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Health Policy Analysis

Reported Challenges in Health Technology Assessment of Complex Health Technologies

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ABSTRACT

Objectives: With complex health technologies entering the market, methods for health technology assessment (HTA) may require changes. This study aimed to identify challenges in HTA of complex health technologies.

Methods: A survey was sent to European HTA organizations participating in European Network for HTA (EUnetHTA). The survey contained open questions and used predefined potentially complex health technologies and 7 case studies to identify types of complex health technologies and challenges faced during HTA. The survey was validated, tested for reliability by an expert panel, and pilot tested before dissemination.

Results: A total of 22 HTA organizations completed the survey (67%). Advanced therapeutic medicinal products (ATMPs) and histology-independent therapies were considered most challenging based on the predefined complex health technologies and case studies. For the case studies, more than half of the reported challenges were "methodological," equal in relative effectiveness assessments as in cost-effectiveness assessments. Through the open questions, we found that most of these challenges actually rooted in data unavailability. Data were reported as "absent," "insufficient," "immature," or "low quality" by 18 of 20 organizations (90%), in particular data on quality of life. Policy and organizational challenges and challenges because of societal or political pressure were reported by 8 (40%) and 4 organizations (20%), respectively. Modeling issues were reported least often (n = 2, 4%).

Conclusions: Most challenges in HTA of complex health technologies root in data insufficiencies rather than in the complexity of health technologies itself. As the number of complex technologies grows, the urgency for new methods and policies to guide HTA decision making increases.

Keywords: challenges, cost-effectiveness assessment, data quality, decision making, health technology assessment, personalized health technologies, relative effectiveness assessment.

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Introduction

Health technology assessment (HTA) is "a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle."[1] Given that the determination of the technology's value is related to the value of other health technologies, the process often includes a "relative effectiveness assessment" (REA), which is sometimes complemented with a cost element, the "cost-effectiveness assessment" (CEA).[2] Over the past decades, the role and importance of HTA have developed gradually in response to greater emphasis on evidence-based decision making in healthcare. At the same time, the treatment of patients has advanced over recent years, because of the development of increasingly tailored health technologies, including combinations of health technologies—consisting of pharmaceuticals, diagnostics, devices, digital tools, and interventions such as wearables and applications—personalized treatments, and treatment pathways, that is, "complex health technologies."[3] These developments happened alongside increasing pressure on financing and delivery of healthcare because of demographic and other changes.[4]

From previous research, we know that these complex health technologies come with new challenges to the existing reimbursement framework.[5-11] Orphan drugs and the trend toward personalized or individualized treatments do not always allow for large randomized controlled trials.[8,9] Increasingly, new trial designs with single arms are used for small populations or interim data are all that is available upon approval.[5-7] The claimed lifelong effects of cell and gene therapies are not feasible to capture in clinical trials before initial market approval and reimbursement decisions.[10,11] A recent example of therapies with challenges to the existing HTA framework are the histology-independent therapies, for example, larotrectinib.[12-14] The prevalence of the mutations targeted by these therapies is rare and spread over various tumor

types. This results in low sample sizes per tumor type and an extremely heterogeneous patient population in these "basket" trials.

In addition to the changing nature of treatments, over the past years, patients request access to new health technologies more early in the lifecycle of technologies and health technologies are more often targeting small patient populations.[15] Exceptional, conditional, and orphan drug approvals have resulted in decreasing amounts and quality of data available at the time of HTA, leading to greater uncertainties and complicating reimbursement decision making.[16-18] To increase certainty in healthcare decisions, the use of real-world data, defined as "everything except randomized controlled trials (RCT)" by the IMI GetReal project,[19,20] is often mentioned as a helpful addition to randomized controlled trials.

It has been recognized since the start of HTA that sound and sufficient data are required and the described developments even further pressurize the HTA decision making process.[21] HTA organizations are expected to make more tailored decisions on more complex health technologies, using more limited data from multiple sources. Therefore, new HTA methods may need to be developed.[22] The HTx project, of which this study is a part, is a Horizon 2020 project supported by the European Union lasting for 5 years from January 2019.[3] The main aim of HTx is to create a framework for the next-generation HTA to support patient-centered, societally oriented, real-time decision making on access to and reimbursement for health technologies throughout Europe. To guide this development of new methodologies for the next-generation HTA, in-depth knowledge is needed of the challenges that are currently faced by HTA organizations during the assessment of complex health technologies. There is ample knowledge available on challenges associated with some specific types of health technologies over the past.[8,23-28] Nevertheless, a comprehensive overview of the challenges in light of the changing nature of health technologies in European HTA practice is missing. Such an overview would be necessary to determine how to mitigate the risks associated with uncertain decision making, for example, through scrutinizing the quality of data generation, development of advanced HTA methods, or employment of more sophisticated reimbursement agreements.

The European Network for HTA (EUnetHTA) has analyzed existing HTA and reimbursement procedures of single health technologies within European countries.[29] Our study builds on this research but focuses on the challenges associated with HTA for complex technologies. We aim to (1) identify which health technologies are perceived as complex and which aspects of HTA are currently considered most challenging, (2) assess the main arguments for perceiving health technologies as complex and HTAs as challenging, and to (3) find the most pressing gaps that can be filled with the development of future-proof methods for HTAs of complex health technologies.

Methods

Data about complex health technologies and challenges in HTA were collected through a survey. This approach was chosen to gain direct insight in daily practice of HTA organizations and to include experiences of the most recent and unpublished cases. The questions were incorporated in a survey that included a variety of topics for multiple HTx deliverables, all focusing on complex therapies.[3]

National and regional European member HTA organizations of EUnetHTA, directly or indirectly involved in decision making, were invited to participate (33 in total), ensuring the representation of a balanced mixture of European countries. The target audience within these organizations was defined as experienced HTA assessors (at least 3-5 years of experience), to ensure sufficient knowledge and experience. Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.11.1356 contains a list of all invited and responding HTA organizations.

Survey Structure

The survey instrument consisted of 3 parts, as illustrated in Figure 1. The first part investigated how often specific types of health technologies were considered complex by HTA organizations, assessed through Likert scales. The second part used prespecified case studies that each comprised one or more of the potentially complex health technologies from the first part. The purpose of the second part was 2-fold. First, by inquiring after the same potentially complex health technologies in a different manner, we aimed to validate the specificity of answers in the first part. Second, the case studies in the second part allowed us to retrieve detailed information on the encountered challenges. A combination of binary, multiple-choice, and open-ended questions was used. The third part of the survey aimed to gather information on complex health technologies and HTA challenges that were not reported elsewhere in the survey, using open-ended questions.

Included Potentially Complex Technologies and Case Studies

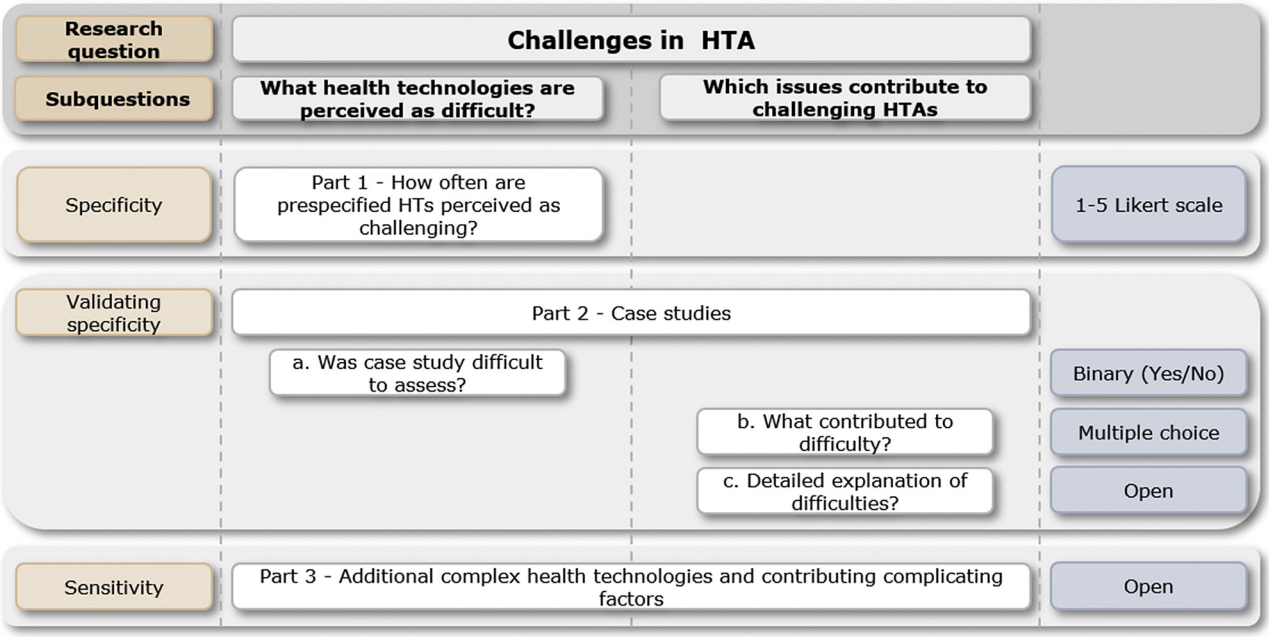
The list of potentially complex types of health technologies was developed based on a gray and scientific literature search. Literature was searched combining "HTA" with the terms "complex," "challenging," "innovative," "combinations of therapies," "personalized medicine," "precision medicine," "treatment pathways," "treatment sequences," "wearables," "digital health technologies," and "devices." Literature was scanned for types of health technologies. We continued scanning literature until a saturated list of potentially complex health technologies was reached, that is, until the continued search did not add any new health technology types. The list was checked by 2 authors (to be added after approval of submission) with experience (>5 years) in the HTA field that confirmed the relevance of included treatments. All identified complex health technology types are listed in the first column of Table 1.

For the selection of case studies, we scanned recently approved health technologies. We aimed at 5 to 7 case studies to keep the survey concise and improve responses. The selection of case studies was random; nevertheless, the cases combined covered the majority of our identified complex types of health technologies to ensure relevance and validation of our previously comprised list of complex types of technologies. The case studies consisted of both pharmaceutical and nonpharmaceutical health technologies. The second column of Table 1 lists the case studies and the complex type of health technology that it covered.

Survey Validation and Testing

Obtaining and testing for validation and reliability of the survey were based on a previously developed strategy.[30-32] The construction of the survey ensured specificity and sensitivity. An expert panel with 2 representatives from academia and 5 from 3 HTA organizations (ie, the National Institute for Health and Care Excellence [NICE], the Dental and Pharmaceutical Benefits Agency [TLV], and the Dutch National Health Care Institute [ZIN]), from in- and outside the HTx project, tested the survey for content and face validity and reliability. The panel verified that the questions together covered the scope of the overarching research aim and

Figure 1. Schematic structure of the survey instrument. The first column in this figure shows the objectives of each part of the questionnaire, the middle column shows questions disseminated and their relation to the sub- and overarching research question, and the rightmost column lists the format of the answer options.



HT indicates health technology; HTA, health technology assessment.

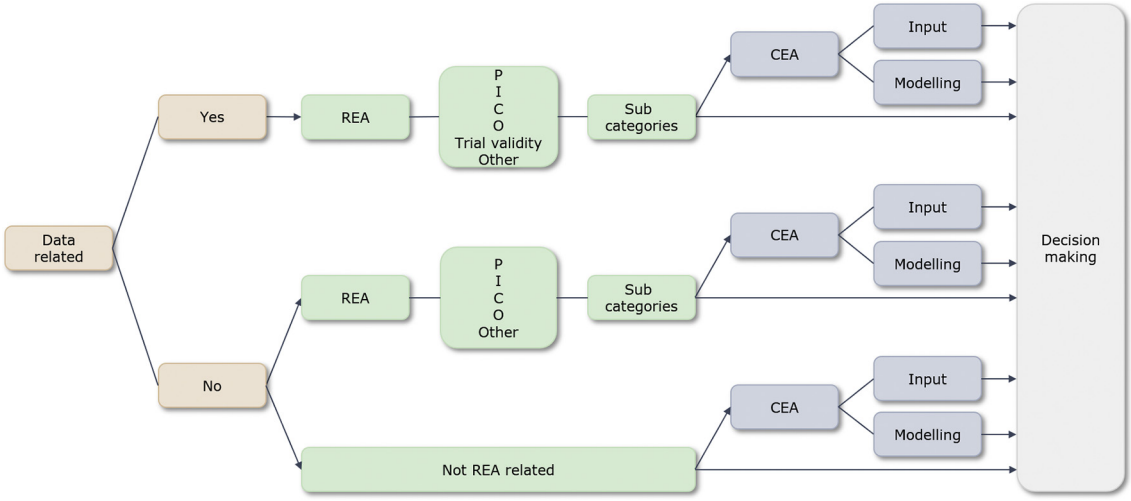
that all questions were relevant to the research aim (ie, content validity). The panel additionally checked the comprehensiveness, structure, and readability in terms of clarity of words and interpretation (face validity) and whether the answer options naturally allow to provide the relevant information (reliability). The same HTA representatives were subsequently involved in a pilot test, where feasibility of completion of the survey and correct interpretation of survey questions was confirmed. The answers from

Table 1. Case studies used in the survey instrument with associated potential complexity as reasons for selection.

Types of complex health technologies	Covered by case studies
ATMPs (advanced therapy medicinal product)	Lux
(Companion) diagnostics	TafMek, Lux, Vit
Advanced surgical interventions	TAVI
Combination of therapies	TafMek, CGM
Digital technologies	CGM
Gene sequencing	Not included in case studies
Histology-independent treatments	Vit
Medical devices or wearables	CGM, rTMS, TAVI
Orphan therapies	Lux
Personalized treatments	TafMek, Lux, Vit
Preventive treatment or vaccine	CGM, HPV
Proton, photon or laser therapy	Not included in case studies
Therapy sequences	TafMek, CGM

Note. The abbreviations for the case studies are as follows: (1) TafMek, "Tafinlar/Mekinist" for the treatment of adults with metastatic or unresectable melanoma with BRAF-V600 mutation; (2) CGM, for example, "Freestyle Libre" to guide treatment of adults and children with type 1 or 2 diabetes mellitus; (3) Lux, voretigene neparvovec "Luxturna" as single-dose gene therapy for adults and children with retinal dystrophy caused by a biallelic RPE65 mutation; (4) rTMS, as treatment for adults with treatment-resistant major depression; (5) HPV, the HPV vaccine, that is, "Gardasil or Cervarix," given to young adolescents for the prevention of cervical cancer; (6) TAVI in adults at intermediate surgical risk; and (7) Vit, larotrectinib "Vitrakvi" as treatment for adults and children with the histology-independent diagnosis of a solid tumor with NTRK-gene fusion.
ATMP indicates advanced therapy medicinal product; CGM, continuous glucose monitoring; HPV, human papillomavirus; rTMS, repetitive transcranial magnetic stimulation; TafMek, dabrafenib/trametinib; TAVI, transcatheter aortic valve implantation.

Figure 2. Decision tree for the categorization of challenges in HTA. The decision tree first splits the reported challenges into data related or not, subsequently into REA related or not (based on PICOT and inductively defined subcategories), followed by an effect on the CEA or not (distinguished between input or modeling). All end in an (in)direct effect on the ultimate decision.



CEA indicates cost-effectiveness analysis; HTA, health technology assessment; PICOT, Population, Intervention, Comparator, Outcomes, Trial; REA, relative effectiveness assessment.

the pilot test were not considered in the results and performed by different persons in the specific HTA organizations than the final participants.

Dissemination

The survey instrument was built in LimeSurvey (LimeSurvey GmBH, Hamburg, Germany) and disseminated in January 2020.[33] An announcement and 3 reminders were sent to increase the response rate until January 2020.

Analysis

Quantitative analyses were performed in Microsoft Excel (Microsoft, Redmond, WA).[34] The open questions were analyzed using NVivo 12 Pro (QRS International, Burlington, MA).[35]

Complex health technologies in HTA

First, averages reported on Likert scales were calculated to quantify how often the participants reported that technologies were perceived as being complex to assess. Second, for each of the 7 case studies, the share of organizations reporting the case study as complex was calculated. Third, a list of additionally reported complex cases was created from the open questions, and it was checked whether any complex health technology was missing from the predefined list.

Challenges in assessments of complex health technologies

First, for each case study that was reported as "complex," respondents were asked to report in which part of HTA the challenge was encountered, defined by 5 domains, being "data," "methods for REA," "methods for CEA," "policies," or "other." We calculated per case study how often challenges were encountered in each of these domains as a share of the total amount of HTA organizations that assessed the case study (eg, if 20 organizations assessed a case study and 8 reported challenges in the REA methods for that case study, it would result in a 40% score). Multiple domains could be selected by each participant. Second, a node structure in NVivo was used to structure the arguments for why health technologies or HTAs were complex, shown in Figure 2. For each argument, it was first determined whether it was caused by data-related issues (eg, a lack of data or low quality). Subsequently, the Population, Intervention, Comparator, Outcomes, Trial (PICOT) was used to organize arguments related to the REA.[36] CEA-related arguments were subcategorized as input and modeling challenges. If an argument was not related to the available data, the REA or the CEA, it was categorized as a policy or "other" challenge (ie, in Fig. 2, these categories fall under directly affecting the "decision making"). The subcategories of the REA arguments and subcategories in "other" were inductively defined based on clustering of likewise arguments. Categorization of arguments was done in a mutually exclusive way.

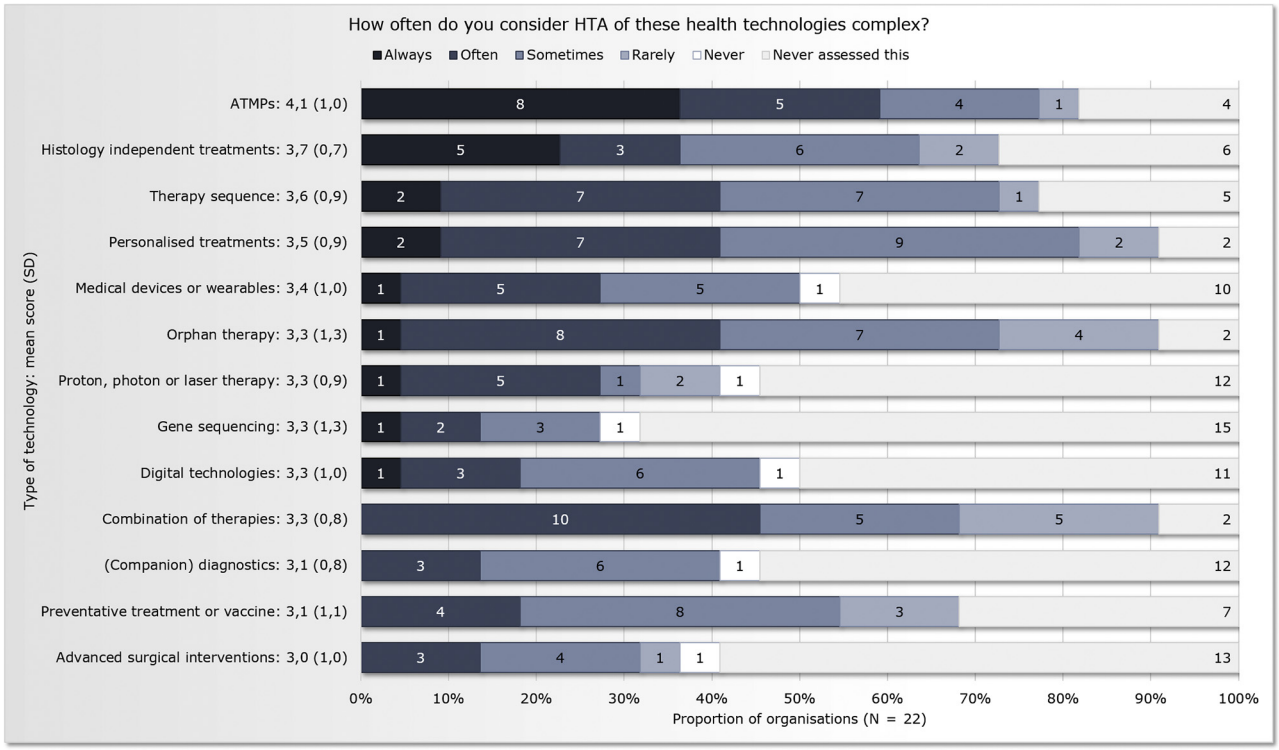
Results

Of 33 invited HTA organizations, 22 organizations from 21 different countries completed the survey (response rate 67%) (see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.11.1356). A total of 21 responding organizations (95%) were responsible for assessing pharmaceuticals, of which 8 (36%) solely assessed pharmaceuticals. A total of 14 organizations (64%) were responsible for assessing nonpharmaceuticals, of which 1 (5%) solely assessed nonpharmaceuticals. Consequently, 13 organizations (59%) were responsible for assessing both pharmaceuticals and nonpharmaceuticals.

Complex Health Technologies in HTA—Closed Questions

Of the prespecified potentially complex therapies, advanced therapeutic medicinal products (ATMPs) were most often considered as challenging to assess, with an average Likert score of 4.1 of 5.0 (SD 1.0); see Figure 3. This score of 4.1 indicates that

Figure 3. How often types of health technologies are complex. The numbers in the bars indicate the absolute amount of organizations that reported the answer. The number behind each of the types of technologies, in the left column before the bars, is the mean score of complexity based on the 1 to 5 Likert scale, including the standard deviation in parenthesis, excluding the organizations that never assessed the technology.



ATMP indicates advanced therapy medicinal product.

among all organizations that ever assessed an ATMP, the average perceived complexity lies between often (score 4.0) and always (5.0). Eight organizations indicated that the assessment of ATMPs was always complex (score 5.0). Second and third, histology-independent therapies scored a 3.7 (SD 0.7) and sequences or pathways of treatments scored a 3.6 (SD 0.9). Surgical interventions, preventive treatments, and diagnostics were considered relatively least challenging to assess. Finally, HTA organizations rarely (in 6 occasions) reported that the HTA of a type of therapy was "never" considered challenging, indicating that we indeed included relatively complex technologies in the survey.

Of the 7 case studies, larotrectinib was perceived complex by 7 of 8 HTA organizations (88%) that had assessed it. In addition, a majority of HTA organizations perceived the assessments of continuous glucose monitoring (6 [67%] of 9 assessing organizations), voretigene neparvovec (6 [67%] of 9 organizations,) and transcatheter aortic valve implantation (3 [60%] of 5 organizations,) as complex. In absolute terms, the combination therapy dabrafenib/trametinib and the histology-independent treatment larotrectinib were most often reported as complex in HTA, by, respectively, 8 of 14 and 7 of 8 of the responding organizations (57% and 88%, respectively). Repetitive transcranial magnetic stimulation was least often assessed (n = 4), and it was reported least often as complex, by 1 of the 4 organizations (25%).

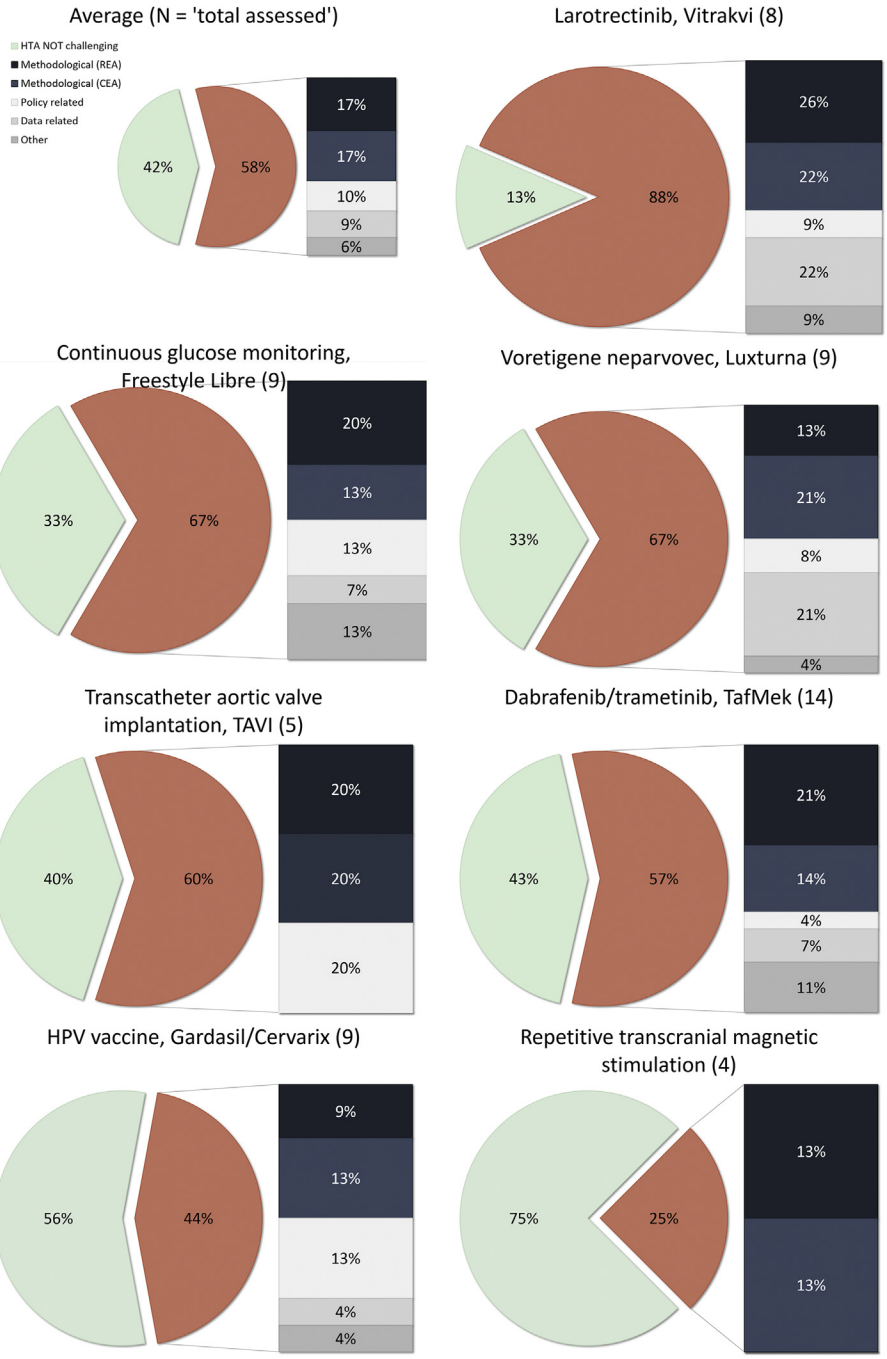
Complex Health Technologies in HTA—Open Questions

In open questions, the HTA organizations reported 41 additional cases of HTAs that had been challenging. Most reported health technologies of these HTAs; 34 (83%) were pharmaceuticals. Antineoplastic treatments were the largest therapeutic category of pharmaceuticals reported (18 of 34), followed by musculoskeletal treatments (6 of 34) and immunotherapies (3 of 34). When grouped according to our list of types of complex health technologies (see Table 1), the top 3 types of reported interventions were orphan designated treatments (25 of 41), personalized therapies (19 of 41), and combinations of therapies (13 of 41). ATMPs were reported 7 times by the HTA organizations. This was consistent with the finding that ATMPs ranked most complex in earlier questions, given the small amount of approved ATMPs compared with orphan designated treatments. The only case that was not yet covered by our predefined categories was 3-dimensional printing. See Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.11.1356 for the detailed list of reported treatments.

Challenges in Assessments of Complex Health Technologies—Closed Questions

Based on the 5 prespecified domains (data, REA, CEA, policy, other) addressing the 7 case studies, methodological challenges in the REA or the CEA together represented a disproportional majority of the reported challenges; see Figure 4. When excluding the responses that indicated that an HTA was not challenging, methodological challenges in the REA were on average responsible for 29% of the total number of challenges (range 19%-50%) reported for each case study by all HTA organizations, equal to those related to the CEA 29% (20%-50%). The least contributing challenges were data related, on average 15% of the reported challenges (0%-25%).

Figure 4. Proportion of HTA organizations reporting on challenges per case study and the domains that the challenges related to. For each case study, the number of HTA organizations reporting no challenges (in green) is visualized as the proportion of the total amount of organizations that has assessed this case study. The red piece of the pie, that is, the sum of the bar, represents the proportion of organizations that did consider this case study challenging. The number in parenthesis behind each case study is the absolute amount of organizations that have assessed this cases study, which makes up 100%. Because organizations were allowed to choose multiple answers, the percentages in the blue part do not directly relate to a number of HTA organizations, rather to the distribution of challenge categories among the organizations that did consider the case study challenging. To illustrate this with an example, the repetitive transcranial magnetic stimulation was assessed by 4 organizations (100%) of which 3 did not consider this challenging (75%) and 1 did (25%). This organization reported both methodological aspects in the REA and CEA to be contributing to the challenge (both 12.5%).



CEA indicates cost-effectiveness analysis; HPV, human papillomavirus; HTA, health technology assessment; REA, relative effectiveness assessment; TafMek: dabrafenib/trametinib; TAVI, transcatheter aortic valve implantation.

Considerable variation in reported answers among the case studies was observed for the nonmethodological challenges (policy, data, other). Only 4 organizations reported solely methodological challenges; all other organizations reported a mixture of all arguments.

Challenges in Assessments of Complex Health Technologies—Open Questions

In the open questions, 20 HTA organizations reported 187 arguments why HTA was challenging, either as a description of the challenges reported for the case studies or as additionally reported challenges. Two-thirds of the reported challenges (n = 128 [68%] of 187) related to issues with available data at the time of assessment (following the predefined HTA domains); see Table 2. In general, the arguments that were data related referred to aspects from the PICOT framework in the REA, predominantly uncertainties around available outcomes data (61 of 128 challenges reported by 13 organizations). In this category, most challenges related to data immaturity (n = 22 of 61). In addition, frequently reported in the outcomes category was that data on outcomes were somehow "limited" (n = 21 of 61), with the precise reasons not being clear. In addition to outcome challenges, organizations often reported challenges because of unreliable data as a consequence of the trial design (n = 12 of 128).

From all the nondata-related arguments (59 [32%] of 187), most were referring to other factors than the PICOT. Policy and organizational elements were mentioned in 13 of 59 challenges by 8 organizations, of which 3 were HTA specific and 9 related to broader healthcare policies (and one other). Societal or political factors were mentioned in 9 of 59 challenges by 4 organizations. A detailed summary of reported challenges per categorized topic is presented in Table 2. Some of the level 2 categories (eg, population, intervention) include a few additional solitary arguments that could not be categorized, resulting in a higher N than the sum of subcategories.

Discussion

This study assessed the experiences of assessors at European HTA organizations regarding challenges in HTA for complex health technologies. HTA organizations perceived ATMPs and histology-independent treatments as most challenging. On average, 58% of the organizations assessed our prespecified case studies and 34% (more than half) reported that methodological challenges were most important, equally distributed over the therapeutic and economic assessment methods. Only 9% of organizations reported that data issues were most challenging in these case studies. Nevertheless, analysis of the follow-up questions demonstrated that the overlap in challenges among the various health technologies lies with the data insufficiencies at time of assessment, despite the challenges being expressed in different domains of the HTA process.

Complex Health Technologies in HTA

Our results are in line with findings on previously reported challenges, which focused specifically on the assessment of ATMPs and histology-independent treatments.[20,23,24,26,29] The scope of our survey covered both pharmaceuticals and nonpharmaceuticals. Only a few nonpharmaceutical products were reported as complex technologies in HTA. Likely this is due to the small share of organizations that assess nonpharmaceuticals, as described by the EUnetHTA joint action 3 report.[29] This overview found that a larger share of European HTA agencies has procedures for HTA of pharmaceuticals compared with nonpharmaceuticals. Further research that systematically assesses the challenges with nonpharmaceuticals and compares these with challenges in pharmaceutical products could provide information on the direction for development of methods and policies for nonpharmaceuticals, if in the future HTA for nonpharmaceuticals becomes more routine.

Challenges in Assessments of Complex Health Technologies

HTA organizations reported challenges in different ways in the closed and open questions. The closed questions on our prespecified case studies suggested that methodological aspects, during REA or CEA, were more often challenging factors than policy- or data-related issues. In contrast, in the open questions, the challenges in HTA seemed to be mostly caused by data issues, in particular due to limited data on relevant outcomes. The construct validity approach in our questionnaire, that is, the questions being formulated in 2 different ways, provided this insight in the data insufficiencies underlying the challenges that are expressed throughout the HTA process.

Few reported challenges related to cost-effectiveness modeling. Most challenges related to the REA and the input parameters for the CEA. This could imply that HTA organizations do not experience many challenges with modeling. Nevertheless, this result might be affected by the fact that not all HTA organizations perform CEAs.[37]

When we specifically look at published cost-effectiveness analyses, previous systematic reviews on the economic evaluations of genetic testing, ATMPs, and sequences of treatment with disease-modifying antirheumatic drugs investigated the quality and approaches of economic evaluations of these challenging health technologies. All 3 concluded that the evidence available for the health technologies is often limited and timely access to these data is of utmost importance, in accordance with our results.[23,24,26] Adding to that, Ten Ham et al[25] concluded in a review on methodological considerations for economic evaluations of gene therapies that the informativeness for HTA decisions is often limited because of uncertainties, nevertheless, that the methods used in economic evaluations can, with minor adjustments, be broadly applied to gene therapies. This underpins our finding that for complex health technologies, data-driven challenges are more important than methodological issues related to the complexity of the technology.

The International Network of Agencies for Health Technology Assessment (INATHA) recently published their perspective on challenges in HTA as surveyed among its members.[38] Although this was a survey among the leadership layer rather than among performing assessors, they also found that inadequate data management systems, having no centralized database, and a sense of declining quality and validity of evidence complicate economic evaluations. Several studies confirm this sense of declining "quality" as the use of innovative trial designs and real-world data sources grows.[5-7,39]

Implications and Directions for Future Research

Improving the quality and quantity of data could be a solution to challenges in HTA. In recognition of this, Naci et al[40] recently published 5 key principles for regulatory bodies and payers to scrutinize the quality of generated data available at time of registration and (re)assessment by HTA organizations. In addition, a large recent systematic review of synergies between regulatory authorities and HTA organizations recognized the necessity of the alignment of evidentiary requirements to improve data quality for

Table 2. Reported challenges in HTA of complex health technologies.

Category	N	Described challenge
Data related	128	
Population	25	
Indication	11	Natural history or disease development unclear, in particular in small populations.
Heterogeneity	7	Data are insufficient on subgroups of patients.
Generalizability	4	Difficult to generalize the used studies to the country's own population, children, or pregnant women.
Diagnostic	3	The diagnosis is complex, eg, if it is based on genetic testing.
Intervention	1	
Intervention	1	Gene therapies are challenging for HTA because data are often insufficient (short follow-up).
Comparator	11	
Indirect	6	Indirect comparisons required, in case the performed RCT used a comparator that is not the (standard) treatment in the assessing country.
Population with comparator	4	A lack of data on outcomes in the population receiving the comparative treatment.
No comparator	1	No available comparator.
Outcomes	61	
Immaturity	22	Study period or follow-up considered too short or use of interim analyses.
Limited	21	Data reported as "limited," "scarce," or "insufficient," in particular data on quality of life, are often "limited."
Interpretation	8	Challenges with interpretation of outcomes that were combined or interrelated or if relevance to clinical practice was uncertain because of the use of "new" outcome measures, that are not often used (in practice).
Absent	6	Sometimes data was reported to be completely absent.
Surrogate	4	Available outcomes were surrogate outcomes, or no data available on overall survival or progression-free survival.
Trial design	12	
Trial design	12	Most often, single-arm trials result in indirect treatment comparisons.
Other	18	
Practice	9	Limited data on daily practice result in uncertain cost calculations, eg, 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, a lack of standardized protocols for administration, a lack of clinical expertise, or the effect of contextual factors on effectiveness.
Policy and organizational	2	The HTA process allows for too few consultation moments with experts; access to data was not arranged timely.
Prices	7	The confidentiality of prices of comparators.
Not data related	59	
Population	5	
Positioning	2	High-prevalence diseases result in various standards of practice and positions of the assessed treatment (and thus comparators).
Heterogeneity	2	Even with data available, heterogeneity causes modeling challenges.
Indication	1	High-prevalence indications can result in challenging models with multiple health states.
Intervention	10	
Positioning	4	Evolving treatment pathways make the position and thus comparator uncertain.
Comparator	6	
Uncertain	3	Uncertainty on which comparator to select.
Multiple	3	Multiple comparators available, because of multiple indications in comparator group; even with data available, this causes challenging modeling issues.
Not REA related	6	
Not REA related	6	The quality of the models delivered by manufacturers was low, because of wrong anticipations or opaque structures. Modeling of cures in gene therapies can lead to challenges.
Other	29	
Policy and organizational	13	The organization of healthcare programs, eg, diagnostic procedures are decentralized whereas subsequent treatment is only given centralized in smaller countries, transparency issues, and challenges with modeling of savings in local vs centralized institutions The organization of HTA, eg, 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.
Societal and political	9	Reimbursement of orphan HTs or ethical issues, including patient's or physician's perspectives and interests on outcomes, or the acceptability of an HT by caregivers of children or adolescents
Payment or reimbursement	4	Concerns about affordability because of high costs, and problems related to different financial streams that were responsible for coverage of the HT.
Practice	3	No standard practice existing or a variety of guidelines, causing uncertainty on how to model the differences, and this results in uncertainty in positioning and in which comparator to use.

HT indicates health technology; HTA, health technology assessment; RCT, randomized controlled trial; REA, relative effectiveness assessment.

both parties. This review identified 4 key activities to effectuate this, among others the early stakeholder dialog and post-authorization data generation. Multiple initiatives in this direction exist, such as early scientific advice of the EMA together with EUnetHTA and national HTA organizations.[41,42] Our research stresses the importance of these initiatives and provides suggestions for technologies with the highest urgency.

Additionally, challenges found in our results highlight the importance of the methodological work that is performed, for example, within the HTx project.[3] The development of evidence-synthesis methods that are able to deal with challenges such as missing data could be one future direction for solving problems faced by HTA organizations.[43,44] Other examples of developed methods that could be of value are the methods that increase certainty around indirect comparisons, enable comparisons with multiple other treatments, and include specific patient characteristics and methods that combine various data sources.[43,45-50] On top of that, machine learning systems are developed and tested to predict health outcomes of treatments based on combined sources of data, which might lead to higher accuracy of predictions in HTA.[51,52]

A third solution that could be further explored for complex health technologies is the financial spread of risks because of outcome uncertainties, by means of pricing and reimbursement schemes.[3,53-55] Our results highlight treatments that could benefit from such agreements, such as ATMPs and histology-independent treatments. Research has focused on explaining which types of financial agreements are suitable in specific situations.[55] Future research should evaluate the effect of some of these agreements and shed light on the trade-off between the complexity of the agreement and the potential benefits they entail. Probably a combination of all these approaches will be needed to ensure sustainable access to new innovative complex health technologies.

Strengths and Limitations

Despite a few larger Central and South European countries such as France, Portugal, and Italy that are missing in our survey, we had a very high response rate (67%) from countries all over Europe. Therefore, the results are likely complete and representative for other European countries. There are no clear indications that the perspectives of missing countries would be very different from the perspectives of the set of included HTA organizations, broadly covering Europe geographically. Second, we aimed to use a concise survey, thus a limited number of questions, to ensure a sufficient response rate. The survey was developed in collaboration with HTA organizations. This approach made sure that the questions were relevant for HTA practice, but more information on certain aspects may in hindsight have been warranted. For example, a "simple" reference case was left out of the set of case studies, which makes it more difficult to compare the reported measures of complexity with what would be considered a "simple" HTA.

Conclusions

European HTA organizations report that challenges in HTAs of complex health technologies mainly root in data insufficiencies rather than in the complexity of the technology itself. This results in outcome uncertainties during the REA and thus in parameter uncertainty in the CEA, ultimately complicating decision making. Potential solutions to these issues could be to improve the data quality and quantity at the time of assessment, to develop evidence-synthesis methods that are able to deal with data insufficiencies, and to develop pricing and reimbursement schemes that mitigate risks because of uncertainty.

Supplemental Material

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REFERENCES

1. O'Rourke B, Oortwijn W, Schuller T, International Joint Task Group. The new definition of health technology assessment: a milestone in international collaboration. *Int J Technol Assess Health Care*. 2020;36(3):187–190.
2. JA WP5 – relative effectiveness assessment of pharmaceuticals. EUnetHTA. https://www.eunethta.eu/ja1-archive/ja-wp5-relative-effectiveness-assessment-of-pharmaceuticals/. Accessed October 4, 2021.
3. HTx project: next generation health technology assessment. HTx. https://www.htx-h2020.eu/. Accessed July 16, 2020.
4. Jacobzone S. Healthy ageing and the challenges of new technologies: can OECD social and health-care systems provide for the future? OECD. http://

www.oecd.org.proxy.library.uu.nl/science/emerging-tech/2487386.pdf. Accessed July 16, 2020.
5. Blagden SP, Billingham L, Brown LC, et al. Effective delivery of Complex Innovative Design (CID) cancer trials - a consensus statement. *Br J Cancer*. 2020;122(4):473–482.
6. Larson L, Walker A, Parow D. Innovative clinical trial designs Welcomed by regulators but what about the payers? ISPOR Glasgow. https://www.ispor.org/docs/default-source/presentations/1330.pdf?sfvrsn=56ed4398_1. Accessed April 17, 2020.
7. Pruce D, Michel S, Theocharous P. Do payers find value in innovative trial designs? The Evidence Form. https://www.evidera.com/wp-content/uploads/2017/05/How-Health-Technology-Assessment-Bodies-See-New-Trial-Design.pdf. Accessed April 17, 2020.
8. Nicod E, Annemans L, Bucsics A, Lee A, Upadhyaya S, Facey K. HTA program response to the challenges of dealing with orphan medicinal products: process evaluation in selected European countries. *Health Policy*. 2019;123(2):140–151.
9. Nicod E, Whittal A, Drummond M, Facey K. Are supplemental appraisal/reimbursement processes needed for rare disease treatments? An international comparison of country approaches. *Orphanet J Rare Dis*. 2020;15(1):189.
10. Coyle D, Durand-Zaleski I, Farrington J, et al. HTA methodology and value frameworks for evaluation and policy making for cell and gene therapies. *Eur J Health Econ*. 2020;21(9):1421–1437.
11. Jönsson B, Hampson G, Michaels J, Towse A, von der Schulenburg JG, Wong O. Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. *Eur J Health Econ*. 2019;20(3):427–438.
12. Cooper S, Bouvy JC, Baker L, et al. How should we assess the clinical and cost effectiveness of histology independent cancer drugs? *BMJ*. 2020;368:l6435.
13. Photopoulos J. The future of tissue-agnostic drugs. *Nature*. 2020;585(7826):S16–S18.
14. Larotrectinib for treating NTRK fusion-positive solid tumours: overview. NICE. https://www.nice.org.uk/guidance/ta630. Accessed March 15, 2021.
15. Leyens L, Brand A. Early patient access to medicines: health technology assessment bodies need to catch up with new marketing authorization methods. *Public Health Genomics*. 2016;19(3):187–191.
16. Vreman RA, Bouvy JC, Bloem LT, et al. Weighing of evidence by health technology assessment bodies: retrospective study of reimbursement recommendations for conditionally approved drugs. *Clin Pharmacol Ther*. 2019;105(3):684–691.
17. Vreman RA, Naci H, Goettsch WG, et al. Decision making under uncertainty: comparing regulatory and health technology assessment reviews of medicines in the United States and Europe. *Clin Pharmacol Ther*. 2020;108(2):350–357.
18. Vreman RA, de Ruijter AS, Zawada A, et al. Assessment of significant benefit for orphan medicinal products by European regulators may support subsequent relative effectiveness assessments by health technology assessment organizations. *Drug Discov Today*. 2020;25(7):1223–1231.
19. R-L Data in drug. Development. IMI GetReal initiative. GetReal. https://www.imi-getreal.eu/. Accessed September 19, 2019.
20. Makady A, van Veelen A, Jonsson P, et al. Using real-world data in health technology assessment (HTA) practice: a comparative study of five HTA agencies. *Pharmacoeconomics*. 2018;36(3):359–368.
21. Abrams HL, Hessel S. Health technology assessment: problems and challenges. *AJR Am J Roentgenol*. 1987;149(6):1127–1132.
22. Reviewing our methods for health technology evaluation: consultation | NICE guidance | Our programmes | What we do | About. NICE. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/chte-methods-consultation. Accessed March 15, 2021.
23. Ghabri S, Lam L, Bocquet F, Spath HM. Systematic literature review of economic evaluations of biological treatment sequences for patients with moderate to severe rheumatoid arthritis previously treated with disease-modifying anti-rheumatic drugs. *Pharmacoeconomics*. 2020;38(5):459–471.
24. Berm EJ, Looff Md, Wilffert B, et al. Economic evaluations of pharmacogenetic and pharmacogenomic screening tests: a systematic review. Second update of the literature. *PLoS One*. 2016;11(1):e0146262.
25. Ten Ham RMT, Klungel OH, Leufkens HGM, Frederix GWJ. A review of methodological considerations for economic evaluations of gene therapies and their application in literature. *Value Health*. 2020;23(9):1268–1280.
26. Lloyd-Williams H, Hughes DA. A systematic review of economic evaluations of advanced therapy medicinal products. *Br J Clin Pharmacol*. 2021;87(6):2428–2443.
27. Chen Q, Staton AD, Ayer T, Goldstein DA, Koff JL, Flowers CR. Exploring the potential cost-effectiveness of precision medicine treatment strategies for diffuse large B-cell lymphoma. *Leuk Lymphoma*. 2018;59(7):1700–1709.
28. Doble B. Budget impact and cost-effectiveness: can we afford precision medicine in oncology? *Scand J Clin Lab Invest Suppl*. 2016;245:S6–S11.
29. An analysis of HTA and reimbursement procedures in EUnetHTA partner countries [final report]. EUnetHTA. https://eunethta.eu/an-analysis-of-hta-and-reimbursement-procedures-in-eunethta-partner-countries-final-report/. Accessed July 16, 2020.
30. Venkitachalam R. Validity and reliability of questionnaires. Slideshare. https://www.slideshare.net/Venkitachalam/validity-and-reliability-of-questionnaires. Accessed July 16, 2020.
31. Bolarinwa OA. Principles and methods of validity and reliability testing of questionnaires used in social and health science researches. *Niger Postgrad Med J*. 2015;22(4):195–201.
32. Kimberlin CL, Winterstein AG. Validity and reliability of measurement instruments used in research. *Am J Health Syst Pharm*. 2008;65(23):2276–2284.
33. Schmitz C. LimeSurvey - the free & open source survey software tool! LimeSurvey. https://www.limesurvey.org/. Accessed March 16, 2020.
34. Microsoft Excel, spreadsheet software, excel free trial. https://www.microsoft.com/nl-nl/microsoft-365/excel. Accessed September 3, 2020.
35. Nvivo: NVivo qualitative data analysis software. QSR International. https://www.qsrinternational.com/nvivo/home. Accessed March 16, 2020.
36. Lampe K, Mäkelä M, Garrido MV, et al. The HTA Core Model: a novel method for producing and reporting health technology assessments. *Int J Technol Assess Health Care*. 2009;25(suppl 2):9–20.
37. Chamova J. Mapping of HTA national organizations, programmes and processes in EU and Norway. Publication Office of the European Union. https://op.europa.eu/en/publication-detail/-/publication/971cf96d-0aef-11e8-966a-01aa75ed71a1. Accessed June 24, 2020.
38. O'Rourke B, Werkö SS, Merlin T, Huang LY, Schuller T. The 'Top 10' challenges for health technology assessment: INAHTA viewpoint. *Int J Technol Assess Health Care*. 2020;36(1):1–4.
39. Verweij J, Hendriks HR, Zwierzina H, Cancer Drug Development Forum. Innovation in oncology clinical trial design. *Cancer Treat Rev*. 2019;74:15–20.
40. Naci H, Salcher-Konrad M, Kesselheim AS, et al. Generating comparative evidence on new drugs and devices before approval [published correction appears in *Lancet*. 2020;395(10242):1972]. *Lancet*. 2020;395(10228):986–997.
41. Parallel consultation with regulators and health technology assessment bodies. European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/parallel-consultation-regulators-health-technology-assessment-bodies. Accessed May 3, 2021.
42. EMA and EUnetHTA step up interaction to align data requirements. European Medicines Agency. https://www.ema.europa.eu/en/news/ema-eunethta-step-interaction-align-data-requirements. Accessed May 3, 2021.
43. Chalkou K, Steyerberg E, Egger M, Manca A, Pellegrini F, Salanti G. A two-stage prediction model for heterogeneous effects of many treatment options: application to drugs for Multiple Sclerosis. *Stat Med*. 2021;40(20):4362–4375.
44. Rekkas A, Paulus JK, Raman G, et al. Predictive approaches to heterogeneous treatment effects: a scoping review. *BMC Med Res Methodol*. 2020;20(1):264.
45. Pooley N, Marjenberg Z, Embleton N, Langham S. PNS299 the increasing use and acceptance of alternative statistical approaches to indirect comparison in the National Institute of Health and Care Excellence (NICE) Health Technology Assessment (HTA) submission process. *Value Health*. 2019;22(suppl 3):S814.
46. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for population-adjusted indirect comparisons in health technology appraisal. *Med Decis Making*. 2018;38(2):200–211.
47. Häggman-Henrikson B, Alstergren P, Davidson T, et al. Pharmacological treatment of oro-facial pain – health technology assessment including a systematic review with network meta-analysis. Wiley Online Library. https://onlinelibrary.wiley.com/doi/full/10.1111/joor.12539?casa_token=T7dHSsd-fBYAAAAA%3Ac-DBXjpkjCiUHwlMdJxLjo3B0JCaMMlB_dfwO7Mze9gtTh1M2ntJqy5gzu0UzWa2UCH4ZJJNJBtEtls. Accessed May 12, 2021.
48. Higgins JP, Welton NJ. Network meta-analysis: a norm for comparative effectiveness? *Lancet*. 2015;386(9994):628–630.
49. Warren RB, Brnabic A, Saure D, et al. Matching-adjusted indirect comparison of efficacy in patients with moderate-to-severe plaque psoriasis treated with ixekizumab vs. secukinumab. *Br J Dermatol*. 2017;178(5):1064–1071.
50. Thom H, Jugl SM, Palaka E, Jawla S. PRM167 Matching adjusted indirect comparisons to assess comparative effectiveness of therapies: usage in scientific literature and health technology appraisals. *Value Health*. 2016;19(3):A100–A101.
51. Collins GS, Moons KGM. Reporting of artificial intelligence prediction models. *Lancet*. 2019;393(10181):1577–1579.
52. Panch T, Szolovits P, Atun R. Artificial intelligence, machine learning and health systems. *J Glob Health*. 2018;8(2):020303.
53. Jönsson B, Oortwijn W, Rutten A, Wailoo A. *Health technology assessment methodology programme review of external evaluation committee*. October 2015.
54. Dabbous M, Chachoua L, Caban A, Toumi M. Managed entry agreements: policy analysis from the European perspective. *Value Health*. 2020;23(4):425–433.
55. Vreman RA, Broekhoff TF, Leufkens HG, Mantel-Teeuwisse AK, Goettsch WG. Application of managed entry agreements for innovative therapies in different settings and combinations: a feasibility analysis. *Int J Environ Res Public Health*. 2020;17(22):8309.