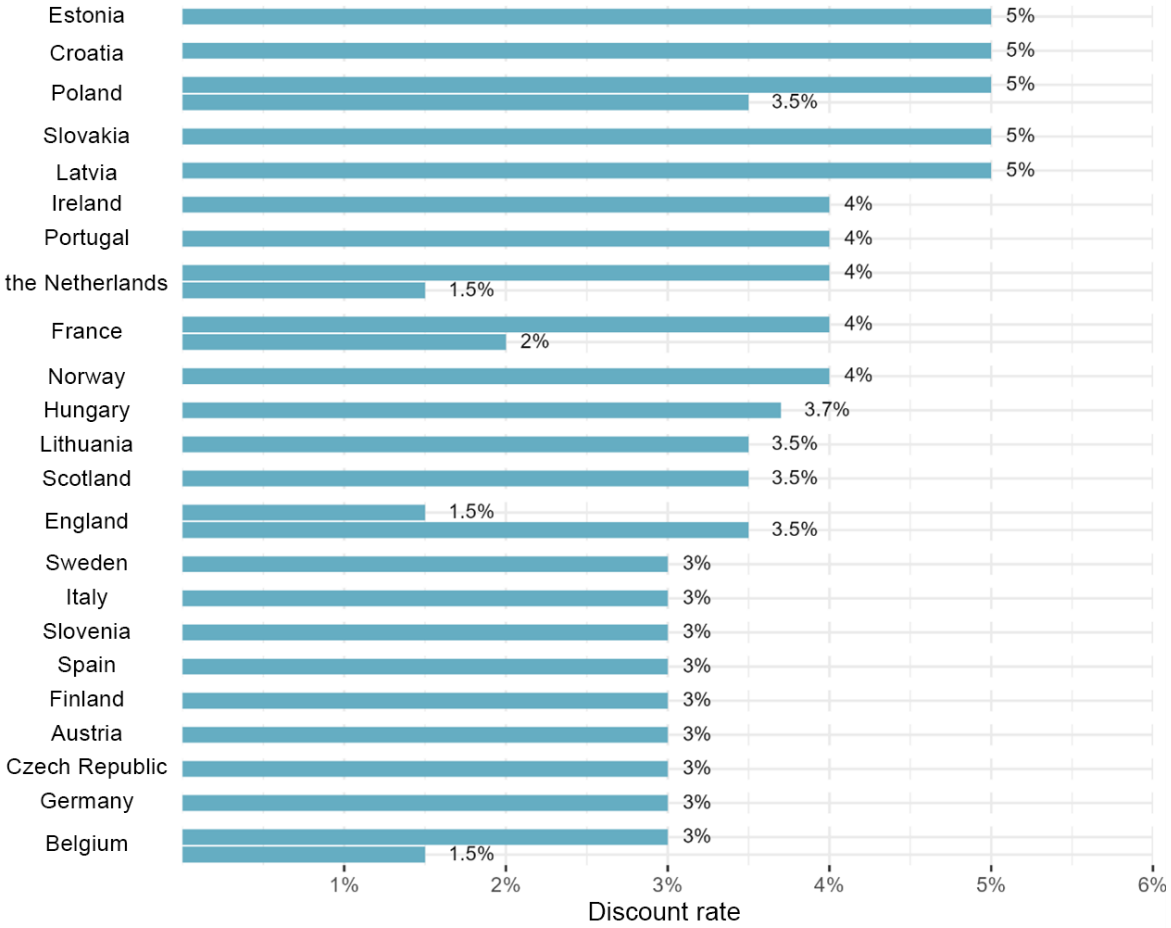
2.6.5. Other countries

The discount rates used in economic analysis in the evaluation of health technologies in selected European countries are presented in the figure below.

As a comment to the comparison of the countries:

- In Poland, the Netherlands, and Belgium, a higher rate is used for costs and a lower one for health outcomes.
- In England, the higher rate (3.5%) is generally applied, and the lower rate (1.5%) is applied for curative treatment of serious illnesses.
- In France, a higher rate of 4% applies for the first 30 years of the analysis period, then a lower rate of 2%.
- In Hungary, the discount rate is derived from the Ramsey equation applied to domestic data.
- In Norway, Ireland, and England, the discount rate established by the Ministry of Finance is applied for use in cost-effectiveness analyses of public projects.
- In Lithuania, the discount rate was recently lowered from 5% to 3.5% (being modelled on the rate used in Scotland).

Figure 4. Discount rates used in the assessment of health technologies in selected European countries.

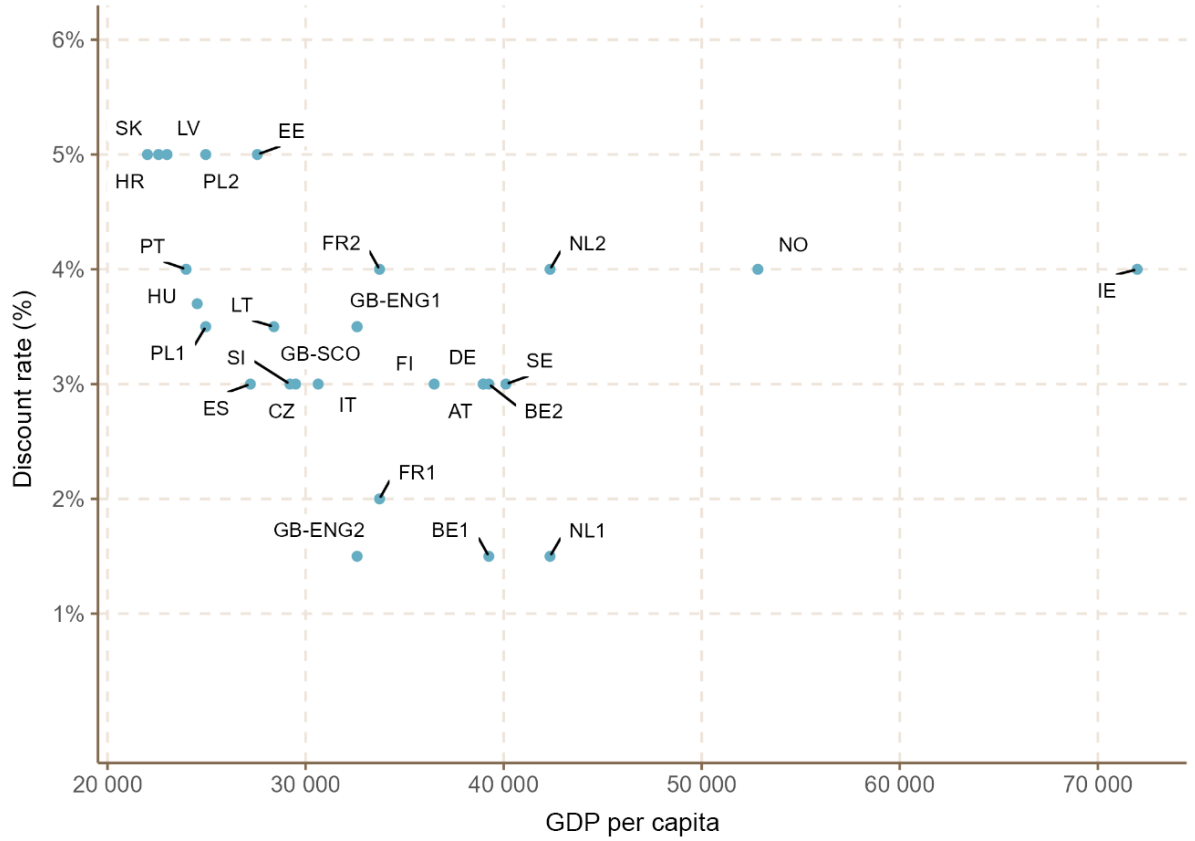


Source: HR, FI, DE, IT, ES, HU, FR, NO, LV, BE, PL: Sharma et al. *(2021); EE, IE, NL, GB-ENG, GB-SCO, SE: National Guides; LT: Lasys (2022); SI: Jurij Fürst, Health Insurance Institute of Slovenia, personal communication; SC: Iveta Palesova, AIFP Slovakia, personal communication; CZ: Leoš Fuksa, SÚKL, personal communication*

As you can see from the figure, the discount rate used in Estonia is among the highest in Europe, sharing first place with Croatia, Latvia, and Slovakia (Poland also has a higher rate of 5%, but only for costs). All other countries, for which data were found, are using a lower discount rate.

A negative relationship appears between the discount rate used and the wealth of the country: lower rates are used in richer countries. The highest rate, 5%, is used only in Central and Eastern European countries. At the same time, there is also variation among the countries of this region, and the discount rate used in, for example, Lithuania, the Czech Republic, Hungary, and Slovenia is below 4%. In addition, among richer Western European countries, the discount rate used varies, typically in the range of 3%–4%, with the exception of the above-mentioned special cases in which a lower rate is used.

Figure 5. Discount rates and GDP per capita (taking into account purchasing power parity) in selected European countries.



Sources: See the previous figure

2.7. Incorporating uncertainty into the analysis

2.7.1. England

An uncertainty estimate is required. It should describe the impact of different types of uncertainty (e.g., parametric or structural) on the cost-effectiveness found, assess whether the sources of uncertainty have been adequately considered in the analyses, and identify sources of uncertainty that are unlikely to be reduced by additional evidence or peer review. The probability that the decision would be different if the actual cost-effectiveness of the technology under consideration were known must be highlighted.

All structural assumptions of the model (e.g., categorisation of health conditions, assumptions about movements between treatment modalities) must be documented and justified, and the impact of variation within plausible limits on cost-effectiveness estimates must be tested. The probabilistic weighting of different structural assumptions can be used while also varying the weights used.

It is also necessary to describe and justify the choices of data sources used (e.g., in terms of cost or efficiency data) in cases where different sources can be used and to point out the impact of the choices made on cost-effectiveness.

The impact of model parameter inaccuracy on the results must also be assessed by assigning a (justified) probability distribution to the parameter estimates. The impact on the results is evaluated through probabilistic sensitivity analysis (if the structure of the model used does not allow this, it must be described, and the choice of the model must be justified). Confidence ellipses and dot plots on the cost-effectiveness plane or cost-effectiveness acceptance curves can be used to describe parameter uncertainty. The probability that the cost-effectiveness of the technology is favourable based on the thresholds used must be presented. With deterministic sensitivity analysis, one must identify the parameters to which the evaluation of the performance indicator is most sensitive and find the values of the parameters at which the cost-effectiveness evaluation changes from favourable to unfavourable. A sensitivity analysis must be performed even if cost minimisation is the chosen method.

2.7.2. Sweden

Based on the guidelines of the TLV (2017), uncertainty should be assessed according to the most important assumptions and parameters. In addition, different discount rates should be used in the sensitivity analysis. The SBU methodology guidelines (SBU, 2020) mention as examples the use of the bootstrap method for empirical analyses and probabilistic sensitivity analysis for models.

2.7.3. Ireland

It is required to perform both univariate and multivariate sensitivity analysis, with reasons for the ranges used for each variable and (if necessary) for excluding variables from the sensitivity analysis. A probabilistic sensitivity analysis (Monte Carlo simulation) must be performed, and an estimate of the full information expected value (EVPI) must be provided. In the sensitivity analysis, the probability that the ICER will be below the threshold (separately for the upper and lower thresholds) must be presented.

Variables, the effect of variation of which must be evaluated in the sensitivity analysis, are defined in the usual way – costs (it is recommended to vary costs by +/- 20%) and other key model input indicators and model parameters, assumptions for the extrapolation of effects beyond the observation period (also including the calculation of results using a time horizon that corresponds to the actual duration of the monitoring period), discount rate (in the range of 0%-10%), comparison of the results of using alternatives in the presence of different source data.

2.8. Handling of new technologies in the HTA

2.8.1. Introduction

In the context of the assessment of health technologies, the treatment of so-called advanced therapy medicinal products (ATMP) deserves special emphasis. This category includes technologies such as medicinal products for gene therapy or somatic cell therapy, or tissue-engineered products. Technologies belonging to this category typically have a number of characteristics that, in one way or another, complicate their evaluation within the framework of the standard procedure. These are often technologies that apply to a small number of patients;

are indicated for the treatment of very serious diseases; are very expensive due to both development and production costs and limited scalability; and offer potentially significant health benefits, in some cases a salutary effect, but with significant uncertainty regarding their proof of effectiveness. The assessment of such technologies presents a number of challenges:

- **Small sample size** in a clinical efficacy study. In the case of rare diseases, the overall patient population is small, and recruitment to the studies is difficult. Also, the patients included in the sample may be very different (e.g., children and adults), which raises questions about the generalisability of the results. There may also be no control arm (e.g., because patients with severe disease do not like the risk of being assigned to the placebo group and prefer to receive the experimental treatment). The use of small, heterogeneous, and non-control arm samples significantly increases the uncertainty in the assessment of clinical efficacy.
- **The use of surrogate endpoints** means that the study has not evaluated the effect of the technology on the primary health outcome of interest to the decision maker (e.g., survival) but on a related intermediate outcome (e.g., tumour progression). In this case, the impact of the technology on the health outcome of interest must be assessed through model forecasts or other assumptions. However, this leads to additional uncertainty about the reliability of the results, especially for rare diseases, where the choice of an appropriate model and assumptions is difficult. In a follow-up analysis of 36 anti-cancer medicinal products approved by surrogate endpoints, Kim and Prasad (2015) found that only five demonstrated improved survival.
- Even if no surrogate endpoints are used, the **short study period** means more generally that the final effect of the technology (and the persistence of the health benefits found in the clinical trial) in the long term is not empirically proven but needs to be evaluated using model predictions. One way to address this problem has been to conduct analyses with **time horizons of different lengths** (calculating the incremental cost-effectiveness rate for each horizon and assigning more weight to the results found with shorter horizons) and combine them with probabilistic sensitivity analysis.
- **The research perspective** becomes especially important in severe diseases. While the economic analysis of technology is often done from the perspective of the healthcare system, in the case of some diseases, the cost-effectiveness is significantly affected by the introduction of a broader perspective – for example, in the case of severe diseases, it is not only the patient's quality of life but also that of his or her relatives and caregivers that suffers significantly (this raises the question of how to handle the economic and ethical aspects of treatment prolonging the survival of a patient with a serious illness, if this is accompanied by a corresponding increase in the burden of care); it may be important to consider the patient's ability to work and productivity, in the case of children, the effects on participation in education and learning results, etc. In the case of treatment that is curative and significantly prolongs life expectancy, long-term costs to the healthcare system that are not related to the disease under consideration should also be taken into account.
- **Determining health benefits and value** is a challenge that arises, especially in severe diseases.

- Conventionally, health benefits are measured in terms of quality-adjusted life years (QALYs), where a change in QALY from, say, 0.1 to 0.2 is typically assumed to be treated as equivalent to a change from 0.8 to 0.9. In the case of severe disease, this assumption has sometimes been challenged, and people have been found to value the health benefits of 0.1 QALY more for severe disease than for mild disease. NICE addresses this difference using so-called **modifiers**, giving greater weight to the health benefits in situations where the absolute and/or relative health loss is greater (for details, see subchapter 2.4.1). In the Netherlands, the choice of the cost-effectiveness threshold is made dependent on relative health damage.
- The definition of added value through technology is also the perspective of the study mentioned in the previous point, e.g., whether or not the reduction of workload, stress, and emotional suffering for caregivers and loved ones is included in the value.
- In the case of technologies that have a potentially curative effect, separate modelling of the probability of a cure and the proportion of cured patients may be necessary to correctly assess the effectiveness of the additional cost (Othus *et al.* 2017).
- It has also been argued (Jena and Lakdawalla 2016) that the so-called insurance value created for the rest of the population through the knowledge that there is a cure for a serious disease that potentially threatens them in the future (analogous to, e.g., vaccines, in which the benefit of protection arises from the vaccine at the moment of receipt, not at the moment of a hypothetical prevented illness occurring in the unknown future) should also be taken into account on the income side.
- A separate category of value is scientific transfer effects, i.e., the knowledge that grows with each new technology, which directly or indirectly contributes to the development of future technologies and makes it easier.

Evaluating the value of different types and including them in the economic analysis of technologies is, of course, difficult, and it may be necessary to go beyond the usual cost-effectiveness analysis and consider benefits and costs in a full-scale cost-effectiveness analysis.

- **The time distribution of the cost** is often different from the norm for new technologies, arising as a single (and large) amount at the beginning of the analysis period, while health outcomes may be spread over a longer period. When discounting costs and health outcomes, maximum weight is given to the cost at the beginning of the period, while future health outcomes receive less weight the further into the future they are. This makes the technology economically disadvantageous. This is addressed in some countries by discounting revenues at a lower rate than costs (Poland, Belgium, the Netherlands); an alternative is to enter into agreements regarding the payment schedule, which allows the cost to be spread over a longer period for the payer.

The mentioned characteristics are not unique to new technologies, but the latter is characterised by the coexistence of many of these factors.

Because evidence obtained from clinical trials is scarce for advanced therapy medicinal products for the reasons described above, attempts are sometimes made to supplement or replace it with the use of **real-life data.** Typically, the lack of randomisation in real-life data compared to randomised control group trials complicates the identification of the causal effect of the technology. However, it has been shown in various studies comparing results from real-life data with results from randomised trials (e.g., Woolacott et al. 2017, Dickerman et al. 2020, and Franklin et al. 2020) that good quality non-randomised data can provide correct estimates of the effects of interventions in many, but not all, situations. It has been found that the following principles of research design help to increase the probability of obtaining a correct assessment, e.g., the use of an active comparison treatment (i.e., the intervention under study is compared not with the absence of treatment but with receiving an alternative treatment) and focusing on new users of the intervention under study (i.e., not those who have already been receiving the corresponding intervention for a while).

A significant challenge with real-life data is ensuring the reliability of the data and research methodology used. There are many factors influencing the results, e.g., the choice of persons included in the participation and comparison groups, the study period, and the analysis methodology. Reliability can be ensured by, e.g., pre-registration of study protocols (to prevent or detect changes in research questions or methodology during the study), disclosure of data and analysis code, or data analysis in a secure environment where no trace of operations is left behind.

Managed entry agreements and risk-sharing agreements are used in many countries as one way to mitigate the uncertainty of evidence. Different types of schemes can be distinguished among such agreements:[31]

- **Financial** agreements where the risks related to the budgetary impact of the introduction of new health technology are mitigated through mechanisms that can be either:
    - **at the patient level** (e.g., establishing a ceiling on the use of the medicinal product per patient or on the cost per patient, if the ceiling is exceeded, the cost is borne by the manufacturer) or
    - **at the level of the patient population** (e.g., a ceiling is agreed on for the total cost of the medicinal product in the population of patients with the corresponding indication, the part of the cost exceeding the ceiling is covered by the manufacturer). For example, an agreement has been used in Australia where a budget ceiling has been agreed upon for the treatment of all hepatitis C patients, and the part of the treatment costs exceeding this is borne by the medicinal product manufacturer.
- **Performance-based agreements** that address uncertainty related to the effectiveness of new health technology, including:
    - **At the patient level,** e.g**.:**

[31] Wenzl and Chapman (2019).

        - temporary funding with the obligation to collect additional evidence, further funding will be decided on the basis of evidence or
        - funding (or continuation of treatment) depends, for each patient, on whether the response meets pre-agreed goals.
    - **At the patient population level,** e.g.:
        - temporary funding with a commitment to gather additional evidence at the patient population level, further funding to be decided based on the evidence, or
        - funding is dependent on achieving a previously agreed upon target for the patient population.

It has been estimated that financial agreements have been used in at least two-thirds of OECD member states, while performance-based agreements have been used to a lesser extent (Wenzl and Chapman 2019).

Price-based and performance-based agreements enable patients to have faster access to new medicinal products, mitigating the risks arising from the budgetary impact of their financing. In some studies, however, it has been found that the experience of countries with the temporary funding of the medicinal product with the obligation to collect additional evidence has not been positive from the financier's point of view: for example, the confidentiality requirements of the agreements have prevented the publication of the evidence (Gerkens *et al.* 2017), or the quality of the collected evidence has turned out to be insufficient (Wenzl and Chapman 2019). The obligation to collect additional evidence also leads to an increased need for data collection, which can increase the administrative burden and requires the development of the necessary infrastructure.

In the Netherlands, before 2012, performance-based agreements were applied to expensive medicinal products used in hospitals that met the following conditions:

- budget impact over €2.5 million per year;
- proven therapeutic value compared to existing reference drugs;
- a well-defined research proposal to address uncertainty about the appropriateness and cost-effectiveness of drug use.

Eligible medicines were granted temporary funding for four years with an obligation to gather additional evidence. The scheme has been evaluated in various studies, which have criticized it for the following shortcomings:

- the evidence collected over four years was, in many cases, insufficient to make a decision on the further continuation of funding for medicinal products or the need for further evidence collection was identified (Makady *et al* 2019);
- the focus of the study plans drawn up for the four-year period did not overlap sufficiently with those aspects for which uncertainty had previously been identified (Pouwels *et al* 2019), in other words, the study plans were not suitable for reducing uncertainty.

The option to enter the scheme was terminated in 2012, after which performance-based risk sharing has no longer been used.

From 2015, the so-called locking system has been applied to expensive medicinal products (the criterion is either a total annual cost of more than €40 million or €50,000 per patient and a total cost of €10 million or more): a medicinal product that meets the criteria is added to the list of locked medicinal products, which means that it will not be reimbursed within the basic health insurance package. This is followed by negotiations with the holder of the medicinal product's marketing authorization regarding the price of the medicinal product and an evaluation by the HTA institution (Zorginstituut, ZIN), during which an assessment of the drug's need, clinical effectiveness and cost-effectiveness is formed.

2.8.2. England

The NICE has not (at least as a general principle) adopted an assessment framework different from the standard methodology for the assessment of novel technologies. However, a **higher incremental cost-effectiveness threshold** (£100,000) can be highlighted as a special treatment that is applied to so-called highly specialised technologies (defined as technology for the treatment of diseases in which the number of patients is small, there is no treatment alternative, and the disease significantly shortens life expectancy or severely impairs the quality of life – see subchapter 4.2.2. for more details). The NICE guidance states bluntly that the programme of highly specialised technologies does not aim to provide treatment in every case where the rare disease population is small, or the evidence is lacking. The formulated goal is rather to strive for a balance between the provision of treatment for rare diseases and the inevitable decrease in overall health benefits in the population. Such wording can be interpreted to mean that

technologies funded under the higher threshold are not treated as cost-effective interventions but as trade-offs made in special cases at the expense of overall health benefits.

As mentioned above, in the context of advanced therapy medicinal products, it is also relevant to note the use **of QALY modifiers** depending on the extent of health damage – although they are also used for medicinal products other than new ones, they also play a role in cost-effectiveness assessments of advanced therapy medicinal products, as they are often intended for the treatment of severe diseases.

The NICE's position on the use of **real-life data** is also important when dealing with advanced therapy medicinal products. The NICE recognizes the need to expand the evidence base beyond randomised clinical trials, using evidence from register data and observational studies. The NICE strategy 2021–2026 (NICE 2021) provides for the use of real-life data in decision-making processes. The NICE has also published guidance material (NICE Real-world Evidence Framework), which helps to define situations where real-world data helps to reduce the uncertainty of evidence and describes good practices for planning studies based on real-world data and reporting results in a high-quality and transparent way. Uses of real-life data at the NICE include:

- **contextualizing** the results of randomised trials, i.e., assessing how well the results of randomised trials apply to the target population of a given country; assessment of treatment adherence, assessment of relationships between surrogate endpoints and definitive endpoints; validation of extrapolated effects outside the time periods of previous studies, etc.
- **impact assessment**, including clinical results and assessments reported by patients, as well as in terms of resource use of the health care system; creating direct comparisons with the reference treatment used in the target country; creating an external control arm for single-arm clinical trials; reweighting the results of randomised trials in such a way that the results reflect the actual distribution of patient subgroups in the target population, etc.

One way to finance innovative medicinal products is to create a separate fund for this purpose. In England, the Cancer Drugs Fund was created in 2011 to finance medicinal products that did not receive a recommendation from the NICE for funding by the NHS. After a significant budget overspend, it was reformed in 2016, and medicinal products began to be financed based on financing agreements with the collection of evidence. An agreement is concluded, and the medicinal product is funded by the Cancer Drugs Fund in situations where the NICE analysis has shown that the effectiveness of the medicinal product in the indication under consideration is plausible but insufficiently proven to recommend it for NHS funding, but that the uncertainty can be reduced by gathering further evidence. After collecting additional evidence during the temporary funding period, the NICE will re-evaluate the medicinal product and make a recommendation for the medicinal product to be funded normally or removed from the Cancer Drugs Fund (Wenzl and Chapman 2019).

One of the more recent types of agreements used in England is **portfolio-based agreements**, in which the conditions for the use of all medicinal products in the manufacturer's product portfolio

for the treatment of a certain disease are agreed upon with the manufacturer. Such agreements can cover both the manufacturer's existing medicinal products and medicinal products that will receive marketing authorisation in the future. For example, in 2018, the NICE, while analysing an innovative therapy for the treatment of cystic fibrosis, found that its cost-effectiveness and budget impact were not favourable due to the high price. However, the NHS and the manufacturer found an opportunity to make the therapy available to patients and mitigate budgetary risks by entering into an agreement for the use of all existing and future cystic fibrosis drugs offered by the manufacturer (Kamphuis *et al.* 2021).

2.8.3. Sweden

In the Swedish evaluation framework, from the point of view of advanced therapy medicinal products, it is appropriate to note the existence of higher cost-effectiveness thresholds depending on the severity of the disease, as well as the general hierarchy of principles underlying health policy (from the highest priority to the lowest: the principle of the value of human life, the principles of need and solidarity, the principle of cost-effectiveness).

Among the risk-sharing agreements and price agreements, temporary financing with the collection of additional evidence can be mentioned, which was used in Sweden until 2015. The manufacturer was required to collect additional data over a fixed period (typically two years). After the end of the period, a decision was made either to fund the product (including collecting additional data, if necessary), to limit the funding, or to end it. The scheme was implemented quite actively from 1998-2009. Sweden was the most active implementer of this type of agreement (Carlson 2010, Andersson *et al.* 2020).

From 2015, a new protocol was implemented for risk-sharing agreements. The Council for New Medicines (*NT-rådet*) carries out so-called horizon monitoring, which identifies technologies of interest based on predetermined criteria (e.g., a large number of potential patients, innovative treatment, high costs). The protocol also provides for an assessment of healthcare economics, preparation of recommendations for implementation, action, and a follow-up action plan. In the case of outpatient treatment, the process is coordinated with the process of adding the medicinal product to the discount list, involving stakeholder groups.

Uncertainty regarding the duration of the treatment, the total volume, and the efficiency of the technologies are the most cited motivations for risk-sharing agreements. However, the agreements used today (unlike the schemes used until 2015) are financial in type, not performance-based. Mechanisms used in contracts include rebates, total cost ceilings per treated patient, and tiered rebates that apply as the duration of treatment increases.

2.8.4. Ireland

Transparency about the use of risk-sharing agreements in Ireland is low, and there is no public data on the existence, form, and number of agreements, which has also been pointed out in

previous review articles (Wenzl and Chapman 2019, Russo *et al.* 2021[32]). However, in a recent comparative analysis of the use of risk-sharing schemes in the financing of Nusinersen, used for the treatment of spinal muscular atrophy and Tisagenlecleucel used for the treatment of cancer in different countries (Facey *et al.* 2021), the implementation of an outcome-based risk-sharing agreement is referred to. As part of the agreement, the collection of additional data has been agreed upon with the aim of reducing uncertainty about the long-term effects of the medicinal products. Data is collected through attending hospital physicians and submitted for analysis to the Medicines Management Program (MMP), the National Health Service's (HSE) multidisciplinary body working on the safety, effectiveness, cost-effectiveness, and accessibility of medicinal products. The collected data is used to perform a second evaluation of the medicinal products.

[32] Russo, P., Carletto, A., Németh, G., & Habl, C. (2021). Medicine price transparency and confidential managed-entry agreements in Europe: findings from the EURIPID survey. Health Policy, 125(9), 1140-1145.

3. The assessment process and decision criteria of health technologies in Estonia

3.1. HTA processes in Estonia

In Estonia, health technology assessments are conducted in three different contexts:

a) HTA assessments within the framework of changing the list of medicinal products, coordinated by the Health Insurance Fund (HIF);
b) HTA assessments within the framework of changing the list of healthcare services, coordinated by the Health Insurance Fund;
c) Health technology assessments are conducted at the Institute of Family Medicine and Public Health of the University of Tartu.

The list of medicinal products is covered by § 43 of the Health Insurance Act. According to this (subsection 1), the list of medicinal products is established by a regulation of the minister in charge of the policy sector on a proposal of the Supervisory Board of the Health Insurance Fund. The following criteria are taken into account when making a proposal to include a medicinal product in the list of medicinal products and when establishing the list of medicinal products (subsection 2):

1) the need of an insured person to obtain a medicinal product as a result of the provision of a health service;
2) the proven medical efficacy of a medicinal product and the need of an insured person to obtain other medicinal products in the course of their treatment;
3) the economic justification of the use of a medicinal product;
4) the existence of alternative medicinal products or treatments;
5) conformity with the financial resources of health insurance and with the principle provided for in subsection 25 (3) of the Health Insurance Act, according to which the expenses of the Health Insurance Fund for medicinal product benefits may not exceed 20% of the costs of health service benefits in the annual health care budget.

The procedure for changing the preparation of the list of medicinal products, the composition and working procedure of the committee, and the content of the decision-making criteria are established by Regulation No. 59 of the Minister of Health and Labour of 19.12.2017 "Procedure for drafting and amendment of a list of medicinal products of the Estonian Health Insurance Fund and the content of criteria for establishing the list and evaluators of compliance with the criteria, and establishment and rules of procedure of a medicinal products committee."

The list of health services of the Health Insurance Fund is covered by §§ 30–31 of the Health Insurance Act. The list is established by the government by regulation on the proposal of the minister responsible for the field, to which is attached the written opinion of the Supervisory Board of the Health Insurance Fund on the proposal (subsection 30 (1) of the Health Insurance Act). The following criteria are taken into account upon entry of a service in the list of health services (subsection 31 (1) of the Health Insurance Act):

1) the proven medical efficacy of the health service;
2) the cost-effectiveness of the health service;
3) the necessity of the health service in society and the compatibility of the service with national health policy;
4) correspondence to the financial resources of health insurance.

The detailed content of the criteria for the list of health services and the assessors of compliance with the criteria are established by Government Regulation No. 62 of 12.07.2018 *"The detailed content of the criteria for the list of health services of the Estonian Health Insurance Fund and the assessors of compliance with the criteria, the conditions, and procedure for evaluating the list of health care services, the formation and work procedures of the committee for the list of health services and the procedure for giving an opinion."*

The criteria used when changing both the list of medicinal products and the list of health services are therefore largely similar, although the wording used is different (the necessity of the service for society vs. the insured person's need to receive a medicinal product; economic justification vs. cost-effectiveness). The differences are, in the case of medicinal products, a reference to the limitation established by §25 of the Health Insurance Act on the share of the pharmaceutical benefit, and in the case of the list of health services, the above-mentioned compliance with the state health policy.

The process of **evaluations of health technologies carried out at UT** is described in the document Methodology of Evaluation of Health Technologies (approved by the Supervisory Board of the HTA on 25.01.2017), which is based on the following description of the process.

In the assessment of health technologies in the different contexts mentioned above, there are differences regarding the process parties, the choice of topics, and the stages, which we describe in the following subsections.

3.2. Stages of HTA processes

3.2.1. Initiating the process

As part of the process of **changing the list of medicinal products**, the first step is to submit an application to the Health Insurance Fund for inclusion in the list of medicinal products. According to § 5 of the regulation "*List of medicinal products of the Estonian Health Insurance Fund…"*, the application may be submitted by the manufacturer of the medicinal product (including the person to whom the marketing authorisation for the medicinal product has been issued). Together with the application, mathematical models must be submitted to support the data contained in the application and, if necessary, the software used for modelling (§ 6).

The application must include, among other things (§ 7)

- characterization of the field of use in Estonia (including the number of patients, treatment methods used, analysis of the possible volume of retail sales of the medicinal product, and the forecast of the volume of retail sales of the medicinal product for three years)
- the expected medical results of using the medicinal product

- a description of the dosage of the medicinal product and the optimal duration of use of the medicinal product
- description of the side effects of the medicinal product and medical-economic assessment of them
- price information and its forecast for the next three years
- a pharmacoeconomic analysis of the use of the medicinal product, which must be prepared in accordance with the guideline for the pharmacoeconomic evaluation of medicinal products published on the website of the Health Insurance Fund in the Baltic States (exceptionally, the analysis does not have to be adapted to Estonian conditions if it is a medicinal product for a rare disease)
- an overview of all scientific publications concerning the medicinal product.

The Health Insurance Fund and the State Agency of Medicines may require the submission of additional data and documents if they are necessary for the correct and quick resolution of the application, in which case the procedural deadlines will be suspended for up to 60 days until the additional data is received. The Health Insurance Fund checks the compliance of the application with the requirements, and if there is a deficiency, it sets a deadline (10-60 days) to eliminate the deficiency within 15 days. During the resolution of the deficiency, the duration of the procedure is suspended (*list of medicinal products of the Estonian Health Insurance Fund*... §§ 7-8).

When changing the list of health services, the first step is also to submit an application to the Health Insurance Fund. Pursuant to subsection 31 (5) of the Health Insurance Act, interested associations of **health service providers and professional associations** may initiate changes to the list by entering into negotiations with the Health Insurance Fund. The **Health Insurance Fund** can also initiate a proposal to change the list of health care services by entering into negotiations with associations of health care providers or professional associations interested in the matter. Adding or changing a service that includes the administration of a medicinal product **can be initiated by the holder of the marketing authorisation for the medicinal product**. The **Ministry of Social Affairs** also has the right to propose to the Health Insurance Fund to enter into negotiations with associations of healthcare providers or professional associations interested in the matter in order to initiate changes to the list of healthcare services if this is necessary for the implementation of the state's health care policy (subsection 31 (5) of the Health Insurance Act).

Patients do not have the right to initiate changes to the list, but they can express their opinion on the contents of the proposed changes to the list from the patient's point of view using the form found on the website of the Health Insurance Fund.[33] The form is used to ask for the following information:

- Symptoms affecting the patient's daily life related to the condition in question

[33] https://haigekassa.ee/sites/default/files/TTL/2020/Arvamuse_vorm.docx

- an assessment of how well the patient's condition can be controlled with the treatment options available in Estonia so far, and in terms of which there is primarily room for improvement
- assessment of whether the service/medicinal product under review improves the patient's quality of life and/or reduces his or her need for care (coping with everyday life, workability, and sociability) and, if so, how
- the effect of the use of the given service/medicinal product on the patient's family and/or caregiver
- what disadvantages may be associated with the use of this service/medicinal product compared to the current standard treatment (e.g., side effects, the complexity of use/administration, the financial impact on the patient and/or caregiver)
- are there groups of patients who would benefit more from the use of this service/medicinal product compared to others (small children, the elderly, etc.)

The submitted opinions will be included in the materials submitted to the TTL committee. According to the interviewed representative of the Health Insurance Fund, the possibility of expressing an opinion through the form is used, but rather rarely.

According to § 9 of the *List of healthcare services of the Estonian Health Insurance Fund*, the application is submitted on the form published on the website of the Health Insurance Fund. The application provides data on compliance with the criteria for assessment, including:

- **The medical indication for the health care service** and the characterisation of the disease or medical condition underlying the indication
- **Evidence-based nature of the health care service**, including a description of the scientific literature search, evidence-based data on the effectiveness of treatment based on clinical studies and meta-analyses, evidence-based data on the safety of treatment, and experience providing the service in global practice
- **Evidence-based nature compared to alternative evidence-based treatment methods**, including a description of alternative evidence-based treatment methods financed by health insurance, the inclusion of requested service and alternative treatment methods in treatment guidelines accepted in European countries, a summary of the evidence-based nature of the treatment compared to alternative evidence-based treatment methods
- Description **of the activities necessary for the provision of the health service**
- **Conditions and readiness of the service provider to** provide high-quality health care service, including the service provider, method of provision (ambulatory, inpatient, and/or day-care/day surgery), medical billing specialty, minimum number of health care appointments to ensure high-quality service, need for personal (additional) training, requirements for the readiness of the service provider
- **Service provision experience in Estonia**, including treatment results
- **Forecast of the number of persons in need of the health care service and number of times the provision of the health care service in Estonia for the** next four years, year by year
- **The relationship of the health care service with the current list**, the list of medicinal products or the list of medical devices and the impact on incapacity for work, including cases of treatment added to the treatment case in the case of the requested and alternative service, replacement of existing services by the requested service, assessment of the addition of new

treatment cases when the service is used, additional need for accompanying services, medicinal products or devices, scientifically proven effect on the duration of incapacity for work compared to an alternative treatment method, assessment of the number of days spent on the certificate of incapacity for work in case of the requested service and an alternative service

- **Summary of the Health Economic Analysis** If it is a matter of adding a new medicinal service or adding a new medicinal product component to an existing medicinal service, the pharmacoeconomic analysis (in accordance with the Baltic States' guideline for the pharmacoeconomic evaluation of the medicinal product) **must be submitted by the marketing authorisation holder** of the medicinal product within one month after the application is published on the HIF website unless there is a good reason not to submit it. When adding technology to the list, it is recommended to submit a summary of the economic analysis.
- **International cost-effectiveness estimates** (by indication)
- **Assessment of the justification of the person's co-payment** and the willingness of the person to pay for the service themselves
- Assessment of the probability of **misuse and overuse of the health care service and** conditions of application.

After the registration of the application, the Health Insurance Fund assesses the compliance of the application with the requirements within 45 calendar days, and if there are deficiencies, it gives 30 calendar days to eliminate the deficiency (List of healthcare services of the Estonian Health Insurance Fund... § 10).

The process of **evaluations of health technologies carried out at UT** begins with the clarification of the need for research, followed by the definition of the topic of HTA and the setting of research questions as a starting task (Methodology for the Assessment of Health Technologies, p. 2). The topics are selected by the Health Technology Assessment Expert Council, which includes up to 10 members from various healthcare fields, including both clinical medicine and healthcare management. Proposals for the selection of topics can be made by all council members, and the decision is made by consensus. Based on the information obtained from the interviews, external input is also obtained, e.g., from the Ministry of Social Affairs, the National Institute for Health Development (e.g., proposals regarding topics related to screening and prevention of infectious diseases), and the Health Insurance Fund. The HTA Council forms a ranking of the suggested topics, based on which the work plan and action plan of the HTA Centre are drawn up with at least a one-year perspective.

Compared to the topics discussed within the process of changing the list of medicinal products and healthcare services, the HTA of UT mainly deals with topics that are more complex or have a broader scope than the verification of the therapeutic value of a specific medicinal product or service by the manufacturer and the evaluation of the verification by the Health Insurance Fund. According to the assessment methodology of health technologies, health technologies are characterised by:

- an expected significant positive impact on the health of the population;
- significant impact on the budget of health insurance and the state budget;

– conflicting evidence of clinical effectiveness and cost-effectiveness;
– lack of a clear overview of the scope of use and target group in Estonia.

In addition to deciding on the topics of HTA reports, the HTA Council is also tasked with approving the initial tasks of HTA reports, appointing experts to be involved in the preparation of HTA reports, reviewing and approving the reports, monitoring the HTA process and ensuring the quality of the reports (Methodology for the Assessment of Health Technologies, p. 3).

3.2.2. Evaluation of evidence

As part of the **list of medicinal products** process, the State Agency of Medicines and the Health Insurance Fund provide an opinion on the application.

- The Health Insurance Fund submits a complete application to the **State Agency of Medicines** within 15 days (subsection 8 (3)). The State Agency of Medicines prepares a written opinion on the application within 30 days, involving external experts, if necessary, without making them public (§ 10).

  The State Agency of Medicines bases its opinion on the following criteria based on the application and other scientific data (§ 11):

  1) the description and prevalence of the disease on which the issuing of the medicinal product on discount conditions is based, importance of pharmacotherapy in treating of the disease;
  2) existence of other medicinal products and treatment methods for the disease on which the issuing on discount conditions is based;
  3) scientifically proven effectiveness of the medicinal product, including a comparison to other medicinal products and treatment methods;
  4) scientifically proven safety of the medicinal product, including a comparison to other medicinal products and treatment methods;
  5) optimum dosing of the medicinal product and duration of use, and a need to receive other medicinal products and treatment or diagnostic procedures during the treatment, including a comparison to other medicinal products and treatment methods;
  6) information regarding the use of the medicinal product under application and other medicinal products used for the disease on which the issuing on discount conditions is based in Estonia and in other countries;
  7) possibility and consequences of misuse and excessive use of the medicinal product;
  8) necessity and possibility of establishing limitations to prescribing of the medicinal product on discount conditions to ensure the rational use of the medicinal product.
- **The Health Insurance Fund** prepares a written opinion on the application within 30 days from the receipt of the opinion of the State Agency of Medicines and immediately forwards it to the manufacturer of the medicinal product.
  The Health Insurance Fund bases its opinion on the following criteria (§ 13):

1) information regarding the facilitation and use of the medicinal product under application and other medicinal products used for the disease on which the issuing on discount conditions is based in Estonia and in other countries;
2) economic justification of using the medicinal product, including a comparison to a disease on which the issuing of other medicinal products and treatment methods on discount conditions is based;
3) possibility and economic consequences of misuse and excessive use of the medicinal product;
4) necessity and possibility of establishing limitations to prescribing of the medicinal product on discount conditions to ensure the economically reasonable use of the medicinal product;
5) estimated retail sales volume of the medicinal product;
6) correspondence of listing of the medicinal product to the financial means of medical insurance, considering the cost of the medicinal product under application in other countries of the European Union, first of all in in the Republic of Latvia, Republic of Lithuania and Republic of Slovakia, and principle provided in subsection 25 (3) of the Health Insurance Act , according to which the expenses incurred by the Health Insurance Fund to provide benefits for medicinal products must not exceed 20% of the expenses prescribed for health service benefits in the annual budget of health care expenses.

As part of the process of changing the list of healthcare services, the following aspects of healthcare services are assessed:

- **proven medical effectiveness**, for which the Health Insurance Fund appoints an expert on the recommendation of the University of Tartu or the State Agency of Medicines;
- **cost efficiency**, for which the Health Insurance Fund appoints an expert;
- **the necessity for society and consistency with the state's health care policy**, which is assessed by the Ministry of Social Affairs;
- **compliance with the financial possibilities of the Health Insurance Fund's budget**, which is assessed by the Health Insurance Fund.

Expert evaluations of proven medical effectiveness and cost-effectiveness shall be submitted to the Health Insurance Fund within 30 days of receiving the application.

The Health Insurance Fund consolidates the applications and submits them together with the used scientific literature to the Ministry of Social Affairs **at least once per calendar year.** The Ministry of Social Affairs submits an assessment of the necessity for society and compatibility with the state's health care policy no later than 45 days after receiving expert assessments from the Health Insurance Fund or 14 days before the meeting of the committee on the list of health care services for those applications that have been submitted to the committee's agenda (§ 10).

One of the differences between the processes of the list of medicinal products and healthcare services is the involvement of external experts in the assessment of the evidence of medical effectiveness – while in the process of the list of health services, an expert is always called to give an assessment, in the case of the list of medicinal products, the assessment is made by the State Agency of Medicines, and external experts are included only if necessary.

In the HTA process carried out at UT, the next stage after initiating a topic is the preparation of a report, during which the following aspects of the technology under consideration are evaluated:

- the quality of existing evidence for the technology, its strengths and weaknesses, and gaps in existing knowledge;
- use in Estonia, comparison with evidence-based data on the clinical effectiveness and cost-effectiveness of the technology;
- the economic impact of the use of technology, including the need for investments and resources and possible organisational changes;
- ethical and organisational aspects related to the use of technology;
- the impact of technology on the patient and their loved ones, addressing changes in patient expectations, need for help and coping;
- the impact of technology on values and the general organisation of life;
- cost-effectiveness of technology;
- uncertainty due to insufficient or contradictory evidence;
- justifications for the choice and availability of technologies for health policy decision-makers and the public.

3.2.3. Drawing up conclusions and recommendations and providing input for funding decisions

In the process of **changing the list of medicinal products,** following the preparation of the opinion of the Health Insurance Fund, it is submitted to the manufacturer of medicinal products (§ 12), who can submit to the committee a written opinion in regard to the opinion within 15 working days (§ 17) and to the Medical Products Committee, which formulates its opinion at a meeting.

The Medical Products Committee is a committee established by the Health Insurance Fund with the right to give opinions to the management of the Health Insurance Fund, which includes representatives of the Estonian Medical Association, the Family Physicians Association of Estonia, the UT Institute of Family Medicine and Public Health, the Estonian Chamber of People with Disabilities, the Estonian Patients' Union, the Ministry of Social Affairs, the State Agency of Medicines and the Health Insurance Fund; if needed, experts are included in the work of the Committee (§ 14).

The opinion of the Medical Products Committee is formed at the meeting based on consensus or by simple majority. Meeting materials are made electronically available to the committee members at least seven days prior to the meeting (§ 16). Among the materials of the meeting are the opinions of the Health Insurance Fund and the State Agency of Medicines and the opinion of the manufacturer of the medicinal product (if any). If the manufacturer of the medicinal product has substantive objections to the opinion of the State Agency of Medicines or the Health Insurance Fund, which have not been previously submitted, the commission may require the State Agency of Medicines and the Health Insurance Fund to submit an additional opinion on the objections of the manufacturer of medicinal products within 15 days (§ 17).

The Committee's opinion must be motivated, in writing, and reasoned. Considerations for not taking into account the opinion and objections of the manufacturer of the medicinal product and

a third party must be noted in the justification (§ 19). The Committee's opinion is forwarded to the manufacturer of the medicinal product.

The Committee's opinion can be conditional, i.e., instead of a definite "yes" or "no" decision, the Committee can also recommend adding the medicinal product to the list, provided that a price agreement is reached with the manufacturer at a price at which the cost-effectiveness of the medicinal product is favourable according to the cost-effectiveness threshold used. At the Committee meeting, it may also be decided to postpone giving the final opinion if it turns out that one or another aspect needs to be further specified with the applicant or a professional expert or if it is necessary to make additional calculations by the Health Insurance Fund.

The Board of the Health Insurance Fund, taking into account the opinion of the State Agency of Medicines, resolves the application within 180 days from the submission of the application. This time does not include the time during which the duration of the procedure was suspended (e.g., during price negotiations with the manufacturer of the medicinal product). If the application is approved, the medicinal product will be added to the list of medicinal products at the suggestion of the Health Insurance Council no later than six months from the expiry of the objection deadline (§ 21).

In the process of **changing the list of health care services,** the expert evaluations are followed by the issuing of an opinion on the applications by **the Committee for the list of health care services**. The Committee for the list of health care services is a committee with the right to advise the management board of the Health Insurance Fund, which includes 13 members:

1) Representative of the Ministry of Social Affairs;
2) External consultant of the Ministry of Social Affairs on surgical specialties;
3) External consultant of the Ministry of Social Affairs on internal medicine specialties;
4) External consultant of clinical-consultative specialties of the Ministry of Social Affairs;
5) External consultant of the Ministry of Social Affairs on dental specialties;
6) External consultant of the Ministry of Social Affairs on psychiatry;
7) representative of the Estonian Hospitals Association;
8) representative of the Family Physicians Association of Estonian;
9) representative of the Estonian Nurses Union;
10) representative of the Estonian Chamber of People with Disabilities;
11) representative of the University of Tartu;
12) representative of the Health Board;
13) representative of the Health Insurance Fund.

Compared to the Medical Products Committee, there are more members, and the composition is different (among the members, there are no representatives of the Estonian Patients' Union, the State Agency of Medicines, or the Estonian Medical Association, but there are representatives of the Family Physicians Association of Estonia, the Estonian Hospitals Association, the Estonian Nurses Union, and the Health Board).

When changing the list of health care services, the **Committee on Hospital Medicines**, whose composition is the same as that of the Medical Products Committee, gives an opinion on the medicinal products (representatives of the State Agency of Medicines, the Health Insurance Fund,

the Estonian Medical Association, the Family Physicians Association of Estonia, the Ministry of Social Affairs, the Estonian Patients' Association, and the Estonian Chamber of People with Disabilities).

The working format of the Committee is a meeting, and the opinion is formed based on consensus or because by a simple majority of the members participating in the meeting. The materials of the meeting shall be made available electronically to the committee members at least seven days before the meeting.

The board of the Health Insurance Fund makes a proposal to the Supervisory Board of the Health Insurance Fund to establish or change the list. The Supervisory Board of the Health Insurance Fund submits a proposal to the minister responsible for the field to make a proposal to the Government of the Republic to establish or change the list, adding the opinion of the Committee on the List of Health Services to the proposal.

If the medical effectiveness or cost-effectiveness of the healthcare service submitted in the application has not been proven and the proposal submitted in the application is not included in the proposal of the Supervisory Board of the Health Insurance Fund provided for in § 10, the application procedure will be terminated. The completed application procedure will be renewed if the applicant submits additional data on medical effectiveness or cost-effectiveness within three months from the entry into force of the list.

In the report produced as a result of **the HTA conducted at UT**, conclusions are formulated compactly, which provide answers to the research questions posed in the initial task. The members of the HTA Council give a written assessment (review) of the report, in which they assess whether the report is suitable for approval. The report's working group answers the questions presented in the review in writing, if necessary, introducing the desired corrections and changes in the report. After the approval of corrections and additions by the reviewers, the report is submitted to the HTA Council for final approval.

Completed reports will be published and made available online and printed in hard copy for delivery to medical facilities and healthcare management agencies, and research libraries. The results will be presented to interested parties at a seminar. Based on the results, scientific works are also prepared, which are published as scientific articles and presented at scientific conferences and seminars organised by stakeholders.

The UT report generally does not give the recommendation to finance or not to finance the technology under review. Rather, the report is an input to the contracting entity, which can design based on it. According to the interviewed UT representative, the Health Insurance Fund does not make funding decisions only based on the results of the UT HTA report, but all such evaluations are also discussed by the Medical Products Committee or the Committee of the List of Healthcare Services, who shape the funding recommendation to the Management Board of the Health Insurance Fund.

3.2.4. Assessments of the interviewees on the process

Initiating the process

According to the interviewed manufacturers of medicinal products, the instructions for submitting applications for discounted medicinal products described in the regulation of the Minister of Health and Labour are **sufficiently clear and detailed**. The annexes and the content to be provided are understandable. The representatives of the interviewed medical professional associations came to the same conclusion.

In the interview of the manufacturers of medicinal products, it was found to be unclear, based on which principles the **UT TTH team makes a choice, in which areas** they make their assessments. It was found that an overview of the priority of the topics and the planned works should also be made available to the manufacturers.

Manufacturers of medicinal products also saw problems in planning the work of the Medical Products Committee. There is a large **variation in the speed at which applications reach the Committee** – for example, some applications reach the Committee's desk in 2 weeks, while others may be left to wait several months. It was found that in such a case, the manufacturer should be given **timely information** on when the medicinal product is planned for the Committee and taking into consideration that the manufacturers have a reasonable time to present their views.

The representative of the professional medical association who was interviewed pointed out a problem that filling out the request to change the list of healthcare services is sometimes **unnecessarily labour-intensive** – instead of translating the tables of performance indicators and moving them into the request, references to relevant scientific articles would essentially be sufficient. Considering the limited time resources of physicians, too much workload can prove to be an obstacle, due to which some applications have not been submitted. The interview also referred to the action plan for cancer control, where it is also stated that for rare diseases and constantly changing treatment indications, professional associations lack the resources to write a separate application for each new indication, which is why it **is not sustainable to leave the responsibility of applying for new medicinal products and treatment services to professional associations** (Cancer Control Action Plan 2021–2030).

Organisation of the process

The representatives of the interviewed manufacturers of medicinal products recognized the speed of the preparation of expert opinions by the Health Insurance Fund and the State Agency of Medicines. Today they are mostly prepared within the prescribed deadlines. The assessments of the State Agency of Medicines are considered well-argued. It was found that the protocols of the Medical Products Committee have become more substantial and clearly structured over time. At the same time, it was criticized that they do not reflect the applicant's views or counterarguments to the Health Insurance Fund's assessments.

The representatives of manufacturers of medicinal products also pointed out the possible place of duplication in the process of the list of medicinal products: it was pointed out that the medical

effectiveness of the medicinal product is assessed by both the State Agency of Medicines and the Health Insurance Fund, while the conclusions may be different (e.g., the assessment of the effectiveness by the State Agency of Medicines is positive and the Health Insurance Fund's is negative).

Manufacturers of medicinal products would like the possibility of more operative communication with a contact person from the Health Insurance Fund, with whom they can discuss the possibilities of finding solutions to the problems that have arisen, receive feedback on the submitted proposals and clarify mutual positions. Currently, communication takes place in writing through the exchange of official letters, which is considered slow and inefficient.

Involvement of the parties

The interviewed members of the Medical Products Committee **generally consider the circle of parties involved in the Committee's work to be optimal.** For pragmatic reasons, it is not considered expedient to expand it excessively – if numerous medicinal products or other technologies are discussed at committee meetings, including for the treatment of various diseases, and the participation of specialist doctors and patient representatives in each field would be required, it would complicate the conduct of the meetings. Therefore, it is preferable to conduct the discussion with a more permanent circle of members who are familiar with the decision-making background system and previous decisions. During the discussion, the conclusion may be reached that the available information is insufficient to make a decision and specific additional input is needed, which is requested from an external expert.

The interviewed manufacturers of medicinal products always involve doctors in the preparation of applications. Patients are not consulted, as the legislation does not allow talking about prescription medicinal products with patients, and the Health Insurance Fund does not ask for input from patients in the application. Manufacturers of medicinal products were of the opinion that a professional expert should always participate in the committee's work. The manufacturers also found that **there is a lack of substantive involvement of sectoral patient associations** in the assessment and decision-making process: today, patient umbrella organisations participate in the committee, and there is no systematic involvement of patient organisations with field-specific knowledge. It was found that the impact of the evaluated technologies on the patient's quality of life should be taken into account more in the decision-making process. According to the interviewed HIF representative, the inclusion of input from patient organisations at least **takes place within the process of the list of healthcare** services (through the opportunity to submit opinions on the services to be discussed in the committee, using the HIF's online form). However, this form of inclusion is not used within the framework of supplementing the list of medicinal products.

The **representatives of the patient organisations participating in the work of the committees were satisfied with** their involvement, the opportunity to present their opinions and positions, and the consideration of the submitted opinions. There were no objections to the committee's work organisation or preparation for the meeting either. The time available to process the materials (seven days) was considered sufficient.

Representatives of patient organisations that are members of the committees **do not collect input from separate sectoral patient associations**. Based on the information from the interviews, this is either **not seen as their role**, or **the members of the committee are sceptical about the patients' ability to** comprehensively assess the decision-making problem, taking into account both medical and economic aspects. One of the interviewees rather saw the risk that the preferences expressed by patients may be essentially unimportant or poorly founded from the point of view of treatment and that the doctors' position regarding the suitability of one or another treatment should be more important.

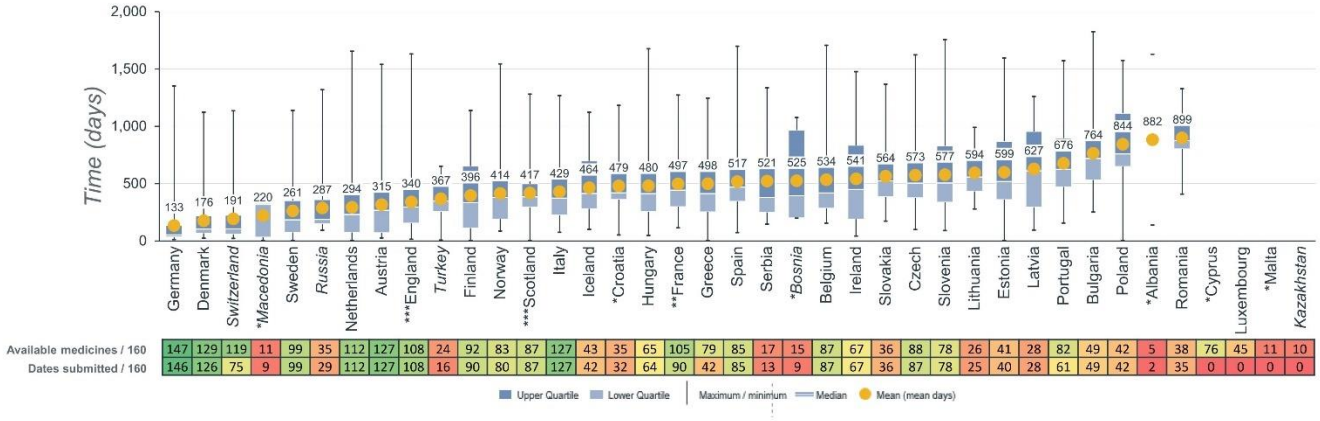
Several interviewees pointed out that **the ability of disease-specific patient associations to have a say in the process and provide meaningful input is very different**. According to one of the interviewees, a more systematic collection of patients' input than before could even lead to unequal treatment of different areas, as more capable representative organisations would be able to justify their needs better than less capable ones, which, however, may not reflect actual differences in treatment needs.

According to the representatives of the interviewed manufacturers of medicinal products, in cases where there have been differences of opinion between the manufacturer of medicinal products and the health insurance fund, the Medical Products Committee usually follows the position of the Health Insurance Fund. The applicants have doubts about whether the counterarguments they presented have reached the committee at all. However, according to the interviewed representative of the Health Insurance Fund, the arguments presented by the manufacturer of the medicinal product are always included in the materials submitted to the committee.

Duration of the process

Previous studies have shown that the process of making medicinal products available to patients is too slow in Estonia. The National Audit Office (Riigikontroll, 2012) has pointed out that in the years 2007–2009, the average time in Estonia from the granting of a marketing authorisation by the European Medicines Agency to the conclusion of a price agreement was 708 days. According to the latest data (see Figure 6), in 2017–2020, the time for medicinal products to become available has shortened by approx. 15% to 599 days, but it is still high compared to many other European countries.

Figure 6. Time in days from the granting of a marketing authorisation for a medicinal product to the time it becomes available to patients (to the entry on the discount list), 2017–2020

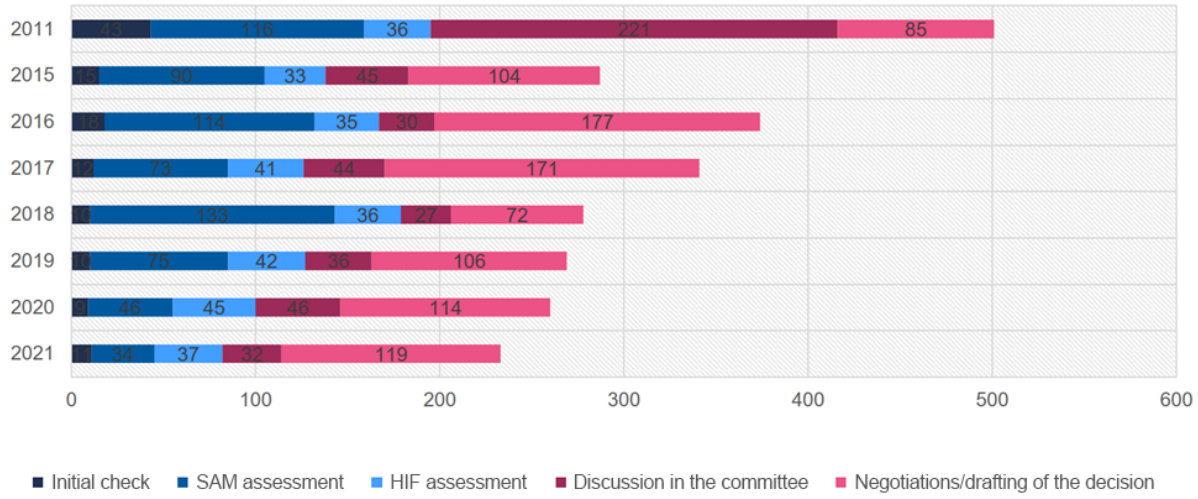


Source: Newton et al. *(2022).*

Here, however, it should be noted that the assessment of health technologies within the processes of the listing of medicinal products or healthcare services constitutes only a part of the time between the granting of central marketing authorisation and the entry into the list – this time also includes the preparation of applications by medical associations or manufacturers of medicinal products and the negotiation and decision-making stage following the assessment process. The latter accounts, for example, for applications processed within the list of medicinal products, the majority of the time between the submission of the application and the final funding decision (seeFigure 7). In addition, this time period includes periods where the progress of procedural deadlines for evaluation processes has stopped on the grounds prescribed by law (e.g., to eliminate deficiencies in the application or to submit additional data).

As can be seen from the figure below, the deadlines for the procedures of the Medical Products Committee have been significantly shortened, especially due to the shortening of the time required to prepare the assessment of the State Agency of Medicines.

Figure 7. Deadlines for processing applications of the Medical Products Committee, 2011–2021.



Source: Danilov (2022).

The representatives of the medical professional associations interviewed were critical of the length of the process **of changing health services**. The problem is that applications are collected and **processed once a year** (in contrast to the Medical Products Committee, where applications are processed continuously throughout the year). The respondents described, for example, the situation where an application was submitted in November, additional comments had to be made on it in August of the following year, and the decision came into effect in January of the following year. The same concern was expressed by representatives of manufacturers of medicinal products, who felt that the list of healthcare services could be changed more often, for example, quarterly.

The interviewed manufacturers of medicinal products also pointed out that the process of **evaluating the model** and the resulting **price negotiations is very long**. The main reason is considered to be the fact that there are no uniform and transparent principles for defining model inputs. The lack of substantive discussion with the Health Insurance Fund is seen as a problem; the exchange of mutual arguments by means of an official letter is considered too time-consuming.

The interviewed Medical Products Committee members **did not see significant opportunities to speed up the evaluation process** – the possibility of shortening the 30-day period prescribed for both the evaluations of the State Agency of Medicines and the Health Insurance Fund was not considered realistic. According to the representative of the State Agency of Medicines, there have been problems with meeting this deadline in the past, but recently it has generally been possible to follow it. No opportunities were also fathomed to speed up the negotiation stage – it is **an inherently unpredictable process**, and the possibility of shortening is limited on the one hand by the state's ability to pay the price asked for the medicinal products and on the other hand by the desire not to end the negotiations too prematurely without reaching an agreement on the price, if there is a medical need for the medicinal product.

The representative of the Health Insurance Fund pointed out that a large part of the delay in the delivery of medicinal products to patients is due to the **delay between the granting of a marketing authorisation and the submission** of applications, which can be shortened by the applicants, not the participants in the procedural process. Manufacturers cited as the main reason for not submitting applications or submitting them significantly later the fact that it is often not possible to meet the current cost-effectiveness thresholds for new medicinal products, or it is already foreseeable that the data from medicinal product studies will be uncertain for the Health Insurance Fund at the time of obtaining a marketing authorisation. For each new medicinal product, manufacturers assess the likelihood of reaching a price agreement, and based on that a choice is made about which applications are submitted and which are not.

3.3. Assessment methodology and decision criteria

3.3.1. Assessment of medical effectiveness

Regulation and practice

The criteria against which the list of medicinal products and the demonstrated medical efficacy of the technology within the TTL process are assessed are listed in the relevant regulations cited above (see subchapter 3.2.2).

In addition to the regulations, the Baltic guidelines for the pharmacoeconomic evaluation of medicinal products also describe the requirements for assessment of the medical effectiveness of the technology. According to this, the basis for measuring the results is **randomised, double-blind clinical trials with a control group** (or open trials, if the latter are relevant), if necessary, adapting the studies conducted in other countries to the Baltic conditions based on circumstances such as the choice of treatment alternative, the demographic characteristics of the patients and the severity of the disease. In the guideline, the quality criteria of the studies used are a clear description of the study plan and questioning, comparable groups of patients at the beginning of the study, a clinically relevant outcome indicator and the duration of the study, an analysis performed based on intention to treat, and the clinical and statistical significance of the results. The guideline does not specifically address indirect comparisons or the use of network meta-analyses, although meta-analyses more generally are noted as a basis for possible economic analysis.

According to the guideline, the treatment under investigation in the study must be compared with standard treatment or common conventional treatment. The guideline specifies that if the new medicinal product belongs to an existing pharmacotherapeutic group, the most used medicinal product belonging to the same group must be used for comparison, while if the new medicinal product belongs to a new group, the medicinal product most used for the same indication must be used for comparison. Non-pharmacological treatments can also be the basis of the comparison if they are the most common treatment for the disease in question. The choice of reference treatment must be justified.

According to UT's methodology, the preferred proof of effectiveness is also randomised controlled studies (and meta-analyses synthesizing them), where the technology under review has been compared with an alternative method corresponding to Estonian treatment practices. In the absence of such studies, other studies with an appropriate structure can be used, taking into account the limitations caused by the lack of randomisation. The PubMed database is used to search for sources.

Assessments of the interviewees

The interviewed manufacturers of medicinal products pointed out several aspects of the practice of assessing medical effectiveness that was critical:

- According to the manufacturers' representatives, the Health Insurance Fund does not accept indirect comparisons, crossover studies, or **the results of network meta-analyses**, citing

uncertainty. According to the descriptions, the Health Insurance Fund requires phase III reference studies and long-term data, but according to the manufacturers, it would also be necessary to take into account the results of phase II studies without a reference group through indirect comparisons, e.g., network meta-analyses and matching-adjusted indirect comparisons, as well as taking into account evidence based on real-life data;

- Manufacturers consider the principles **of reference treatment selection** unclear. A difficult situation is, for example, when the Health Insurance Fund has chosen an off-label treatment used in Estonian clinical practice as the reference treatment for the technology under review. It is not possible to rely on the studies that have been done to make such a comparison because there is no reason for manufacturers to plan a study to compare a treatment with a treatment that is not indicated for the given disease.

However, according to the interviewed representative of the Health Insurance Fund, the results of the network's meta-analyses are still accepted if they are of high quality. According to the representative of the State Agency of Medicines, the results of indirect comparisons and network meta-analyses are used if they allow meaningful conclusions to be drawn (while pointing out quality problems with the evidence).

According to the representative of the Health Insurance Fund, it is increasingly happening that the quality of the evidence presented in applications is poor. This was attributed to the pressure to bring the products to market as soon as possible by providing the data used to obtain the marketing authorisation as evidence. Often, however, they come from studies whose focus is different from what is necessary for the decision to grant funding to medicinal products – for example, the safety and effectiveness of the medicinal product have been evaluated compared to a placebo but not to an alternative medicinal product in use. Some applications have used data that are immature—median survival has not been reached, and it is difficult to estimate how much the medicinal product extends survival. It also happens that the technology has been compared with a treatment alternative that is not in use in Estonia. In such a situation, the decision-maker does not get a good picture of the advantages and disadvantages of the technology compared to the already-funded alternative. Also, according to the representative of the State Agency of Medicines, in the case of most applications, the evidence leaves something to be desired, either for the aforementioned reasons or because the primary outcome indicator is the progression period or another indicator (which is not the main indicator of interest from the point of view of decision-making).

The prospect of using studies based on real-life data was seen as rather risky in the interviews with the members of the pharmaceutical committee due to the lack of randomisation: if comparable medicinal products are systematically given to different groups of patients (e.g., a new medicinal product to young patients with a good outlook and an old medicinal product to older patients), it biases the results. Small samples were seen as an obstacle to the collection and use of real-life data of Estonian patients: the number of patients with rarer diseases would be so small under Estonian conditions that the data collected from their database would not have very high generalisability. The data collection and storage infrastructure, which today is insufficient, was also seen as a problem: currently, there is not enough aggregated data on the

prescribing of medicinal products, treatment use, and outcomes, including outcomes after hospitalisation, in hospitals.

3.3.2. Economic analysis

3.3.2.1. Methods used

According to the regulation on the Amending the List of Medicinal Products..., when choosing a cost-effectiveness analysis, a **cost-utility** analysis is presented unless there is a compelling reason to waive it (§ 7). The regulation on Amending the List of Health Services does not specify the method, but the practice is the same. Also, according to the UT guideline, cost-utility analysis is the preferred method.

In practice, both the Health Insurance Fund and UT also **use cost minimisation** in cases where the effectiveness of comparable interventions can be considered equal based on the scientific literature.

The Baltic guideline and UT methodology do not specify the prerequisites for using the cost minimisation method. In the guidelines of Sweden, England, and Ireland, the cost minimisation method is separately mentioned as a possible method. At the same time, the guidelines in England and Ireland emphasise that an important prerequisite for the use of cost minimisation is the certainty that the effects of the compared interventions are equal (i.e., it is not considered sufficient simply that the difference between two interventions is statistically insignificant).

The interviews did not provide comments on the choice of methods used for economic analysis but on the methodological choices made during their implementation (see below).

3.3.2.2. The perspective of the analysis

Regulation and practice

According to the Baltic guidelines, the analysis is carried out from a healthcare perspective (including only direct healthcare costs and benefits in this area). In addition, analyses based on society's perspective (taking into account all costs and results outside the healthcare system) can be presented separately, with the aim of justifying the reimbursement of the medicinal product.

The UT cost-effectiveness analysis guideline provides that the analysis perspective is chosen based on the research question. According to the guideline, the perspective of the health care funder (the party incurring significant direct medical costs of implementing the technologies) is most often used, but in some cases, it may be important to consider non-medical (e.g., the patient's own transport costs) and indirect costs (e.g., reduced productivity due to illness).

The practices of the foreign countries discussed in the study are different in terms of the perspective of the analysis. According to the guidelines of England and Ireland, it is necessary to proceed from the perspective of the health and social care system, in the case of Sweden from the perspective of the entire society as broadly as possible. In England, in addition to health outcomes for the patient, effects on caregivers can also be taken into account, if necessary.

In the literature, the use of a society-as-a-whole perspective has been described as one of the core principles of good HTA practice (e.g., Drummond *et al.,* 2008). Its use contributes to the optimal use of public resources in society and avoids making decisions that may be optimal from the point of view of one part of the system (e.g., the healthcare system) but not if all parts of the system were taken into account (e.g., social security, labour market subsidies, the labour market as a whole). However, the application of the perspective of society as a whole is hindered by a significantly higher need for data – it is much easier to map the costs related to the use of one or another technology in the healthcare system than to gather and process information from various national databases in order to assess the effects on the largest possible part of the costs of public services and subsidies.

Assessments of the interviewees

The interviewees generally agreed that using a societal perspective can be appropriate and desirable. At the same time, the interviewed members of the Medical Products Committee mentioned a number of practical issues regarding its possible implementation. Various challenges were pointed out, both methodological (e.g., how to systematically take into account the non-health effects on the patient), budgetary (if the use of a broader perspective leads to the evaluation of a larger number of technologies as cost-effective than before, does this meet the budget's possibilities) as well as the need for large data. According to the representatives of the Health Insurance Fund and the State Agency of Medicines, the Medical Products Committee is actually willing to take into account the external effects of the healthcare system if they are convincingly substantiated in the application.

3.3.2.3. Incremental cost-effectiveness threshold

Practice

The cost-effectiveness criteria used in Estonia are implicit, i.e., they are not established in the guideline materials or normative documents. However, references to these levels are sometimes found in committee minutes and cost-effectiveness and budget impact assessments and are common knowledge among stakeholders in the assessment process.

Two levels are available: €20,000, which is applied to the treatment of chronic diseases (but also, for example, to some anti-cancer medicinal products), and €40,000, which is applied to end-of-life diseases. Since these are implicit thresholds, there are no more precise criteria in the guideline materials, as in which threshold is used in which case.

According to the information obtained from the interviews, the above-mentioned levels (at the same level as absolute amounts) have been in use for approximately the last ten years. As a ratio to GDP per capita in 2021, the levels are 0.9 and 1.8, respectively. As a ratio to GDP per capita in 2012, these levels would be 1.54 and 3.1, respectively. In other words, measured in GDP per capita (which can be used as an indicator of society's ability to pay), the thresholds have fallen significantly over the decade, as GDP per capita has increased by 74% over that period. Also, due to inflation (measured as an increase in the consumer price index), the real value of the thresholds has fallen (see figures below).

Figure 8. The value of thresholds in euros, at constant prices of 2011

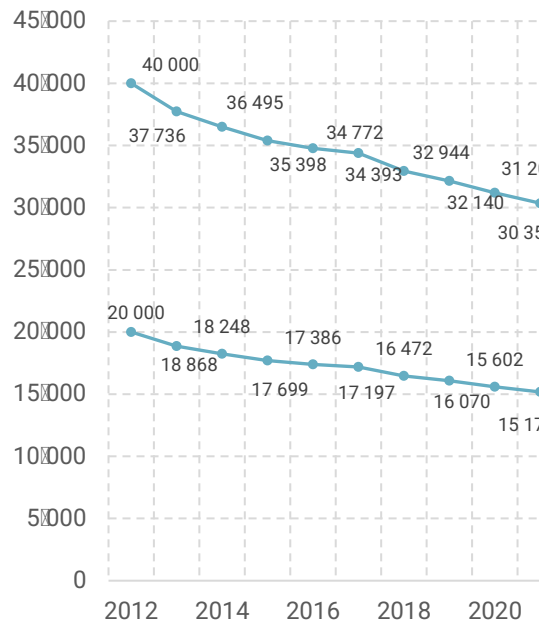
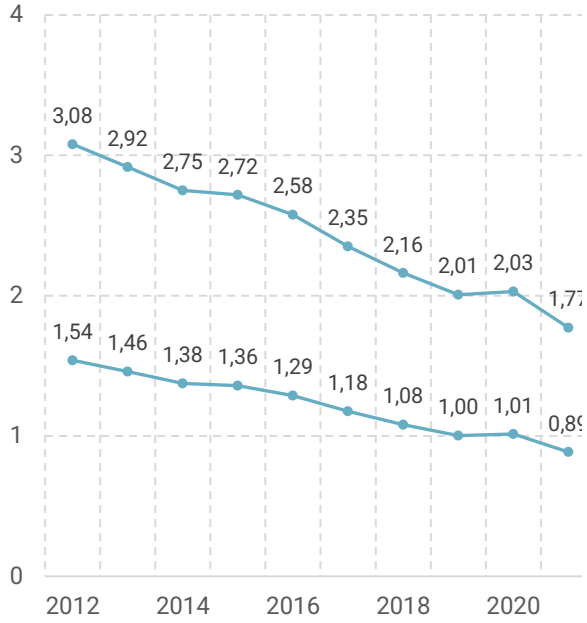


Figure 9. Value of thresholds as a ratio of GDP per capita



In the international comparison (see subchapter 2.3.5, page 26) one can make the following observations:

- **In absolute terms**, Estonia has a lower threshold:
  - lower than CZ, BG, HU, SI, SK, NO, ENG, also IE considering VAT treatment
  - same as the lower level of LT
  - same or higher than the lower level of the ranges of NL, and SE.
- Estonia's higher threshold is compared to the corresponding threshold of other countries:[34]
  - Lower than CZ, ENG,[35] IE, NL, NO, PL, SE, LV, LT, SK, HU
  - Higher than SI (roughly the same considering VAT treatment), BG.
- **In relation to GDP,** Estonia has a lower threshold:
  - lower than BG, HU, LV, PL, CZ, SK, SI, LT
  - higher than the lower level of the ranges IE, NL, SE, NO
- Estonia's higher threshold:
  - Lower than BG, HU, LV, LT, SK, and SE.
  - Higher than SI, NL, NO, and IE.

[34] In countries where a single threshold is in use, comparisons have been made with it. Countries with multiple thresholds have been compared with a higher threshold, except for countries where a threshold of more than 3x GDP is used for special cases (e.g. Latvia, England, Slovakia) – for these countries, the next highest threshold has been used for comparison.

[35] In the case of England, Estonia's higher threshold was compared with the £50,000 threshold (application of modifiers based on the loss of health criterion).

In several countries, unlike Estonia, either a separate higher level has been established for medicinal products for more serious and rare diseases (e.g., England, Lithuania, Latvia, Slovakia), or separate procedures have been created for highly innovative and expensive medicinal products without a mandatory cost-effectiveness threshold (e.g., Czech Republic, Poland).

It must be remembered that the threshold levels are not comparable from country to country, if the criteria for their application are different, because the thresholds of different countries can be used in different situations and if different preconditions are met. For example, if the higher threshold of €40,000 in Estonia exceeds the level of £30,000 in England, the conditions for their implementation are very different – if in Estonia it applies to end-of-life diseases, in England, remaining at the upper end of the range of 20,000–30,000 means the highest requirements for proof and greater attention focusing on benefits not covered by QALYs (NICE, 2022).

In addition, practices differ from country to country in terms of whether costs without VAT (e.g., England, Ireland, and Slovenia) or with VAT (Estonia, Czech Republic, Slovakia) are taken into account in the cost-effectiveness analysis.

Compared to countries with a per capita GDP similar to Estonia (see Figure 2), the threshold of €20,000 in Estonia is lower than in most other countries (with the exception of Lithuania's lowest threshold). Looking at the richest countries, however, one may also come across countries such as Sweden or the Netherlands, where the lowest threshold of the several thresholds in use is lower in absolute terms than the one in use in Estonia. At the same time, the comparison is again complicated by the differences in the conditions of applying the threshold: unlike in Estonia, according to the criteria revealed in the interviews, a lower threshold is applied to chronic diseases, so, for example, in England or Ireland, the guidance material does not state such a restriction. It should also be taken into account that in countries using implicit thresholds, including Estonia, the criteria for using thresholds may not be uniform and strict, and in practice, there may be flexibility in the selection and implementation of thresholds, which is not reflected in a simple comparison of thresholds.

Estonia's higher threshold is slightly higher than Slovenia's threshold (considering the different treatment of VAT in the analysis, approximately the same) and Bulgaria's threshold but lower than the Czech Republic's, Poland's, Hungary's, and Latvia's thresholds, and Slovakia's and Lithuania's higher thresholds.

In international practice, there are analogies to both the implicitness (e.g., Sweden, etc.) and the explicitness (England) of the threshold. There are also examples of using a fixed and non-GDP-related level over a longer period (Western European countries) than GDP-related thresholds (several Central and Eastern European countries). It should be noted that the use of non-GDP thresholds does not necessarily mean that the thresholds have been completely static – e.g., in countries where the thresholds are defined as ranges, the highest values within the range may have been used for decision-making. Over time, countries have also introduced additional thresholds for special cases (e.g., modifier rules in England).

Assessments of the interviewees

The interviewed manufacturers of medicinal products considered the threshold levels insufficient because the prices of many new medicinal products are no longer able to remain within these thresholds. This was also cited as a reason why applications are not submitted for many new medicinal products. There was also criticism of the lack of transparency: it is not always clear for medicinal product manufacturers in which cases a higher threshold applies and when a lower one is used (e.g., a chronic disease threshold of 20,000 is required for certain anti-cancer medicinal products). It was found that in order to increase transparency, it would be desirable to link the thresholds to the severity of the disease, as is done, for example, in England, the Netherlands, Norway, and Lithuania.

In other interviews, different assessments were brought out – both doctors and patients expressed the opinion that after the thresholds have remained at the same level for a long time, it would be appropriate to update them. At the same time, doubts were also expressed as to whether the financial capabilities of the Estonian healthcare system would support it. Some of the interviewees also considered the current levels of the thresholds to be sufficient.

Among the more sceptical views regarding raising the thresholds, the risk was pointed out that linking the cost-effectiveness threshold to GDP will only lead to an increase in the prices of products by producers and increase costs in the healthcare system without expanding real treatment options for patients. It was also questioned why the amount paid for technologies should be related to Estonia's GDP if the costs of technology development are not dependent on it.

3.3.2.4. Discounting

Regulation and practice

According to the guideline of the Baltic States for the pharmacoeconomic evaluation of medicinal products referred to in the Regulation on the List of Medicinal Products, future expenses, and income must be discounted. Both costs and revenues arising during the time period are discounted at a rate of 5%. If a different discount rate is used, a justification must be given. The guidelines do not provide examples of possible reasons or situations that would justify the use of a different discount rate. According to UT's methodology, the discount rate usually used is 5%.

As far as the interviewees know, there have been no cases in practice where the applicant could have successfully justified the use of a different discount rate. According to the representatives of the interviewed medicinal product manufacturers, it is not clear in which cases the use of a different discount rate instead of 5% is allowed.

Compared to other European countries, **the discount rate used in Estonia is high** (see Figure 6) – apart from Estonia, Croatia, Slovakia, and Latvia (income and expenses) and Poland (expenses 5%, income 3.5%) also use the 5% rate. A lower rate is used in the rest of the countries.

Among the reference countries considered in this study, in the case of Ireland and England, when choosing the discount rate, reference is made to the regulation established by the Ministry of Finance regarding the methodology used in economic analysis. It is also expected that decisions

on the use of public money will be based on uniform rules and analysis parameters, which will allow assessing the optimal use of limited resources – this is a reasonable approach even if health care financing takes place in a system defined and separated from the rest of the public budget. In health economics, arguments have been given about why health outcomes should be treated differently when discounting, discounting them at a lower rate (as mentioned above, no consensus has developed on this issue, although some countries apply it in practice). However, there are no arguments why healthcare expenditures and health outcomes should be discounted at a higher rate than, for example, public investments.

Discounting is rarely dealt with in **Estonian regulation**. There are no valid national guidelines for the cost-effectiveness analysis of projects. The reason for this is probably the lack of a direct need – e.g., public projects financed by EU stimulus funds are based on the European Commission's regulation,[36] according to which a real financial discount rate of 4% is used as the recommended base rate for public investment activities co-financed by ESI funds (Article 19, paragraph 3). Member States may use a financial discount rate other than 4% if they provide reasons for choosing such a basis, which may be

a) the specific macroeconomic conditions of the member state and international macroeconomic developments and economic conditions,
b) the nature of the investor or implementing a structure, such as a public-private partnership, or
c) the nature of the sector concerned.

Based on the briefly described theoretical foundations of discounting in subchapter 2.6.1, macroeconomic conditions and the economic situation can influence the choice of the discount rate primarily through the fast growth rate of consumption – the faster the country's economy and thus consumption grows, the higher the discount rate should be. In the last decade, however, the growth of the total production and consumption of the domestic economy has been significantly slower compared to this period, which reduces the need to establish a discount rate that is different from the rate recommended by the EC.

Analogous to the above-mentioned EC regulation, § 48 of the Estonian Minister of Finance's Regulation *guideline to public sector financial accounting and reporting* also refers to the discount rate level of 4%, according to which long-term non-interest-earning claims, long-term provisions, and long-term liabilities must be discounted at a rate of 4%.

However, from the point of view of evaluating health technologies, it is more appropriate to look at the **social discount rate used** in other fields as a comparison. In this regard, too, Estonia has followed EU regulations – according to the cost-effectiveness analysis guide for projects financed by EU funds for the period 2014–2020, 5% was used as the social discount rate among the countries receiving support from the Cohesion Fund, and 3% among the other countries.[37]

[36] Commission Delegated Regulation (EU) No 480/2014, 3 March 2014. https://eur-lex.europa.eu/legal-content/ET/TXT/HTML/?uri=CELEX:02014R0480-20190530&from=EN

[37] https://ec.europa.eu/regional_policy/sources/docgener/studies/pdf/cba_guide.pdf

However, the period covered by the guideline has now passed and a newer guideline[38] for the period 2021–2027 provides for the use of a **social discount rate of 3%** in all member states. As stated above, the transition to a lower discount rate is also supported by Estonia's macroeconomic background – current and projected GDP growth has slowed down compared to the last decade. In the case of Estonia, there is no data yet on the extent to which the new social discount rate is used in today's practice. However, as a general principle, a recommendation can be formulated that **the discount rate used in the evaluation of health technologies should not exceed the discount rate used in other areas of the country** so that decisions regarding the use of public resources can be optimal. Therefore, it was necessary to monitor the development of regulations and practices regarding the discount rates used and, if necessary, adjust the rate used.

3.3.2.5. Choice of time horizon

Regulation and practice

The guidelines of the Baltic States do not specify the time horizon used in analyses for the pharmacoeconomic evaluation of medicinal products. According to the UT guideline, the choice of time horizon depends on the nature of the health problem and the technologies used; in the case of chronic diseases, the rule is to use a lifetime perspective.

The definition of the time horizon is quite general, even in the observed foreign country guidelines. The guidelines in all the observed countries include the requirement that the time horizon must correspond to the period during which the main health effects and costs appear, but the guidelines also provide additional clarifications:

- English and Swedish guidelines state that if the technology under consideration has an effect on survival compared to the reference treatment, a lifetime time horizon should be used. According to English guidance, using a time horizon shorter than a lifetime is justified if there is no effect on survival and the differences in costs and health outcomes persist for a relatively short period of time.
- The Irish guidance states that, as a rule, a different time horizon must be used; the use of a shorter time horizon needs to be justified (it can be used for acute health problems where no difference in mortality is expected when using comparable health technologies) and the impact of this choice on the results of the analysis must be highlighted.
- The Swedish guideline recommends analysing treatment periods of one to five years for chronic diseases so that the cost-effectiveness rate takes into account the cost-effectiveness at different ages.

Assessments of the interviewees

According to the interviewed manufacturers of medicinal products, it is not clear what principles and data are used to select the time horizon. According to them, the Health Insurance Fund very

38 https://ec.europa.eu/regional_policy/sources/docgener/guides/vademecum_2127/vademecum_2127_en.pdf

often shortens the time horizon compared to the analysis originally presented in the application, without sufficient justification, according to applicants. This is an important parameter affecting the evaluation of the effectiveness of additional costs, and the development of this choice is not transparent for applicants. For example, a case was described where the Health Insurance Fund shortened the time horizon to 10 years, while 15 years had been used in the analysis of other countries. At the same time, a case was cited as a positive example where the commission agreed to use a 32-year time horizon, similar to the practice of other countries, even though the Health Insurance Fund had used a 10-year period in its assessment.

According to the interviewed representative of the Health Insurance Fund, the use of a longer time horizon is often associated with greater uncertainty. If only a small part of the health benefits attributed to a health technology can be substantiated by the results of actual clinical trials, and the rest is an estimate based on model predictions, the uncertainty regarding the total health benefits is correspondingly large and may turn out to be unacceptable. Therefore, the time horizon used in the analysis is selected for each case separately, taking into account the survival rate in the case of the respective disease and avoiding the use of a time horizon significantly longer than the survival rate.

3.3.3. Price agreements and risk-sharing agreements

The opinion of the committee on the list of medicinal products or healthcare services is followed by a negotiation stage, during which the conditions for the promotion of health technology are agreed upon. When shaping the negotiation position, the opinion of the commission is the input for the Health Insurance Fund, including the assessment of cost-effectiveness and related uncertainty. If the cost-effectiveness of the technology is unfavourable at a price stated in the application, the commission's decision may be conditional, i.e., the price at which the additional cost-effectiveness of the technology is in line with the threshold is stated. Expert opinions and the committee's opinion may indicate significant uncertainty regarding either the medical effectiveness or cost-effectiveness of the technology. To mitigate the risk associated with uncertainty to the payer, either a price reduction or the implementation of a performance-based risk-sharing scheme may be agreed upon. Different types of agreements are used: purely financial agreements are used, which include a price reduction and a ceiling on the volume of service provision (e.g., an upper limit on the number of patients receiving treatment), the cost of which is exceeded by the manufacturer in whole or in part; as well as result-based agreements, in which the costs of providing treatment are borne by the manufacturer for a certain period, and if the agreed performance indicators are achieved, the health insurance fund takes over the financing.

Pharmaceutical manufacturers had several comments regarding price negotiations and agreements:

- They are not satisfied with the discounts required to compensate for the uncertainty associated with the immaturity of the data (for example, in a situation where results based on median progression-free survival have been demonstrated, but median overall survival data are not yet available).

- In the case of direct discount-based contracts where repayment is made, the problem for manufacturers is double VAT payment.
- In the case of contracts where the treatment is started at the manufacturer's expense, and if the treatment works, the Health Insurance Fund takes over the financing, it is considered fairer for the Health Insurance Fund to make an additional payment for the first three months, if the treatment has worked.
- It has happened that the committee makes a decision that the promotion of the medicinal product requires additional data in a situation where no follow-up studies have been planned for the medicinal product. In this case, the medicinal product has no chance of reaching the patients, and the solution should be sought rather from a conditional financing decision or innovative risk-cost-sharing contracts, where payment is based on results based on real-life data.
- Clear and transparent rules need to be formulated in a situation where an application is submitted for a medicinal product for which medicinal products with equivalent efficacy are already available on the market. In practice, the position of the Health Insurance Fund has been different in the case of such medicinal products – both a price corresponding to the existing most used medicinal product and a -5% discount have been demanded for the new medicinal product. The non-transparency of the rules causes the process to drag on and adds time and labour to the negotiations for both parties.
- Several types of agreements were brought out, the implementation of which, according to the manufacturers, would improve patients' access to medicinal products but which are not used in Estonia today:
    - Agreements in which payment is made for the achievement of the **actual treatment result**, measuring the achievement of the agreed performance indicators on a patient-by-patient basis based on real-life data and agreeing that the Health Insurance Fund will pay for the treatment only for those patients whose treatment was effective; otherwise, the cost would be reimbursed by the manufacturer;
    - Conditional financing agreements for **the period when the data is still arriving**;
    - **Portfolio-based contracts**, in which the conditions for the use of all medicinal products in the manufacturer's product portfolio for the treatment of a certain disease are agreed upon with the manufacturer (such agreements can cover both the manufacturer's existing medicinal products and medicinal products that will receive marketing authorisation in the future).

Manufacturers would expect more proactive cooperation from the Health Insurance Fund in the implementation of various contracts and schemes.

In the foreign countries considered in the study, there is quite a large variation in the species of agreements in use. There are countries that use portfolio-based agreements (England), conditional agreements with a collection of evidence (England), as well as examples of countries where agreements with a collection of evidence have been used in the past but have been abandoned (Sweden). Discounts and refunds are available on agreements in Slovenia;[39] in

[39] Jurij Fürst (ZZZS), personal communication.

Slovakia, discounts, budget ceilings, portfolio-based agreements, and (less often) performance-based agreements are used;[40] in the Czech Republic, rebates, budget ceilings, and portfolio-based agreements (temporary financing with evidence gathering has been used in the past for advanced therapy medicinal products, but has been abandoned).[41]

[40] Iveta Pálešová, AIFP Slovakia, personal communication.

[41] Leoš Fuksa (SÚKL), personal communication.

4. Summary

In this work, the process of assessment of health technologies and the main parameters of the economic analysis used in the evaluation were compared in Estonia and in selected foreign countries (England, Sweden, Ireland; in the comparison of cost-effectiveness thresholds and discount rates, also a selection of other European countries). In the case of Estonia, the guidelines used in the process of changing the list of healthcare services and the list of medicinal products, and the guidelines of HTA of UT were examined. Various parties in the assessment processes were also interviewed to map practices and evaluations.

As a more general conclusion, it can be said that the key stages of the evaluation process are quite similar in the reference countries and in Estonia:

- assessment of medical effectiveness, in which double-blind, randomised studies with a reference group are preferably used as evidence, where the assessed technology has been compared with a treatment regimen already in use in the given country;
- this is followed by a cost-effectiveness analysis, where the cost per quality-adjusted life-year added when using the technology and its compliance with a given threshold are assessed; and
- sensitivity analysis, during which the impact of uncertainty in the data and model parameters used in the analysis on the results is assessed.

However, there are numerous differences between countries in the details of their implementation.

For example, in the assessment of **medical effectiveness**, an increasing number of situations are encountered where the quality of the evidence material fails to meet the ideal: e.g., studies with a randomised comparison group have not been conducted (or cannot be conducted), the samples used are small, the data are immature, etc. Different countries have tried to solve these challenges in different ways: e.g., by trying to use evidence that is less preferable to ideal evidence (real-life data, observational data, indirect comparisons of technologies, etc.) as evidence and to more precisely define the prerequisites for their use. Another way to deal with the risks associated with the use of insufficient evidence goes beyond the scope of the HTA assessment and consists in mitigating the risks by means of price and risk-sharing agreements. The practices of countries regarding the types of agreements used are also quite different.

In addition, in Estonia, it is often a challenge in the assessment process that the decision has to be based on evidence of less than ideal-quality, while the TTH instructional materials do not deal with the use of such evidence. From the interviews of the members of the Medical Products Committee, it is clear that the quality of the **evidence** presented in the applications **is often poor** due to the immaturity of the data (e.g., applications for obtaining a marketing authorisation are based on studies in which the necessary comparisons with the relevant comparative treatment have not been made; patients have been monitored for too short a time in the studies). In the interview, the manufacturers of medicinal products found that the Health Insurance Fund could be more flexible when considering the evidence, e.g., indirect comparisons (e.g., network meta-analyses) could be taken into account. According to the interviewed members of the Medical

Products Committee, network meta-analyses are still taken into account when making decisions if they are of high quality. The views on the evidence accepted in the assessment are thus different; manufacturers of medicinal products expressed a desire for clearer and more transparent regulation of the practice.

There are also quite a lot of differences between countries in the **cost-effectiveness analysis** methodology. Among the fundamental differences, **the perspective of the analysis can be pointed out:** if in England and Ireland the analysis is carried out from the perspective of the health and social system, in Sweden, the perspective is society as a whole, including costs and other effects arising both in the health system and outside it. In Estonia, the analysis is mainly based on the perspective of healthcare; in addition to that, an analysis based on the perspective of society can be presented as a separate analysis. The representatives of the parties and stakeholders interviewed in the evaluation process found that the perspective of society would be appropriate, but the challenges related to its use were also pointed out – since the use of a broader perspective would make more health technologies cost-effective, there may not be enough money for this. Also, using a broader perspective would require more data from different data sources, making the preparation of a high-quality analysis more laborious and time-consuming.

Another important difference is **the time horizon used in the analysis** – its choice can significantly affect the results of the analysis. As a general principle, all the reviewed guidelines of foreign countries state that the time horizon must be long enough to highlight differences in costs or output between comparable technologies. In the guidelines of different countries, however, additional guidelines have been added to it. Thus, the Irish guideline points out that the time horizon is, as a general rule, a lifetime; a shorter horizon must be justified; However, the Swedish guidelines say that if the treatment affects survival, a lifetime time horizon should be used. The Baltic guideline used in Estonia for the pharmacoeconomic assessment of medicinal products does not give instructions on the time horizon; according to the UT guideline, the rule is to use a lifespan perspective for chronic diseases. The interview with manufacturers of medicinal products revealed that the principles of choosing the time horizon in the current practice of the Health Insurance Fund are unclear; it would be necessary to specify them in the manual and justify them in more detail in the cost-effectiveness assessments.

An important decision criterion, on the basis of which the cost-effectiveness of the technology under consideration is evaluated as favourable or unfavourable, is the **cost-effectiveness threshold,** which expresses the willingness to pay for a quality-adjusted life year. During the last decade, the thresholds used in Estonia (€20,000–40,000) **have remained absolutely the same.** In conditions of economic growth, this has led to their decrease as a share of GDP per person – if ten years ago the thresholds were about 1.5 and 3 GDP per person, now they **have fallen** to 0.9 and 1.8, respectively.

The study compared cost-effectiveness thresholds in selected European countries. The comparison of thresholds between countries is rather complicated – in some countries, there is one threshold; in others, several thresholds or a range of thresholds; the criteria for applying

different thresholds are different; the comparison is also complicated by the different treatment of VAT in the analysis. As general observations, it can be stated that:

- **In absolute terms**, Estonia's lower threshold used for chronic diseases is below the thresholds used in other Central and Eastern Europe countries and, given the different treatment of VAT, also the lower values of the threshold ranges used in Western Europe (with the exception of the lower value of the indicative Swedish range).
- **As a ratio to GDP** per capita, Estonian thresholds are lower than the thresholds used in most CEE countries and the same or higher than in most Western European countries.
- In several European countries, the choice of the threshold depends on **the severity of the disease**.
- Several European countries have introduced a separate **high threshold level**, which is used for decision-making in special situations defined based on different criteria (e.g., rare diseases, orphan medicinal products, novel technologies).
- National practice varies as to whether thresholds are **linked to GDP per capita** or not. Indexing with GDP is common among Central and Eastern European countries, and it is not used in Western Europe. This does not necessarily mean that thresholds in Western Europe have been static – e.g., England has reformed the rules for implementing thresholds. Also, in Central and Eastern Europe, including Latvia and Lithuania, there have been changes regarding thresholds in recent years (e.g., the addition of new high thresholds).

Determining the optimal cost-effectiveness threshold is a difficult task, the answer to which was beyond the scope of this work. To solve this, either a survey study should be conducted to determine the willingness of members of society to pay for health benefits or a study based on the opportunity cost approach (based on the fact that financing each intervention to achieve one additional QALY replaces another intervention in the health care system). The comparison between countries alone does not allow for defining the optimal threshold; the position of the Estonian threshold in the comparison between countries can only serve as background information when assessing the threshold. Also, the trend of the relationship between the threshold and GDP over the last decade can also be considered as telling background information – if we assume that the cost-effectiveness threshold should correspond to the willingness of society members to pay (which no study has been conducted to determine and which is therefore unknown), then it is most likely correlated with their ability to pay (expressed by GDP per person). If the threshold has changed significantly as a ratio to GDP, it means that either at the beginning or at the end of the period, the threshold was probably at a suboptimal level.

The scientific literature has not taken the position that the optimal threshold should be one-to-one with GDP, but it has been shown to be positively correlated with GDP (Danzon *et al.,* 2013). The automatic update of the threshold involves a complex compromise – on the one hand, the risk must be taken into account that manufacturers of technologies in a monopoly or quasi-monopoly position will start pricing their products higher when the threshold rises. On the other hand, if the threshold is not raised, there is a risk that the necessary technologies will be left unfunded at a price level that would have been acceptable, considering the increased willingness of society to pay.

The **discount rate** expressing the time value of money is an important parameter in the evaluation of health technologies, the effects of which may extend into the distant future. The discount rate used in Estonia is 5%, and the use of other rates must be justified (examples of using a different rate were not revealed in the survey). The discount rates used in the evaluation of health technologies differ from country to country, being in the range of 3-4% in most countries. The **5%** used in Estonia and some other Central and Eastern European countries **is the highest applicable rate in Europe**. Most countries, like Estonia, use the same discount rate for costs and health outcomes, but there are also countries where health outcomes are discounted at a lower rate.

In the manuals of other countries, when discussing the choice of the discount rate, reference is made to the regulation established by the ministries of finance, with which a uniform discount rate has been established for use in public finances, investment profitability analyses, etc., in situations where the time value of money must be taken into account. In Estonia, too, it would be important to ensure that the discount rate used in evaluating health technologies is in line with general practice. Estonian domestic regulation deals with the discount rate only in the general rules of state accounting, and it is a financial discount rate. In the context of HTA, however, the social discount rate is important, which in Estonia is typically based on EU regulation and guidance materials. When economic growth slows down, the social discount rate used by countries typically decreases. Previously (in the period 2014–2020), for example, the EU project cost-effectiveness analysis manual provided for a social discount rate of 5% in countries receiving support from the Cohesion Fund (including Estonia) and 3% in other countries, but according to the new manual, a discount rate of 3% should be used, in the event that the national regulation does not provide otherwise rate usage. The guideline is not mandatory for use in the context of HTA, but as a general principle, it would be reasonable to ensure that the discount rate used in health care is not higher than that used when deciding on the use of public money in other areas. Although the scientific literature has expressed the opinion that the use of a lower discount rate for health outcomes would be justified due to the special nature of the consumption value of health as a commodity, there should be no reason why a higher discount rate should be used in the assessment of health technologies than in other public sector investment projects.

In terms of the assessment process of health technologies, the **involvement of stakeholders in the assessment process** has been described more thoroughly in foreign countries than in Estonia. Compared to the discussed foreign countries, Estonia has a more modest involvement of patients – according to the HTA guidelines of other countries, it has a significant role in the HTA processes; the same cannot be said about the Estonian guidelines. Although patient umbrella organisations are represented in the medicinal products and healthcare service listing committees, they do not see it as their role to consult with sectoral patient associations as part of the assessment of applications. In the interviews, various obstacles to involving patients to a greater extent than before were pointed out: the ability of patient associations to have a say in the assessment process was considered uneven; finding an appropriate form of involvement was considered a challenge; there was also a risk that involvement would increase the duration of the process.

In interviews with representatives of stakeholders involved in the submission of applications (manufacturers of medicinal products and professional associations of doctors), various **bottlenecks in the application preparation and assessment processes** were pointed out:

- Unlike the list of medicinal products, the list of healthcare services is updated in too long an increment (once a year), which increases the time between the submission of the request and the service becoming available to patients.
- Translating published evidence into Estonian and reformatting it for application purposes is a time-consuming process for which medical professional associations do not always have the resources, and because of this, some applications are not submitted.
- Manufacturers of medicinal products recognized the speed of preparation of expert opinions by the Health Insurance Fund and the State Agency of Medicines, which has improved over time, as well as the assessments of the State Agency of Medicines. The protocols of the Medical Products Committee have also become more substantial and clearly structured over time. However, it was found that they could reflect the applicant's views and counter-arguments to the Health Insurance Fund's assessments and the Committee's reasons for not taking them into account.
- Although according to the representatives of the Medical Products Committee interviewed, the arguments and proposals forwarded by the manufacturers of medicinal products always make it to the materials submitted to the Committee, the manufacturers perceive that they have not been sufficiently taken into account in the Committee's discussion.
- In the opinion of manufacturers of medicinal products, the Baltic guidelines for the pharmacoeconomic evaluation of medicinal products remain too general in important aspects and need to be modernised. Clearer and more uniform principles and criteria would create the assumption that the submitted applications more closely meet the expectations of the application assessor. This would also help to reduce the time required to process applications, as well as if the Health Insurance Fund were more proactive and solution-oriented in the negotiation process.

It is also important to mention the limitations of this study. The study is based on a comparison of a limited number of practices in foreign countries with Estonia and on interviews with a limited number of representatives of stakeholders. This makes it possible to point out the differences and similarities between the practice of Estonia and foreign countries, as well as potential areas of concern revealed in the interviews. The purpose of the study was not to assess how exactly the methodology and decision criteria for assessing health technologies have affected the availability of specific treatment options for patients or whether the decisions and price agreements made have been useful for society or not. The authors of the study did not have access to confidential information about the progress or content of the price agreements.

5. Suggestions and recommendations

Based on the results of the study, we present the following proposals and recommendations:

1. The cost-effectiveness thresholds used have changed significantly in relation to GDP per capita. **Therefore, the change in the cost-effectiveness threshold in relation to GDP should be monitored, and the need to update it should be regularly assessed.** Ideally, a study should be conducted (either based on the willingness to pay or the opportunity cost approach), and an expert working group should be created, for example, to define the optimal level of the threshold.
2. The principles **of choosing the time horizon** used in cost-effectiveness analysis need more clarity and transparency (they are not discussed at all in the Baltic guideline). The guidelines of foreign countries also describe the principles of choosing a time horizon quite briefly, but at least they give guidelines on which cases a lifetime time horizon must be applied and in which cases not. Even if it is not possible in the guideline to formulate precise principles for the selection of the time horizon in all possible special cases, it is important for the sake of clarity and transparency **to open and justify the** time horizon selection considerations in the cost-effectiveness assessments of the Health Insurance Fund, so that the selection is more transparent and applicants can have a better understanding of the practice used. In situations where there is significant uncertainty in extrapolations made for distant future periods, the analysis should be carried out using different time horizons (as recommended by, e.g., Drummond *et al* 2019), which allows highlighting the impact of the choice of time horizon on the performance indicators and the uncertainty associated with them.
3. It is worth considering **introducing an additional higher threshold for limited situations**, as has been done in many countries (e.g., the highly specialized technologies programme in England, the levels applied based on the major health harm criterion in the Netherlands and Sweden, the rates applied to the financing of advanced therapy medicinal products in Slovakia). The introduction of such a threshold would make decision-making in special situations more transparent and would help to avoid situations where the request is not submitted by the manufacturer, as the prospects for obtaining a favourable cost-effectiveness assessment are slim in the case of thresholds used.
4. The **discount rate** (5%) used in evaluating the cost-effectiveness of health technologies should not be higher than the discount rate used in other areas when deciding on the use of public money. Therefore, **developments in national and international regulation and practice regarding discounting should be monitored** – the new period EU guidance recommends using 3% as the social discount rate if national regulation has not established a different rate. The international comparison also shows that most other European HTA institutions use a discount rate of 4% or lower (with the exception of a small number of Central and Eastern European countries).
5. Currently, cost-effectiveness analyses are primarily based on the perspective of the healthcare system, supplementing the analysis with the perspective of society if necessary. In the interviews with the parties and stakeholders of the process, the value was seen in **using a broader societal perspective**, but risks were also pointed out (budgetary impact if, due to the use of a broader perspective, more technologies should

turn out to be cost-effective than before) and challenges related to the greater need for data. It would be advisable to take steps to create the capacity so that at least the effects arising within the national tax and social protection system (employment and labour taxes, social benefits external to the Health Insurance Fund, such as work capacity support, disability benefits, unemployment benefits, etc.) could be taken into account in the analysis, if necessary.

6. For the sake of transparency, it would be wise to formulate **clearer principles in the guidelines, which type and which evidence material that meets the requirements** is taken into account when making a decision. The Baltic guideline for pharmacoeconomic evaluations of medicinal products names only randomised, double-blind clinical trials with a control group or open studies. In practice, such studies are not applicable in some situations, or studies have not been conducted to compare the technology under consideration and the treatment used in Estonia. Despite the fact that other evidence (e.g., analyses based on indirect comparisons) is taken into account in the decision-making process, manufacturers do not have sufficient clarity about what evidence is acceptable and what is not. There are examples from other countries (e.g., England) where the guidance materials are more detailed in this regard and describe the principles and limitations of using indirect comparisons, observational data, and real-life data.
7. As already stated in the points discussed above, the **Baltic guideline for the pharmacoeconomic assessment of medicinal products remains too general in various important aspects.** The other Baltic countries also no longer use it – both Latvia and Lithuania have recently changed their systems. It needs to be replaced by guidance that provides clearer and more detailed guidelines regarding acceptable methodological choices both in the evaluation of medical effectiveness and cost-effectiveness, as well as in the use of a time horizon and a different discount rate than usual.
8. Although according to the representatives of the Medical Products Committee interviewed, the arguments and proposals forwarded by the manufacturers of medicinal products always make it to the materials submitted to the Committee, the manufacturers perceive that they have not been sufficiently taken into account in the Committee's discussion. For the sake of transparency in the decision-making process, **the minutes of the committees should state the reasons** why the manufacturers' positions have not been accepted.

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