Next Generation Health Technology Assessment

Next Generation Health Technology Assessment (HTx) to support patient-centred, societally oriented, real-time decision-making on access and reimbursement for health technologies throughout Europe

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Systematic review on how (cost-) effectiveness of combinations of health technologies,

individualised/personalised treatments and treatment pathways is currently being assessed by HTA bodies

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Next Generation Health Technology Assessment

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EXECUTIVE SUMMARY

A GAP ANALYSIS OF THE CHALLENGES IN HEALTH TECHNOLOGY ASSESSMENT OF COMPLEX HEALTH TECHNOLOGIES

Descriptive study on how (cost-)effectiveness of combinations of health technologies, individualized/personalised treatments and treatment pathways is currently being assessed by health technology assessment (HTA) organisations; Lead Partner: UU (M1-M11)

Introduction
With more advanced health technologies (HTs) entering the healthcare market, also the requirements for methodologies to assess these HTs for reimbursement will or need to change. However at this moment, detailed insight in how HTA organisations perceive HTAs of these more advanced HTs is missing. Therefore, there is a need to assess in greater depth the HTAs that are performed for more advanced HTs to identify what European HTA organisations perceive as challenging in the HTAs of these advanced HTs and what the role of traditional randomized controlled trial (RCT) and real-world data (RWD) sources are. The aim of this study is to collect this detailed insight because it will be an important starting point for the methodological work in the HTx project that aims to provide solutions for the identified methodological and data related challenges.

Aim
This study aims to perform a gap analysis to find the needs for improvement in HTA methodology by 1) identifying which HTAs are considered challenging and which HTs are perceived as complex, 2) assessing what the main arguments are that make therapies complex and HTAs challenging, 3) investigating the relationship between the use of real-world data (RWD) and challenging HTAs of complex therapies, and by 4) finding the most pressing gaps that can be filled with the development of novel methodologies for challenging HTAs of complex HTs.

Methods
This study builds on recent work conducted as part of the European network for HTA (EUnetHTA) Joint Action 3 (JA3) which provided a more general overview on the activities of HTA organisations within Europe and focused mostly on the assessment of single HTs.

To identify HTs and assessment issues that are perceived as complex, we sent out a questionnaire to European HTA organisations that are members of EUnetHTA. This questionnaire was validated and tested for reliability and disseminated via the online tool LimeSurvey. Questions included whether seven specified case examples of complex HTs (ranging from a gene therapy to surgical interventions) were perceived as complex on a 5-point scale from never to always; rating of specific elements that could make an assessment challenging on a 1-5 Likert scale; and open questions asking for additional complex cases and issues that make HTA challenging. Subsequently, we investigated data sources that are accepted by the

organisations; the likeliness of using RWD in prespecified challenging situations on a 1-5 Likert scale; ranking of 9 prespecified reasons for not using RWD; an open question for other circumstances that promote the use of RWD or other hurdles preventing the organisations from using RWD sources. The analysis of closed and quantifiable questions was done in Excel (version 2016), whereas the open questions were analysed using a decision node tree in NVivo (version 12).

Results

In total, 22 out of 33 invited HTA organisations from 21/27 countries completed the questionnaire. This was, despite a slight overrepresentation of the Nordic countries, a balanced mixture. ATMPs were in general considered as the types of therapies most challenging for HTA. Out of seven prespecified case studies, the histology independent therapy was reported as most challenging by organisations that assessed it. Additionally reported complex HTs were mostly pharmaceuticals, oncology products, designated orphan medicines, personalised treatments and combinations of treatments. ATMPs were reported often given to the relatively small amount of existing ATMPs on the market.

For the case studies, methodological issues in the REA or CEA were more often reported to be contributing to HTA challenges than policy- or data related issues. In open questions, the reported challenges were most often data related; absent, insufficient, immature or of low quality. These data insufficiencies resulted in uncertainties around desired outcomes according to 13 organisations, subsequently creating uncertainty around input parameters for the CEA. The non-data related arguments were most often societal- or political pressure (4 organisations) or organisational- and policy related problems (8 organisations), resulting in uncertainties around the input parameters in the CEA or created challenges in decision making. Direct modelling issues in the CEA were less often reported. The arguments showed considerable variety per case, although data issues were reported for these case studies.

All participating organisations reported accepting traditional data sources. For RWD sources, this varied from 19 out of 22 organisations to 8/22, with patient registries being the most accepted source. In challenging circumstances, organisations tended to be likely to accept RWD, scores ranging from 3.2 – 4.3 out of 5.0. Additionally reported circumstances to accept RWD mostly related to insufficient outcomes data from RCTs. More than half of the organisations ranked '*lacking necessary RWD sources*' and '*existing policy structures or information governance*' most important barriers for not accepting the RWD sources.

Conclusions

HTA challenges faced by European HTA organisations mainly root in data insufficiencies at time of assessment, and result in outcome uncertainties in the REA and input parameters for the CEA. Complex HTs, for example gene therapies, sometimes inherently cause data insufficiencies, making some complex HTs more challenging for HTA. In challenging HTA circumstances, HTA organisations tend to be positive towards accepting RWD to supplement traditional data sources. However, this is only if these sources are timely available and policies do not hinder their utilisation. These results highlight the importance of the work that is done in the methodological work packages of HTx and support the implementation work packages.

A GAP ANALYSIS OF THE CHALLENGES IN HEALTH TECHNOLOGY ASSESSMENT OF COMPLEX HEALTH TECHNOLOGIES

Descriptive study on how (cost-)effectiveness of combinations of health technologies, individualized/personalised treatments and treatment pathways is currently being assessed by health technology assessment (HTA) organisations

Introduction

HTA is the systematic evaluation of the properties and effects of a health technology (HT), according to the World Health Organisation (WHO) definition(1). Direct and intended effects of this HT, and to a lesser extend also indirect and unintended consequences are hereby addressed. It is aimed mainly at informing decision making regarding HTs. Despite some relatively recently established collaborations among European member states, most countries have their own HTA organisations.

Over the past few decades, the role and importance of HTA has developed gradually. This development is in response to greater emphasis on evidence-based decision-making in healthcare. At the same time, the treatment of patients has become more complicated over recent years due to the development of increasingly tailored HTs including combinations of HTs – consisting of pharmaceuticals, diagnostics, wearables, devices, digital tools and interventions – precision or personalised treatments, treatment pathways or sequences, and an improved use of Patient Reported Outcome Measures (PROMs). These HTs are hereafter referred to as '*complex HTs*'.(2) This all happened alongside increasing pressures on financing and delivery of healthcare, caused by, among other things, an increasing elderly population(3).

Developments in the use of HTA and its outputs have been reactive to political, societal and financial needs rather than being proactively 'designed' to address the needs of diverse and changing healthcare systems. Even though the need for information that is necessary for decisions on reimbursement often arises within a small timeframe in all member states, this might explain why current HTA procedures and its use as supporting tool for decision-making varies considerably across European healthcare systems. This is causing inefficiencies and a duplication of effort in European HTA. (2)

Due to the complex nature of European HTA collaborations, these collaborations have mostly focused on producing joint clinical assessments and developing joint methods for the relative effectiveness assessments (REA). The European Network for HTA (EUnetHTA) is such a collaboration. EUnetHTA has developed the joint rapid REA, however, this focused predominantly on *single HTs*.(2,4)

Access for patients to new HTs is requested more early in the authorisation and reimbursement process than before(5). Due to stimulation of development of HTs for rare diseases, access of newly available HTs is more often for small patient populations. This results in decreasing amounts and quality of data available at the time of the HTA process. Often single arm studies are used for small populations and interim data is all that is available upon approval of a newly developed intervention(6–8). To increase certainty in HTA-informed healthcare decisions, real world data (RWD), defined as 'everything except randomized controlled trials (RCT)' by the IMI GetReal project, is often mentioned as a helpful addition to the traditional data sources like RCTs(9,10).

To date, the tools to adequately inform decisions on these *complex HTs* still do not exist. Data sets of innovative medicines and medical devices are often limited, and companion diagnostics, target therapies and digital health interventions are being introduced into healthcare systems while no HTA frameworks exist for their assessment. If HTA organisations are expected to make more tailored decisions on *complex HTs* using more complicated data, often from different sources, new HTA methods need to be developed for this *next generation of healthcare*.

As a result, the need has arisen for (collaboration on) personalised HTA that is capable of identifying for whom HTs work and for whom they are not essential, hereby guaranteeing that the right treatment is provided, to the right patient, at the right time and leading to an increase in societal healthcare benefits. In order to properly feed these HTA frameworks, methods to combine RWD in a quality assured way with traditional data sources like RCTs need to be developed. The HTx project for next generation HTA aims to develop these methods for future proof HTA, while combining different sources of data.

This specific study builds on the report work from the EUnetHTA JA3 work package (WP) 7, which analysed existing HTA and reimbursement procedures of *single HTs* within EUnetHTA partner countries and provided a more general overview on the activities of HTA organisations within EU.(4)

This study assesses in greater depth HTAs that HTA organisations in Europe performed on *complex HTs*. The study assesses to which extent HTA organisations currently perceive HTAs of *complex therapies* as *challenging* and what the main challenges are in these HTAs, including the use of real world data (RWD) in these particular HTAs. This gap analysis defines the current issues that HTA organisations face in relation to these challenging HTAs and their needs for improved assessment methodologies. This forms the basis for future methodological work in the HTx project.

Aim

This study aims to perform a gap analysis to find the needs for improvement in HTA methodologies by 1) identifying which HTAs are considered *challenging* and which HTs are perceived as *complex,* 2) assessing what the main arguments are that make HTs *complex* and HTAs *challenging*, 3) investigating the relationship between the use of RWD and *challenging* HTAs of *complex* HTs and lastly by 4) finding the most pressing gaps that can be filled with the development of future proof methodologies for *challenging* HTAs of complex HTs.

Methods

Data about complex HTs and challenges in HTAs were gathered from HTA organisations through a questionnaire. The use of a questionnaire gives direct insight in challenges that are experienced in the daily practice of HTA organisations, as well as access to data on the most recent and unpublished experiences. For the development, validity and reliability testing we used five steps of the methodology from Venkitachalam et al, Bolarinwa and Kimberlin and Winterstein(11–13). The theories of these authors were clearly connected and complemented and fitted well to our development of this questionnaire in the HTA field.

Questionnaire development and testing

1. *Participant selection and scope*

The target audience was defined as experienced HTA assessors, to ensure sufficient knowledge and experience to accurately answer the questions about performed HTAs. HTA organisations from all EUnetHTA member states were invited to participate for two reasons. These member states ensured the representation of the whole of Europe, as was the scope of the study, and it ensured our deliberate aim for a balanced mixture of Western and Eastern European countries for transferability and implementation reasons. One specification was that HTA organisations had to be directly or indirectly involved in decision making in order to identify hurdles that actually impacted decision makers. HTA organisations operating either on a national or regional level, and both organisations that assess pharmaceuticals and non-pharmaceuticals were included, to capture all in the HTA field. See appendix 1 for the list of invited organisations.

2. *Conceptualisation*

The overarching research question of the questionnaire were similar to this report's research questions: 'which HTs were perceived as challenging to assess?' and 'what were the main issues that contributed to these challenges during assessment?'. We aimed to measure the difference in challenge of assessment of various types of HTs and the contributing factors that are either inherent to the HT or to the assessment process.

3. *Format and data analysis*

All formulated questions focused on answering the two overarching research questions. The questionnaire consisted of four parts, as illustrated in figure 1. The first part investigated how often specific issues contributed to challenges during assessments. Our list with complicating issues was created by literature search and by input from individuals with practical experience. The second part used prespecified case studies that each contained one or more of the complicating issues as questioned in the first part. Therefore, in the second part, the same question was incorporated indirectly, to confirm the specificity of the first part. See table 1 for the list of case studies with the challenges that each contains. The third part of the questionnaire had specific questions regarding additional cases that had been challenging to assess, and additional issues that contributed to the challenge of HTAs. This approach aimed to identify issues that were missed in the first two parts, since this was only a selection, and thus ensured sensitivity. The fourth and last part of the questionnaire focused on RWD by asking for data sources that are accepted in the organisation, reasons for not accepting RWD and circumstances

that would increase the likelihood of accepting RWD. For the full list of questions as they were sent, see appendix 2.

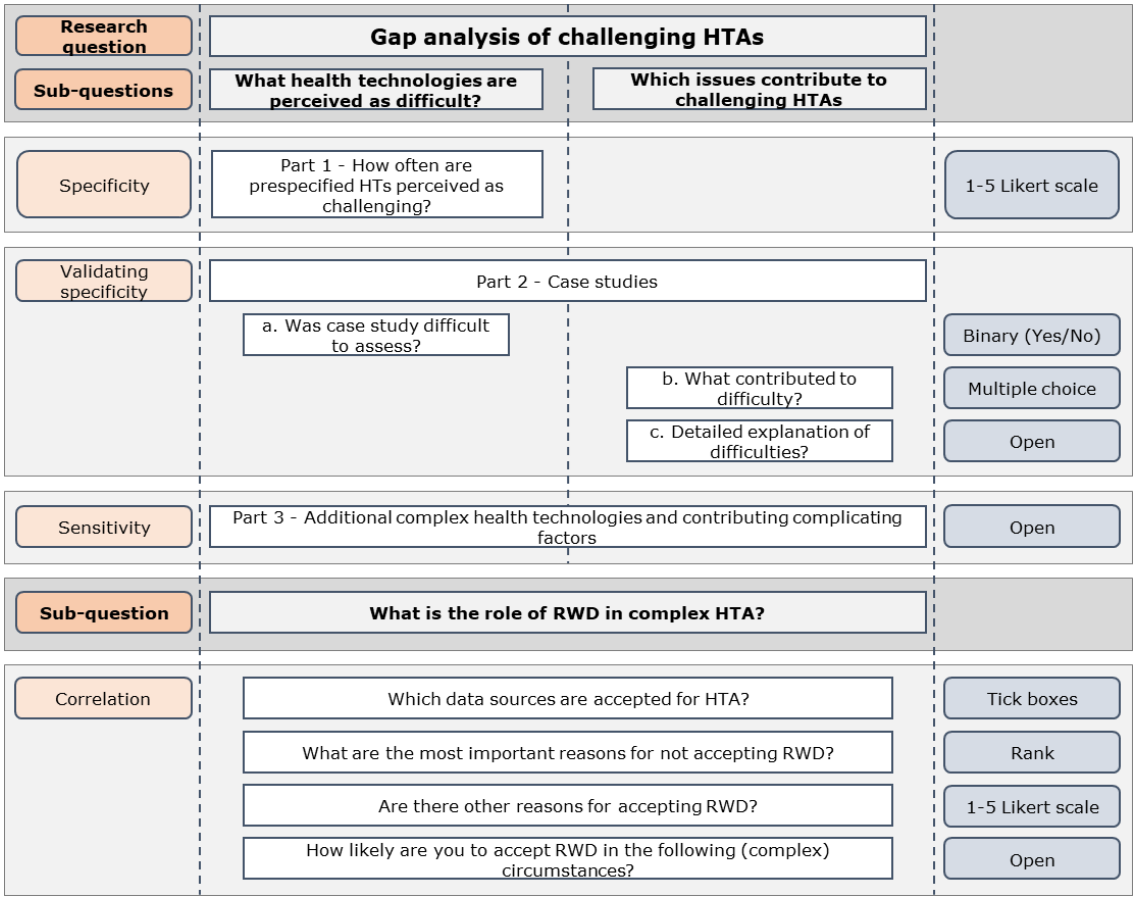

Figure 1. | Schematic structure of the questionnaire. The first column shows the objectives of each part of the questionnaire, The middle part the questions disseminated and their relation to the sub- and overarching research question and in the most right column the answer options. HTA = health technology assessment; HT = health technology; RWD = real world data

The case studies were chosen based on challenges that each case contained, see table 1. First, a long list of HTs that had been assessed in recent years was established. Hereafter, possible issues that could have made these HTAs complex were added, based on what we found in literature and input from two representatives from the HTA field. From the complete list of HTAs and challenges a few were chosen to keep the questionnaire concise, taking into account that the selection represented a balanced mixture of pharmaceuticals and non-pharmaceuticals and a selection of different types of challenges that were also questioned in the first part.

Table 1. | The 7 case studies that were used in the second part of the questionnaire to measure what type of HTs were considered 'challenging to assess' and the issues that made these HTAs complex. These case studies contain a selection of issues that could be perceived as 'complex' to assess in HTA, representing a broader list of challenges in the first part of the questionnaire. These challenges do not cover all existing challenges, follow-up questions questioned for additional issues that were missed in our prespecified list.

Health technology	Indication	Challenge

Dabrafenib/trametinib (TafMek)	Treatment of adults with metastatic or unresectable melanoma with BRAF-V600 mutation	Combination, interim analysis data, precision medicine, sequence of therapies, companion diagnostic
Continuous glucose monitoring (e.g. Freestyle Libre)	Guide treatment of adults and children with diabetes mellitus type 1 or 2	Combination, medical device, digital technology, both preventative and managing
Voretigene neparvovec (Luxturna)	Single dose gene therapy for adults and children with retinal dystrophy caused by a bi-allelic RPE65 mutation	Orphan designation, precision medicine, curative treatment, ATMP, companion diagnostic
Repetitive transcranial magnetic stimulation	Treatment of adults with treatment-resistant major depression	Medical device
HPV vaccine (Gardasil/Cervarix)	Given to young adolescents for the prevention of cervical cancer	Preventative treatment
Transcatheter aortic valve implantation (TAVI)	In adults at intermediate surgical risk	Surgical intervention, medical device
Larotrectinib (Vitrakvi)	Treatment of adults and children with the histology independent diagnosis of a solid tumour with NTRK-gene fusion	Histology independent, precision medicine, companion diagnostic

4. Validity

To validate that the questionnaire did measure what it was intended to measure, we tested for construct, content and face validity, as described by Venkitachalam et al, Bolarinwa and Kimberlin and Winterstein(11–13). See table 2 for a short description of and methodology for testing these types of validity.

The questions were built up in a way to ensure construct validity (table 2, row 1). In the first two parts of the questionnaire the same question about the challenge of HTA was incorporated twice, using different wording. This strategy established the specificity of the questionnaire, i.e. more certainty of the previous answers. A reference for the degree of challenge was created by including known complicating factors and a known complicated HT. In order to keep the questionnaire concise, aiming for a high response rate, we limited the amount of complicating issues and prespecified case studies. The third part of the questionnaire inquired additional suggestions on complicating issues and challenging cases to ensure the sensitivity of the questionnaire. Using this reference framework for 'challenging HTA' from the first three parts, we lastly questioned the organisations about the likelihood of accepting RWD in prespecified circumstances. A last open question inquiring for additional circumstances to accept RWD, ensured the sensitivity of this last part as well.

An expert panel with representatives from both academia (UoC[1], UU[2]) and HTA organisations (NICE[3], SMC[4], SRI[5], TLV[6], ZIN[7]), most working for the HTx project, verified that the questions together covered the overarching research aim, that all

[1] University of Copenhagen, UoC, Denmark
[2] Utrecht University, UU, the Netherlands
[3] National Institute for Health and Care Excellence, NICE, UK
[4] Scottish Medicines Consortium, SMC, Scotland
[5] Syreon Research Institute, SRI, Hungary
[6] Dental and Pharmaceutical Benefits Agency, TLV, Sweden
[7] Dutch National Health Care Institute, ZIN, the Netherlands

questions were relevant and covering the content, and that the questionnaire was comprehensive (table 2, row 2 and 3). The expert panel also tested for readability of the questionnaire and the clarity of wording to ensure correct interpretation of the questions. The representatives were chosen based on their field of research, amount of practical experience, involvement in the HTx consortium and availability. For the representatives involved in the expert panel and pilot test, see appendix 3.

The HTA representatives from this expert panel were subsequently involved in the pilot test with the complete set of questions in the *Lime Survey* tool, that was used for dissemination. The pilot test was done to ensure feasibility of completing the questionnaire, a clear structure and right interpretation of the questions (table 2, row 2 and 3). These results were not included in our final results. For the final results, other people in each organisation were asked.

Table 2. | Three types of validities that the questionnaire was tested for during the development phase. The identification of and methodology for testing for these types of validity were based on articles by Venkitachalam et al, Bolarinwa and Kimberlin and Winterstein(11–13).

Type of validity	Meaning	Methodology of testing
Construct	The extent to which the data extraction tool accurately measures the theoretical construct that is was designed to measure.	We identified issues and cases known to be complicating, based on literature and practical experience, and used these as reference for new issues and cases in the questionnaire. Specificity and sensitivity were ensured by the structure of the questionnaire.
Content	The extent to which the data extraction tool covers all concepts necessary to answer the overarching research question and does not include concepts irrelevant to this overarching research question.	The questionnaire was tested by a panel of experts in the field (academia and HTA), to assess whether the specific concepts in the questionnaire represented the full domain of content that is relevant to the overarching research question.
Face	The extent to which the surface of the data extraction tool has a clear structure linking the all the items in a logical way to the overarching research objective.	The questionnaire was tested by a panel of experts (academia and HTA) for readability by our target population, clarity of wording to ensure the correct interpretation and the questionnaire was piloted among a group of people from the target population (and expert panel) to ensure a well-structured layout and style and the feasibility of completing it in the given estimated time frame.

5. *Reliability*

The reliability of a questionnaire refers to any random error in measurement. Reliability indicates the accuracy or precision of the measuring instrument. Does the questionnaire consistently measure what it intends to measure? During the expert panel testing and pilot testing, the experts considered the reliability of the questionnaire by assessing the clarity of words and thus the right interpretation of the questions, the clear structure and the feasibility of completing it in the given time frame. Minor textual and structural adjustments were made based on these tests.

Dissemination

The questionnaire was sent out to experienced assessors in HTA organisations simultaneously with questions from other parties in the HTx project to prevent that multiple surveys would be sent out with overlapping questions, in different style

and structure, within the same time frame. Collaboration therefore lessened the burden of time in HTA organisations and ensured a comprehensive set of questions. The link to the questionnaire was disseminated via a centralized HTx e-mail address.

The questions were formulated in the survey tool *Lime Survey*, freely available at Utrecht University. We additionally distributed the questions in a Word document to participants experiencing difficulties with the tool. A number of weeks in advance of sending out the questionnaire, an announcement was sent to all participants to notify them about the questionnaire and our project, and to exclude potential organisations that were not interested in participating. The link to the questions was send with a corresponding e-mail explaining the purpose and importance. After a few more weeks, one more reminder with the link was distributed. One week before the deadline, we used the authors' network to send out a last reminder to obtain some additional responses. The questionnaire was anonymised and privacy was assured according to European legislation (EU) 2016/679.

Analysis

Closed and quantifiable questions
Analysing the results of the quantifiable questions was done in Excel, exported from the *Lime Survey* back-office.

First, to analyse how often the participants thought that certain HTs were perceived as having challenging HTAs, the answers 'never', 'rarely', 'sometimes', 'often', 'always' were translated into 1-5 to calculate averages, never being 1 and always being 5.

Second, for each of the case studies the percentage of organisations categorising it as complex was calculated, as share of the total amount of organisations that assessed the case study. Accordingly, for the cases that were considered complex, the percentage of each category of challenges was calculated per case study, as share of the total amount of HTA organisations that assessed the case study.

Third, the amount of times that a data source was categorised as 'accepted' by the HTA organisation was calculated. Hereafter, the weighted average was calculated for each of the 9 reasons for not accepting RWD, using a weight from 1-9 for each rank, 9 to the most important reason, 1 to the least. Lastly, the averages were calculated from the 1-5 Likert scale, the average indicating the likeliness of accepting RWD in HTA in each of the circumstances.

Open questions
The open questions, containing lengthy text, were analysed using NVivo. The node structure that was used to identify and structure the arguments for why HTs or HTAs are complex, is shown in figure 2 below.

Answers from all the open questions were combined in one document and collectively assessed. The PICO[8] framework was used to organize arguments

[8] PICO framework = often used to guide the relative effectiveness assessment. PICO stands for the targeted patient **p**opulation in the assessment, the assessed **i**ntervention, the used **c**omparator and the relevant **o**utcomes.

related to the REA, and the CEA related arguments were subcategorized in input and modelling issues. Data related issues were subcategorized into lack of data and low quality data. The policy related issues as well as all the other non-prespecified categories fall under the category other reasons for challenges.

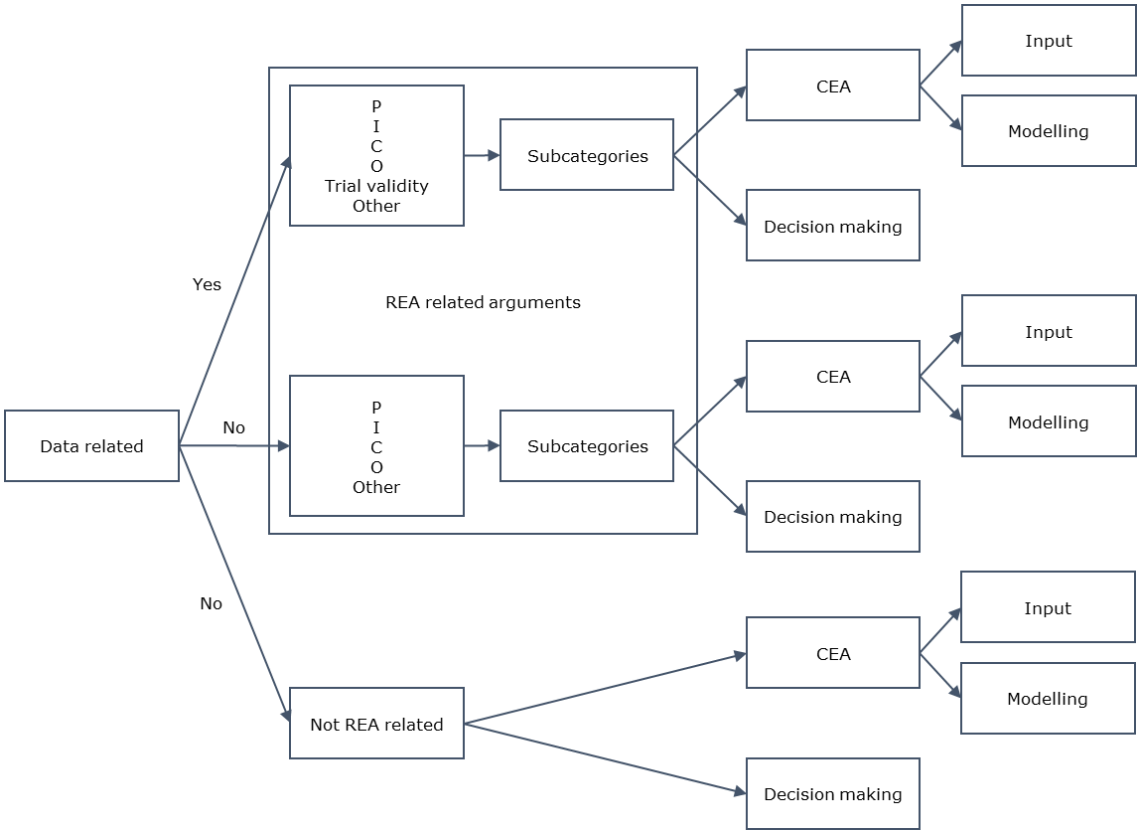

Figure 2. | The decision tree that was used to categorise arguments from the open questions that could make HTA more complex. First arguments were categorised into data related or not, subsequently into REA (PICO) related or not, followed by the effect of the argument on the CEA or decision making. CEA = cost-effectiveness analysis; PICO framework = Population, Intervention, Comparator, Outcomes; REA = relative effectiveness assessment.

Results

Out of 33 invited HTA organisations, 22 organisations from 21 different countries completed the questionnaire (response rate 67%), see appendix 4. There was a relatively balanced spread of organisations throughout Europe, with a slight overrepresentation from the Nordic countries, as seen in figure 3. Twenty-one responding organisations (95%) were responsible for assessing pharmaceuticals, of which 9 (41%) are assessing solely pharmaceuticals. Ten organisations (45%) were responsible for assessment of non-pharmaceuticals, of which 1 (5%) solely assesses non-pharmaceuticals. Twelve organisations (55%) were responsible for assessing both pharmaceuticals and non-pharmaceuticals.

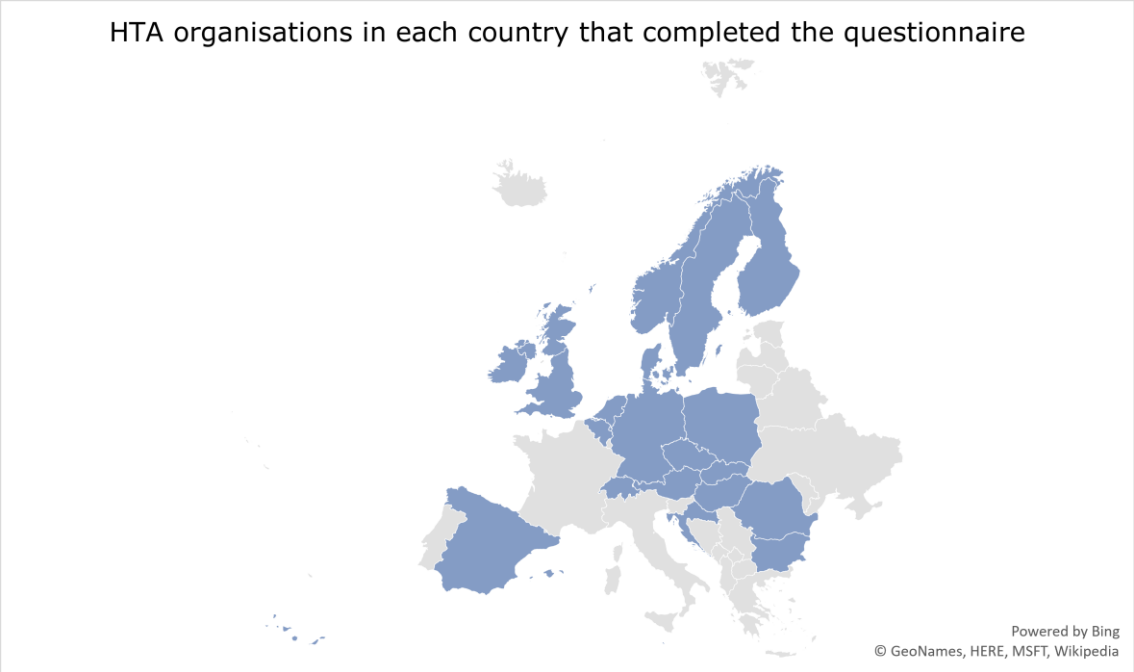

Figure 3. | Map with highlighted countries with HTA organisations that completed the questionnaire. The spread is quite balanced with 8 Northern, 5 Eastern, 3 Southern and 6 Western countries that responded, according to UN definitions. In every country there was one HTA organisation that completed the questionnaire, except for one country that had two organisations completing the questionnaire.

How often are assessments of prespecified complex types of HTs considered 'challenging'?

This question was answered by all 22 HTA organisations. ATMPs were considered challenging to assess most often, with an average weighed score of 4.1 out of 5.0. Eight organisations answered that ATMPs are 'always' challenging to assess, 6 'often', 4 'sometimes', 1 'rarely' and 0 'never'. Second and third, histology independent therapies scored 3.7/5.0 and sequences or pathways of treatments scored 3.6/5.0, see figure 4. Surgical interventions, preventative treatments, diagnostics and were considered least challenging for assessment, respectively scoring 3.1, 3.1 and 3.2 out of 5.0. The average weighed scores do not show large gaps in ranking, except for the gap between ATMPs in the first place and histology independent therapies in the second, with a 0.4 difference. Only six times, an HTA organisation reported that the HTA of a type of therapy was 'never' considered challenging (lightest blue bar in figure 4). There did not seem to be any large contradictions in the answers reported within the specific therapies.

Were the assessments of the complex HTs in prespecified case studies perceived as 'challenging' assessments?

Larotrectinib (Vitrakvi) was rated as the case study that was most challenging to assess. Seven out of the eight HTA organisations (88%) that assessed the histology independent treatment, reported that this HTA had been complex, see table 3.

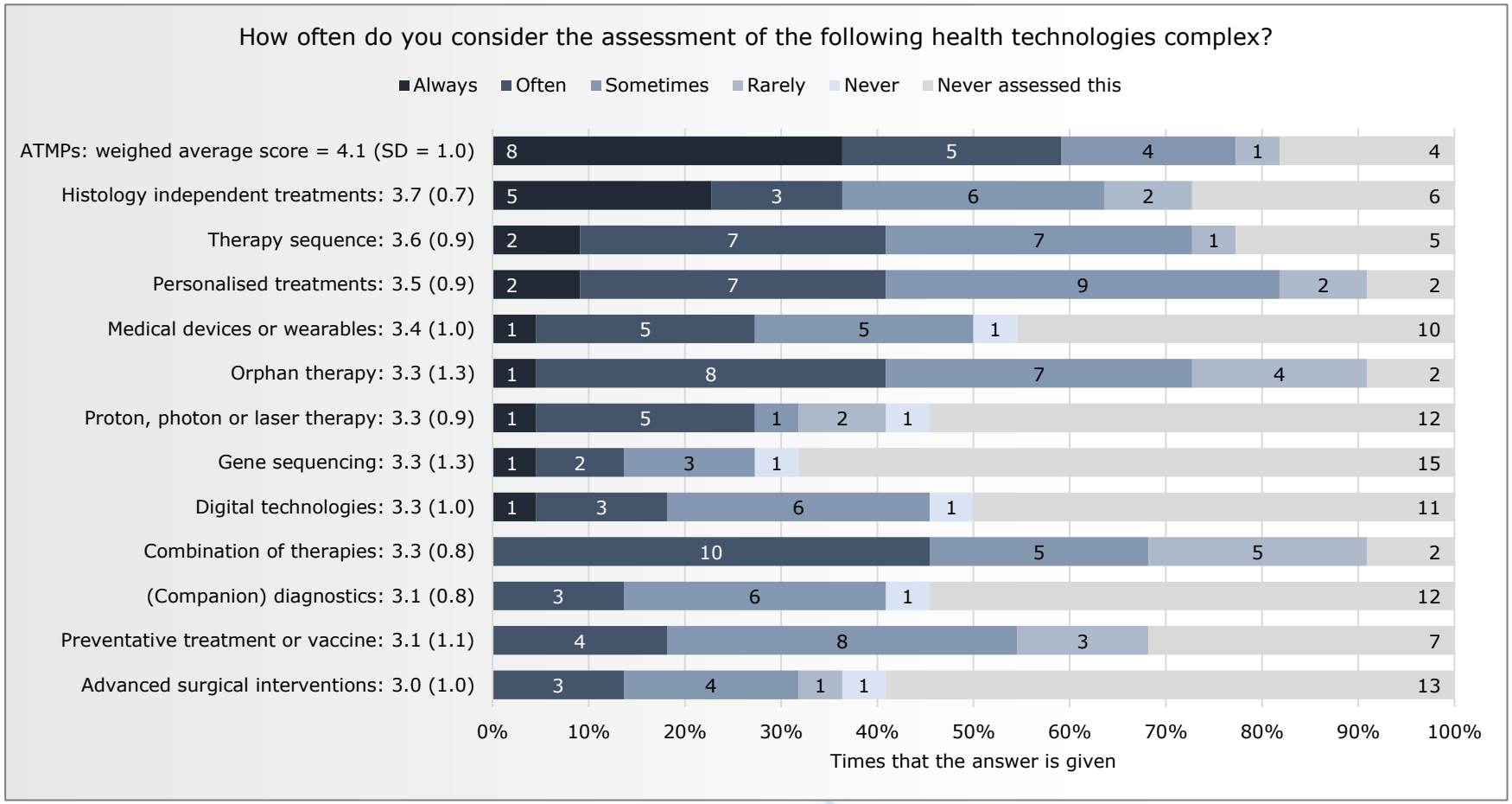

Figure 4. | Per type of HT, this graph shows the amount of HTA organisations reporting that this HT was 'never', 'rarely', 'sometimes', 'often' or 'always' considered as having challenging HTAs. In grey, it shows the amount of organisations that never assessed the type of HT. The number behind each of the HTs, in the column before the graph, is the calculated average weighed score for its complexity. ATMPs = advanced therapy medicinal products; HT = health technology.

In absolute terms, the combination therapy dabrafenib/trametinib (TafMek) was reported by most HTA organisations to have been a challenging HTA, 8 (36%) of the 22 responding HTA organisations, whereas larotrectinib (Vitrakvi) scored second in absolute numbers, with 7 (32%) of the 22 organisations reporting this to be a challenging HTA. Repetitive transcranial magnetic stimulation was in both absolute, 1 out of 4 (25%), and relative numbers, 1 out of 22 (5%), reported as having been the least challenging HTA. These results align with the results found in the question before, asking for the complexity of different types of HTs.

Table 3. Share of HTA organisations reporting case studies as challenging. | This table shows the share of organisations that pointed out that the HTAs of the case studies below were challenging. The first column shows the amount of organisations that said the HTA was challenging as share of the total amount of organisations that assessed the case study, whereas the second column shows it as share of the total amount of organisations that participated in the questionnaire. The number in brackets behind the case study indicates the number of HTA organisations that have assessed this case.

Case study (No. organisations assessed)	Share "yes"/ assessing organisations	Share "yes"/ total organisations (n=22)
Larotrectinib, Vitrakvi (8)	**88%**	32%
Continuous glucose monitoring, Freestyle Libre (9)	67%	27%
Voretigene neparvovec, Luxturna (9)	67%	27%
transcatheter aortic valve implantation, TAVI (5)	60%	14%
Dabrafenib/trametinib, Tafinlar/Mekinist (14)	57%	**36%**
HPV vaccine, Gardasil/Cervarix (9)	44%	18%
Repetitive transcranial magnetic stimulation (4)	25%	5%

Arguments for why complex case studies made HTA challenging – closed questions

In all 7 of the case studies, the majority of the HTA organisations reported that methodological issues in either the REA or the cost-effectiveness assessment (CEA) were contributing to an HTA being complex, see figure 5 and 6. Methodological aspects during the REA were in 9% - 26% of the time reported and the methodological aspects in the CEA were in 13 – 22% of the time reported. Data related issues were on average least contributing as reported by the HTA organisations, in 13% of the times for the assessed case studies. In general, for reasons other than the methodological, considerable variation was observed among the case studies. Looking at the results per organisation, four organisations reported solely the methodological aspects in the REA and/or CEA as contributing factors to challenging HTA. In the other countries, a mixture of all arguments was reported.

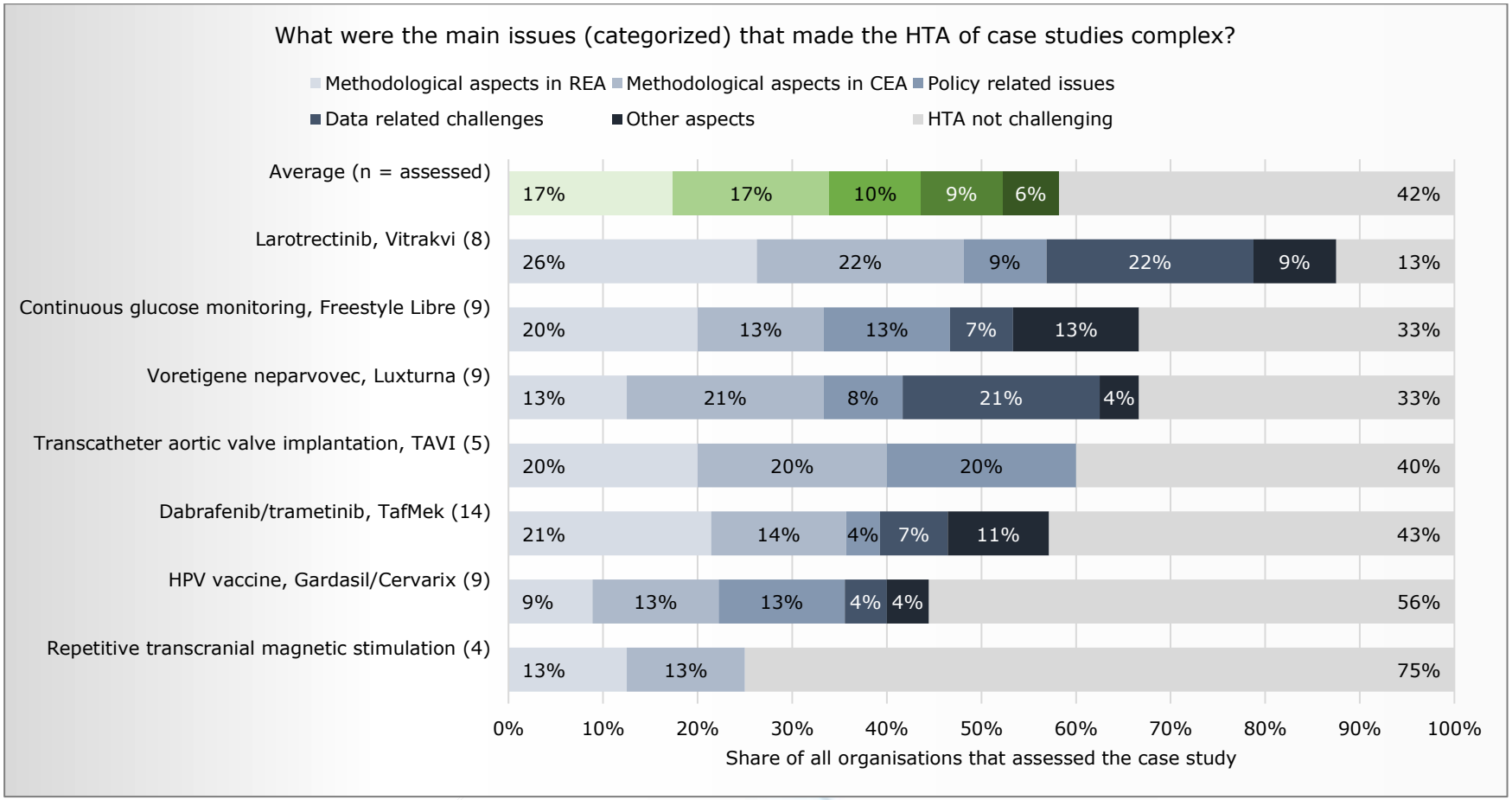

Figure 5. | For each case study that the HTA organisations marked as being challenging to assess, they were requested to report in which part of the HTA the challenges were encountered. The issues that could be found to be challenging were categorized in methodological aspects in the relative effectiveness assessment (REA), cost-effectiveness assessment (CEA) or other methodological aspects and data or policy related issues. Multiple answers could be chosen. The answers are given as share of the total amount of organisations that had assessed the case study. The figure behind the case studies are the number of organisations that did assess this particular case study. The share of HTA organisations that reported that the HTA was *not* challenging is shown in grey.

Arguments for what makes HTAs challenging – open questions

All 22 HTA organisations contributed to arguments on why HTA was considered challenging, either in the case studies or with additional reported arguments. The analysis showed that two third of the reported arguments related to issues with available data during the assessment, see the first level ring of the sunburst graph in figure 6. One third was related to other reasons than issues with data. In general, the arguments that were *data related,* mostly referred to aspects from the *PICO* framework, predominantly uncertainties around outcomes data (reported by 13 organisations), and were most likely to be expressed during the *REA*. Most of these arguments resulted in uncertainties around *input* parameters during the CEA. Arguments that were *not data related* were referring more often to '*other*' factors than the PICO, such as organisational elements (8 organisations), practice or political factors (4 organisations). These arguments were more often than the data related arguments likely to result in *modelling* issues during the CEA or directly affect *decision making*. All arguments inherently affect *decision making* due to uncertainties in either REA, CEA or both. A detailed description of the reported arguments per case study can be found in appendix 5. Table 4 shows more detail on arguments per categorised topic as shown in figure 2.

Table 4. | By the HTA organisations reported arguments from the open questions on why an HTA is challenging. The categories data related and not data related are presented separately, both ordered from most reported argument to least reported argument.

Category	Argument	Effect
Data related		
Outcomes		
Immaturity	Study period or follow-up considered too short ore use of interim analyses.	Input & model
Limited	Data reported as '*limited*', 'scarce' or 'insufficient', in particular data on quality of life (QoL) was often called '*limited*'.	Input & model
Interpretation	Challenges with *interpretation* of outcomes that were combined, interrelated or if relevance to clinical practice was uncertain due to the use of 'new' outcome measures, not used often (in practice).	Decision making
Absent	Sometimes reported to be completely *absent.*	Input
Surrogate	Available outcomes were *surrogate* outcomes, or it was reported as no data on overall survival or progression free survival.	Input
Population		
Indication	Natural history or disease development and in particular small populations.	Input
Heterogeneity	Data are insufficient on subgroups of patients.	Input
Generalisability	*Generalisability* of literature to the country's own population, children or pregnant women.	Input
Diagnostic	The *diagnosis* is complex, for example if it is based on genetic testing.	CEA
Comparator		
Prices	The *confidentiality of prices* of comparators	Input
Indirect	*indirect comparisons*, in case the performed RCT used a comparator which is no (standard) treatment in the assessing country.	Input
Population with comparator	Lack of data on outcomes in *population receiving comparative treatment.*	Input
No comparator	No available comparator	Input
Trial design		
Trial design	Most often single arm trials, results in indirect treatment comparisons.	Input
Other		
Practice	Limited data on daily practice results in uncertain *cost calculations*, e.g. unknown if vial sharing was possible or how spillage was handled. Limited knowledge about treatment sequences followed in practice, thus the *positioning* of therapy, results in *uncertain comparator.* Role of physicians in management of therapies, lack of	Input

	standardised protocols for administration, a lack of clinical expertise or the effect of contextual factors on effectiveness.	
Policy and organisational	HTA allows for too few consultation moments with experts, access to data was not arranged timely.	Input
Intervention		
Intervention	One HTA organisation reported that gene therapies were challenging for HTA because data is often insufficient (short follow-up).	Input
Not data related		
Other		
Policy and organisational	*Organisation of healthcare programs*, e.g. diagnostic procedures done decentralised whereas subsequent treatment only given centralised in smaller countries, transparency issues, challenges with modelling of savings in local versus centralised institutions. *Organisation of HTA*, e.g. short periods of time for assessments, HTA framework is built for single technology assessments in a specifically defined patient population, not always appropriate for new treatment modalities.	Input & model
Societal and political	Reimbursement of orphan HTs or ethical issues, patient's or physician's *perspectives* and *interests* on outcomes, or *acceptability* of an HT by care givers of children or adolescents.	Input & decision making
Payment or reimbursement	Concerns about affordability due to high costs, problems related to different financial streams that were responsible for coverage of the HT.	Decision making
Practice	*No standard practice* existing or a variety of guidelines, causing uncertainty on how to model the differences and result in uncertainty *positioning* and in which comparator.	Input & model
Intervention		
Positioning	Evolving treatment pathways make the position and thus comparator uncertain.	CEA
Not REA related		
Not REA related	*Quality of the models* delivered by manufacturers were of low quality, due to wrong anticipations or 'opaque' structures. *Modelling of cures* in gene therapies was reported.	Model
Comparator		
Uncertain	*Uncertain* which comparator to select	Input
Multiple	*Multiple* comparators due to multiple indications in comparator group, even with data available this causes challenging *modelling* issues.	Model
Population		
Positioning	High prevalence diseases result in various standards of practice, *positioning* of the assessed treatment and thus *comparators.*	CEA
Heterogeneity	Even with data available, heterogeneity was reported to cause modelling challenges.	Model
Indication	High prevalence indications can result in challenging models with multiple health states.	Model

Figure 6. | This sunburst graph shows all the reported arguments explaining why the case studies and other HTAs were considered as complex by all HTA organisations. Arguments are categorized based on the PICO framework, as shown in figure 2. Some arguments end in the last layer in 'problems with decision making'. These arguments were solely related to decision making. All other arguments resulting in issues in the CEA, inherently also results in decision making issues. The blank shares clock wise, starting at the top, are: Not data related – Population - Indication – CEA – Model; Data related – Comparator – No comparator – CEA – Input; Data related – Intervention – CEA – Input; and Not data related – Other issues – Practice – Positioning – Uncertain comparator - CEA. CEA = cost-effectiveness assessment; REA = relative effectiveness assessment; QoL = quality of life.

Which other examples of HTA of complex HTs were challenging?

The 22 HTA organisations reported 41 cases of HTAs that had been challenging. Most of the reported HTs, 34 (83%), were *pharmaceuticals*, see table 5. Within the reported pharmaceuticals, *antineoplastic treatments* were the largest category of therapies reported (18/34), followed by *musculo-skeletal treatments* and *immunotherapies*. ATMPs were reported 7 times by HTA organisations, which was consistent with the finding of ATMPs ranking most complex in earlier questions given the small amount of existing ATMPs compared to oncology treatments. Based on our classification of challenging issues, the top three types of interventions were *orphan designated treatments* (25/41), *personalised therapies* (19/41) and *combinations of therapies* (13/41), see table 6. See appendix 6 for the detailed list of reported treatments.

Table 5. | This table shows the indication areas of the HTs that were reported by the HTA organisations as cases with challenging HTA. The classification of the cases was done based on the first to levels of ATC-codes developed by the WHO.

Drug class	Times mentioned
Antineoplastic	18
Musculo-skeletal system	6
Immunosuppressant	3
Nervous system	2
Cardiovascular system	1
Endocrine therapy	1
Alimentary tract and metabolism	1
Anti-infectives	1
Respiratory	1
Total	34

Table 6. | This table shows the types of HTs that were reported by the HTA organisations as cases with a challenging HTA. This classification was based on the table with issues identified by us, used in the first question measuring which types of therapies were considered complex.

Complicating issue in mentioned therapies	***Times mentioned***
An orphan designated therapy	25
Personalised treatments, based on a biomarker or gene	19
A combination of therapies	13
Advanced therapy medicinal products (ATMPs)	7
(Companion) diagnostic procedures	4
A preventative treatment or vaccine	3
Histology independent treatments, based on biomarkers	2
A sequence of therapies	2
Medical devices or wearables	2
Digital technologies	1
Advanced surgical interventions, such as managing surgical robots from a distance	1
Proton, photon or laser therapy	0
Gene sequencing	0

Which data sources are accepted for HTA or decision making?

All 22 organisations completed this question. The traditional data sources, *meta-analyses*, *systematic reviews* and *randomized controlled trials (RCTs),* were the top three accepted data sources for HTAs in Europe. All three data sources were accepted by every participating organisation. The RWD sources *case reports*, *unpublished data* and *editorial and expert opinions* were among the least accepted data sources, each accepted by one third of the organisations. See table 7 for all the data sources that were ranked.

Table 7. | This table shows the results of the different existing data sources that are used by the HTA organisations.

Data source	Amount of organisations using this source
Meta-analysis	22
Systematic review	22
RCT	22
Patient registries	19
Interim data from RCT	18
Cohort study (prospective observational)	17
Case-control study	13
Cross-sectional study	12
Case reports and series	9
Unpublished data	9
Editorials/expert opinions	8

How likely are you to accept RWD for HTA or decision making in challenging circumstances?

All 22 organisations completed this question. The average scores on the Likert scale followed small steps without large gaps among succeeding issues. The scores ranged between 3.2-4.3 out of 5.0, making the gap between the first and last issue considerable. The results indicate that in these circumstances the attitude towards RWD acceptance leans more to positive than to negative. HTs with an *orphan designation* or treatments for indications with a very small patient population would create the most likely scenario for organisations to accept RWD HTAs (4.3/5.0). This was closely followed by (companion) *diagnostic procedures* and *surgical interventions*, scoring respectively 4.2 and 4.1 out of 5.0. Organisations would be least likely to accept RWD in HTA if this data came from countries in regions outside their own region, despite it being the only available data source (3.2/5.0). See table 8.

Table 8. | The average scores (1-5) from the questions under which circumstances HTA organisations would be more likely to use (additional) RWD in their HTAs.

Complicating issue	Average score (SD)
Orphan designation or small patient population	4.3 (1.0)
(companion) diagnostic procedures or tests	4.2 (0.7)
Advanced surgical interventions	4.1 (0.9)
Medical devices or wearables	4.1 (1.2)
ATMPs	4.1 (0.9)
Gene sequencing	4.0 (0.9)
A sequence of therapies	3.9 (1.2)

Digital technologies	3.9 (0.9)
Treatments approved based on interim data or with limited follow-up time	3.8 (1.4)
Histology independent treatments, based on biomarkers	3.8 (1.2)
Proton, photon or laser therapies	3.7 (1.1)
RWD only available from other countries IN your region	3.7 (1.1)
Single arm trials	3.6 (1.3)
A preventative treatment or vaccine	3.5 (1.4)
Personalised medicine, based on a biomarker or gene	3.5 (1.2)
A combination of therapies	3.4 (1.3)
Comparison treatments with completely different mechanisms of action	3.3 (1.3)
RWD only available from other countries OUTSIDE your region	3.2 (1.2)

Are there other circumstances where you are more likely to accept the use of RWD for assessments or decision making?

Seven organisations reported additional circumstances where RWD may be accepted. It was reported that RWD would not be accepted as the sole source of evidence, it would be supplementary to traditional RCT evidence. In case of no available RCT data, single-arm studies could be accepted. However, a high level of uncertainty would still be a concern in this case. Table 9 shows all reported circumstances in which organisations would be willing to accept RWD, organised by the PICO framework as in earlier questions.

Table 9. | Additional circumstances in which the HTA organisations would be willing to accept RWD for their assessments. RWD = real world data; RCT = randomized clinical trial; CEA = cost-effectiveness analysis.

Category argument	***Argument***
Population related	RWD would be accepted in case of a high burden of disease, if the indications of the assessed treatment are very severe or even fatal.
Intervention related	RWD would be used in case of highly innovative HTs which are just approaching marketing readiness. Additionally, if the treatment would otherwise not be available or accessible.
Outcome related	RWD would be used in case of a lack of robust evidence, however highly promising results based on the literature that is available. RWD would be accepted when the findings of the research are outdated, or in case of considerable contradictories in the available RCT literature. RWD are more likely to be used where the data has potential to resolve areas of uncertainty in the clinical case.
Comparator	Where the trials used for licensing compare against treatments that are not used in the country's practice, which is similar to issue with single arm trials, RWD would be accepted.
CEA	In case of considerably high uncertainties in the cost-effectiveness analysis, RWD would be used to feed into the assessment.
Policy	RWD would be used in case of pharmaceuticals that are authorized under the European WEU[9] legislation, because this approval is inherently based on RWD. Additionally, in the case of interventions requiring informed consent schemes.
Practice	In the case where there is uncertainty over resource utilisation in clinical practice.

[9] Well-established use: this is the case if the active compound in a pharmaceutical has been used for more than 10 years and the efficacy and safety are thus 'well-established'. WEU product dossiers need to fulfil legislative requirements of Directive 2001/83/EC by showing that the product applying for market access is safe and efficacious and of high quality.

What are reasons for not accepting RWD?

All 22 organisations ranked the set of prespecified reasons for not accepting RWD in HTA or decision making. On average, the organisations ranked '*lacking necessary RWD sources*' as the most important barrier for not being able to accept RWD in HTA, see figure 7. This reason was followed by '*existing policy structures or information governance*' that prevented the organisations from accepting RWD, and that there was '*no possibility to interpret or verify data, or that it was challenging to do so*' was ranked third. Financial reasons and personnel issues were ranked as least contributing to the acceptance of RWD. When considering the median, the order of ranking is almost similar, except for '*lack of methods to use RWD*', due to a the spread of rankings skewed towards lower ranks. See figure 7 for the boxplots of all ranked reasons not to use RWD. There was a considerable variation in responses of HTA agencies. '*no possibility to interpret or verify data, or that it was challenging to do so*' showed the most consistent ranking of all reasons. Additionally, the medians of '*lacking necessary RWD sources*' (2.5) and '*existing policy structures or information governance*' (3.0) show that, despite the wide range of ranks, more than half the HTA organisations ranked these two reason in the top 3.

Discussion

Summary of findings

Our study demonstrated that HTA challenges faced by European HTA organisations mainly rooted in data insufficiencies at time of assessment, and resulted in outcome uncertainties in the REA and input parameters for the CEA. Complex HTs, for example gene therapies, sometimes inherently caused data insufficiencies, making some complex HTs more challenging for HTA. In challenging HTA circumstances, HTA organisations tended to be positive towards accepting RWD to supplement traditional data sources. However, this was only if these sources were timely available and policies did not hinder their utilisation.

In total, 22 out of 33 invited HTA organisations from 21 out of 27 countries completed the questionnaire. This was, despite a slight overrepresentation of the Nordic countries, a balanced mixture. ATMPs were in general considered as the types of therapies most challenging for HTA. Out of seven prespecified case studies, the histology independent therapy was reported as most challenging by organisations that assessed it. Additionally reported complex HTs were mostly pharmaceuticals, oncology products, designated orphan medicines, personalised treatments and combinations of treatments. ATMPs were reported often given to the relatively small amount of existing ATMPs on the market.

In the case studies, methodological issues in the REA or CEA were more often reported to be contributing to HTA challenges than policy- or data related issues. In open questions, the reported challenges were most often data related; absent, insufficient, immature or of low quality. These data insufficiencies resulted in uncertainties around desired outcomes, subsequently creating uncertainty around input parameters for the CEA. The non-data related arguments were most often societal- or political pressure or organisational- and policy related problems, resulting in uncertainties around the input parameters in the CEA or created challenges in decision making. Direct modelling issues in the CEA were less often

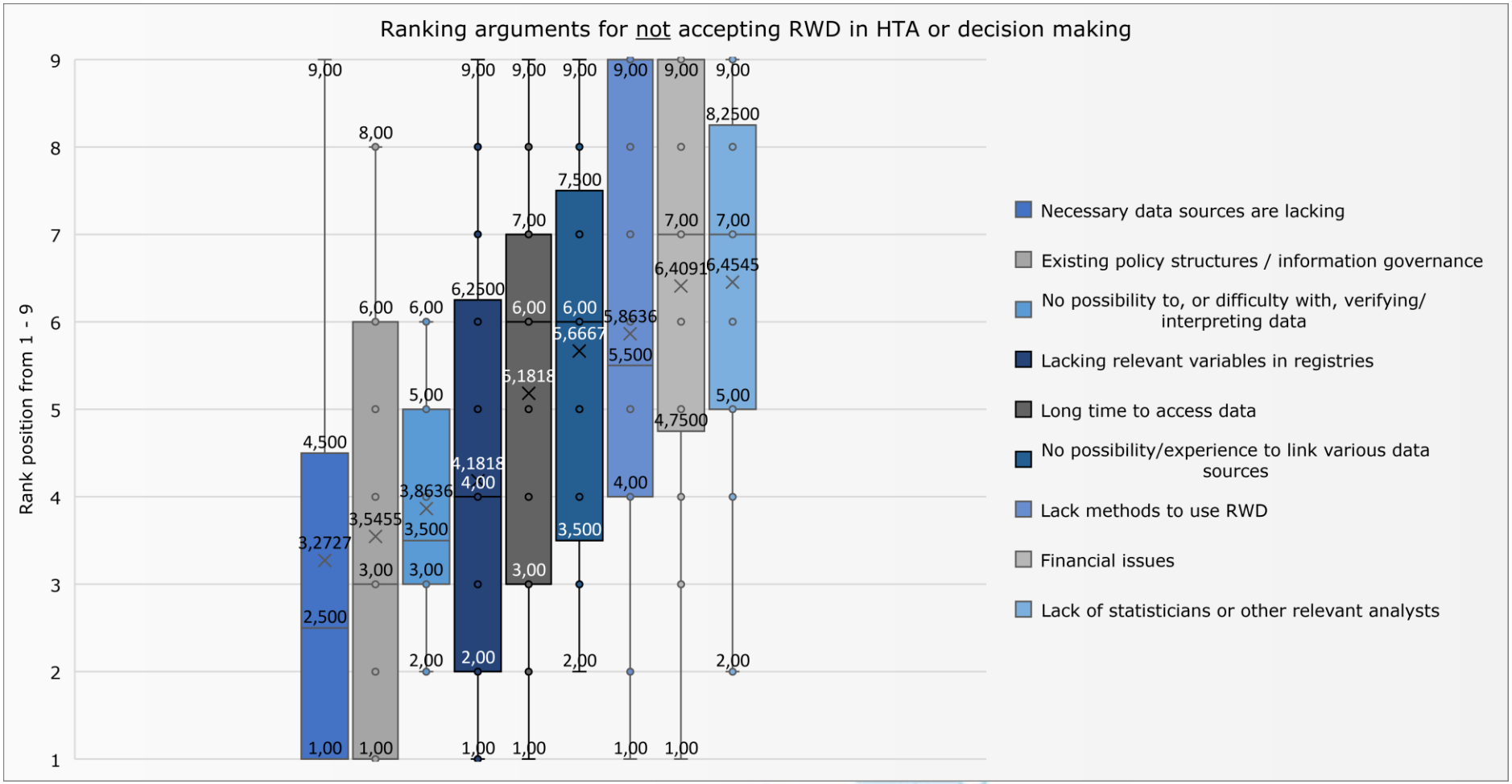

Figure 7. | Boxplot results of the ranking of arguments for not accepting RWD in HTA or decision making. Arguments were placed on a rank from 1 to 9, with 1 being the highest rank and 9 the lowest. The arguments are arranged based on the average scored rank, shown at the cross (x), from left (highest ranked = 3.3) to right (lowest ranked = 6.5). The median rank is shown at the middle stripe (-).

reported. The arguments showed considerable variety per case, although data issues were reported for these case studies.

All participating organisations reported accepting traditional data sources. For RWD sources, this varied from 19 out of 22 organisations to 8 out of 22, with patient registries being the most accepted source. In challenging circumstances, organisations tended to be likely to accept RWD, scores ranging from 3.2 – 4.3 out of 5.0. Additionally reported circumstances to accept RWD mostly related to insufficient outcomes data from RCTs. As barrier for not accepting RWD, more than half of the organisations ranked '*lacking necessary RWD sources*' and '*existing policy structures or information governance*' in the top 3 reasons for not accepting the RWD sources.

In perspective

Overall, this study does not show many unexpected results, rather most of it confirms what's signalled from practice(4,10,14–16). However, we did expect that the challenges in HTA of complex HTs would also be more related to the complexity of the HT. Although sometimes the HT inherently restricts the possibility of gathering necessary data, i.e. orphan designated therapies or curative HTs, most of the arguments by HTA organisations were related to issues with the available data at time of assessment. Additionally, more challenges related to actual modelling work were expected. Our results show that most challenges are with the REA and the input parameters for the CEA model. One possible explanation for this, might be that for some HTA organisations 'complex' HTs are not part of the selection of assessed HTs. This might be reflected in the low number of organisations that we found to have (yet) assessed our case study examples. Additionally, not all HTA organisations perform CEAs which would explain the focus on data- and REA related arguments.

Our results are in line with earlier studies. Research from the EUnetHTA joint action (JA)3, focussing on single technology assessments, found that the larger share of European HTA agencies has procedures for HTA of pharmaceuticals as compared to non-pharmaceuticals. This seemed to be reflected in our results where most of the challenging HTAs reported by the organisations were pharmaceuticals. The JA3 also demonstrated that a minority of the organisations uses horizon scanning to support topic selection nor do they prepare with defining the assessment scope or decision problem in advance of the HTA. Both these could be useful tools to foresee complex HTs and challenges in HTA and prepare in advance relevant HTA procedures and methodology needed for these challenging HTAs. JA3 also concludes that working procedures in HTA organisations in Europe vary widely, which is, again, reflected in our results regarding reasons for not accepting RWD in HTA for example. (4)

Multiple factors are contributing to the challenges of HTA. HTA organisations reported considering ATMPs, in general, as the type of HT that is most complex in HTA. However, based on specified case studies, the ATMP case was not scored most complex. Histology independent treatments, devices, combinations or preventative HTs scored similar or higher, suggesting other contributing factors.

In questions with categorised options, HTA organisations reported that methodological aspects, either in REA or CEA, were more often contributing factors

to challenges in our prespecified case studies than policy- or data related issues. Based on our open questions, the complexity in HTs seems to be mostly caused by data issues, in particular by uncertainty around available outcomes. This could be explained by our assessment approach. Organisations would likely have filled in the issues in the case studies at the point where they encountered them, whereas in our assessment, we located the problem in the category where it is rooted, starting to look at data issues. Outcome uncertainties mostly affects the REAs of HTs, indirectly, it also affects certainty about the outcomes required in the CEAs, which in turn translates into uncertainty around the decisions made.

Systematic reviews on the economic evaluations of genetic testing, ATMPs and sequences of treatment with disease-modifying anti-rheumatic drugs (DMARDs), investigated the quality and approaches of economic evaluations of these challenging HTs. All three articles conclude that the evidence available for the HTs is often limited and timely access to this data is of utmost importance, as in accordance to our results. (14–16)

Makady demonstrated that policies and guidelines from HTA agencies in 6 European countries did in general not actively encourage the use of RWD(17). Certainly this was the case in REAs, whereas the interest in RWD in the case of CEAs was wider, sometimes even requested. In the practice of HTA of oncological drugs for the treatment of melanoma, another study of Makady showed that in 5 European countries, the use of RWD was indeed higher in the CEA than in the REA, although a lot of differences among the countries were still visible(10). Similarly, our results on the acceptance of RWD in challenging HTA seemed positive, although it is not accepted by all organisations. This might be related to existing policy structures.

Strengths and Limitations

A strength of our study was to directly approach assessing individuals at European HTA organisations, in a validated way, gathering additional information about currently faced challenges, rather than solely challenges explicitly described in published documents. Secondly, using the questionnaire allowed us to gather information from both published assessments as well as still ongoing HTAs. Third, the response rate to our questionnaire was satisfying, 61%, and the participants represent a balanced spread throughout Europe, ensuring transferability of results to most or even all European countries. Lastly, the questionnaire was developed, tested and validated in a collaboration with both academic institutions and HTA organisations, ensuring robustness of the methodology while enhancing the relevance of our questions to the HTA practice.

A limitation of our study, despite including most of the European countries, larger countries like France, Portugal and Italy are missing. However, we have no information that their perspectives would be very different from the perspective of the included HTA organisations. Secondly, due to the collaborative dissemination of our questionnaire, we aimed at a concise questionnaire to ensure a sufficient response rate. Because of this, a 'simple' reference case was left out of the set of case studies. The same was done for the question, scoring general types of technologies for their complexities. Our results should therefore be interpreted in relation to each other, not to 'simple' HTA. Third, a large share of the participating HTA organisations solely assesses pharmaceuticals. This seems to be reflected in

our results, e.g. where organisations were inquired to report additional complex cases of HTA, which were mostly limited to pharmaceutical HTs. This means that currently we lack an overview of the extent to which combinations of HTs, digital HTs, treatment pathways etc. will induce more challenges in HTAs in the future.

Implications

Challenges found in our results highlight the importance of the methodological work that is done in HTx. Both the artificial intelligence endeavours in work package 3 and prediction modelling in work package 2, aim to develop methods for combining data sources and build models that increase outcomes certainty. Additionally, our results provide new, practically relevant, starting points for further research in both packages. The relevance of challenges found in this study and the large representation of European HTA organisations that provided information for our results will support implementation and ease uptake of developed methods by HTA organisations.

HTx uses four case studies for novel methodology development; proton therapy by head and neck cancer, diabetes mellitus (DM), multiple sclerosis (MS) and myelodysplastic syndromes (MDS). All case studies hold some of the challenges found in this study. Small patient populations are reflected in our MDS case study and treatment sequences in MS provide an example for challenges due to data limitations in case of varieties of treatment positioning. DM reflects combinations of therapies, such as the continuous glucose monitoring device with medication, challenges with uncertain outcomes due to interrelation or the influence of system factors and patient and physician perspectives. Proton or photon therapy for head and neck cancer will provide models that carefully estimate the individual effectiveness based on many different individual characteristics, system factors and physician perspectives.

Future research

In-depth research focussing on the most challenging case studies, i.e. ATMPs and histology independent treatments, would be necessary to find details of the methodological issues faced. Detailed knowledge would further support methodological work in HTx. This would also give insight in variations in approach between HTA organisations or could focus on improvements of methodology proposed by HTA organisations, supporting implementation. Given the focus of our results on pharmaceuticals and differences in regulatory environments, additional research would be needed to inform our understanding of the differences in challenges between pharmaceuticals and non-pharmaceuticals. The most pressing challenges found in this study, insufficiencies in available data, societal and organisational issues and regulations around and availability of RWD in HTA, could possibly be improved with policies. To give recommendations on possible regulatory measures, comparative policy analyses would be necessary.

Conclusions

HTA challenges faced by European HTA organisations mainly root in data insufficiencies at time of assessment, and result in outcome uncertainties in the REA and input parameters for the CEA, which translate into uncertainty in decision

making. Complex HTs, for example gene therapies, sometimes inherently cause data insufficiencies, making some complex HTs more challenging for HTA. In challenging HTA circumstances, HTA organisations tend to be positive towards accepting RWD to supplement traditional data sources. However, this is true only if these sources are timely available and policies do not hinder their utilisation. These results highlight the importance of the work that is done in the methodological work packages of HTx, and support the implementation work packages. More detailed research on methodologies used in challenging HTA, acceptance of RWD and policy recommendations are necessary to further support the implementation of the next generation of HTA.

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Appendices

Appendix 1. | Organisations invited to complete the questionnaire

Table 1. | Table of all organisation in European countries invited to fill in the questionnaire. These are all EUnetHTA member countries, HTA organisations (in)directly involved in decision making which assess both pharmaceuticals and non-pharmaceuticals.

Country	Organisation
Austria	Austrian Social Insurance (HBV)
België	"Rijksinstituut voor Ziekte- en Invaliditeitsverzekering" (RIZIV INAMI)
Bulgaria	National Center of Public Health and Anlayses (NCPHA)
Croatia	Croatian Health Insurance Fund (HZZO)
Cyprus	Ministry of Health
Czech Republic	State Institute for Drug Control (SUKL)
Denmark	Danish Medicines Council (DMA)
Finland	Finnish Medicines Agency (FIMEA)
France	"Haute Autorité de Santé" (HAS)
Germany	Gemeinsamer Bundesausschluss (B-GA)
Hungary	National Institute of Pharmacy and Nutrition (NIPN)
Hungary	Department of Technology Assessment
Ireland	National Centre for Pharmacoeconomics (NCPE)
Italy	The Italian Medicines Agency (AIFA)
Lithuania	State Health Care Accreditation Agency under the Ministry of Heatlh of the Republic of Lithuania (VASPVT)
Malta	Directorate for Pharmaceutical Affairs, Ministry for Health Malta (DPA/MFH)
Netherlands	The Dutch National Health Care Institute (ZIN)
Norway	Norwegian Medicines Agency (NOMA)
Poland	Agency for Health Technology Assessment and Tariff System (AOTMiT)
Portugal	National Authority of Medicines and Health Products (INFARMED)
Romania	National School of Public Health, Management and Professional Development Bucharest (NSPHMPDB)
Scotland	Scottish Health Technologies Group (SHTG)
Scotland	Scottish Medicines Consortium (SMC)
Slovakia	Comenius University in Bratislava Faculty of Pharmacy (UNIBA-FoF)
Slovakia	Ministry of Health
Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)
Slovenia	Ministry of Health
Spain	Basque Office for Health Technology Assessment (OSTEBA)
Spain	The Spanish Agency of Medicines and Medical Devices (AEMPS)
Spain	Galician Agency for Health Technology Assessment (AVALIA-T)
Sweden	The Dental and Pharmaceutical Benefits Agency (TLV)
Switzerland	Federal Office of Public Health (FOPH - BAG)
United Kingdom	the National Institute for Health and Care Excellence (NICE)

***Appendix 2.* | List of all the questions disseminated to the HTA organisations.**

General information

What is the name of your organisation?

What is your current position within this organisation?

Defining 'challenging' HTA

The first set of questions aims to identify certain types of complex technologies that are perceived as having challenging assessments by HTA organisations. By doing so, we hope that we can identify the gaps in methodology, data sources, tools, policy structures that would facilitate the assessment of these 'complex' technologies. The questions in this section focus on technologies that you might have assessed in the past years. In order to adequately answer the questions, we hope that someone involved in the assessment of these technologies can (help) answer the questions. The following case studies will be questioned:

- *Dabrafenib/trametinib (TafMek) for the treatment of adults with metastatic or unresectable melanoma with BRAF V600 mutation*
- *Continuous glucose monitoring (Freestyle Libre) to guide treatment of adults and children with diabetes mellitus type 1 or 2*
- *Voretigene neparvovec (Luxturna) as single dose gene therapy for adults and children with retinal dystrophy caused by a bi-allelic RPE65 mutation*
- *Repetitive transcranial magnetic stimulation for treatment of adults with treatment-resistant major depression*
- *HPV vaccine (Gardasil/Cervarix) given to young adolescent women for the prevention of cervical cancer*
- *Transcatheter aortic valve implantation (TAVI) in adults at intermediate surgical risk*
- *Larotrectinib (Vitrakvi) for adults and children with the histology independent diagnosis of a solid tumour with NTRK gene fusion*

In general, how often do you consider an assessment of a new health technology 'complex', in case of assessing:

Case	Never	Rarely	Sometimes	Often	Always	Never assessed/ unable to answer
A combination of therapies						
A sequence of therapies						
Personalised treatments, based on a biomarker or gene						
An orphan designated therapy						
A preventative treatment or vaccine						
Histology independent treatments, based on biomarkers						
Advanced therapy medicinal products (ATMPs), like somatic-cell therapy, curative gene therapies, tissue engineered medicines						
Medical devices or wearables						

Digital technologies						
Gene sequencing						
(Companion) diagnostic procedures						
Advanced surgical interventions, such as managing surgical robots from a distance						
Proton, photon or laser therapy						

Case 1. **| Dabrafenib/trametinib (TafMek) for the treatment of adults with metastatic or unresectable melanoma with BRAF V600 mutation**

Was the assessment of this health technology perceived as a 'complex' assessment by the agency?

- Yes
- No
- Did not assess

Case 1: If yes, in what aspect was the assessment perceived as complex? Multiple answers are possible.

- Methodological aspects in the relative effectiveness assessment
- Methodological aspects in the cost-effectiveness assessment
- Other methodological aspects
- Policy related issues
- Data related challenges

Case 1: If yes, can you very briefly explain what the main issues were, that made this assessment challenging? Explain in 2-3 sentences or key words per selected item in the previous question.

Case 2. **| Continuous glucose monitoring (Freestyle Libre) to guide treatment of adults and children with diabetes mellitus type 1 or 2**

Was the assessment of this health technology perceived as a 'complex' assessment by the agency?

- Yes
- No
- Did not assess

Case 2: If yes, in what aspect was the assessment perceived as complex? Multiple answers are possible.

- Methodological aspects in the relative effectiveness assessment
- Methodological aspects in the cost-effectiveness assessment
- Other methodological aspects
- Policy related issues
- Data related challenges

Case 2: If yes, can you very briefly explain what the main issues were, that made this assessment challenging? Explain in 2-3 sentences or key words per selected item in the previous question.

Case 3. **| Voretigene neparvovec (Luxturna) as single dose gene therapy for adults and children with retinal dystrophy caused by a bi-allelic RPE65 mutation**

Was the assessment of this health technology perceived as a 'complex' assessment by the agency?

- Yes
- No
- Did not assess

Case 3: If yes, n what aspect was the assessment perceived as complex? Multiple answers are possible.

- Methodological aspects in the relative effectiveness assessment
- Methodological aspects in the cost-effectiveness assessment
- Other methodological aspects
- Policy related issues
- Data related challenges

Case 3: If yes, can you very briefly explain what the main issues were, that made this assessment challenging? Explain in 2-3 sentences or key words per selected item in the previous question.

Case 4. **| Repetitive transcranial magnetic stimulation for treatment of adults with treatment-resistant major depression**

Was the assessment of this health technology perceived as a 'complex' assessment by the agency?

- Yes
- No
- Did not assess

Case 4: If yes, in what aspect was the assessment perceived as complex? Multiple answers are possible.

- Methodological aspects in the relative effectiveness assessment
- Methodological aspects in the cost-effectiveness assessment
- Other methodological aspects
- Policy related issues
- Data related challenges

Case 4: If yes, can you very briefly explain what the main issues were, that made this assessment challenging? Explain in 2-3 sentences or key words per selected item in the previous question.

Case 5. **| HPV vaccine (Gardasil/Cervarix) given to young adolescent women for the prevention of cervical cancer**

Was the assessment of this health technology perceived as a 'complex' assessment by the agency?

- Yes
- No
- Did not assess

Case 5: If yes, in what aspect was the assessment perceived as complex? Multiple answers are possible.

- Methodological aspects in the relative effectiveness assessment
- Methodological aspects in the cost-effectiveness assessment

- Other methodological aspects
- Policy related issues
- Data related challenges

Case 5: If yes, can you very briefly explain what the main issues were, that made this assessment challenging? Explain in 2-3 sentences or key words per selected item in the previous question.

Case 6. **| Transcatheter aortic valve implantation (TAVI) in adults at intermediate surgical risk**

Was the assessment of this health technology perceived as a 'complex' assessment by the agency?

- Yes
- No
- Did not assess

Case 6: If yes, n what aspect was the assessment perceived as complex? Multiple answers are possible.

- Methodological aspects in the relative effectiveness assessment
- Methodological aspects in the cost-effectiveness assessment
- Other methodological aspects
- Policy related issues
- Data related challenges

Case 6: If yes, can you very briefly explain what the main issues were, that made this assessment challenging? Explain in 2-3 sentences or key words per selected item in the previous question.

Case 7. **| Larotrectinib (Vitrakvi) for adults and children with the histology independent diagnosis of a solid tumour with NTRK gene fusion**

Was the assessment of this health technology perceived as a 'complex' assessment by the agency?

- Yes
- No
- Did not assess

Case 7: If yes, n what aspect was the assessment perceived as complex? Multiple answers are possible.

- Methodological aspects in the relative effectiveness assessment
- Methodological aspects in the cost-effectiveness assessment
- Other methodological aspects
- Policy related issues
- Data related challenges

Case 7: If yes, can you very briefly explain what the main issues were, that made this assessment challenging? Explain in 2-3 sentences or key words per selected item in the previous question.

Can you give other examples of assessments of complex therapies, that were challenging? Please add a reference in the form of the name of the technology assessed and where we can find a document about this assessment.

Can you think of other reasons, besides the ones discussed in this survey (methodological, policy related, amount or quality of data), that can make an assessment of a complex therapy challenging? If this reason is related to a specific technology, please give the name of this technology.

Tick the boxes of the data sources that you do accept for assessments or decision making at your agency. Multiple answers are possible.

- Meta-analysis
- Systematic review
- RCT
- Interim data from RCT
- Cohort study (prospective observational
- Case-control study
- Cross-sectional study
- Case reports and series
- Editorials/expert opinions
- Unpublished data
- Patient registries

Rank the following issues of reasons for not using RWD from top (most important reason) down (least important or no reason at all).

1. Existing policy structures / information governance (e.g. rules complicating or prohibiting use of RWD)
2. Data sources lacking
3. Long time to access data
4. Lacking relevant variables in registries
5. Financial issues
6. Lack of statisticians or other relevant analysts
7. No possibility to or difficulty with verifying/interpreting data
8. No possibility/experience to link various data sources
9. Lack methods to use RWD

How likely are you (or would you be) to accept RWD sources for assessment and appraisal in the following circumstances? In other words, how much would you want to use RWD sources because you consider that it is needed under each of the circumstances? Please see the given definition of RWD in the introduction.
1 = not likely at all
5 = most likely

Circumstance	1	2	3	4	5	Never assessed/ unable to answer
A combination of therapies						
A sequence of therapies						
Personalised medicine, based on a biomarker or gene						
A preventative treatment or vaccine						
Histology independent treatments, based on biomarkers						
advanced therapy medicinal product (ATMP) like somatic-cell therapy, curative gene therapies, tissue engineered medicines						
Medical devices or wearables						
Digital technologies						
Gene sequencing						
(Companion) diagnostic procedures/tests						
Advanced surgical interventions						
Proton, photon or laser therapies						
Comparison treatments with completely different mechanisms of action						
Treatments approved based on interim data or with limited follow-up time						
Orphan designation or small patient population						
Single arm trials						
RWD that's not available from your country, but only available from other country(ies) in your region						
RWD that's not available from your country, only available from other country(ies) OUTSIDE your region						

Can you think of any other circumstances where you are (or would be) more likely to accept the use of RWD for assessments or decision making?

Appendix 3. | Representatives involved in the Expert Panel and Pilot Testing

From an academic perspective, Utrecht University and the University of Copenhagen were involved in the expert panel based on the established collaboration for dissemination of questions for the HTx project. The National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Dental and Pharmaceutical Benefits Agency (TLV) and the Dutch National Health Care Institute (ZIN) were involved in the expert panel and pilot testing, for input from a practical perspective and knowledge. Most HTA organisations are involved in the HTx project, one organisation was involved based on the authors network.

Table 1. | Representatives involved in the expert panel and pilot test of the questionnaire. People were selected based on research field, practical experience, relationship to the HTx consortium and their availability.

Organisation	**People involved**
Utrecht University	Dr. W.G. Goettsch, R.A. Vreman, prof. A.K. Mantel-Teeuwisse, M.A. Hogervorst
University of Copenhagen	Prof. M. de Bruin, dr. R. Ofori-Asenso
NICE	Dr. D. Dawoud
SMC	Dr. J. Jones
TLV	A. Strömgren, J. Pontén
ZIN	R. Kalf, A. Lokhorst, prof. D. Delnoij
SRI	Prof. dr. Z Kaló, I. Jakab, B. Németh

Appendix 4. | Countries that completed the questionnaire

Table 1. | Table of countries and organisations that completed the questionnaire, including the positions of the person that completed the questionnaire.

Country	**Organisation**	**Function**	**pharmaceuticals / medical technologies**
Austria	Austrian Social Insurance (HBV)	Medical Evaluator	Both
Belgium	"Rijksinstituut voor Ziekte- en Invaliditeitsverzekering" (RIZIV INAMI)	coordinator expertise pharmaceuticals	Both
Bulgaria	National Center of Public Health and Anlayses (NCPHA)	Head of Department	Pharma
Croatia	Ministry of Health Croatia (CHIF/HZZO)	Senior Advisor Specialist	Both
Czech Republic	State Institute for Drug Control (SUKL)	senior assessor	Pharma
Denmark	Danish Medicines Council (DMA)	Health Science Officer	Pharma
Finland	Finnish Medicines Agency (FIMEA)	Pharmacoeconomist	Pharma
Germany	Gemeinsamer Bundesausschluss (B-GA)	Department Head, Department of Methodological Advice	Both
Hungary	National Institute of Pharmacy and Nutrition (NIPN)	Head of Department	Both
Ireland	National Centre for Pharmacoeconomics (NCPE)	Deputy Head and Member of Senior Management Team	Pharma
Malta	Directorate for Pharmaceutical Affairs, Ministry for Health Malta (DPA/MFH)	Director Pharmaceutical Affairs	Pharma
Netherlands	The Dutch National Health Care Institute (ZIN)	Assessor	Both
Norway	Norwegian Medicines Agency (NOMA)	Senior Pharmaceutical Advisor HTA	Pharma
Poland	Agency for Health Technology Assessment and Tariff System (AOTMiT)	HTA analyst	Both
Romania	National School of Public Health, Management and Professional Development Bucharest (NSPHMPDB)	Senior Public Health & Management Specialist	Pharma
Scotland	Scottish Health Technologies Group (SHTG)	Lead Health Services Researcher	MedTech
Scotland	Scottish Medicines Consortium (SMC)	Principal Pharmacist	Pharma
Slovakia	Comenius University in Bratislava Faculty of Pharmacy (UNIBA-FoF)	Head of department	Both
Spain	Basque Office for Health Technology Assessment (OSTEBA)	Senior researcher	Both
Sweden	The Dental and Pharmaceutical Benefits Agency (TLV)	Head of Unit	Both
Swiss	Federal Office of Public Health (FOPH - BAG)	Head Section HTA	Both
UK	the National Institute for Health and Care Excellence (NICE)	Scientific Adviser	Both

Appendix 5. | Detailed description of the arguments for challenging HTA per case study

Case study 1: dabrafenib/trametinib (TafMek)

TafMek was assessed by most, 14/22, HTA organisations, and ranked 5/7 with 57% reporting it as challenging. The main arguments for the challenge of the HTA, were due to data. In available literature, TafMek was compared to observation. An appropriate comparator needed to be selected, which was complicated by variations in standard of care. Inherently, an indirect comparison was necessary. Prices of the comparators were reported to be confidential. The TafMek study was published after interim analysis and therefore available data was immature, creating uncertainty about overall survival. Additionally, data on TafMek in second or further line therapy was absent. Additionally, organisations reported that the QoL measurement was biased and that the period for assessment was too short.

Case study 2: continuous glucose monitoring (Freestyle Libre)

CGM was assessed by 9/22 organisations and ranked a shared second place with 67% of the organisations reporting the HTA as challenging. The reported arguments were various. In this field, many different medical devices are available and the clinical superiority over other devices was unclear. This was reported due to manufacturer data that was challenging to compare and that outcomes were interrelated. HbA1c as outcome in patients with a glucose level on target and receiving insulin, aim for prevention of hypoglycaemia, whereas patients with high blood glucose level aim to prevent hyperglycaemia and complications. Both aims should be proven to properly assess the HT in HTA. Limited evidence was available and thus patients and physician perspectives were required, from which there was large social pressure. Additionally related to the data, the QoL was measured with TTO and considered uncertain. The generalisability to pregnant women and children was reported as complicated. Reported lastly, was that the role of physicians in management of the HT and way of financing was unclear. There was no data on the 'consumption' of the device, which made input parameters uncertain.

Case study 3: voretigene neparvovec (Luxturna)

Luxturna was assessed by 9/22 organisations and ranked a shared second place with 67% of the organisations reporting it as challenging. Long-term data was missing in this assessment, making extrapolations on disease development challenging, while the long-term effect was claimed by the manufacturer. This HT is not a lifesaving treatment, it aims at improving QoL. This was considered uncertain by the organisations and the used outcome measure was unusual and complex to interpret. A small number of patients are eligible for receiving the treatment, and the clinical diagnosis is based on genetics and is complicated. The studied patient population was heterogeneous. Due to high costs, the affordability was under discussion. The savings possibly made in municipalities could not be incorporated into the model.

Case study 4: repetitive transcranial magnetic stimulation

Only 4/22 organisations assessed this HT and it was considered least complex of the case studies with only one organisation (25%) reporting it to be challenging. It

was reported that data on the HT was needed in order to develop protocols for the administration; localisation, frequency, intensity, number of pulses, maintenance regimen, concurrent medication and various other issues.

Case study 5: HPV vaccine (Gardasil/Cervarix)

The HPV vaccine was assessed by 9/22 organisations and ranked 6/7 with 44% of the organisations reporting it as challenging. The challenge of this HTA was in the modelling of the long-term effect of the HT. There was uncertainty about the development of herd immunity. Available literature used surrogate outcomes as end-point and the study population was hard to generalise to the whole population. For one organisation, it was uncertain how the vaccine should be covered and how the program should be organised. The acceptability of the HT by tutors, that sometimes decide for young adolescents was unknown.

Case study 6: transcatheter aortic valve implantation (TAVI)

In the fourth place (60%) was the case stud on TAVI, which was assessed by only 5/22 organisations. The main issue was uncertainty about the available evidence on medium-term outcomes in a specific patient population. One HTA organisation reported that a limited number of clinical experts was available, and all had an interest in providing the HT at their own centres, while decentralised provision was not considered appropriate.

Case study 7: larotrectinib (Vitrakvi)

By 8/22 organisations, Vitrakvi was ranked the most complex case study to assess, with 88% reporting it as challenging. The challenges were caused by various issues. Data was reported as limited and immature, and in particular data on appropriate comparators was scarce. The clinical relevance of the studied outcome was uncertain. The patient population was heterogeneous due to various tumour sides that could show NTRK-gene fusion presence. Not for all tumour sides, the effect of NTRK-gene fusion was known, and for some of these sides there was no data on the population specific with this gene presence. Therefore, the natural history of the disease with or without comparator was unclear. For each tumour side, the studied population was small. Due to the heterogeneity, there were plenty of comparators that needed to be considered. Additionally, one organisation reported here that wastage of the medicine and adherence was unknown, hindering accurate costs estimations.

Appendix 6. | Answers to the open question requesting additional cases that were perceived as challenging to assess by the HTA organisation.

Table 1. | Answers to: "Can you give other examples of assessments of complex therapies, that were challenging? Please add a reference in the form of the name of the technology assessed and where we can find a document about this assessment."? Mentioned cases were organized by 'pharmaceutical/non-pharmaceutical' (second column) and categorized by type of intervention (last column).

Type of health technology	Can you give other examples of assessments of complex therapies, that were challenging?	Brand name	Therapeutic area	Therapeutic area classification
Pharmaceutical	Afostase alfa	Strensiq	Hereditary transthyretin amyloidosis	Genetic
Pharmaceutical	Alectinib	Alecensa	Non-small cell lung carcinoma	Oncology
Pharmaceutical	PCSK9 inhibitors: Alirocumab and Evolocumab	Praluent and Repatha	Hypercholesterolemia	Metabolic
Pharmaceutical	Atezolizumab with bevacizumab, paclitaxel, carboplatin	Tecentriq	Non-small cell lung carcinoma	Oncology
Pharmaceutical	Burosumab	Crysvita	X-dependent hypophosphatemia	Metabolic
Pharmaceutical	CAR-T	CAR-T cell therapies	Diffuse large B cell lymphoma	Oncology
Pharmaceutical	CAR-T	CAR-T cell therapies	Diffuse large B cell lymphoma	Oncology
Pharmaceutical	CAR-T: tisagenlecleucel and axicabtagene ciloleucel	Kymriah and Yescarta	Diffuse large B cell lymphoma	Oncology
Pharmaceutical	CAR-T: axicabtagene ciloleucel	Yescarta	Diffuse large B cell lymphoma	Oncology
Pharmaceutical	Darvadsrocel	Alofisel	Crohn's disease	Inflammatory
Pharmaceutical	Dinutuximab	Qarziba	High risk neuroblastoma	Oncology
Pharmaceutical	Enzalutamide	Xtandi	non-metastatic castration-resistant prostate carcinoma	Oncology
Pharmaceutical	Erenumab and fremanezumab	Aimovig	Migraine	Neurological
Pharmaceutical	Gene therapies	Gene therapies	Various indications	Various
Pharmaceutical	Ibrutinib	Imbruvica	Chronic Lymphatic Leukemia	Oncology
Pharmaceutical	Inotersen	Tegsedi	hypophosphatasia	Metabolic
Pharmaceutical	Lenvatinib	Lenvima	Renal cell carcinoma	Oncology
Pharmaceutical	Lesinurad	Zurampic	Gout	Inflammatory
Pharmaceutical	Lorlatinib	Lorviqua	Non-small cell lung carcinoma	Oncology

Pharmaceutical	Nivolumab	Opdivo	Melanoma (carcinoma)	Oncology
Pharmaceutical	Nusinersen	Spinraza	SMA disease	Neurological
Pharmaceutical	Nusinersen	Spinraza	SMA disease	Neurological
Pharmaceutical	Nusinersen and other Highly specialised technologies (HST)	Spinraza	SMA disease	Neurological
Pharmaceutical	Nusinersen	Spiranza	SMA disease	Neurological
Pharmaceutical	Ocrelizumab	Ocrevus	RRMS	Neurological
Pharmaceutical	Ocrelizumab	Ocrevus	RRMS	Neurological
Pharmaceutical	Olaparib	Lynparza	Ovarian carcinoma	Oncology
Pharmaceutical	Olaparib	Lynparza	Epithelial ovarian, fallopian tube, or primary peritoneal carcinoma's	Oncology
Pharmaceutical	Oncology drugs	Oncology	Various carcinoma's	Oncology
Pharmaceutical	Oncology drugs	Oncology products	Various carcinoma's	Oncology
Pharmaceutical	Sofosbuvir	Sovaldi	Hepatitis C	Infectious
Pharmaceutical	Stem cell treatment	Holoclar	Cornea epithelium damage	Inflammatory
Device	Alphadefensin lateral flow test	Synovasure	Periprosthetic Joint Infection	Inflammatory
Device	Direct liver test	Various	Various liver conditions	Various
Device	Newborn screening for systic fybrosis	Guthrie card	Cystisc Fibrosis	Genetic
Device	Trisomy testing	non-invasive testing for trisomy 21, 18 and 13	Trisomy 21, 18, 13	Genetic
Device	3D printers	Various	N/A	Various
Device	Optune	Optune	Glioblastoma	Oncology
Device	Diabetes Home and Health monitoring	Various	Diabetes mellitus	Metabolic