TALLINN UNIVERSITY OF TECHNOLOGY
School of Information Technologies
Department of Health Technologies

Brigitha Kask 192540YVEM

MULTI CRITERIA DECISION ANALYSIS AS PART OF HEALTH TECHNOLOGY ASSESSMENT: A CASE STUDY ON METASTATIC TRIPLE-NEGATIVE BREAST CANCER

Master`s thesis

Supervisor: Riina Hallik
M.Sc, MMS
Co-supervisor: Tanel Ross
M.Sc

Tallinn 2021

TALLINNA TEHNIKAÜLIKOOL
Infotehnoloogia teaduskond
Tervisetehnoloogiate instituut

Brigitha Kask 192540YVEM

MITME-KRITEERIUMILISE OTSUSTE ANALÜÜSI KAASAMINE TERVISETEHNOLOOGIATE HINDAMISSE: JUHTUMIUURING METASTAATILISE KOLMIKNEGATIIVSE RINNAVÄHI PÕHJAL

Magistritöö

Juhendaja: Riina Hallik
M.Sc, MMS
Kaasjuhendaja: Tanel Ross
M.Sc

Tallinn 2021

Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature, and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

Author: Brigitha Kask

10.05.2021

Abstract

Background: Multi criteria decision analysis (MCDA) is a methodology that allows including different stakeholder preferences and wide value dimensions in a systematic, structured, and transparent way. The thesis aimed to design and co-create a new multi criteria evaluation model and test through a practical case study on what level it is adaptable to pharmaceutical reimbursement decision-making in Estonia. The breast cancer treatments in first-line locally advanced or metastatic triple-negative breast cancer (mTNBC) in programmed death-ligand 1 (PD-L1) immune cell-positive patients subgroup (≥1% PD-L1 expression) were evaluated. *Methods*: The state of the art review was used to identify the criteria and stakeholders. The first four stages of a multi-attribute value theory (problem structuring, model building, model assessment, model appraisal) were adopted. A facilitated decision analysis modeling approach was used during the mini focus group seminars with feedback questionnaire. The MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique) technique was used and operationalized with M-MACBETH software. *Results:* The MCDA model designing process includes eight steps according to international research and guidelines. The final mTNBC value tree based on the Estonian case study includes four attributes. The overall weighted preference value score achieved by Atezolizumab + Nab-paclitaxel was 61 – 65, followed by Nab-paclitaxel with 27 – 45 out of 100. *Conclusions:* Using the MCDA as part of health technology assessment (HTA) can help to map all relevant aspects for decision-making, identify the criteria contributing the most to the overall value score of the treatment and engage relevant stakeholders in balanced and transparent decision-making. However, the MCDA model building process requires several iterations to define all relevant attributes and back up the appraisal with high-quality evidence to reduce the subjectivity inherent in all decision-making. The study's relevance is in the comparison of the current HTA and MCDA processes involving key stakeholders in the discussion. The hypothesis was not fully proven, but all the research questions were answered. The thesis is written in English and has 71 pages, including 6 chapters, 11 figures and 3 tables.

Annotatsioon

Taust: Mitme-kriteeriumiline otsuste analüüs ehk MCDA on metoodika, mis võimaldab ostustamisse süsteemselt, stuktureeritult ja läbipaistvalt kaasata oluliste huvigruppide hinnanguid ja laiemaid väärtusdimensioone. Magistritöö eesmärk on praktilise näite abi disainida ja koos luua MCDA mudel ning testida, kas ja mil määral on seda võimalik rakendada Eesti ravimite rahastuse otsustusprotsessis. Juhtumiuuringus hinnati mitteresetseeritava lokaalselt levinud või metastaatilise kolmiknegatiivse rinnanäärmevähi ravimeid patsientide alagrupis, kelle PD-L1 ekspressioon on kasvajat infiltreerivatel immuunrakkudel ≥ 1%. *Metoodika:* Kirjanduse ülevaade teostati, et teha kindlaks milliseid kriteeriume ja huvigruppe kaasata. Rakendati MAVT esimest nelja etappi (probleemi struktureerimine, mudeli ehitamine, hindamine ning kriteeriumitele hinnangute andmine). Mini fookusgrupi seminaridel kasutati juhendatud otsuse analüüsi modelleerimist ning osalejad vastasid tagasiside küsimustikule. Hindamisel kasutati MACBETH tehnikat ning M-MACBETH tarkvara. *Tulemused:* MCDA mudeli disainimise protsess koosneb kaheksast etapist. Lõplik metastaatilise kolmiknegatiivse rinnavähi väärtuspuu koosneb neljast atribuudist. Atezolizumab + Nab-paclitaxel saavutas maksimaalsest võimalikust skoorist (100-st), kõrgema lõpliku kaalutud väärtusskoori, mis jäi vahemikku 61 – 65. Nab-paclitaxeli lõplik kaalutud väärtusskoor jäi vahemikku 27 – 45. *Järeldused:* MCDA kasutamine HTA osana aitab kaardistada olulisi aspekte, mis mõjutavad otsustusprotsessi ning kindlaks teha millisele hindamiskriteeriumile omistatakse suurim kaal, kaasates seejuures erinevaid huviguppe tasakaalustatud ning läbipaistvate otsuste tegemisse. MCDA mudeli ülesehitamine on mitmeid kordusi nõudev protsess, mille käigus on vaja kindlaks teha kõik hindamiseks olulised atribuudid ning leida andmekogud heade otsuste tegemiseks, et vähendada ostustusprotsessile iseloomulikku subjektiivsust. Magistritöö olulisus seisneb hetkel kasutuses oleva tervistehnoloogiate hindamise protsessi ja MCDA võrdluses ning oluliste huviguppide esindjate kaasamises antud arutellu. Töös püstitatud hüpotees ei leidnud täiel määral kinnitust, kuid kõik uurimuse küsimused said vastuse. Magistritöö on kirjutatud inglise keeles ning sisaldab teksti 71 leheküljel, 6 peatükki, 11 joonist, 3 tabelit.

List of abbreviations and terms

AHP	Analytical Hierarchy Process
AVF	The Advanced Value Framework
CAUSE	Criteria, Alternatives, Uncertainties, Stakeholders, Environmental factors
CI	Confidence interval
DOR	Duration of response
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHIF	Estonian Health Insurance Fund
EMA	European Medicine Agency
EU	European Union
EUnetHTA	European Network of Health Technology Assessment
FDA	U.S. Food and Drug Administration
GDP	Gross domestic product
HER 2	Hormone epidermal growth factor receptor 2
HQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICVR	Incremental cost-value ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MACBETH	Measuring Attractiveness by a Categorical Based Evaluation Technique
MAVT	Multi-attribute value theory
MCDA	Multi criteria decision analysis
mTNBC	Metastatic triple-negative breast cancer
MVP	Minimum viable product
NICE	National Institute for Health and Care Excellence
OS	Overall survival
ORR	Objective response rate
PAPRIKA	Potentially All Pairwise RanKings of all possible Alternatives
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
QoL	quality of life

RWD	Real-world data
TNBC	Triple-negative breast cancer
QALY	Quality-adjusted life year
W.A.I.T.	Waiting to Access Innovative Therapies
WHO	World Health Organization
WPV	Weighted preference value

Table of contents

List of figures

List of tables

1 Introduction

The need for healthcare services is rapidly growing due to reasons such as increasing prevalence of preventable illnesses and the aging population, which increases living with comorbidities. New innovative treatments make it possible to help more patients. However, the time, complexity, and investment needed for developing a valuable, novel pharmaceutical makes it usually very expensive, and providing patients with the best possible care requires additional yearly funding from the state. With scarce resources, dividing the limited budget between different healthcare services is very challenging. In Estonia, the investment into the healthcare system is below the EU average [1]. Society expects healthcare decisions to be transparent, which can only be achieved when the health technologies are assessed, appraised, and the final decisions are made under the systematic construct of benefit assessment [2]. Moreover, healthcare strives to move from quantification to measuring the value of the provided services. The term *value* is very subjective and can have different meanings to stakeholders. The most value-creating and optimal use of resources must be the aim of all healthcare decision-making processes. Many studies point out that the health technology assessment (HTA) process, using incremental cost-effectiveness ratio (ICER) as the main driver in decision-making, is not sustainable. Additionally, the reimbursement of rare disease (including rare cancers) pharmaceuticals requires a different decision-making approach. The evidence presented for the orphan drug reimbursement usually differs significantly from the evidence available for more conventional treatments. Thus, the assessment should be based on different criteria, considering equity, disease burden, severity, and innovation. The metastatic triple-negative breast cancer treatments, which is the focus of the current research case study, are not orphan drugs by definition but pose similar challenges. These are end-of-life treatments for a relatively small patient pool, and reimbursement decision-making involves several uncertainties.

One possible solution in addressing these issues could be using the multi criteria decision analysis (MCDA), which can support the HTA process. MCDA helps to systematically determine the optimal solutions, make value judgments, and integrate different

stakeholder preferences into the decision-making process [2]. Including the MCDA in decision-making helps to define and transparently measure the healthcare technologies' overall value. However, when implementing MCDA, all relevant stakeholders, especially policymakers and payers, have to commit to changing the process. Committing is not easy when the exact benefit is not fully understood. The database search (conducted in Google Scholar and PubMed) to find the existing and available research on utilization of MCDA in the pharmaceutical reimbursement process in Estonia gave no result.

The study is the first step towards understanding, providing theoretical guidance, practical example, and experience in designing and building an MCDA model. The aim is to adopt an MCDA methodology to design and co-create a new multi criteria evaluation model and test through a practical case study on what level it is adaptable to pharmaceutical reimbursement decision-making in Estonia. Moreover, the intention is to initiate a discussion on the possible advantages, disadvantages, and on potential of MCDA adding value to the current Estonian reimbursement process. The study is relevant because it compares the current HTA and MCDA processes, involves the key stakeholders in discussion, and can be used to develop the MCDA model further.

The thesis consists of six chapters. The first chapter is an introduction to the topic. The second chapter gives an overview of multi criteria decision analysis in general, the current reimbursement process and access to pharmaceuticals in Estonia, and metastatic triple-negative breast cancer (mTNBC). Methodology and methods are explained in the third chapter, and the results are presented in the fourth chapter. The fifth chapter discusses the case study results and feedback, points out the limitations and future research opportunities. Finally, chapter six presents the conclusions of the study.

2 Background

2.1 The reimbursement process and access to pharmaceuticals in Estonia

The Estonian public health insurance system follows a solidarity principle. All medically insured people must get the same quality healthcare, and the costs will be covered by the Estonian Health Insurance Fund (EHIF). In the year 2019, 95.28% of the Estonian population had insurance coverage [3]. Health insurance funding is connected to social tax, an obligatory labor force tax [4]. According to the World Bank, the Estonian health expenditure percentage of GDP (gross domestic product) in 2018 was 6.69%, which was significantly lower than the European Union average (9.85%) [1].

In 2019, 16.65% of Estonia healthcare costs were allocated to pharmaceuticals. The hospital pharmaceutical costs formed 5.02% of total healthcare costs [3]. Prescription medicines, which are on the positive list of reimbursed pharmaceuticals, will be reimbursed by EHIF with the following rates: 100%, 90%, 75%, or 50%. Pharmaceuticals used in hospitals are included in a health service code (or have a separate code in the list of health services) and are reimbursed accordingly by the EHIF [5]. The Hospital Pharmaceutical Committee is responsible for providing opinions regarding amendments to the list of medicinal products. The committee acts as an advisory body to the EHIF and involves different stakeholders like healthcare professionals, payers, patient representatives, regulators, and the Ministry of Social Affairs [6], [7]. The list of healthcare services is renewed and updated yearly.

The criteria currently assessed are:

- proved medical effectiveness
- cost-effectiveness
- the societal need and the accordance with governmental healthcare politics
- accordance with the EHIF budget possibilities [7].

The European Federation of Pharmaceutical Industries and Associations (EFPIA) published the Patients Waiting to Access Innovative Therapies (W.A.I.T.) survey: *"The INDICATOR provides a benchmark of the rate of availability and waiting times in European countries"* [8]. In the scope of the W.A.I.T. indicator survey were 172 products, approved by the European Medicine Agency (EMA) in the period of 01.01.2015 – 31.12.2018. The rate of availability shows the point at which the product gets access to the reimbursement list. Estonia ranks 25th among the 34 countries, as shown in Figure 1 [8]**.**

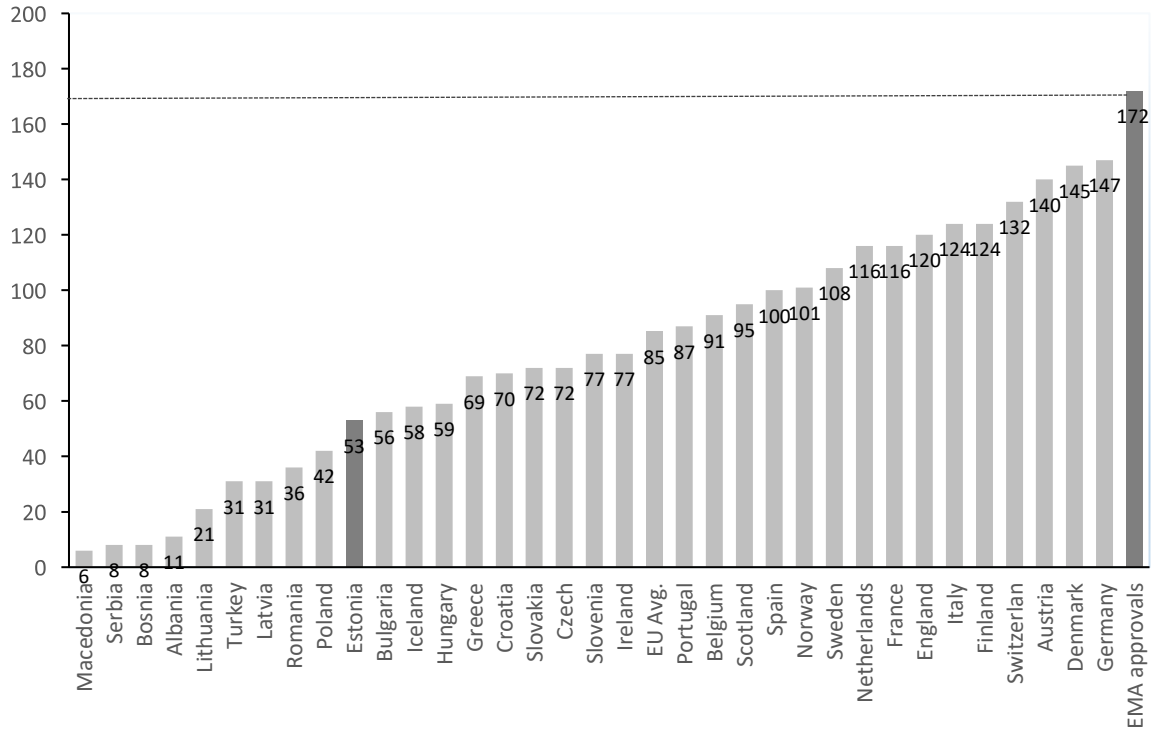


Figure 1. The rate of availability [8].

2.2 Multi criteria decision-making

In 1976 Keeney and Raiffa first introduced the MCDA, defining it as *"an extension of decision theory that covers any decision with multiple objectives. A methodology for*

appraising options on the individual, often conflicting criteria, and combining them into one overall appraisal" [2], [9].

A decision is a fundamental tool when people face opportunities, challenges, and uncertainties. An effective decision-making process focuses on the essential. It is straightforward, flexible, promotes and guides the collection of relevant information, acknowledges subjective and objective factors, supports resolving dilemmas, and is logical and consistent [10].

Criteria in decision-making can be seen as a standard based on which one particular choice or course of action is considered more desirable than the other. When there are several choices to be considered which are conflicting, it becomes a multi criteria decision-making problem. A wide range of criteria has to be considered in a group of stakeholders with different interests. This requires balancing the criteria and sometimes considering various alternatives before making the decision [11].

2.3 Metastatic triple-negative breast cancer

Cancer is a common term used for a group of diseases that can affect any part of the human body. It refers to the fast creation of abnormal cells, which grow beyond their usual boundaries and spread to other organs, ultimately metastasizing [12]. It is estimated that in 2018, 9.6 million deaths were caused by cancer globally, ranking it the second largest cause of death among all diseases [12]. In the European Union (EU), the estimated burden of cancer for 2020 is 2.7 million new cancer cases (excluding non-melanoma skin cancer) and 1.3 million cancer deaths [13].

By WHO estimations, breast cancer ranks second in new cancer cases (2.09 million cases) and is the fifth most significant cause of death in all cancer types globally (627000 deaths) [12]. Breast cancer is a leading cancer cause among Estonian women, with cases rising from 763 in 2016 to 836 in 2018 [14].

About 12 – 15% of breast cancers are triple-negative breast cancers (TNBC) [6]. Diagnosis of TNBC means that the cancer cells tested negative for estrogen receptors, progesterone receptors, and HER 2 (hormone epidermal growth factor receptor 2). TNBC is aggressive and challenging to treat. It has a higher likelihood of spreading and recurring

than other types of breast cancer [15]. The metastatic triple-negative breast cancer (mTNBC) is not curable, and the survival median with chemotherapy is 12 – 18 months. In Estonia, the estimated number of patients per year is 10 – 16 [6].

2.4 The scope, aim and study outline with research questions

In general, the field under research is HTA, specifically the use of MCDA and reimbursement of pharmaceuticals. The thesis is further focused on the mTNBC and further narrowed to the programmed PD-L1 immune cell-positive patients subgroup (≥1% PD-L1 expression). The treatment alternatives under evaluation for the use of MCDA are Nab-paclitaxel and Atezolizumab + Nab-paclitaxel. The mTNBC treatments were chosen because the utilization of MCDA is widely researched for cancer treatments and orphan drugs in other countries. The assessment of these treatments poses many challenges, and the need to consider additional equity-related criteria is often highlighted.

The thesis is applied research with design science research methodology involving induction and deduction phases with methods such as state of the art review, case study, and mini focus group. MCDA model building is an iterative process, and the case study result is a Minimum Viable Product (MVP), needing follow-up actions.

The thesis aims to adopt an MCDA methodology to design and co-create a new multi criteria evaluation model and test through a practical case study on what level it is adaptable to pharmaceutical reimbursement decision-making in Estonia. It is hypothesized that utilizing MCDA as part of the HTA allows the inclusion of a broader value dimension, is more transparent, inclusive, and structured, offering better and more informed decision-making than the current pharmaceutical reimbursement process.

The induction phase concentrates on descriptive research, describing the best-known MCDA methods and guidelines. The state of the art review is conducted to find the long

list of the MCDA values, criteria, attributes, and weighting techniques used in other studies [16]. The empirical analysis of the thesis is based on the MCDA practices from countries using it as part of the HTA. The research induction phase involves descriptive questions to describe the current pharmaceutical reimbursement decision-making process and the existing MCDA guidelines and practices [16].

The research questions in the induction phase were:

- What are the necessary steps for building a valid and transparent multi criteria evaluation model?
- What are the values, criteria, and attributes to include in the MCDA?

In the deduction phase, the previously gained knowledge is used to design and co-create the MCDA model with stakeholders participating in mini focus group seminars. It involves evaluating and designing questions to assess the current pharmaceutical reimbursement process's advantages and disadvantages and design a new MCDA model [16].

The research questions in the deduction phase were:

- How to assign transparent and structured measures to the MCDA model?
- How different are the stakeholders' value preferences?
- What are the differences in reimbursement process and outcome when adopting the MCDA as part of HTA?

3 Methodology and methods

3.1 Methodological process

The thesis represents a pragmatic world view, advocated by David L. Morgan [17], used within mixed-methods research. The pragmatic approach converts observations into theories and then evaluates these theories through practical action [17]. The study is based on design science research, defined as *"a research paradigm in which a designer answers questions relevant to human problems via the creation of innovative artifacts, thereby contributing new knowledge to the body of scientific evidence"* [18].

The data gathering within mixed-methods research is based on the concurrent embedded strategy. The strategy allows simultaneous collection of both qualitative and quantitative data [19].

The thesis adopts The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) MCDA Good Practice Guidelines Checklist [20], with key considerations to think about when designing, reporting, and conducting a critical assessment of MCDA studies. Furthermore, the checklist guides how to validate the process to ensure that the MCDA design, input, and output are plausible and in line with decision-makers' goals and stakeholders' preferences [20].

3.2 State of the art review

The State of the art review was conducted to find criteria, attributes, and stakeholders included in the MCDA model building process in other countries. The review results shown in Appendix 1 helped prepare for the case study.

A systematic search was done on 06.01.2021 in the following databases: PubMed, Google Scholar. The keywords used in both searches were variations of MCDA, HTA, and pharmaceuticals. The research protocol can be seen in Appendix 2. The filters applied in

all searches were English (language) and the period from 2015 to 2020. Additional filters applied in PubMed were Mesh Humans and free full text. The studies were imported to FMendeley software, where duplicates were removed. The inclusion and exclusion criteria and the result with the final literature used for the review are presented as a PRISMA flowchart in Figure 2.

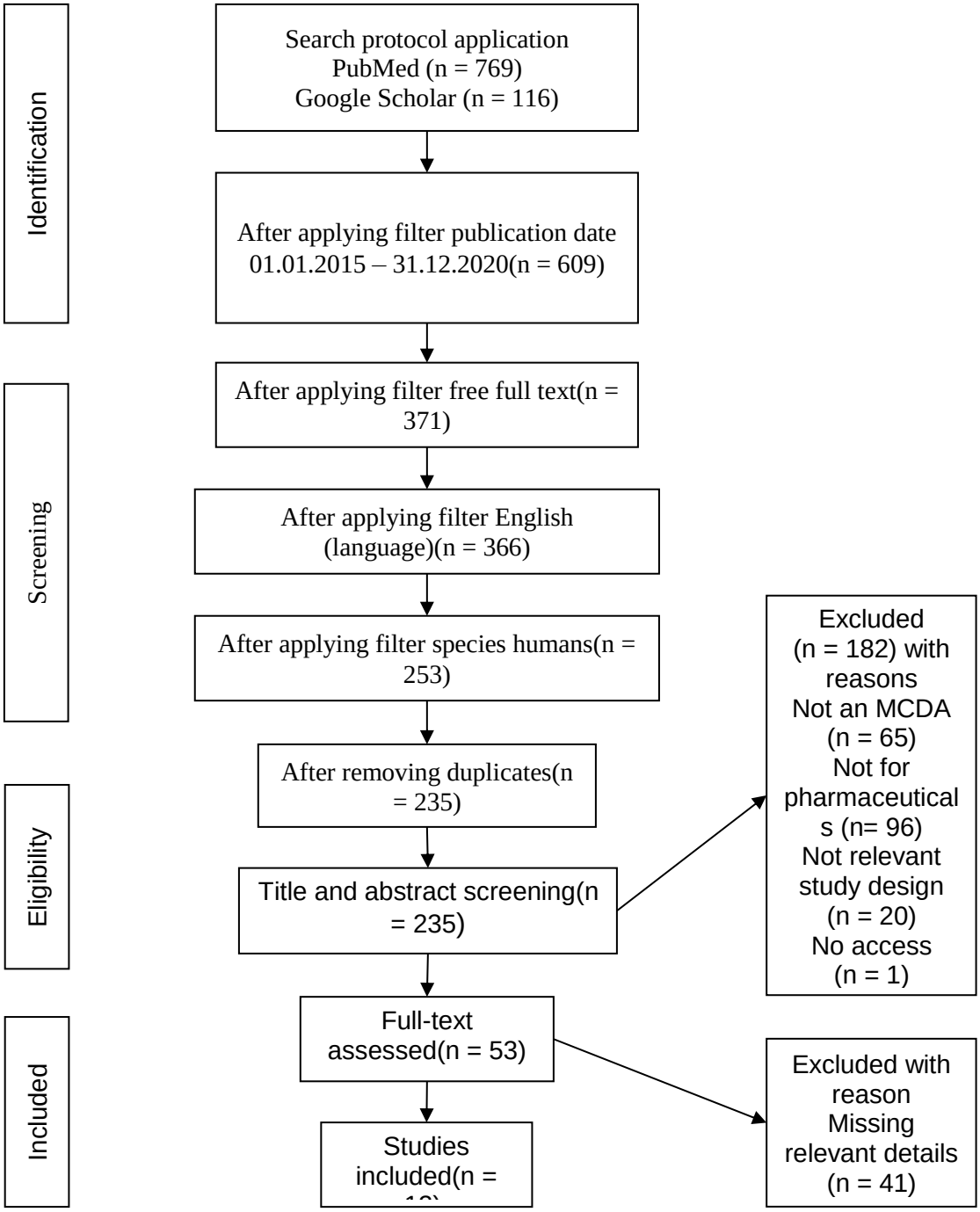


Figure 2. PRISMA flowchart describing literature selection. Source: author, adapted from [21].

3.3 Mini focus group

The first four stages (problem structuring, model building, model assessment, model appraisal) of the multi-attribute value theory (MAVT) were used in the MCDA case study [11], [22]. The sensitivity analysis, robustness analysis, and development of the action plan were not in the scope of the case study.

A facilitated decision analysis modeling approach was used during the mini focus group seminars. Typically focus group contains 6 – 12 people, and one meeting lasts about two hours, covering the carefully selected and predetermined topics. The focus group is considered suitable for understanding and involving a range of opinions provided by different people [18]. The mini focus group is allowed when participants have a particular experience and expertise for discussion. Mini focus groups include 3 – 4 participants, and the advantage of a smaller group is that all participants can feel safer sharing their beliefs, opinions, and experiences [23]. Due to the pandemic situation, the seminars were held virtually using the Google Meet platform. All meetings were recorded via Google Meet. The summary of the first and second Google Meet recordings is shown in Appendix 3. The virtual meetings took place in the period of 11.03.2021 – 26.03.2021. Participants signed the consent agreeing to the data collection, disclosure procedure, and seminar recordings. The consent form in the original language can be seen in Appendix 4. All the focus group members and their preferences are published as categories (stakeholder groups). The participants belong to four key stakeholder categories: doctor, patient, payer, and regulatory. All selected focus group participants, besides the patient, have experience in the Estonian pharmaceutical reimbursement decision-making process. The MCDA studies in the literature review include the same stakeholder categories.

After the virtual meetings, the participants answered a feedback questionnaire (Appendix 5). The questionnaire comprises three sections. The questions in the first section aim to map the participants' views on the advantages and disadvantages of MCDA. In the second section, the participants were asked to judge how well the core values of the MCDA theory were opened during the focus group seminars. The last section aimed to collect the participants' views about the possible additional value that MCDA could bring when used as part of HTA in Estonia. The questionnaire was sent to

all participants via e-mail using the Google Form, and the collected answers were anonymous.

3.3.1 Case study problem structuring

In the case study, MCDA methodology was used to estimate the overall value of the first line locally advanced or metastatic triple-negative breast cancer (mTNBC) treatments in the PD-L1 immune cell-positive patients subgroup (≥1% PD-L1 expression). The treatment alternatives were selected based on the amendment application of the healthcare services list No. 1417 submitted to the Estonian Health Insurance Fund by the Estonian Association of Oncotherapy on November 30, 2019 [24], [7]. The treatment alternatives are Nab-paclitaxel and Atezolizumab in combination with Nab-paclitaxel.

The first focus group seminar concentrated on problem structuring and selecting the appropriate value tree criteria. Before the first seminar, all participants received a video introduction and access to the Google Jamboard. Google Jamboard was used as an assisting tool to facilitate the virtual seminars. The following guiding materials were entered into Google Jamboard before the first seminar:

- CAUSE checklist (Criteria, Alternatives, Uncertainties, Stakeholders, Environmental factors) [11]
- preliminary generic value tree (Appendix 6).

3.3.2 Case study model building

The "value-alternative hybrid thinking" and the generic value tree proposed by Angelis and Kanavos [25] in The Advance Value Framework (AVF) were adopted as the model building starting point. The AVF obtained the results through a five-stage process, including a literature review to discover the value dimensions considered during HTA in eight EU countries (France, Germany, Sweden, England, Italy, Netherlands, Poland, Spain). The results were validated with the HTA experts from the same countries [25].

The value tree's core structure was built using the top-down approach, while when defining the attributes, the bottom-up approach was used [25].

The terms *criterion* and *attribute* are sometimes used as synonyms in the MCDA studies. Current study differentiates these terms, using the term attribute only for measurable criterion. The case study value tree criteria selection process is shown in Figure 3.

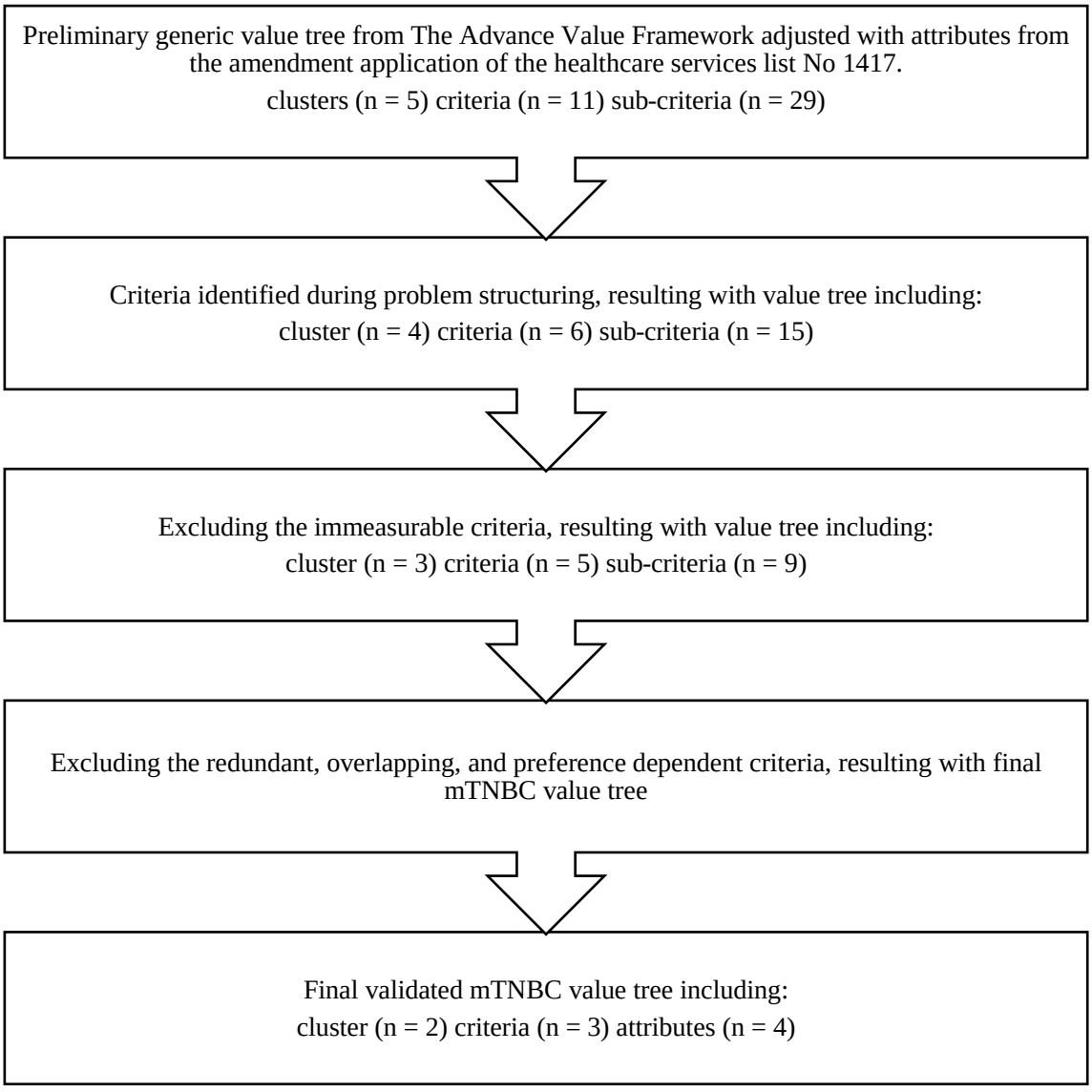


Figure 3. Case study criteria selection process.

The second focus group seminar concentrated on defining and validating the performance matrix, including the “lower” and “higher” reference levels. The following materials were prepared and sent to all focus group participants via e-mail before the second seminar:

- mTNBC value tree with measurable attributes, shown in Figure 5
- attribute definitions and sources of evidence, shown in Appendixes 7 and 8
- the preliminary performance matrix, shown in Appendix 9.

After the seminars, the necessary changes and outcomes were entered into the M-MACBETH software. The final scoring and weighting meeting was held individually with all participants.

3.3.3 Case study model assessment and appraisal

During the focus group seminars, the qualitative data on the stakeholders' opinions about the essential evaluation criteria and attributes to address the decision problem and measure the treatment alternatives performance was collected. Later the performance was measured by scoring and weighting all criteria, resulting in the overall weighted preference value (WPV) score for each treatment alternative. All focus group members had an individual meeting to give their scores and weights. The individual scoring meeting was chosen to assure uninfluenced judgments. The process was operationalized using the M-MACBETH software, which uses the questioning protocol to obtain the stakeholders' qualitative judgments about the differences in value. Based on this approach, the stakeholders pairwise compared the alternatives difference in attractiveness using the semantic scale – no, very weak, weak, moderated, õstrong, very strong, extreme [26], [27]. The M-MACBETH uses the stakeholders' qualitative judgments to generate a numerical score and construct a quantitative evaluation model. It has automated judgment consistency checks and offers suggestions on how to remove the inconsistencies [27]. When changes are made in judgments, the overall scores will be updated automatically by the software. M-MACBETH was introduced to stakeholders, but they were not asked to enter any data. The data analysis was performed using the M-MACBETH software and Excel. The following analysis and visuals were prepared based on the judgments in M-MACBETH and displayed in the results: value trees, table of performance, histogram of scores, histogram of weights, histogram of the overall WPV scores.

4 Results

4.1 Steps for MCDA model building

The thesis is built up based on the ISPOR MCDA Good Practice Guidelines Checklist [20], which lists the key aspects to consider when designing, reporting, and conducting a critical assessment of MCDA studies. Furthermore, the checklist guides how to validate the process to ensure that the MCDA design, input, and output are plausible and in line with decision maker goals and stakeholder preferences [20]. This chapter gives a theoretical overview of the recommended MCDA model building steps.

The three main MCDA modeling methods are value-measurement methods, reference-level methods, and outranking methods [28]:

- The value-measurement methods use the numerical score to identify and compare how much one decision alternative is preferred over another. These methods commonly involve additive models, which multiply a score for each decision criterion with the relative weight of the criterion and finally sum these weighted scores to get the overall value score [28].

- Reference-level methods aim to discover the alternative that is closest to achieving the predefined minimum satisfactory achievement levels on each criterion [28].

- Outranking methods compare each decision alternative pairwise on each criterion to identify how much one alternative is preferred over the other, then aggregate the preference across all criteria and compare each alternative to the top-ranked alternative [28].

All MCDA methods have certain advantages and disadvantages, and the choice of the method depends on the type of the decision problem, whether used to address the sorting, choice, or ranking problem [29].

The ISPOR Task Force reports focus primarily on the value-measurement methods because the other methods are used less in healthcare [28].

4.1.1 Defining the decision problem

The first step of the MCDA model building is understanding and defining the decision's aim and the problem which decision-makers want to solve. This step involves identifying the relevant stakeholders, required output, and the considered alternatives [28].

Problem categories where utilizing MCDA can be beneficial are:

- choice problems – making a simple choice between different alternatives
- sorting problems – dividing the alternatives into different categories, like acceptable, not acceptable, somewhat acceptable, more information needed
- ranking problems – ranking the action or alternatives in some preferred order
- description problems – explaining the actions and outcomes in a systematic way so that the decision-makers can evaluate them
- design problems – identifying new decision alternatives to meet the aims and aspirations through the MCDA process
- portfolio problems – selecting a subset of alternatives from a more extensive set of options, considering the characteristics of the different alternatives and the manner in which they interact [11].

There are different tools available, like the CAUSE checklist, to guide the problem structuring process [11].

4.1.2 Selecting and structuring criteria

Selecting the proper criteria, assessing them with valid attributes in a multi-stakeholder group is vital for MCDA [22]. There are different ways criteria can be identified, such as the reviews of previous decision-making processes, focus group seminars, and facilitated workshops [28].

The criteria representing the decision-makers' key concerns and objectives can be structured using the value tree. After structuring the value tree, the decision alternatives and the attributes allowing to measure the performance of these alternatives must be defined [25].

The value tree can be structured by using either the top-down or bottom-up approach. The top-down approach is also known as value-focused thinking, where overall value concern is broken down into lower-level sub-concerns. The bottom-up approach is also known as alternative-focused thinking, where the alternative considered options (based on the specific attributes used to distinguish between them) are grouped into a higher level of value-concerns [25], [30]. Keeney [30] suggests using value-focused thinking as it gives better results in most situations [30].

The selected criteria must have the following properties:

- completeness – criterion is complete when it captures all relevant decision factors [20]
- nonredundancy – when decision alternatives achieve the same level of performance on a criterion, the criterion can be regarded redundant. To avoid the scoring and weighting of the criterion that, in this case, has no impact, the criterion must be removed [20]
- nonoverlap – avoiding double-counting by not allowing two criteria to measure the same factor and giving too much weight to some value dimension [20]
- preference independence – preference concerning one criterion should not depend on another's performance [11], [20]
- value relevance – it is essential that decision-makers can link the concept to their higher goals [11]
- understandability – the decision-makers must understand all concepts used in the analysis [11]
- measurability – it is essential to decompose criteria to a level of detail, which makes it possible to measure the performance of alternatives [11]
- operationality and simplicity – the model containing different criteria should have a simple representation and should be usable with reasonable effort [11].

According to ISPOR MCDA Emerging Good Practices Task Force Report [20], the average number of criteria used in MCDA is 8.2. The recommendation is to have as few criteria as needed for making a well-founded decision [20].

4.1.3 Measuring performance

After the criteria are defined and validated, it is essential to measure the performance of alternatives on each criterion. The performance measurement should be based on evidence-based medicine principles (clinical trial data) and recommended guidelines, for example, National Institute for Health and Care Excellence (NICE) guidelines [20].

One of the challenges of the MCDA is that there is often not enough existing data to measure the performance of treatment alternatives on a particular criterion, for example, the criterion disease severity. For filling this data cap, expert opinion can be used [20].

To display the performance of alternatives on all relevant criteria in a structured way, it is recommended to use the performance matrix [20].

4.1.4 Scoring alternatives

Scoring and weighting aim to capture different stakeholders' preferences for criteria, which, together with performance data, can be used to assess the relative overall value of alternatives [26].

The scores are used to capture intra-criterion performance and preferences [11]. The scores can be derived by determining specific rules for converting the performance measurements into scores. This helps to translate the performance measures using non-identical units for each criterion onto a standard scale. When converting the performance measures into scores, it should be consistent, and the exact change along the scoring scale should be equally preferred (e.g., 30 – 40 or 70 – 80) [28].

The scale must include two reference points with numerical values, the bottom and the top of the scale, with the maximum and minimum points [11].

There are local and global scales. A local scale is defined by all alternatives under decision-makers consideration, scoring the alternative performing the best on a particular criterion with maximum points and the alternative performing the worst with minimum points. On a global scale, reference points can be defined by best and worst supposable performance on the particular criterion, which could realistically happen [11].

The main types of scoring elicitation methods are compositional and decompositional methods. The compositional methods view each criterion independently and build up the overall value. These methods generate separate estimates of scores and weights, after which they are combined to get the aggregated scores. The compositional methods include direct rating, Simple Multi Attribute Rating Technique, Measuring attractiveness by a Categorical Based Evaluation Technique (MACBETH), and pairwise comparison (Analytical Hierarchy Process) [28].

The decompositional methods view the overall value of alternatives and derive the weights and scores for each criterion. These methods include conjoint analysis and Potentially All Pairwise RanKings of all possible Alternatives (PAPRIKA) [28].

4.1.5 Weighting criteria

While the scoring captures the preferences within the criterion, the weighting captures the preferences between the criteria [26]. Weights allow the decision-makers to make trade-offs between the criteria and can be thought of as exchange rates. There are different weighting methods [28]. The "swing weight" method considers the value range from the worst to the best of each criterion. Decision-makers must estimate the value of the swing in order to assign values to the weights. The prerequisite for assigning the swing weights is that the scoring scales for each criterion have been defined [11]. The other methods used to generate the weights include direct rating, Simple Multi Attribute Rating Technique, and Pairwise Comparison Using Ordinal Scales and Discrete Choice Experiment [28], [26].

4.1.6 Calculating the aggregated score

The aggregation aims to select the proper function that makes it possible to combine the scores and weights to follow stakeholder preferences. The most straightforward aggregation function in healthcare MCDA is the additive model, used with compositional and decompositional approaches [20]. For the additive model to be appropriate, the criteria should be preferentially independent, meaning the trade-offs that the decision-maker is willing to make between any two criteria should not be dependent on any other criteria [11].

The additive function formula can be expressed as $Vj = \sum_{i=1}^{n} \quad Sij * Wi$

With: Vj as the overall value of the intervention j; Sij as the score for the intervention j on criterion I; Wi as the weight assigned to criterion i [20].

4.1.7 Dealing with uncertainty

There are different ways to handle uncertainty. Understanding the nature of uncertainty and the existing possibilities to reduce it can be achieved by proper and sufficient problem structuring, data gathering, and analysis. It is helpful to differentiate the internal and external uncertainties [11].

Internal uncertainties are related to the process of problem structuring and analysis, and these uncertainties can be resolvable or unresolvable. Resolvable uncertainties are usually associated with the ambiguity of the concept meaning. The unresolvable uncertainties do not give any explicit knowledge to make the most appropriate choice, for example, choosing between the different criteria sets coming from the problem structuring [11].

The lack of knowledge about the outcome of the particular choice refers to *external uncertainties* [11].

Approaches helping to estimate the impact of uncertainties include having uncertainty as one criterion in the MCDA model or conducting the sensitivity analysis. The choice of the approach depends on the stakeholder risk attitude and how easy it is to capture various forms of uncertainty in a single MCDA criterion [20].

4.1.8 Reporting and examining of findings

When reporting the MCDA results back to decision-makers, it is necessary to consider the initial problem. The MCDA results should be transparent, easy to understand, and accessible to all decision-makers. To make the inputs and outputs transparent and understandable, MCDA software can be used. The software allows creating different visuals and supports the decision-making, but the results should still reflect stakeholder preferences. Hence, the stakeholders must understand and agree with the results created by the software [20].

4.2 MCDA case study

4.2.1 mTNBC problem structuring

At the beginning of the first focus group seminar, the participants were asked the following question: *"What is the purpose of reimbursing a new pharmaceutical for mTNBC in the PD-L1 positive patient subgroup?"* The focus group listed the following goals: save and prolong lives, prolong quality of life (QoL), effective treatment, best possible care, relieve complaints, not cause redundant adverse effects. Next, the discussion focused on identifying the aspects, which can influence the decision-making. The discussion was guided using the CAUSE checklist [11]. The summary of problem structuring is shown in Table 1.

Table 1. mTNBC problem structuring with CAUSE checklist [11].

Criteria	**A**lternatives	**U**ncertainties	**S**takeholders	**E**nvironment
What are essential criteria for evaluating the treatment alternatives?	What are the treatment alternatives currently available? What are the differences between treatment alternatives?	What are the uncertainties to consider by reimbursement decision-making?	Who is the patient (characteristics)? Who are the other stakeholders able to influence the decision or influenced by the decision?	What are the influencing environmental factors?
Therapeutic impact (OS, PFS, ORR, DOR); QoL; Safety; Restrictions; (contraindications, interactions); The general condition of the patient; Cost-effectiveness; Posology administration;	Chemotherapy combinations; Stereotactic radiation therapy; Palliative care; Alternative care; Participation in a clinical trial.	Adverse events; The number of elderly patients in Estonia; The risk and time, duration of adverse effects; The right instrument to measure QoL; Patients preferences and risk willingness; Long-term efficacy;	Patient; Doctor; Payer; Regulator; Politicians; Pharma industry; Charity funds; Decision-making committee; Society; Taxpayers.	First two treatment months the patient is incapable of work; During the rest of the treatment, the patient can work; No caregiver needed; After treatment, the patient needs a caregiver;

Socioeconomic impact.	Actual patient pool; Treatment duration.	Psychological burden to patients and families.

4.2.2 mTNBC value tree

The final version of the mTNBC value tree was achieved after the third iteration. First, the generic value tree from The AVF [25] was offered to stakeholders to support the discussion and was sent to all participants via e-mail before the first focus group seminar (see Appendix 6). The preliminary generic value tree for mTNBC included five criteria clusters: the burden of disease, therapeutic impact, safety profile, innovation level, and socioeconomic impact [25]. Additionally, the attributes previously evaluated in application No. 1417 were added to the generic value tree.

In the first focus group seminar, the burden of disease was excluded from the value tree. The spill-over effect and mechanism of action criteria were removed; only the posology was judged to be relevant in the innovation level cluster. The direct medical cost criterion was considered important but was not included in the value tree because the aim was to calculate the total weighted preference value score, which later can be compared to the costs. The initial mTNBC value tree after problem structuring is shown in Figure 4.

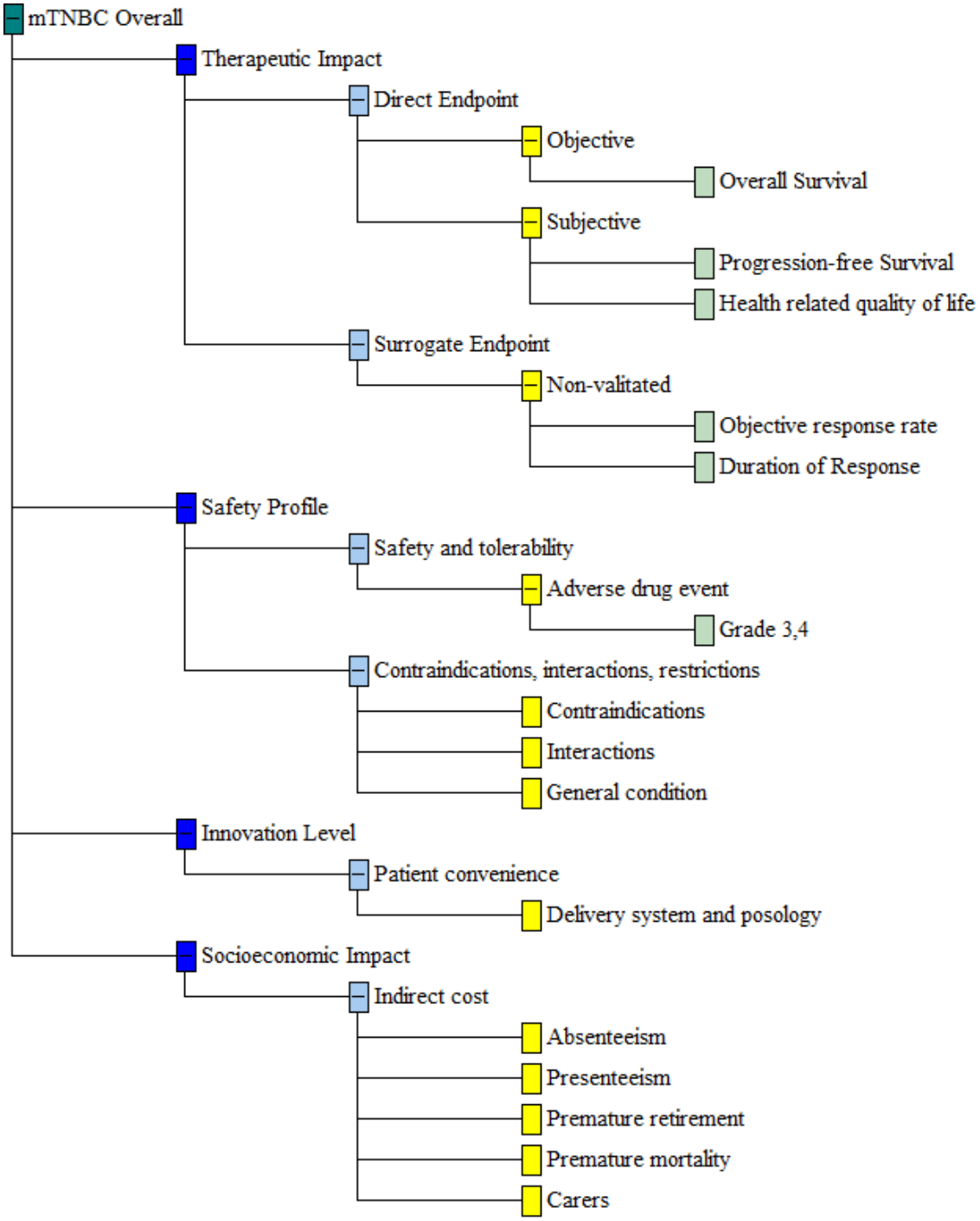


Figure 4. mTNBC value tree after problem structuring (image from M-MACBETH software).

After the second iteration, the immeasurable criteria were removed from the value tree. The socioeconomic impact cluster and the general condition criteria were removed. The mTNBC value tree with measurable attributes is shown in Figure 5.

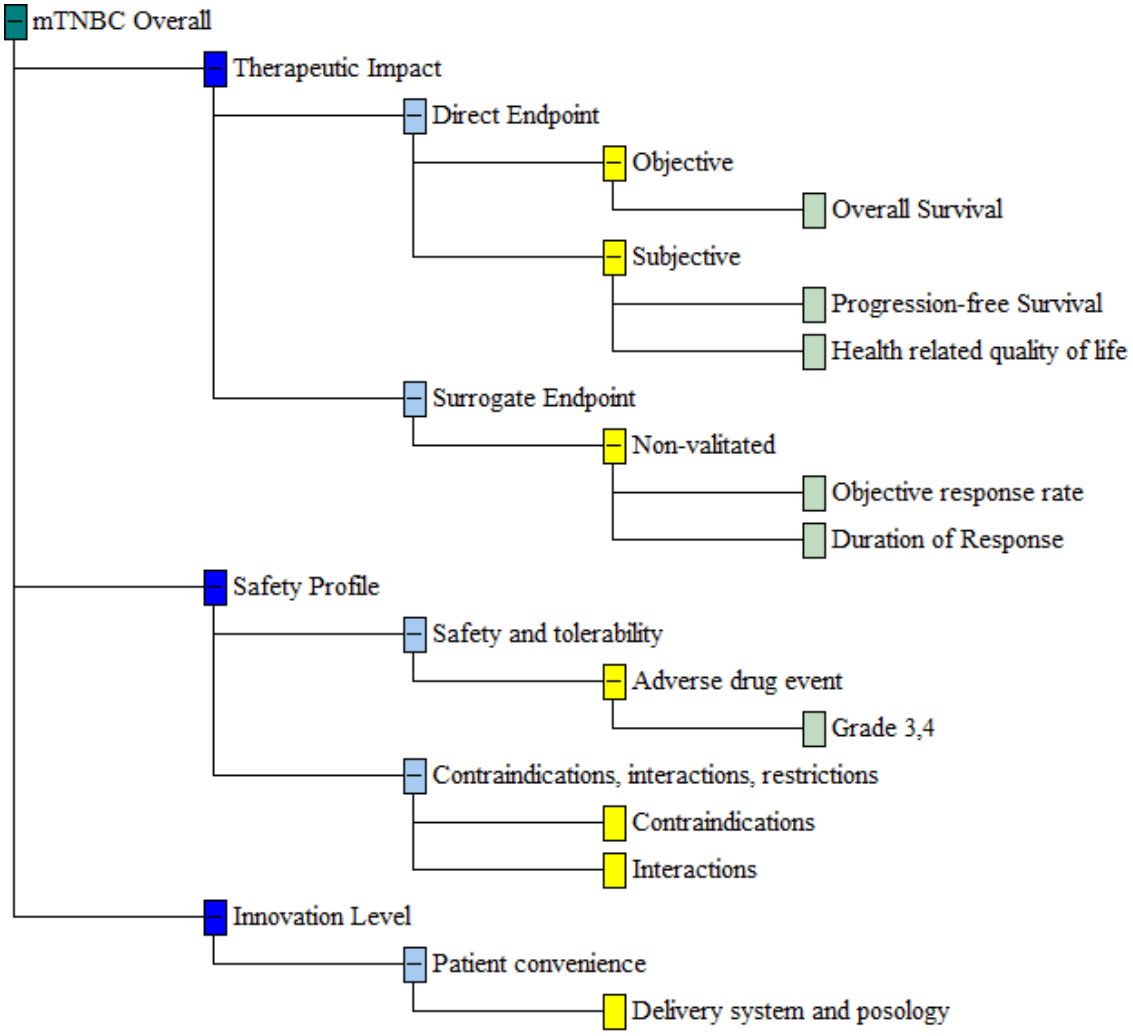


Figure 5. mTNBC value tree with measurable attributes (image for M-MACBETH software).

Afterwards, the criteria were assessed to determine if there are some preference-dependent, redundant, or overlapping criteria in the value tree. Health-related quality of life (HQoL), adverse drug events grade 3 – 4, contraindication and interactions were considered redundant because both treatment alternatives reached a similar performance level. The criteria duration of response (DOR) and progression-free survival (PFS) were considered overlapping, and the criterion DOR was removed from the value tree. The final mTNBC value tree contains two criteria clusters, therapeutic impact and innovation level, with four attributes, shown in Figure 6.

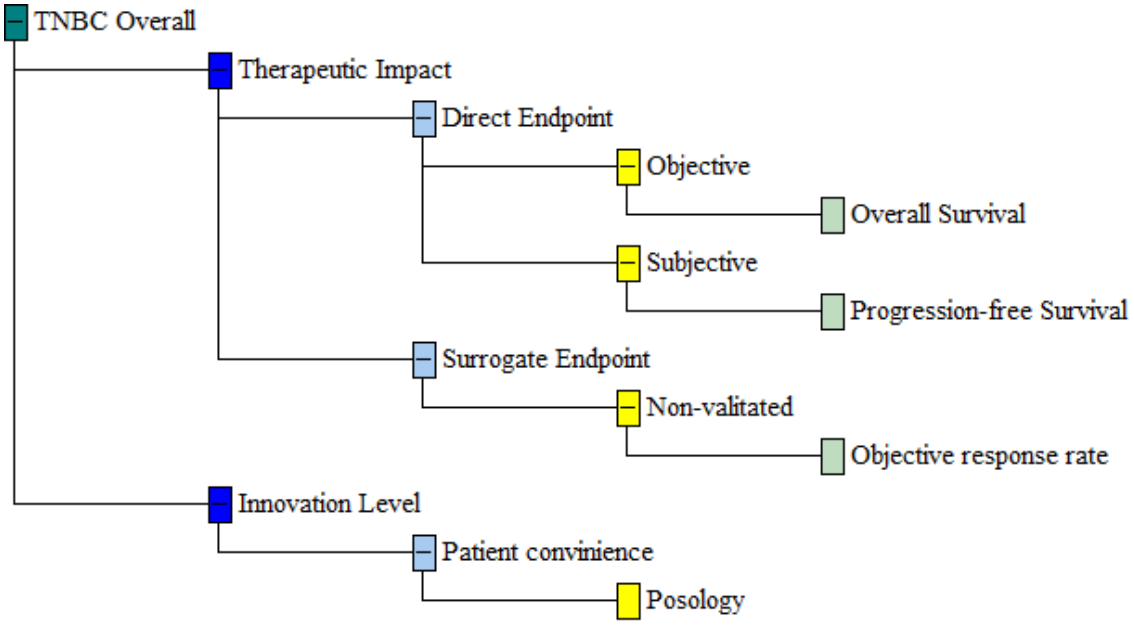


Figure 6. Final value tree for mTNBC (image from M-MACBETH software).

4.2.3 mTNBC performance matrix

The performance matrix includes two treatment alternatives: Nab-paclitaxel and Atezolizumab + Nab-paclitaxel. The validated performance attribute definitions are shown in Appendix 7. The references for the performance data are shown in Appendix 8. The 95% confidence interval (CI) values were used to define the attributes "lower" and "higher" performance levels, which act as anchors in the weighting scale and count for 0 and 100 scores. The final mTNBC treatments performance matrix is shown in Table 2.

Table 2. mTNBC performance matrix.

Attribute	Metric	Lower Level	Basis	Atezolizumab + Nab-paclitaxel	Nab-paclitaxel	Higher level	Basis
OS	month	13.6	CI 95%	24.5	17.9	30.7	CI 95%
PFS	month	3.8	CI 95%	7.5	5.3	9.2	CI 95%
ORR	%	35.4	CI 95%	58.9	42.6	66.1	CI 95%
Posology	28-day cycle time / hour	2.6	best performance	2.6	1.5	1.5	worst performance

4.2.4 mTNBC treatment alternatives scores

The focus group members scored both treatment alternatives, and Atezolizumab + Nab-paclitaxel scored highest in all criteria besides the posology. The scores for treatment alternatives are shown in Figures 7 and 8.

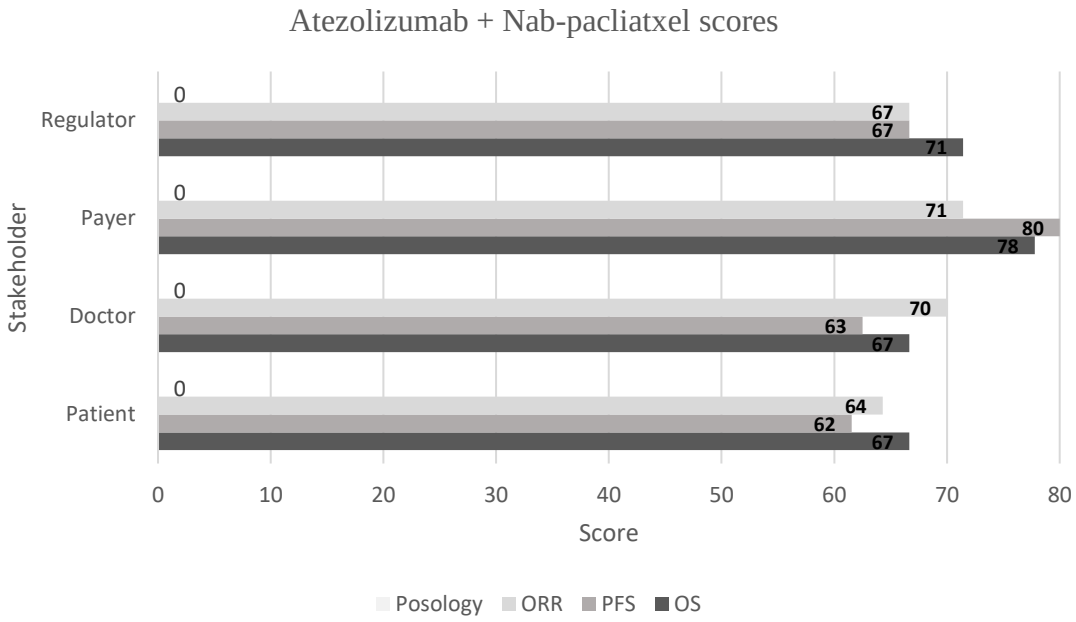


Figure 7. Atezolizumab + Nab-paclitaxel criteria scores.

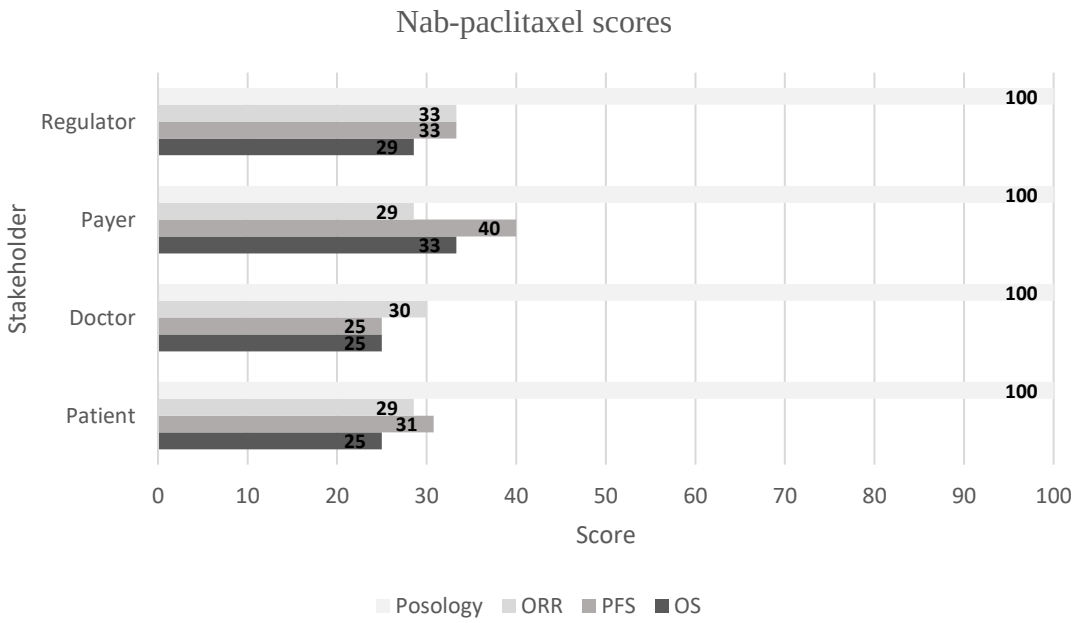


Figure 8. Nab-paclitaxel criteria scores.

4.2.5 mTNBC criteria weights

Focus group members judged the relative importance of criteria by weighting. The ranking of the value criteria differed between the participants. All stakeholders besides the patient ranked the criteria overall survival (OS) highest. The weights for OS were in the range of 35 – 63. The PFS was ranked highest by the patient and as second-highest by all other stakeholders. The weights for PFS were in the range of 16 – 40. The weights for objective response rate (ORR) were in the range of 7 – 20. The weights for posology were in the range of 2 – 16. The weights assigned to the criteria are shown in Figure 9.

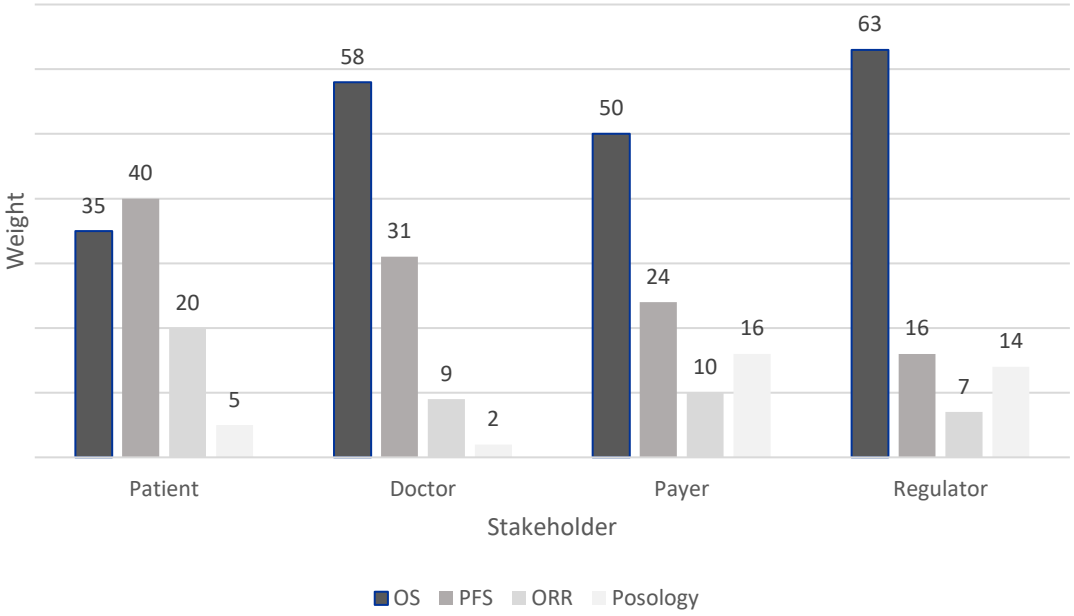


Figure 9. The stakeholder criteria weights.

4.2.6 mTNBC treatment alternatives weighted preference value scores

The scores and weights were combined, calculating the weighted preference value (WPV) scores for both treatment alternatives are shown in Figure 10. Between the two treatment options, Atezolizumab + Nab-paclitaxel scored highest, with the WPV score in the range of 61 – 65. Nab-paclitaxel overall WPV score was in the range of 27 – 45.

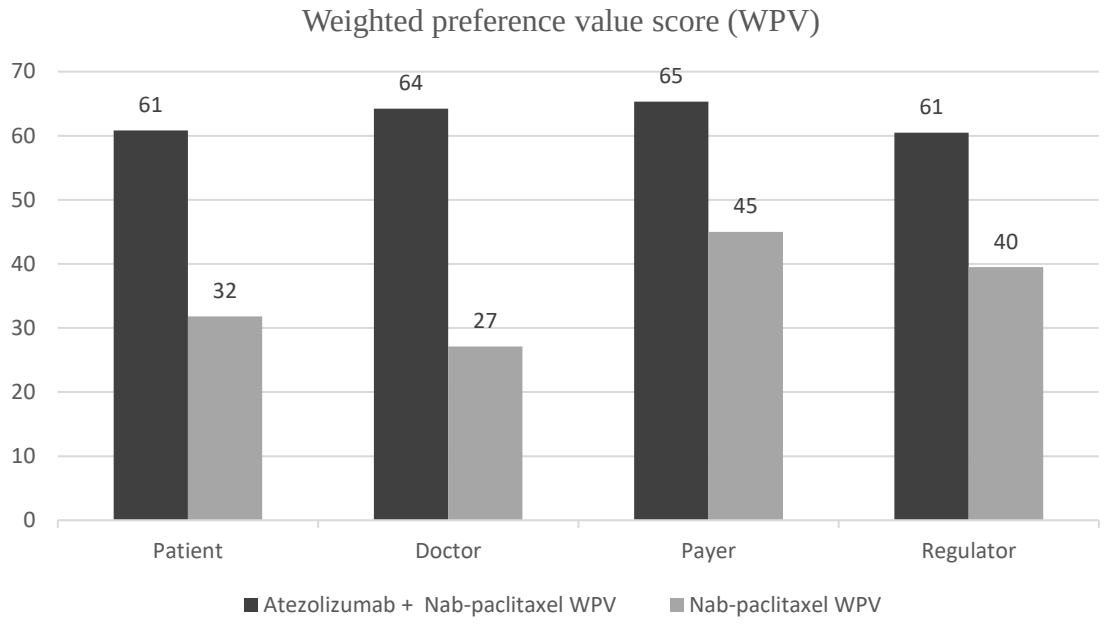


Figure 10. mTNBC treatment alternatives WPV scores.

4.2.7 Feedback questionnaire

From the four focus group members, three answered the questionnaire.

In the first section of the questionnaire, the participants were asked to express their opinion about the potential advantages and disadvantages of the MCDA. The answers are shown in Table 3.

Table 3. Questionnaire section 1 answers.

Advantage	**Disadvantage**
"Allows making the impression that the assessment is done in more "scientific and methodological" bases."	"For common citizen abstruse. Too complicated and time-consuming, and because of that, in practice, hard to implement. The advantage compared to the current approach unclear."
"Effectiveness, safety, impact on the quality of life."	"Superficial, unrealistic."
"I believe that it is easier to use it by so-called widespread pharmaceutical reimbursement decision-making. It is possible to avoid focusing too much on one question, possible to consider several questions and impacts."	"Criteria assessment subjective (cost part: direct and indirect costs)."

In the second section of the questionnaire, the participants were asked to judge how well the core values of the MCDA theory came out during the focus group seminars. The evaluation was performed on a five-point scale (Appendix 5), and the summary reflecting the assessed MCDA core values with keywords is shown in Figure 11.

	Disagree			Fully agree
Question 1 *clear structure*		2 x	1 x	
Question 2 *disease-specific criteria*	2 x		1 x	
Question 3 *inclusive*	1 x		2 x	
Question 4 *transparent*	1 x	1 x	1 x	
Question 5 *simple, understandable*	1 x	2 x		

Figure 11. Questionnaire section 2 answers.

The third section questions focused on the potential use and added value of MCDA when used as part of HTA in Estonia. The questions did not get conclusive answers, but all respondents agreed that the assessment criteria must be disease-specific. There was no consensus on the need to include additional criteria into reimbursement decision-making (two considered it necessary, one did not). All agreed that it is vital to measure the importance of the different assessment criteria. The need to include the reference levels in the assessment was not clear for two respondents and was considered necessary by one. Whether the value score calculated with MCDA could be an alternative to the currently used quality-adjusted life year (QALY) got different answers. One respondent said: *"No. Both of them have their pros and cons. The value score is less validated and for the public even less clear."* The other noted: *"They could be used in parallel,"* and the third could not answer. Assessing the possible value of using the MCDA in Estonia, the answers differed ("yes", "no", and "did not know"). For the most likely disease area to utilize the MCDA in Estonia, one respondent commented: *"It is hard to say. We could try it in the area where the use of QALY is very complicated."* The other two could not answer.

5 Discussion

The aim of the thesis – to design and co-create an MCDA model and test through a practical case study the potential of the MCDA to add value to the current Estonian HTA process – was fulfilled. However, the set hypothesis that utilizing MCDA as part of the HTA allows the inclusion of a broader value dimension, is more transparent, inclusive, and structured, offering better and more informed decision-making than the current pharmaceutical reimbursement process, was not fully proven. The hypothesis was mainly tested through the case study process feedback after the focus group seminars; however, the shown benefits from the international research did not become apparent to the key stakeholders participating in the focus group seminars. The differences in the hypothesis and the respondents' opinions can be seen in Figure 11. The reasons behind the different opinions can vary. One plausible explanation can be that when testing a new process, especially as complex as MCDA, all the benefits cannot be revealed at once, and it requires more profound understanding and experience to draw the final conclusions for the mentioned benefits. Another aspect can be that MCDA is a compound process and needs multiple iterations. Thus, experts in their field, whose time is scarce, can also be hard-pressed for time and fearful for the uptake of the entire MCDA process. Possibly the author's novice in the field and as a moderator played a role as well. All in all, it can also be that the shown benefits would not be revealed strongly in the Estonian setting at all.

One of the main results that emerged from the thesis is the full overview of the MCDA model building process with the theoretical foundation, including the eight steps explained in detail in chapters 4.1.1 – 4.1.8. Moreover, the chapters answer the primary research question from the induction phase: *"What are the necessary steps for building a valid and transparent multi criteria evaluation model?"* However, understanding the model-building steps is just the beginning of the MCDA designing process. There are many different MCDA techniques available, and all have strengths and weaknesses. The MACBETH technique was used in the case study because it had supporting software M-MACBETH, and it was previously used in some studies identified with literature review. Furthermore, MACBETH uses semantic scoring scales, which is considered to reduce the

cognitive load for assessors. However, it can be argued that using a different MCDA technique would have resulted non-identical results, either given more weight on the use of MCDA and it's possible benefits or even less.

The second research question in the induction phase: *"What are the values, criteria, and attributes to include in the MCDA,"* was answered by the state of the art review, and later during the focus group discussions by identification of the criteria and attributes relevant to the case study. The more detailed arguments and insights of why these criteria and attributes were selected in the case study are discussed in chapter 5.1.

In regard to the deduction phase research questions, the principal query the author was most interested in was asked by the third research question: *"What are the differences in reimbursement process and outcome when adopting the MCDA as part of HTA?"* This question needed to have the combination of both induction and deduction phase knowledge. Before the differences are brought out, the author also saw some similarities when comparing the MCDA literature with the current HTA process in Estonia which are worth pointing out. Firstly, some aspects of the CAUSE checklist are discussed in the current reimbursement process; secondly, many same essential criteria are evaluated. Additionally, the current reimbursement decision-making is done in a multi-stakeholder group. Even though there are some similarities within the processes, the author also perceives many additional advantages for the use of MCDA, thereby answering the research question. Contrary to the current HTA process, where the assessment criteria are defined by law, MCDA promotes defining the assessment criteria based on the decision problem. In theory, an exhaustive problem structuring process to map all the relevant aspects first and later focusing on how to measure them helps to concentrate on the ideal outcome and will influence the decision-making process and also helps to identify the assessment criteria [11], [20]. Instead of assessing the criteria that we can and should measure, the process focuses on what is essential to measure. The problem structuring also helps to identify the gaps in the assessment and points out the topics that might need the involvement of additional experts.

In the current HTA process, the driving metric for decision-making is ICER, calculated as cost per QALY, which has been used for over 40 years and is the standard for economic evaluation in many countries, including Estonia [31]. The QALY is the only benefit

included in the calculation. Other values are addressed just in the discussion and not involved in the actual value calculation. However, the QALY cannot capture the holistic value of the treatment. In some cases, like rare diseases, the lack of cost-effectiveness does not mean that the benefit for the patient is marginal, and the access to treatment should be rejected [32]. The MCDA has a different approach for cost-effectiveness calculation using the incremental cost-value ratio (ICVR) [22]. The ratio calculation includes all relevant assessment criteria, different stakeholders' preferences [11], [20], and therefore is a more value-based approach.

Although the current HTA process includes relevant criteria, it does not involve transparent measurement of the importance of these criteria. Making transparent trade-offs between criteria is not possible. However, the MCDA allows transparent measurement of the importance of criteria and enables transparent trade-offs between criteria [11], [20], [25], [28], which makes it possible to incorporate the relative importance of various value dimensions, involve different stakeholders' preferences, and assure transparency [2], [29]. Next to the quantitative weights assigned across different evaluation criteria, when measuring the performance of treatment alternatives, MCDA allows constructing the scoring scales that consider a broader context by defining the "higher" and "lower" reference levels. There are different ways to define the "higher" and "lower" levels of the scoring scale. For example, it can be based on the available real-world data (RWD) or best supportive care data; additionally, experts can define it.

5.2 Review on the mini focus group

This chapter will share more details of the focus group discussions (covering the six steps of MCDA model building), participants' opinions, and value preferences. Moreover, it answers the following research questions: *"How to assign transparent and structured measures to the MCDA model?"* and *"How different are the stakeholders' value preferences?"*

The first step of MCDA modelling is problem structuring, which starts with mapping the involved stakeholders, treatment alternatives, environment, and uncertainties, then defining the assessment criteria and attributes, which are most suitable to measure the treatments' overall value. The focus group problem structuring discussion was inspiring

and patient-centric, concentrating on the value for the patient and society. Moreover, the mTNBC patient profile was described – a young patient with fast-progressing, usually non-curable disease. Additionally, all the stakeholders that could influence the decision-making or who would be influenced by the decision were mapped. The need to involve patients with different cancer types in the decision-making and prioritization process was emphasized. *"I really would like to know what the Estonian patient says. What is missing? Who to prefer?"* Involving patients can give a more profound understanding of what matters to patients. The patients representative empathized: *"The time that is additionally given, or what exists, should be in every way comfortable and good [---] Let the remaining time be shorter but with high-quality."*

The focus group also found it essential to add broad stakeholder groups like society and taxpayers to the stakeholder map, pointing out the importance of understanding the overall societal preferences, priorities, and the benefits new treatments can bring to society. It is understandable, that prioritization in healthcare will always remain challenging, especially in a small country like Estonia, where the investment into healthcare is below the European average. However, Estonian patients have access only to 31% of new innovative medicines approved by EMA (see Figure 1) [8]. The possibility to make more innovative pharmaceuticals available for patients also calls for additional investment, and the taxpayers must be willing to contribute more. These broad stakeholders are influential and should be considered by decision-making. The current HTA process does not include this kind of stakeholder mapping.

Evaluating the available treatment alternatives, their advantages, and disadvantages is essential and present in both assessment processes, in MCDA, and in HTA. The alternatives currently available for mTNBC patients are different chemotherapy combinations, achieving the survival median of 12 – 18 months [24]. The focus group discussed that the immunotherapy treatment duration is not precisely known and needs further investigation.

The MCDA problem structuring includes mapping the environmental factors influenced by the reimbursement decision-making. These environmental factors get little attention in the current reimbursement process, but their indirect impact on the overall value of treatment should not be overlooked. The disease and treatment are affecting the patient

and the environment around her, including her family. The family members often must make some changes to their daily lives, such as finding time to transport the patient to the hospital for infusion or hiring a caregiver. The focus group discussed how the mTNBC could influence the patients' family and work-life. During the first couple of months of the treatment, the mTNBC patients are usually incapable of working. However, most patients will go back to work afterwards. When the treatment stops, the patient is usually again incapable of working and might need a caregiver to help her. Besides, there is a heavy psychological burden for patients and their families.

The following aspects mapped during the MCDA problem structuring are treatment-related uncertainties, which are discussed at some level in the current HTA process. In a focus group, the discussion involved the following uncertainties: the long-term treatment effects, quality of life, the number of patients, the actual duration of treatment, and the budget impact. Additionally, the group discussed how to define the right instrument to measure the quality of life. *"What is the instrument used to measure it? What exactly does it measure? On the one hand, we wish for something that could be used for all diseases equally, and on the other hand, we know that it is not sensitive enough to capture the disease-specific changes."* The focus group further discussed how to determine what the patients want and what is their level of risk-willingness. *"We often assume what patients want. We have not measured patients' preferences."* Measuring the patients' preferences and risk-willingness is important but a challenging task. The preferences can depend on the patient's disease, how far it has progressed, age, family status, and multiple other factors.

The final step of the MCDA problem structuring is to define the assessment criteria, which considers all previous mappings and can support the measurement of the treatment's overall value. The focus group received some supporting materials before the first seminar: the reimbursement application No. 1417 [24] (where the same mTNBC treatment alternatives were assessed with the current HTA assessment criteria) and the generic value tree from The AVF [25]. The materials were offered to initiate the discussion and provide some additional examples of assessment criteria used in other countries. All the assessment criteria in the current reimbursement process are relevant, and they are also included in most of the MCDA studies. The criteria clusters of therapeutic impact and safety profile were considered very important by the focus group.

Additionally, the group discussed the need to include the assessment of the patients' general condition as a criterion. *"What we should include more often, is that we are also assessing the patients' general condition while evaluating the treatments, and include as well her list of comorbidities and concomitant medications."* The assessment of contraindications and interactions was also considered essential. One participant said: *"For me, it is one thing that describes the treatments universal goodness."* All these criteria are discussed during the current reimbursement decision-making, but not all are included in the actual calculation of the benefit or value score.

The treatments' direct medical costs were not included as a separate criterion in the value tree. The value tree was constructed to obtain the pure overall value score of the treatments, which later can be compared to costs. Understandably, the payer needs to assess the budget impact and affordability of treatments and understand the incremental benefit and cost of the new treatment. MCDA allows the calculation of the incremental cost-value ratio (ICVR). The difference between ICVR and currently used ICER is that it uses WPV (weighted preference value score) instead of QALY. The benefit of the latter is discussed on page 42.

There are contradictory opinions on how to assess the value of the innovation in healthcare and whether it should be separately considered during the reimbursement decision making. Many MCDA studies have defined innovation as a separate assessment criterion and have identified different attributes for performance measurement. The most common attributes are the mechanism of action, spill-over effect, and patient convenience [25]. In the Estonian reimbursement process, only the pharmaceutical administration regime is described. However, patient convenience is not yet considered as an essential value factor by decision-makers. The focus group decided to include patient convenience as a criterion for assessment but concluded that innovation must be translatable into the therapeutic impact, and there is no need to separately measure other innovation attributes. Nevertheless, it was discussed that the posology criterion should get less weight as the infusion's frequency is the same for both treatment alternatives. Only the infusion time and the length of the stay in the hospital was different between treatment alternatives.

The mTNBC treatments are end-of-life treatments, and the alternatives currently available for patients are just chemotherapy combinations. In many countries, the HTA

for these treatments includes the equity concerns like rarity and unmet need. Discussing the importance of the criteria burden of disease and unmet need, the focus group concluded that this assessment requires societal agreement and priority setting. *"How should it be, if it is end-of-life treatment or beginning-of-life treatment, which one is better?"* When allocating additional funds to one disease area, fewer resources can be allocated for other disease areas. However, some areas like rare diseases need exceptions. *"One thing is how these treatments are at all allowed to the market. We cannot demand from them the same things that we request from the usual treatments. The other thing is that somehow the industry must earn back their costs …. the question is that we have crossed the line in both dimensions; reasonable sums are not asked for them anymore."* Knowledge about the diseases is increasing, as well as the ability to diagnose them more precisely. The treatments are personalized, targeting minor patient populations, and as a result, more treatments can be defined as rare disease treatments. There is a need to find a healthy balance between the pharmaceutical companies earning back their research and development investments and the affordability for the healthcare system.

The criteria cluster socioeconomic impact was considered necessary by the focus group. The current Estonian HTA process includes this criterion, but there is no good process for systematic data gathering to support the performance measurement of treatments. Currently, the reimbursement application submitter is responsible for providing data about the socioeconomic impact. However, there is a possibility to gather data on early retirement and absenteeism from the EHIF database. The issue remaining is how to connect this data with the pharmaceuticals during the reimbursement process.

The first iteration of problem structuring in the focus group resulted in a value tree including all essential criteria for assessing the mTNBC treatments (shown in Figure 4). However, for socioeconomic impact cluster and general condition criterion, the attribute or evidence to measure the performance of the treatment alternatives could not be assigned. These criteria were excluded from the value tree, and the possibility of involving these criteria requires further research.

According to MCDA methodology, all criteria must possess specific properties, including nonoverlap, nonredundancy, and preference independence [11]. Comparing the mTNBC treatment alternatives and assessing their performance, the focus group concluded some

criteria redundant: quality of life and all criteria under safety profile. The grade 3 – 4 adverse events were experienced in the Atezolizumab + Nab-paclitaxel treatment group by 49.4% of patients and in the Nab-paclitaxel + placebo group by 42.8% of patients [24]. The difference between the two groups was just 6%, which was considered clinically irrelevant. Comparing the contraindications and the interactions, the focus group believed, that there is no such difference based on which one treatment could be preferred. PFS and DOR's attributes were considered overlapping, and only PFS as the direct endpoint was included in the final value tree. It was also emphasized that the criteria ORR should get less weight: *"The response rate can be very short while cost very much."* In the current HTA process, these property rules are useless as the benefit score is calculated only based on the quality of life and survival attributes. However, in the context of the MCDA, the criteria property rules assure that one value dimension does not get too much attention. Excluding the redundant criteria reduces the assessment burden. When the alternatives achieve the same performance level on criterion, it will not affect the difference between their overall value score.

The final mTNBC value tree includes four attributes. The number of attributes in the final value tree is not significant, and the value tree could be improved by finding the missing attribute information and evidence. Nevertheless, the aim should not be to measure every criterion but to measure all meaningful criteria.

When measuring the performance of treatment alternatives, the focus group decided to define the therapeutic impact criteria cluster scoring scales "lower" and "higher" reference levels, using the 95% CI from the clinical trial. The RWD for mTNBC treatments was not available, and the use of the best supportive care data was not possible as the specific data for the PD-L1 positive patients was missing.

One of the thesis research questions was: *"How different are the stakeholders' value preferences?"* Hence, in the case study, all the focus group members gave their individual judgments. Even though only four criteria and four stakeholders were involved in the final assessment, the judgments still differed. The highest-ranked criterion for doctor, payer, and regulator was OS. For the patient, the most important criterion was PFS, even though the treatment alternatives performance difference was just 2.2 months [24]. This illustrates well why it is crucial to involve all relevant stakeholders and their value

judgments. The assessment process can be considered subjective, as judgments depend on the stakeholders' preferences. However, it can also be argued that not calculating the scores is even more subjective as in this case, the value judgments are only in stakeholders' heads, and there is no clear understanding of the importance of criteria.

The feedback received after the focus group seminars showed that the MCDA has potential for some participants at some level. However, the concrete disease areas where the use of the MCDA would be most valuable were not identified. Furthermore, the model itself needs to be improved by finding the missing attribute information and evidence to measure all criteria considered essential by the focus group.

5.3 Limitations and biases

The study results should be interpreted carefully, considering it as a first iteration of the MCDA model designing process. The results should be considered a minimum viable product (MVP), not a final model.

The small number of focus group participants can be perceived as one limitation. The focus group included only the key stakeholders, and the study was done as a simulation exercise, not an actual reimbursement decision-making process. Also, it was the first MCDA co-creation experience for all the participants, which certainly creates several limitations. The participants had limited knowledge and difficulties understanding all MCDA model building tasks, and the theoretical overview of MCDA was relatively short. Additionally, not all participants were thoroughly acquainted with the current HTA process. Furthermore, the facilitation skill and the restrictions coming from the virtual meeting can affect the study results. Finally, the author had no prior experience in moderating this kind of seminar on the topic.

The strength of the evidence can be considered as a limitation. The lack of evidence and the limited time to perform the more profound research were the reasons why some attributes were not included in the final value tree. There was little clinical evidence available for the PD-L1 immune cell-positive patients subgroup. The assessments of the socioeconomic impact and patients' general condition were not performed due to a lack of performance evidence.

Possible bias may arise because the author's views on the process can be influenced by employment in a pharmaceutical company and because one of the case study treatment alternatives belongs to the pharmaceutical company's product portfolio.

5.4 Future research

The practical case study focused only on the problem structuring and model building, sensitivity analysis, robustness analysis, and development of action plan were out of scope, and a follow-up case study is needed.

Analyzing the process and the results of the case study, the following areas for future investigation were identified:

- The need to identify the most relevant disease areas where utilization of MCDA can give the most significant benefit in Estonia.
- Several criteria were not included in the assessment, as they were missing a good attribute or evidence for performance measurement. There is a need to investigate further how these criteria can be measured and included in the MCDA model.
- When the payer wishes to use the incremental cost-value ratio (ICVR), there is a need to investigate how to determine relevant thresholds for ICVR.
- To minimize the administrative burden of decision-makers, the investigation of possible assisting tools should be conducted, finding out the possible alternatives for M_MACBETH and listing the advantages and disadvantages of the different tools.

6 Conclusions

The thesis attempts to start a discussion on the current reimbursement process in Estonia and gives a thorough theory by the state-of-the-art review on possible benefits of including MCDA in the HTA process. Moreover, it is an example of design science research. The aim of the thesis was fulfilled, and all the research questions posed prior to the study were answered. The hypothesis was not fully proven, but the case study is an initial MVP showing the need for further action with research and discussion on the evaluator level.

The study's central argument is that the core of the HTA should be to measure the holistic value of treatments. The assessment of novel personalized treatments requires advancements in reimbursement decision-making processes. However, the decision-makers need to acknowledge that the current HTA process is not sustainable and requires improvements. As per exhaustive literature review, using the MCDA as part of HTA can help to map all relevant aspects for decision-making, identify the criteria contributing the most to the overall value score of the treatment and engage relevant stakeholders in balanced and transparent decision-making.

By the mini focus group seminars and feedback questionnaire for the explicit case study, this research provides insights into the stakeholders' value perceptions and their opinions on what needs to be improved in the current reimbursement process. Even though the focus group participants' feedback did not provide conclusive answers about the potential value of using the MCDA in Estonia, some aspects of MCDA, like the inclusion of disease-specific assessment criteria and transparent measurement of these criteria, were considered important by all respondents. There was no consensus on whether MCDA should be included in the current HTA process and what would be the disease area where the utilization of MCDA would be most beneficial. Currently, only a subset of benefits and costs are included in the assessments. The HTA is not considering all long-term benefits to society, achieved with timely and patient-centric care. The complex discussion around the equity in healthcare and assessing the criteria like the burden of disease, unmet need, disease severity is highly dependent on society's priorities and willingness to invest.

However, the meaning of these criteria must be defined and understood by all involved stakeholders unambiguously; only after that, the valid measurement attribute can be chosen. Value-based decision-making should focus on finding the possibilities to measure all relevant assessment criteria transparently.

All in all, the MCDA model building process is very complex and requires several iterations to identify all relevant attributes and back up the appraisal with high-quality evidence to reduce the subjectivity inherent in all decision-making. Hence, the current MCDA model needs improvements which can be achieved by future research.

▪ Acknowledgments

I would like to express my sincere gratitude to my supervisor Riina Hallik and co-supervisor Tanel Ross for their support and guidance throughout the thesis writing process.

Furthermore, I would like to thank Anneli Elme, Riina Laurimaa, Alar Irs, Erki Laidmäe for participating and contributing to the focus group seminars.

Last but not least, special thanks go to my family and friends for their encouragement, support, and patience.

▪ References

[1] The World Bank, “Current health expenditure (% of GDP) - European Union | Data.” [Online]. Available: https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS?locations=EU. [Accessed: 10-Feb-2021].

[2] A. C. Mühlbacher and A. Kaczynski, “Making Good Decisions in Healthcare with Multi-Criteria Decision Analysis: The Use, Current Research and Future Development of MCDA,” *Appl. Health Econ. Health Policy*, vol. 14, no. 1, pp. 29–40, 2016.

[3] Eesti Haigekassa, “Eesti Haigekassa majandusaasta aruanne 2019.” [Online]. Available: https://www.haigekassa.ee/haigekassa/majandusaruanded-ja-eelarve. [Accessed: 03-Jul-2020].

[4] Eesti Haigekassa, “Ravikindlustus.” [Online]. Available: https://www.haigekassa.ee/inimesele/ravikindlustus. [Accessed: 25-Nov-2019].

[5] T. Habicht, M. Reinap, K. Kasekamp, R. Sikkut, L. A. Ewout, and V. Ginneken, “Health Systems in Transition Estonia Health system review,” 2018. [Online]. Available: www.healthobservatory.eu. [Accessed: 25-Nov-2019].

[6] Eesti Haigekassa, “HAIGLARAVIMITE KOMISJONI KOOSOLEKU PROTOKOLL 08.07.20,” 2020. [Online]. Available: https://www.haigekassa.ee/haiglaravimite-komisjoni-koosolekute-protokollid. [Accessed: 21-Nov-2020].

[7] Riigi Teataja, “Eesti Haigekassa tervishoiuteenuste loetelu kriteeriumide täpsem sisu ning kriteeriumidele vastavuse hindajad, tervishoiuteenuste loetelu hindamise tingimused ja kord, tervishoiuteenuste loetelu komisjoni moodustamine ja töökord ning arvamuse andmise kord.” [Online]. Available: https://www.riigiteataja.ee/akt/114072018010. [Accessed: 12-Feb-2020].

[8] European Federation of Pharmaceutical Industries and Associations, “EFPIA Patients W.A.I.T. Indicator 2019 Survey.” [Online]. Available: https://www.efpia.eu/publications/downloads/efpia/efpia-patients-wait-indicator-2019-survey/. [Accessed: 10-Feb-2021].

[9] R. L. Keeney and H. Raiffa, *Decision analysis with multiple conflicting objectives*. New York, NY: Wiley& Sons, 1976.

[10] J. S. Hammond, R. L. Keeney, and H. Raiffa, *Smart Choices: A Practical Guide to Making Better Life Decisions*. New York, NY: Broadway Books, 1999.

[11] V. Belton and T. J. Stewart, *MULTIPLE CRITERIA DECISION ANALYSIS An Integrated*

Approach. USA: Kluwer Academic Publishers, 2003.

[12] World Health Organization, “Cancer.” [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/cancer. [Accessed: 20-Dec-2019].

[13] European Commission, “2020 Cancer incidence and mortality in EU-27 countries | EU Science Hub.” [Online]. Available: https://ec.europa.eu/jrc/en/news/2020-cancer-incidence-and-mortality-eu-27-countries. [Accessed: 21-Nov-2020].

[14] Tervisestatistika ja terviseuuringute andmebaas, “PK10: Pahaloomuliste kasvajate esmasjuhud paikme, soo ja vanuserühma järgi. PxWeb.” [Online]. Available: https://statistika.tai.ee/pxweb/et/Andmebaas/Andmebaas__02Haigestumus__04PahaloomulisedKasvajad/PK10.px/table/tableViewLayout2/. [Accessed: 03-Jan-2021].

[15] National Breast Cancer Foundation, “Triple Negative Breast Cancer.” [Online]. Available: https://www.nationalbreastcancer.org/triple-negative-breast-cancer. [Accessed: 21-Nov-2020].

[16] S. Van Thiel, *Research methods in public administration and public management: An introduction*. Routledge, 2014.

[17] D. L. Morgan, “Paradigms Lost and Pragmatism Regained: Methodological Implications of Combining Qualitative and Quantitative Methods,” *J. Mix. Methods Res.*, vol. 1, no. 1, pp. 48–76, 2007.

[18] A. Hevner and S. Chatterjee, *Design Research in Information Systems Theory and Practice*. New York, NY: Springer Science+Business Media, 2010.

[19] J. W. Creswell, *RESEARCH DESIGN Qualitative, Quantitative, and Mixed Methods Approaches*. SAGE Publications, 2009.

[20] K. Marsh *et al.*, “Multiple Criteria Decision Analysis for Health Care Decision Making--Emerging Good Practices: Report 2 of the ISPOR MCDA Emerging Good Practices Task Force.,” *Value Health*, vol. 19, no. 2, pp. 125–37.

[21] “PRISMA flow diagram. Presentation of the procedure of literature... | Download Scientific Diagram.” [Online]. Available: https://www.researchgate.net/figure/PRISMA-flow-diagram-Presentation-of-the-procedure-of-literature-searching-and-selection_fig4_257302282. [Accessed: 19-Apr-2021].

[22] A. Angelis, G. Montibeller, D. Hochhauser, and P. Kanavos, “Multiple criteria decision analysis in the context of health technology assessment: a simulation exercise on metastatic colorectal cancer with multiple stakeholders in the English setting,” *BMC Med. Inform. Decis. Mak.*, vol. 17, no. 1, p. 149, Oct. 2017.

[23] A. J. Onwuegbuzie, W. B. Dickinson, N. L. Leech, and A. G. Zoran, “A Qualitative Framework for Collecting and Analyzing Data in Focus Group Research,” *Int. J. Qual. Methods*, vol. 8, no. 3, pp. 1–21, Sep. 2009.

[24] Eesti Haigekassa, “Loetelu muutmine 2013-2021 | EESTI HAIGEKASSA

TERVISHOIUTEENUSTE LOETELU MUUTMISE TAOTLUS KOOS TÄITMISJUHISTEGA nr. 1417." [Online]. Available: https://www.haigekassa.ee/partnerile/raviasutusele/tervishoiuteenuste-loetelu/loetelu-muutmine-2013-2021#tab-2020. [Accessed: 28-Dec-2020].

[25] A. Angelis and P. Kanavos, "Multiple Criteria Decision Analysis (MCDA) for evaluating new medicines in Health Technology Assessment and beyond: The Advance Value Framework," *Soc. Sci. Med.*, vol. 188, pp. 137–156, Sep. 2017.

[26] K. Marsh, M. Goetghebeur, P. Thokala, and R. Baltussen, Eds., *Multi-Criteria Decision Analysis to Support Healthcare Decisions*. Cham: Springer International Publishing, 2017.

[27] M-MACBETH, "M-MACBETH User's Guide," 2017. [Online]. Available: http://m-macbeth.com/demo/. [Accessed: 23-Feb-2021].

[28] P. Thokala *et al.*, "Multiple Criteria Decision Analysis for Health Care Decision Making—An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force," *Value Heal.*, vol. 19, no. 1, pp. 1–13, Jan. 2016.

[29] A. Angelis and P. Kanavos, "Value-Based Assessment of New Medical Technologies: Towards a Robust Methodological Framework for the Application of Multiple Criteria Decision Analysis in the Context of Health Technology Assessment," *Pharmacoeconomics*, vol. 34, no. 5, pp. 435–446, May 2016.

[30] R. L. Keeney, *Value-Focused Thinking*. London: Harvard University Press, 1996.

[31] L. P. Garrison, B. Zamora, M. Li, and A. Towse, "Augmenting cost-effectiveness analysis for uncertainty: The implications for value assessment—rationale and empirical support," *Journal of Managed Care and Specialty Pharmacy*, vol. 26, no. 4. Academy of Managed Care Pharmacy (AMCP), pp. 400–406, 01-Apr-2020.

[32] J. I. Drake, J. C. T. de Hart, C. Monleón, W. Toro, and J. Valentim, "Utilization of multiple-criteria decision analysis (MCDA) to support healthcare decision-making FIFARMA, 2016," *J. Mark. Access Heal. Policy*, vol. 5, no. 1, p. 1360545, Jan. 2017.

[33] A. Angelis, "Evaluating the Benefits of New Drugs in Health Technology Assessment Using Multiple Criteria Decision Analysis: A Case Study on Metastatic Prostate Cancer With the Dental and Pharmaceuticals Benefits Agency (TLV) in Sweden," *MDM Policy Pract.*, vol. 3, no. 2, pp. 1–17, 2018.

[34] M. Wagner *et al.*, "Appraising the holistic value of Lenvatinib for radio-iodine refractory differentiated thyroid cancer: A multi-country study applying pragmatic MCDA.," *BMC Cancer*, vol. 17, no. 1, p. 272, 2017.

[35] A. Jiménez, A. Ais, A. Beaudet, and A. Gil, "Determining the value contribution of selexipag for the treatment of pulmonary arterial hypertension (PAH) in Spain using reflective multi-criteria decision analysis (MCDA).," *Orphanet J. Rare Dis.*, vol. 13, no. 1, p. 220, Dec. 2018.

[36] P. Wahlster, M. Goetghebeur, S. Schaller, C. Kriza, and P. Kolominsky-Rabas, "Exploring

the perspectives and preferences for HTA across German healthcare stakeholders using a multi-criteria assessment of a pulmonary heart sensor as a case study," *Heal. Res. Policy Syst.*, vol. 13, no. 1, Apr. 2015.

[37] Y. Yu *et al.*, "Method Development for Clinical Comprehensive Evaluation of Pediatric Drugs Based on Multi-Criteria Decision Analysis: Application to Inhaled Corticosteroids for Children with Asthma," *Pediatr. Drugs*, vol. 20, no. 2, pp. 195–204, Apr. 2018.

[38] N. Zozaya *et al.*, "Determining the Value of Two Biologic Drugs for Chronic Inflammatory Skin Diseases: Results of a Multi-Criteria Decision Analysis," *BioDrugs*, vol. 32, no. 3, pp. 281–291, Jun. 2018.

[39] K. Kolasa, K. M. Zwolinski, V. Zah, Z. Kaló, and T. Lewandowski, "Revealed preferences towards the appraisal of orphan drugs in Poland - multi criteria decision analysis," *Orphanet J. Rare Dis.*, vol. 13, no. 1, p. 67, Dec. 2018.

[40] K. Marsh *et al.*, "Evaluation of COPD Treatments: A Multicriteria Decision Analysis of Aclidinium and Tiotropium in the United States," *Value Heal.*, vol. 20, no. 1, pp. 132–140, Jan. 2017.

[41] M. Mobinizadeh, P. Raeissi, A. A. Nasiripour, A. Olyaeemanesh, and S. J. Tabibi, "A model for priority setting of health technology assessment: The experience of AHP-TOPSIS combination approach," *DARU, J. Pharm. Sci.*, vol. 24, no. 1, Apr. 2016.

[42] M. G. M. Weernink, M. C. W. Vaanholt, C. G. M. Groothuis-Oudshoorn, C. von Birgelen, M. J. IJzerman, and J. A. van Til, "Patients' Priorities for Oral Anticoagulation Therapy in Non-valvular Atrial Fibrillation: a Multi-criteria Decision Analysis," *Am. J. Cardiovasc. Drugs*, vol. 18, no. 6, pp. 493–502, Dec. 2018.

[43] G. Iskrov, T. Miteva-Katrandzhieva, and R. Stefanov, "Multi-criteria decision analysis for assessment and appraisal of orphan drugs," *Front. Public Heal.*, vol. 4, no. SEP, Sep. 2016.

[44] Ravimiregister, "I LISA RAVIMI OMADUSTE KOKKUVÕTE TECENTRIQ." [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_et.pdf. [Accessed: 28-Mar-2021].

[45] Ravimiregister, "I LISA RAVIMI OMADUSTE KOKKUVÕTE ABRAXANE." [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/abraxane-epar-product-information_et.pdf. [Accessed: 28-Mar-2021].

▪ Appendix 1 – The state of the art review results

Assessment field	Criteria	Stakeholders	MCDA technique	Country	Source
Metastatic castrate-resistant prostate cancer treatments	Overall Survival, Health-related Quality of life, Radigraphis tumor progression, Treatment discontinuation, Contraindications, Delivery posology, Special instructions, Medical costs impact	Swedish Dental and Pharmaceutical Benefits Agency – one medical investigator, one pharmacist, and two health economists	MACBETH	Sweden	[33]
Metastatic colorectal cancer treatments	Overall Survival, Grade 4 EA, HRQol, Medical cost impact, Posology, ATC Level 4, Progression Free Survival, Marketing Authorisation, Phase 3 CT	Medical oncologist, consultant (community pediatrician), public health expert, pharmacist, health economist, HTA expert, medical statistician, patient, patient carer, patient advocate	MACBETH	England	[22]
Orphan drugs (radioiodine refractory differentiated thyroid cancer)	Disease severity, Size of affected population, Expert consensus/CPGs, Unmet needs, Comparative effectiveness, Comparative safety/tolerability, Comparative patient-perceived health/PROS, Type of preventive benefit, Type of therapeutic benefit, Comparative cost consequences - cost of intervention, Comparative cost consequences - other costs, Quality of evidence, Mandate and scope of healthcare system, Population priorities and access, Opportunity costs and affordability, System capacity and appropriate use of intervention, Common goal and special interests, Political, historical and cultural context, Environmental impact	Policy decision makers, specialists, patient representatives, methodologists with decision-making expertise	EVIDEM	France, Italy, Spain	[34]

Pulmonary Arterial Hypertension treatments	Disease severity, Unmet needs, Comparative efficacy/effectiveness, Comparative safety/tolerability, Comparative patient-perceived health/patient reported outcomes (PRO), Type of preventive benefit, Type of therapeutic benefit, Comparative cost of intervention, Comparative other medical costs, Comparative other non-medical costs, Quality of evidence Expert consensus/clinical practice guidelines (CPG), Population priorities and access, Common goals and specific interests, System capacity and appropriate use of intervention, Opportunity costs and affordability	Evaluators, clinicians, regional decision makers, hospital pharmacists, patients	EVIDEM	Spain	[35]
Pulmonary heart sensor	Relevance and Validity of evidence, Completeness and consistency of reporting, Impact on other spending, Cost-effectiveness of intervention, Budget impact on health plan, Type of medical service, Public health interest, Improvement of patient reported outcomes, Improvement of safety and tolerability, Improvement of efficacy/effectiveness, Comparative interventions limitations, Clinical guidelines, Size of the population affected by the disease, Disease severity	Health professionals, health policymakers, industry, citizens, researchers	EVIDEM	Germany	[36]
Pediatric asthma treatments	Guideline/HTA, SR/meta-analysis, RCT, Healthcare professional recommendation, Irreplaceability, Number of contraindications, Use restrictions, Reversibility of overdose, Common adverse reactions, Serious adverse reactions, Drug-drug/food–drug	Pediatricians, clinical pharmacists, pharmacists trained in pharmacoeconomics, pharmaceutical specialists, pharmacoepidemiology specialists, pharmacologists, drug policy and	AHP	China	[37]

	interactions, Width of therapeutic window, Suitability of dosage form, Suitability of strength, Drug instruction, Medicine packaging, Monitoring of medication, Dose frequency, Restriction conditions during dosing interval, Storage and transportation conditions, Drug dispensing and administration, Price, DDDc, Treatment course cost, Pharmacoeconomic evaluation, Protein binding rate and distribution characteristics, Necessity of a dose adjustment in cases of kidney or liver dysfunction, Gene polymorphism, Elimination half-life, Peak concentration, Time to peak, Bioavailability and bioequivalence	administration specialists			
Chronic Inflammatory Skin Disease treatments	Comparative effectiveness/efficacy, Disease severity, Unmet needs, Quality of evidence, Comparative PROs type of therapeutic benefit, Size of affected population, Comparative safety/tolerability, Type of preventive benefit, Comparative cost consequences - cost of intervention, Comparative cost consequences - medical costs, Comparative cost consequences - non-medical costs, Expert consensus/clinical practice guidelines	Clinicians (dermatologists), patients (two with severe psoriasis and two with severe AD), regional payers, health economist	EVIDEM	Spain	[38]
Orphan drugs treatments	Indication uniqueness, Disease rarity, Disease severity, Advancement of technology, Manufacturing technology, Therapeutic alternative, Scientific evidence for clinical efficiency, Benefits from use of medicine (safety aspects), Cost-effectiveness	The President of the HTA agency, members of the Appraisal Committee (representatives of the Ministry of Health, the National Health Fund, regulatory body, and patients ombudsman)	AHP	Poland	[39]

	analysis, Budget impact analysis, Therapy cost, HTA recommendations issued elsewhere, Rationalization analysis				
Chronic obstructive pulmonary disease treatments	Rescue medication use, Symptom severity, Early morning activity limitation, Night-time awakening, Exacerbations, Confirmation of dose delivered, Portability, Preloading, Dosing per day, Anticholinergic side effects, Cardiovascular side effects, Other side effects	Clinicians, pulmonologists, family practitioners	MAVT	USA	[40]
Supraventricular tachycardia and stroke treatments	Efficiency/effectiveness, Safety, Population size, Vulnerable population size, Availability of alternative technologies, Cost-effectiveness in other countries, Budget impact, Financial protection, Quality of evidence	Experts from official committee of HTA in Iranian ministry of health and medical education	AHP-TOPSIS	Iran	[41]
Oral Anticoagulants	Effectiveness, Out-of-pocket cost, Major bleedings, Minor bleedings, Gastrointestinal complaints, Routine blood monitoring, Food restrictions, Intake frequency, Pill type/intake instructions	Patients	AHP	Spain, Germany, France, Italy, United Kingdom	[42]
Orphan drugs	Health benefits, Clinical effectiveness, Life-saving, Safety, Alternative, Disease severity, Disease burden, Budget impact, Cost-effectiveness, Strenght of evidence, Vulnerable groups	Medical professionals, heading university hospital clinics, chair of rare disease patient organizations, health authorities (reimbursement decision-makers), market access and governmental affairs executives of pharmaceutical companies	AHP	Bulgaria	[43]

▪ Appendix 2 – Search strategy in databases PubMed, Google Scholar

<table>
<tr><td colspan="2">The search for the literature of MCDA studies in HTA, the following formula was adopted in PubMed: [(“A“ OR “C“ OR “D“ OR “E“ OR “F“ OR “G“) AND (“H“ OR “I“ OR “J“]. The fields used in PubMed were title and abstract.</td></tr>
<tr><td>A: ”multicriteria analysis“ OR “multi criteria analysis“ OR “multiple criteria analysis“</td><td>F: “MAUT” OR “multi attribute utility theory” OR “multi attribute decision analysis” OR “multi attribute decision making”</td></tr>
<tr><td>B: ”MCDA” OR “multicriteria decision analysis” OR “multi criteria decision analysis” OR “multiple criteria decision analysis”</td><td>G: “MAVT” OR “multi attribute value theory” OR “multi-attribute value theory”</td></tr>
<tr><td>C: “MCDM” OR “multicriteria decision making” OR “multi criteria decision making” OR “multiple criteria decision making”</td><td>H: “medical” OR “clinical” OR “hospital” OR “health”</td></tr>
<tr><td>D: “multicriteria decision aiding” OR multi criteria decision aiding” OR “multiple criteria decision aiding”</td><td>I: “drug” OR “pharmaceutical” OR medicine”</td></tr>
<tr><td>E: “multicriteria resource allocation” OR “multi criteria resource allocation” OR multiple criteria resource allocation”</td><td>J: “HTA” OR “health technology assessment” OR “health technology appraisal” OR “health technology evaluation” OR “benefit risk assessment” OR “value measurement” OR “value based measurement” OR “value assessment” OR value based assessment”</td></tr>
<tr><td colspan="2">In the search for the literature of MCDA studies in HTA, the following search was conducted in Google Scholar.</td></tr>
<tr><td colspan="2">“multi criteria decision analysis” OR “multi criteria decision making” OR “multi criteria decision aiding” OR “multi attribute decision making” OR “multi attribute decision analysis” OR “MCDA” AND “health technology assessment” OR “HTA” OR “benefit risk assessment” AND “drug”</td></tr>
</table>

- # Appendix 3 – Summary of virtual focus group seminars recordings

Focus group participants: Anneli Elme, Riina Laurimaa, Alar Irs, Erki Laidmäe

Facilitator: Brigitha Kask

Seminar Date: 11/03/2021

Google Meet recording

Thesis and MCDA overview	14:00	The facilitator set the agenda for the day and introduced the definition of MCDA by Keeney and Raiffa, pilots in other countries, three main phases of the process, set of reports by ISPOR, eight essential steps for MCDA and master's thesis focus (no sensitivity analysis and action plan development). Three groups of MCDA models (referents-level models, ranking models, value measurement models).Using the MCDA technique MACBETH. The aim of the seminars (to co-create and design the MCDA model). Overview of today's and the next meetings. Advantages of the MCDA. Some examples (reference levels, value for different stakeholders, cost-effectiveness calculation). mTNBC treatments reimbursement problem definition and structuring. Reference to the introduction video. Elaboration on the specific rules for selecting criteria. Reference to the pre-sent generic value tree. Overview of the breast cancer statistics. Essential aspects to evaluate TNBC.
Problem structuring in Google Jamboard	14:28	Focus group participants tried to define the mTNBC treatments reimbursement problem and aim with their own words. Following page in Jamboard, CAUSE checklist. Mapping the stakeholders. Discussion about who are the stakeholders who are affected? Stakeholders who can influence the decision? Mapping of the treatment alternatives. Currently available treatment alternatives and differences between them. Mapping of the environmental factors. Overview on the influence on the close-ones, families, need for caregivers, patient’s ability to work. Mapping of the uncertainties (patient number, quality of life measurement instrument, long-term efficacy outcomes, adverse events, actual treatment duration, budget impact, and patient preferences).
Break	15:16	

Problem structuring (criteria selection) in Google Jamboard	15:23	Attributes from the application added to the value tree (therapeutic impact, adverse events, posology, cost-effectiveness). What are other important criteria? Can we assess and measure them? Assessment of patients' general condition. Assessment of restricting factors. Innovation should be reflected in clinical outcomes. The burden of disease, unmet need, equity, end-of-life category depends on societal preferences. Exceptions for rare diseases. Socioeconomic impact (patient incapable of working). It can be measured using the EHIF database, studies from other countries. Next steps and materials.

Focus group participants: Anneli Elme, Riina Laurimaa, Erki Laidmäe

Facilitator: Brigitha Kask

Seminar Date: 19/03/2021

Google Meet recording

Validation of criteria	14:00	The facilitator summarised the previous meeting and set the agenda for the day. Reference to preparation materials. Health-related quality of life score achieved similar outcomes, excluded. Exclusion of costs explained. Inclusion and exclusion of therapeutic impact criteria. DOR and PFS overlapping, DOR excluded. ORR criterion is less important. Discussion about safety profile criteria. Evaluation of contraindications and interactions, general condition, adverse events, and discontinuations. ECOG data for comparison not found. In the current context, contraindications and interactions not important. Posology, number of infusions versus time of infusions. The number of infusions is the same. Infusion frequency and patients travel time and distance. Time of infusions included. The posology criterion is less important.
Overview of M-MACBETH	14:41	Overview of the measurement scales. The “higher” and “lower” levels explained. Judgment scales and local and global scales explained.
Selection of measurement scales	14:47	Importance of the “higher” and “lower” levels discussed. CI 95% for therapeutic impact cluster. Adverse events levels selection. Adverse event difference between treatments clinically irrelevant. Adverse events excluded. Four attributes included in the final mTNBC value tree.

▪ Appendix 4 – Consent form

INFORMEERITUD NÕUSOLEK MCDA MUDELI DISAINIMISEKS JA KOOSLOOMISEKS

Minu nimi on Brigitha Kask ning olen Tallinna Tehnikaülikooli Infotehnoloogia teaduskonna Tervisetehnoloogiate Instituudi magistritudeng ja kutsun teid osalema fookusgrupi seminaridel, mille sisust valmib minu magistritöö „Multi Criteria Decision Analysis (MCDA) as part of Health Technology Assessment: a case study on metastatic triple-negative breast cancer“
Huvi antud teema vastu tekkis seoses töökohaga Roche Eesti OÜ-s. Magistritöö juhendajaks on Riina Hallik ja kaasjuhendajaks Tanel Ross.
Magistritöö eesmärk on praktilise näite abi disainida ja koosluua MCDA mudel ning testida, kas ja mil määral seda on võimalik rakendada Eesti ravimite rahastuse otsustusprotsessis.
Antud töö on oluline, kuna MCDA on otsustusaluste analüüs, mille kasutamine tervisetehnoloogiate hindamise kontekstis võimaldab teha keerulisi otsuseid kaasates laiemaid väärtusdimensioone ning erinevate huvigruppide hinnanguid. Fookusgrupi seminaride tulemina võiks tekkida arutelu MCDA mudeli kasutamisest vastates ennekõike küsimustele, mis valdkonnas võiks MCDA kasutada, ning kas ja millist lisaväärtust selle kasutamine loob.
Töös osalemine, ajakulu ja aktiivne panustamine ei ruugi teile otseselt kasu tuua, kuid annab võimaluse kaasa mõelda ja panustada antud valdkonna arendamisse. Luban saata kokkuvõtva e-maili fookusgrupi seminaride tulemustest ning soovi korral ka magistritöö lõpliku versiooni.
Ootused magistritöö raames korraldatud virtuaalsetel fookusgrupi seminaridel osalemiseks :
Palun...
...Igale fookusgrupi seminarile eelnevalt tutvuda e-mailile saadetud eelinfoga ning panustada aktiivselt koosloome protsessi.
...Anda tagasisidet seminaride põhjal koostatud tulemitele ning võimalike vajalike muudatuste kohta:

- väärtuspuu
- kriteeriumite mõõdikute definitsioonid
- alternatiivide toimimise maatriks, sisaldab muuhulgas hindamiseks kasutatud allikaid ning väärtuse hindamise skaalat (sh. kõrgem ja madalam väärtus).

...Viimasel virtuaalsel kohtumisel, anda isiklik individuaalne hinnang (skooride ja kaalude näol) kõigile väärtuskriteeriumitele.
...Vastata lühikesele tagasiside küsitlusele.
...Lubada virtuaalsete seminaride salvestamist andmeanalüüsiks ning seminaridel käsitletud ja kogutud info avaldamist antud magistritöös isikustatud kujul.

Annan oma nõusoleku aktiivseks osalemiseks ning andmete töötlemiseks ja avalikustamiseks isikustatud kujul.

Nimi / allkiri (digitaalne) / kuupäev

▪ Appendix 5 – Focus group feedback questionnaire

Section 1

1. Please describe the potential advantages of using the MCDA for pharmaceutical reimbursement decision-making?

2. Please describe the potential disadvantages or shortcomings of using the MCDA for pharmaceutical reimbursement decision-making?

Section 2

Did the following theoretical advantages of using the MCDA open up during the focus group seminars while assessing the TNBC treatments?

1. The treatments assessment process had a clear structure?

Disagree ○ ○ ○ ○ ○ Fully agree

2. The treatments assessment process allowed identification and inclusion of broader disease-specific assessment criteria?

Disagree ○ ○ ○ ○ ○ Fully agree

3. The treatments assessment process was inclusive, including different stakeholders?

Disagree ○ ○ ○ ○ ○ Fully agree

4. The treatments assessment process was transparent and enabled the measurement of importance of the different assessment criteria?

Disagree ○ ○ ○ ○ ○ Fully agree

5. The treatments assessment process was simple and understandable?

Section 3

Answering the following questions, please explain your opinion.

1. Is the inclusion of additional assessment criteria (in addition to the criteria in the current reimbursement application) into pharmaceutical reimbursement decision-making important?

2. Is it important that the treatment assessment criteria are disease-specific?

3. Is it important to measure the importance or weight of the different assessment criteria during pharmaceutical reimbursement decision-making?

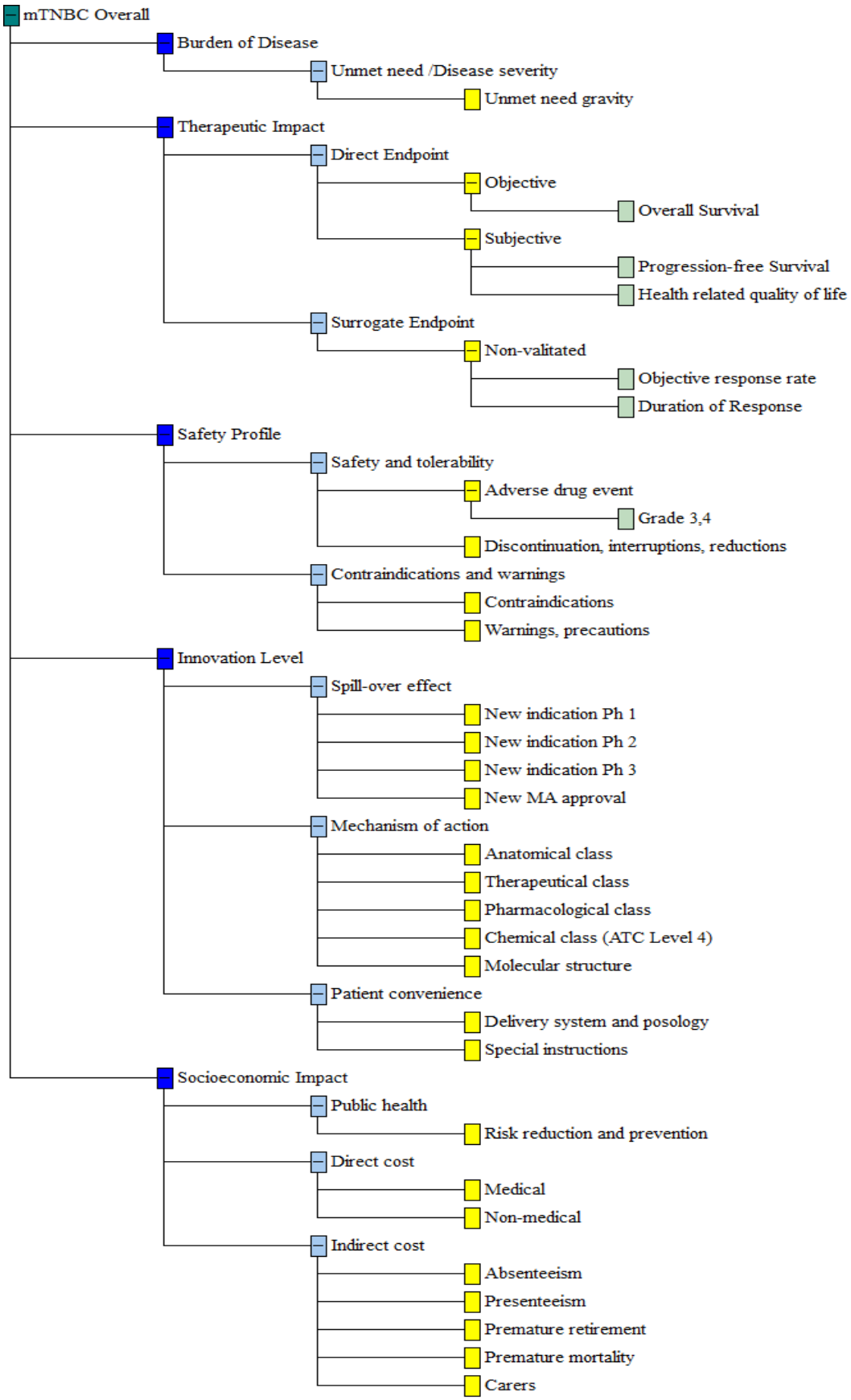
4. Is it important that besides the different treatment alternatives performance median, the reference levels ("lower" and "higher" level) are as well included in the assessment?

5. Could the MCDA value score be an alternative for QALY during cost-effectiveness assessment?

6. Would the inclusion of MCDA into the treatments assessment process be beneficial in Estonia?

7. What would be the most likely disease area to utilize the MCDA in Estonia?

- **Appendix 6 – mTNBC preliminary generic value tree**


mTNBC Overall
Burden of Disease
Unmet need /Disease severity
Unmet need gravity
Therapeutic Impact
Direct Endpoint
Objective
Overall Survival
Subjective
Progression-free Survival
Health related quality of life
Surrogate Endpoint
Non-valitated
Objective response rate
Duration of Response
Safety Profile
Safety and tolerability
Adverse drug event
Grade 3,4
Discontinuation, interruptions, reductions
Contraindications and warnings
Contraindications
Warnings, precautions
Innovation Level
Spill-over effect
New indication Ph 1
New indication Ph 2
New indication Ph 3
New MA approval
Mechanism of action
Anatomical class
Therapeutical class
Pharmacological class
Chemical class (ATC Level 4)
Molecular structure
Patient convenience
Delivery system and posology
Special instructions
Socioeconomic Impact
Public health
Risk reduction and prevention
Direct cost
Medical
Non-medical
Indirect cost
Absenteeism
Presenteeism
Premature retirement
Premature mortality
Carers

▪ Appendix 7 – mTNBC attributes definitions

Cluster	Attribute	Definition
Therapeutic Impact	Overall Survival	The median time from the randomization to death
	Progression-free Survival	The median survival time during which the patients' disease has not progressed
	Objective response rate	The percentage of people who have received a partial or complete response to the treatment (RECIST 1.1)
	Duration of Response	The median time of the treatment response
Safety Profile	Grade 3 – 4 Adverse events (AE)	% of patients who experienced Grade 3 – 4 Adverse events
	Contraindications	Conditions or diseases which make the use of particular pharmaceutical unadvisable
	Interactions	Simultaneously used pharmaceuticals interactions (pharmacokinetic and pharmacodynamics) which can affect the pharmaceuticals performance or the treatment outcome
Innovation Level	Posology	Frequency of doses during the 28-day treatment cycle in combination with the duration of the administration

- **Appendix 8 – mTNBC treatments performance data references**

Cluster	Attribute	Evidence source	
		Atezolizumab+ Nab-paclitaxel	**Nab-paclitaxel**
Therapeutic Impact	Overall Survival	CHMP product information [44]	CHMP product information [44]
	Progression-free Survival	CHMP product information [44]	CHMP product information [44]
	Objective response rate	CHMP product information [44]	CHMP product information [44]
	Duration of response	CHMP product information [44]	CHMP product information [44]
Safety Profile	Grade 3 – 4 Adverse events	Application No 1417 [24]	Application No 1417 [24]
	Contraindications	CHMP product information [44], [45]	CHMP product information [45]
	Interactions	CHMP product information [44], [45]	CHMP product information [45]
Innovation Level	Posology	CHMP product information [44], [45]	CHMP product information [45]

-

▪ Appendix 9 – mTNBC preliminary performance matrix

Attribute	Metric	Atezolizumab + Nab-paclitaxel	Nab – paclitaxel
Overall survival	month	25.4	17.9
Progression-free survival	month	7.5	5.3
Objective response rate	% of patients	58.9	42.6
Duration of Response	% of patients	8.5	5.5
Grade 3 – 4 Adverse events	% of patients	49.4	42.8
Contraindications	type	1. Hypersensitivity to Atezolizumab or to any of the excipients (L-histidine, Glacial acetic acid, Sucrose, Polysorbate 20, Water for injections) + all for Nab-paclitaxel	1. Hypersensitivity to the active substance or to any of the excipients (human albumin solution (containing sodium, sodium caprylate, and N-acetyl DL tryptophanate)) 2. Lactation 3. Patients who have baseline neutrophil counts < 1500 cells/mm3
Interactions	type	1. The use of systemic corticosteroids or immunosuppressants before starting Atezolizumab should be avoided + all for Nab-paclitaxel	1. Medicines known to inhibit either CYP2C8 or CYP3A4 (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) 2. Medicines known to induce either CYP2C8 or CYP3A4 (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine)