Next Generation Health Technology Assessment

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

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TABLE OF CONTENTS

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Description of the deliverable	We will provide a review in which we will compare market authorisations, HTA assessments and clinical guidelines for the areas/interventions for which we will perform our case studies. This will be done at the start of the project in order to have a clear starting point for the available information from clinical societies, regulatory authorities and HTA organisations. The focus will be on assessment of evidence using the PICO framework as a starting point.
Key words	Synergies, alignment, HTA, clinical guidelines, patient access

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EXECUTIVE SUMMARY

Introduction

Patient access to novel pharmaceutical treatments may be facilitated by a smooth process of market approval, reimbursement and uptake in clinical guidelines (CGs). The three responsible stakeholders (regulators, health technology assessment [HTA] organisations and clinicians) have different goals but their work overlaps in balancing the drug risks against benefits, although the scope of included benefits and risks varies. Alignment of their clinical evaluation processes might increase efficiency and result in earlier patient access. This study aimed to assess synergies between recommendations in HTA reports and clinical guidelines for multiple sclerosis (MS) medicines.

This study aimed to quantify the alignment and discrepancies between published documents from five European HTA organisations, including the therapeutic and economic assessment, and CG documents of the respective countries for MS medicines, and identify any references they make to each other.

Methods

HTA reports and corresponding CGs were assessed to find synergies and discrepancies in recommendations of the two stakeholder groups and any references they make to each other. Documents from the UK, France, Germany, the Netherlands and Poland were assessed. Data was extracted using a data extraction tool. This study is part of a larger project that includes questionnaires and a workshop for regulators, payers and clinicians to discuss potential areas for improvement.

Results

We assessed 113 HTA reports for 16 MS treatments (approved 1995-2020) and 7 CGs. After 2010, nearly half (47%) of the HTA reports referred to the use of CGs, mostly to determine the appropriate comparator. Differences in referencing were more visible between countries than over time. This same pattern was detected for references to consultations with clinical experts while developing HTA reports (reference in 43% of the HTA reports). A consultation sometimes entailed written feedback (29%) and generally focused on foreseen treatment positioning, specific eligible populations and consequences of adverse events. CGs often referred to final recommendations of HTA reports (5/7). Consulting HTA representatives, on the other hand, was not observed, unless the CG was developed by an institution that is formally related to the HTA organisation (2/7). CGs referenced pharmaco-economic studies (4/7) for details on costs and cost-effectiveness. In none of the included countries, publishing HTA reports directly triggered updates of CGs. To date, not all new treatments for MS and current HTA recommendations are included in CGs.

Final recommendations made by HTA reports and CGs on reimbursement and inclusion in the treatment algorithm were mostly in synergy (46 of 51 treatment algorithms (90%)). If not, the negative (therapeutic) HTA recommendation was overruled by a positive reimbursement decision

after which the treatments were included in the CG. When looking in more detail, differences became visible. Different treatment positions were recommended in 41% of the compared cases. Differences occurred when the treatment was recommended to start in a different treatment line (12%), the recommendation was extended to additional sub-indications (30%) or to completely different sub-indications (10%).

Conclusion

Generally, the final recommendations on reimbursement and treatment position were similar among stakeholders. Differences were visible when zooming into details of the recommendations. The organizational process from reimbursement to uptake in clinical treatment guidelines is not very well aligned in the case of MS. It seemed that the two stakeholder groups did not always systematically access each other's knowledge. Additionally, actions by one stakeholder did not always seem to trigger action by the other stakeholder, such as timely updates of guidelines. These results indicate that steps to improve the process towards patient access are feasible and worthwhile.

Results from this study will inform the discussion among stakeholders groups, including regulators, during a workshop on improving the alignment of the process. Ultimately, this data combined with stakeholder input will lead to policy recommendations that would facilitate the improved synergies among the three stakeholder groups. Increased efficiency in the process would ensure earlier and more sustainable access to required treatments.

OVERVIEW OF THE CURRENT SYNERGIES BETWEEN HTA ORGANISATIONS AND CLINICAL GUIDELINE DEVELOPERS: A CASE STUDY ON MULTIPLE SCLEROSIS

Introduction

Background

Health technology assessment (HTA) can be used to compare new health technologies to existing standard of care in order to inform policy and decision making, usually for pricing and reimbursement and in some cases for clinical practice(1). HTA recommendations in Europe are still predominantly made on a national level. Differences in context (e.g. a country's gross domestic product), scope and methodology in each country may cause divergence in the recommendations(2,3). In the field of multiple sclerosis (MS) this divergence clearly exist(4,5).

Due to a continuous increase in health care expenditure, researchers focused on frameworks to incorporate HTA recommendations in evidence based treatment practices(6–9). Clinical treatment guidelines (CGs) are generally used as a tool to ensure guidance of evidence based medicine, aiming to advance quality of care but also increasingly aiming to treat in a cost-effective manner(10).

Given the likewise purpose of informing decision-making, albeit in a different context, it is no surprise that the processes of relative effectiveness assessment (REA) in HTA and CG development contain considerable overlap. CGs, however, do not usually use full HTA reports during development(11). Collaboration and alignment among HTA organisations and between HTA and CG developers could prevent double efforts and facilitate equality in patients' access to evidence-based and cost-effective treatments among European countries.

In the field of MS, nine relatively expensive disease-modifying treatments entered the market in the past decade(12). The variety of treatment options with costly medication requires evidence-based guidance for neurologists allowing them to make a personalised decision for the best treatment for that patient at that moment while taking into account the budgetary limitations. The divergence in HTA recommendations and variation in different CGs complicates this decision(13). The European Commission funded (H2020) HTx project aims to develop methods for complex HTA assessments such as for MS(14). The large number of expensive immunomodulating treatments with widely varying treatment algorithms and reimbursement recommendations were reason to include MS as a case study in this project.

Initiatives for collaboration among HTA organisations and between HTA and CGs have emerged. The European Network for HTA (EUNetHTA) is the largest HTA collaboration in Europe, and raised the issue in 2015 as methodological issue that requires further research(15). GINAHTA, a

collaboration between Guidelines International (G-I-N) and the International Network of Agencies for HTA (INHATA), is a global initiative established in 2015, with the purpose '*to explore common methods and to facilitate collaboration and sharing of products between the HTA and guideline communities*'(16). The working group did not publish any findings to this date.

The appraisal and development of clinical guidelines was a preferred services of focus for HTA organisations among decision makers in Spain, according to Andradas and colleagues in 2008(17). Also, among healthcare providers there was a wide interest in assessments relevant to clinical decision making. The Belgian Health Care Knowledge Centre (KCE) and the English National Institute for Health and Care Excellence (NICE) already (co)produce clinical guidelines, while considering HTA. However, to our knowledge there is no research performed on the synergies between HTA documents and clinical guidelines.

Aim

This study aimed to quantify the alignment and discrepancies between published documents from five European HTA organisations, including the therapeutic and economic assessment, and CG documents of the respective countries for MS medicines, and identify any references they make to each other.

Scope

All in the European Union (EU) available treatments for multiple sclerosis were used as a case study for the analysis. Potential synergies were sought in the process of developing HTA documents and CGs as well as the conclusions that these documents draw.

This study has been performed as part of the European Commission funded HTx project, in which implementation of the methods developed in HTx in the practice of participating HTA agencies is a major task(14). This study is a subtask of the overarching task looking at the synergies between regulatory agencies, HTA organisations and clinical guideline developers. This task will conclude with a workshop involving all three stakeholder groups to identify how the existing synergies may be improved and new collaboration may be facilitated in the future. The synergies between clinicians and regulators, as described for this deliverable in the HTx proposal, will be included in the following studies undertaken in this task.

Report outlay

This report starts with a description of the methods for collecting relevant documents and extracting data from the documents via a data extraction tool, followed by the analysis of the data. Then, the results give an overview of HTA documents and clinical guidelines that were assessed. Accordingly, an overview of the process related synergies between the documents are given, such as 'do these documents refer to each other?' and 'did consultations between the parties take place?'. Hereafter, the report shows the synergies in recommendations made between the parties; 'do they recommend treatments for the same population?' or 'do they recommend the treatment in the same place in the treatment algorithm?'. The results will be discussed and finally the report draws a conclusion on the synergies between HTA documents and clinical guidelines.

Methods

We performed a document analysis in which we systematically extracted data from published HTA reports and CGs. Among the data that were gathered were the references to the other stakeholder described and to each other's documents and we compared the recommended line of therapy and patient population, to find synergies and discrepancies (see details below).

Country and document selection

France, Germany, the Netherlands, Poland and the United Kingdom (UK), were selected for inclusion. For inclusion were considered the larger jurisdictions, thus with large impact of their policies, methods and guidelines (Germany, France, Poland, UK). Additionally, we selected countries with pioneering HTA organisations, involved in the development of guidelines (France, Germany, Netherlands, UK), or involved in the HTx project (Netherlands, UK)(18). In addition, we aimed for a balanced spread throughout the EU. Included countries all have HTA organisations performing both therapeutic and economic assessments and are directly or indirectly involved in the country's decision-making process. Lastly, the language proficiency of the involved authors to accurately assess the documents and the availability of public documents were considered. The latter two were reasons to exclude Sweden, which was initially included as their HTA organisation, the dental and pharmaceutical benefits agency (TLV), is partner in the HTx project. The websites from all national HTA organisations in each country were searched for documents on each of the included MS treatments. National CGs for each country were searched for and were included if they at least evaluated the disease modifying therapies for MS. In the UK two CGs were available, one written by the Association of British Neurologists (ABN) and one from the National Health Service (NHS)(18,19). A European guideline for MS treatment (a joint effort from the European Committee for Treatment and Research in MS and the European Academy of Neurology) and the reports on the included MS pharmaceuticals published by EUnetHTA were included as a comparison(20,21). See table 1 for the selected HTA organisations and included CGs.

Table 1: Overview of included countries with relevant HTA organisations and clinical guidelines

Country	HTA organisation	Clinical guideline developer
United Kingdom	The National Institute for Health and Care Excellence (NICE)(22)	NHS Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies, 2019(18). Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis(19).
France	Haute Autorité de Santé (HAS)(23)	HAS, Actes et prestations, affection de longue durée, Sclérose en plaques, 2015(24)
Germany	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)(25) Der Gemeinsame Bundesausschuss (G-BA)(26)	DGN / KKNMS Leitlinie zur Diagnose und Therapie der MS, 2014(27).
Netherlands	Dutch National Healthcare Institute (ZIN)(28)	Nederlandse Vereniging voor Neurologie, Multipele Sclerose, 2012(29). Ziektemodulerende Behandeling van Multiple Sclerose bij volwassenen, Addendum bij de richtlijn Multiple Sclerose 2012, 2020(30).

Poland	Agency for Health Technology Assessment and Tariff System (AOTMiT)(31)	Leczenie stwardnienia rozsianego Zalecenia Polskiego Towarzystwa Neurologicznego, 2016(32).
European	European Network for Health Technology Assessment (EUnetHTA)(21)	ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis, 2018(20).

Treatment selection

All in the EU patented treatments with an approved indication for MS, including (active) relapsing remitting MS, relapsing MS, primary progressive MS, (active) secondary progressive MS and progressive MS were included. For generics it was assumed that no HTA was performed, thus they were excluded. This accounted only for glatiramer acetate and rituximab, where there are generic or biosimilar versions available. All pharmaceuticals were approved between 1995-2020(33). Subsequently, all treatments that were not assessed by any of the HTA organisations were excluded, as well as treatments that were withdrawn from the market.

Data extraction

A data extraction tool was developed in two steps, see appendix 1 for the final data extraction tool. The first step was a deductive approach, where parameters were included that could show the synergies or explain potential differences. The final recommendation, positioning, specified population and additional restrictions or comments were extracted to identify synergies among outcomes. To identify process related synergies, we documented the literature and comparator used, references to the other stakeholder's documents or consultation and the time gap between publication of both documents. Finally, we documented the main argument leading to the final recommendation. The final recommendation, the main argument for this recommendation and consultation of CG developers were reported for the relative and cost-effectiveness assessment separately. In the second step, the data extraction tool was tested with one treatment, fingolimod, and complemented with inductive parameters (reason of HTA assessment and the initiating stakeholder, the final recommendation of HTA reports separated by therapeutic and economic recommendation, the reason for guideline update and reference to pharmaco-economic studies).

Data for France, Germany, the Netherlands, the UK and EU was extracted by one author (MH). During the data extraction process, most of the parameters could be extracted from summaries or other fixed paragraphs. For the references to clinical guidelines, consulted physicians, the reference to HTA reports, pharmaco-economic studies and consulted HTA organisations we used a prespecified search strategy consisting of three steps. First, a list of general search terms was developed during the fingolimod test case. This list consisted of main concepts that described the extracted information (e.g. 'guideline', 'neurologist', 'expert'). This was done for each language. Second, these search terms were used to extract these parameters for all other medicines. Third and last, we fully analysed 1-2 documents from each language, to verify that our search terms identified all the necessary information. The used search terms are listed in appendix 2. A second author (RV) extracted data from a small selection of documents (all documents for teriflunomide), after which the results were compared and with any discrepancies consensus was reached through discussion. The Polish data extraction was performed by two separate native Polish authors (AZ, MZ), via a similar approach.

Data analysis

Completed data extraction tables for each country were analysed in Excel (Excel for Windows, 2012, Microsoft Corp.). For this report, we assessed the references that were included in each document; i.e. references in HTA documents to available CGs or to consulting CG developers and references in CGs to published HTA reports and consulting HTA representatives. This provides insight in the development processes of both types of documents. Additionally, we assessed the recommendations that were prepared in each of the documents; i.e. the similarities between HTA reports and CGs regarding recommendations on treatment inclusion, treatment positioning and the eligible patient population. This latter analysis demonstrates insight in the content and outcomes of the processes of both stakeholder groups. All data was presented as absolute numbers or percentages, except for the reported reasons for using the other stakeholder's documents or having a consultation. This was described qualitatively using examples to illustrate the cases. A timeline was created for all events of market authorisation, HTA assessment and CG publications, visualizing time lags and synergies and discrepancies in final recommendations.

Results

Included MS treatments

In total, 21 treatments for MS were identified, of which one often used off-label (rituximab). Five treatments were subsequently excluded because these were either not yet assessed by any of the HTA organisations at time of document selection in August 2020 (N = 4, cannabidiol, ofatumumab, ozanimod, rituximab) or the treatment was, after approval, withdrawn from the market (N = 1, daclizumab). Table 2 shows in bold all the included treatments (N = 16).

Table 2: Overview of the included MS treatments

Trade name	Active Substance	Authorized (EMA)	Type of treatment
Betaferon	interferon beta-1b	1995	Disease modifying treatment (DMT)
Avonex	**interferon beta-1a**	1997	DMT
Rebif	**interferon beta-1a**	1998	DMT
Novantrone / Eslep	**mitoxantrone**	1998	DMT
Copaxone	**glatiramer acetate**	2004	DMT
Tysabri	**natalizumab**	2006	DMT
Extavia	**interferon beta-1b**	2008	DMT
Gilenya	**fingolimod**	2011	DMT
Sativex	cannabidiol / delta-9-tetrahydrocannabinol	2011	Symptomatic
Fampyra	**fampridine**	2017	Symptomatic
Lemtrada	**alemtuzumab**	2013	DMT
Aubagio	**teriflunomide**	2013	DMT
Tecfidera	**dimethyl fumarate**	2014	DMT
Plegridy	**peginterferon beta 1-a**	2014	DMT
Mavenclad	**cladribine**	2017	DMT
Ocrevus	**ocrelizumab**	2018	DMT
Zinbryta	daclizumab	2018	DMT
Mayzent	**siponimod**	2020	DMT
Zeposia	ozanimod	2020	DMT
Kesimpta	ofatumumab	2021?	DMT
Rituxan + generics	rituximab	Not for MS	DMT

Included documents

In total, we collected 113 published HTA reports from the organisation's websites, including initial assessments (N = 56), reassessments (N = 44) and assessments for extension of indications within the MS scope (N = 13), see Figure 1. The majority of these reports made a positive reimbursement recommendation, ranging from 63-70% for initial assessments, reassessments and indication extensions. Most HTA reports were collected from HAS (France, N = 46) as HAS periodically reassesses treatments. Seven guidelines published between 2014 and 2020 were identified for all countries in total, of which two were developed for the UK setting.

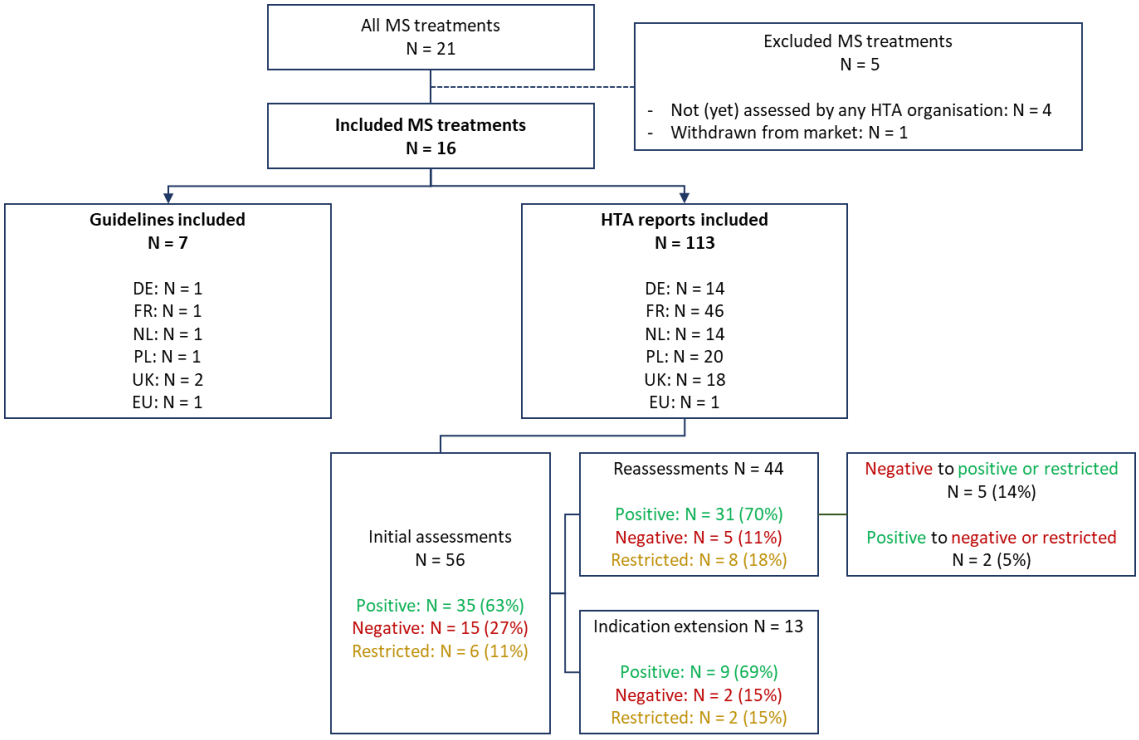

Figure 1: Included documents

Using each other's work: HTA referring to guidelines

Two HTA reports were not considered in this assessment because the data on references were not available. Figure 2 shows that out of 111 HTA reports, only 45 (41%) referred to a CG. Most HTA reports that referred to CGs included multiple CGs often from multiple countries (N = 27, 60%). Five HTA reports (11%) only mentioned CGs indirectly by using information that was received from the manufacturer or an external stakeholder that referred to CGs. HTA reports indicated that CGs are generally used for determining the appropriate comparator and sometimes for (diagnostic) start and stop criteria. The referral of CGs in HTA reports seemed to have taken off after 2010, as the percentage referring to a CG before 2010 was 6% (N = 16) whereas the percentage of referring to a CG was 47% after 2010 (N = 97). From 2010 onwards, the differences over time are not so apparent. More interestingly we observed differences between countries. In France and Germany for example, HTA bodies rarely mentioned CGs compared to HTA bodies in the Netherlands, Poland and the UK that reported the use CGs more commonly.

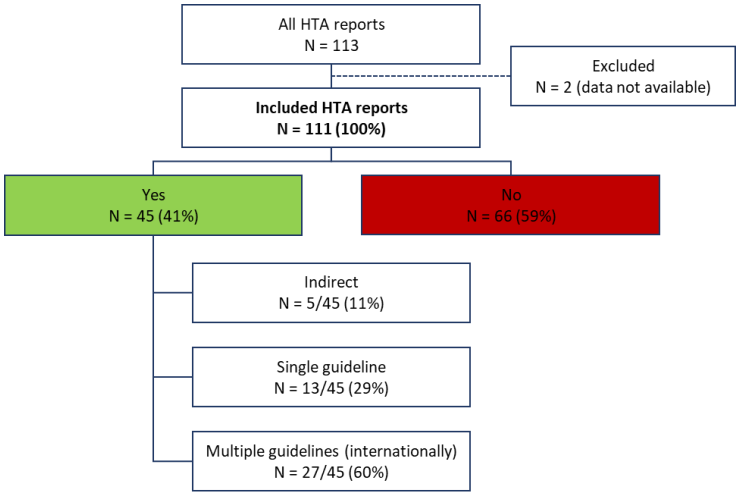

Figure 2: References in HTA reports to clinical guidelines

Utilising practical expertise: HTA referring to clinician consults

As shown in Figure 3, out of 111 HTA reports, 48 (43%) reported a consultation with 'clinicians' or 'experts' to gather input. Two third (69%) of these consultations covered both therapeutic topics as well as topics necessary for the economic assessment (CEA). In one third of the cases (29%) the consultation took place in a 'written' format, i.e. the clinicians could provide written feedback on the draft report instead of during a face to face discussion. HTA organisations reached out to both individuals (41% a single expert, 46% multiple experts) and clinician organisations (33%) for consultations. Usually the same strategy was used within countries for every new assessment. HTA reports indicated that consultations were used to supplement information from CGs with practical considerations by acquiring information on the foreseen treatment position, specific patient populations and (treatment, costs, prevalence of) adverse events. Similar to trends for references to CGs, the reported number of consultations did not change much over time, although differences among countries were visible.

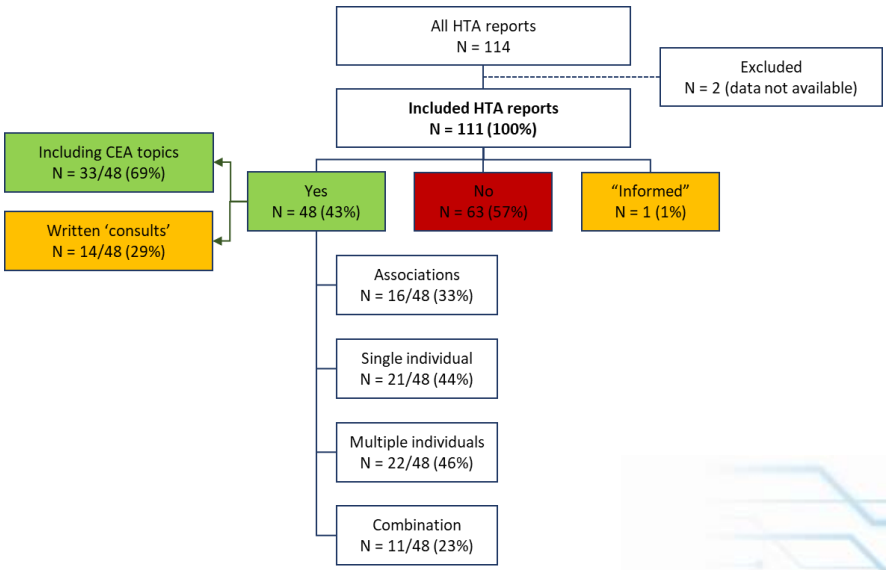

Figure 3: Clinical experts, potential guideline developers, consulted during HTA procedure

Recycling the other's efforts: guidelines referring to HTA

Among seven guidelines shown in Figure 4, five referred to published HTA reports in their respective country. Two of these CGs also reported consulting HTA representatives. Of these two CGs, one was written by HAS itself and one by the NHS England, which is legally obliged to fund treatments recommended by NICE. No independent guideline reported a consultation with HTA representatives in their development process, only two CGs referred to HTA reports. These references were made for the final HTA recommendation and the specific patient population to which this recommendation applies, not for the content of their assessment. Four guidelines reported using pharmaco-economic studies other than HTA reports for their recommendation, of which one CG reported searching for studies but not finding any. When referring to pharmaco-economic studies, this was generally done to acquire more details on costs and cost-effectiveness.

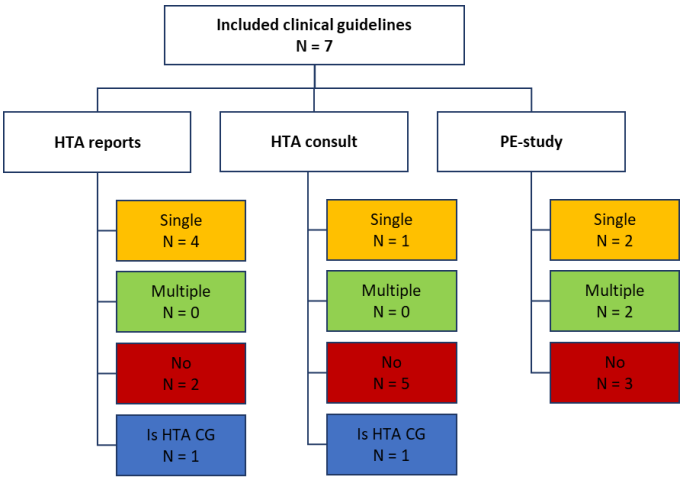

Figure 4: References to HTA reports in clinical guidelines

Timing of events

Figure 5 shows a timeline with market authorisations, HTA assessments and the CG publications, all with their respective outcomes. This timeline visualises discrepancies in timing of the subsequent events. The grey areas in the timeline represent a time lag between market authorisation and HTA, or between HTA and CG updates. The grey cells under CG visualise the number of treatments that has not yet been taken up in national CGs. A similar time related phenomenon is demonstrated by the case of alemtuzumab in France. The initial assessment of alemtuzumab by HAS resulted in a negative advice that was adopted in the HAS CG. Reassessments that were performed in 2016, 2017 and 2018 that were all positive, were not yet implemented in the CG at time of this present study, giving the impression that contradicting recommendations were made. As another example, in the Netherlands siponimod was positively assessed by ZIN and received a positive recommendation just before publication of the CG. Siponimod was not yet included in the CG, while development processes had at least partly been parallel. A different approach for a similar timing issue was visible in the UK in the case of peginterferon β-1a. The NHS guideline reported no information on this treatment in the treatment algorithm, only listed it as pending for NICE recommendation until the CG will be revised.

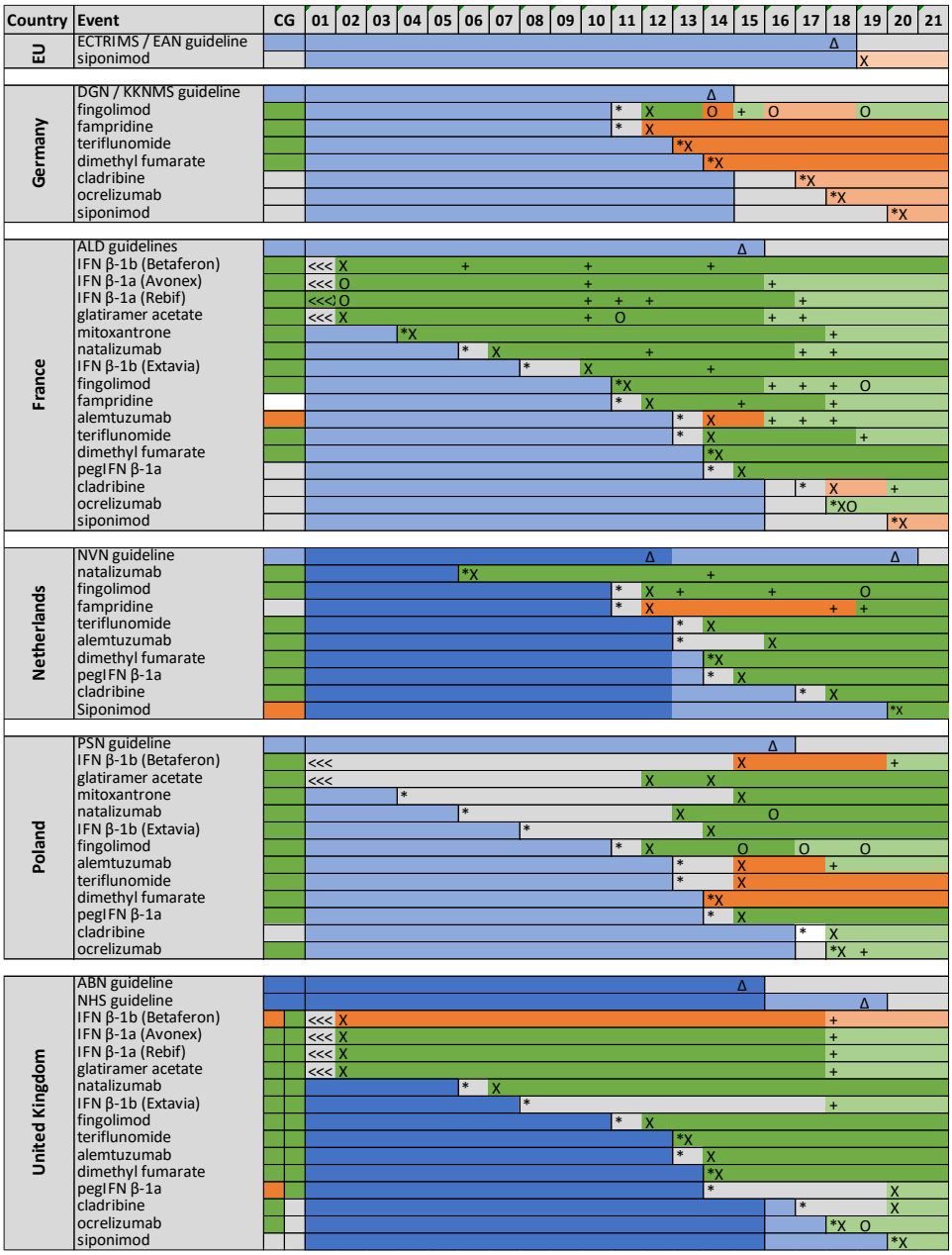

Figure 5: Timeline showing events of market authorisation, HTA assessments and CG publications with their respective outcomes.

This timeline shows major patient access events for MS treatments in our selected countries. The top row shows what each column covers: the country, treatment, CG shows recommendations for each treatment in guidelines (white: out of scope, grey: unable due to timing, green: included, orange: not included) and the timeline running from 2001 (01) to 2021 (21). For the UK, two guidelines were included, the left column representing NHS recommendations and the right column those of the ABN guideline. Blue areas show the period that is covered by each guideline. Light blue means that there is one guideline, dark blue means there is a second or updated guideline. The green and orange coloured parts in each row represent the HTA recommendation, green being a positive recommendation and orange negative. HTA recommendations made after the last update of the guideline, thus which could not have been included, are visualised with a lighter green and orange colour. Each event is indicated with a symbol: * = market authorisation, X = initial HTA recommendation, + = HTA reassessment, O = HTA assessment of an indication extension, <<< = published before the start of this timeline, Δ = publication of clinical treatment guideline.

Final recommendations

As shown in Figure 5, in five cases the HTA recommendations contradicted the recommendation in the CG. Teriflunomide (TF) and dimethyl fumarate (DMF) were not recommended for reimbursement by AOTMiT, whereas the CG of the Polish Neurological Society does recommend these. Both treatments were considered safe and effective and were included in the list of reimbursed treatments by the minister of health. The main reasons for AOTMiT's negative advice were both clinical and economic. Evidence for effectiveness in the population as broad as for comparable treatments was lacking, in combination with a methodological unsound economic model (TF) and there was weak evidence for added clinical benefit while costs were higher than for comparators (DMF). Similar contradictions were visible in the German CG developed by the Deutsche Gesellschaft für Neurologie. They included fampridine (FP), TF and DMF in the treatment algorithm as the G-Ba decided positively on the treatment's reimbursement despite a negative therapeutic evaluation by IQWIG, which found 'no added benefit' for all three treatments. Data was considered not suitable for proving hard endpoints and did not include the right comparator (FP, TF and DMF). Arguments for inclusion of TF and DMF in the CG, on the other hand, focused on the safety profile, as all treatments were considered long-term safe and well tolerable. In the case of FP, the CG concluded on significant effectiveness for a subgroup of the population. In the Netherlands, which has a similar HTA system with separated institutions for assessment and decision making, no such contradictions were visible in the case of MS treatments.

A last discrepancy visible in the timeline, is the case of interferons in the UK. NICE recommended three out of four available interferons. Betaferon received a negative advice as it was valued equal to the other assessed interferon β-1b, only at a higher price. The NHS England adopted this recommendation in the CG whereas the ABN CG recommended the use of interferon β-1b generically, without distinguishment between brands. It is worth flagging that the ABN guideline would be used not only to England, where both NHS England and NICE recommendations apply, but also to other parts of the UK (Scotland, Wales and Northern Ireland).

Positioning of treatments

A total of 51 comparisons of treatment positions (i.e. the line of treatment) between HTA reports and CGs could be made. Treatments with a negative HTA recommendation were excluded, as they were not recommended for the specific treatment line. Cases where the negative HTA recommendation was overruled by a positive final reimbursement decision were included. The NICE recommendation was separately compared with the NHS and ABN guideline. Many minor differences could be noted due to differences in wording, the use of a different definition of 'treatment line' and differences in recommendations for 'sub-indications' within MS, such as clinically isolated syndrome (CIS) or rapidly evolving severe (RES) MS.

We divided the compared treatment lines into three general categories: 'similar' (green in Figure 6), 'minor differences' (yellow in Figure 6) and 'major differences' (red in Figure 6). Twenty-nine compared treatment line recommendations (59%) fall under the former category 'similar', of which 25 treatment line recommendations (50% of total) were exactly the same in the HTA report and in the CG. In four cases (8%), the recommended treatment line was similar, i.e. it started the same and applied to the same sub-indication, only the CG extended this to further treatment lines. An example is natalizumab in the UK that was recommended by NICE as a first line treatment for

RES-MS, and the NHS extended this to the use of natalizumab in the second and third line RES MS as well, after failure of previous treatments. Fifteen treatment line comparisons (30%) fall under the category ‘minor differences’. These cases differed not in the treatment line that was recommended, but the indication for the recommendation was extended. Teriflunomide in the Netherlands was recommended by ZIN as first line treatment for relapsing-remitting MS (RRMS). The CG recommended this treatment for the first line as well, but extended the indication to CIS and active secondary progressive MS (SPMS). Eight cases (16%) fall under the latter category ‘major differences’. In five cases (10%), the recommended treatment line was the same but the indication was different (not only extended as in the case of ‘minor differences’). In six cases (12%) the treatment line recommended was actually different. Ocrelizumab was recommended by NICE as a first line treatment for primary progressive MS (PPMS), whereas in the NHS guideline the first line treatment recommendation was made for RRMS and RES-MS. NICE did recommend ocrelizumab for RRMS in the second line, which also includes this case in the last subcategory, where treatments are recommended for the same sub-indication only starting in a different line of treatment. Another example for this is fingolimod, that was recommended as a second line treatment by NICE whereas the ABN CG described the use of it as a first line treatment.

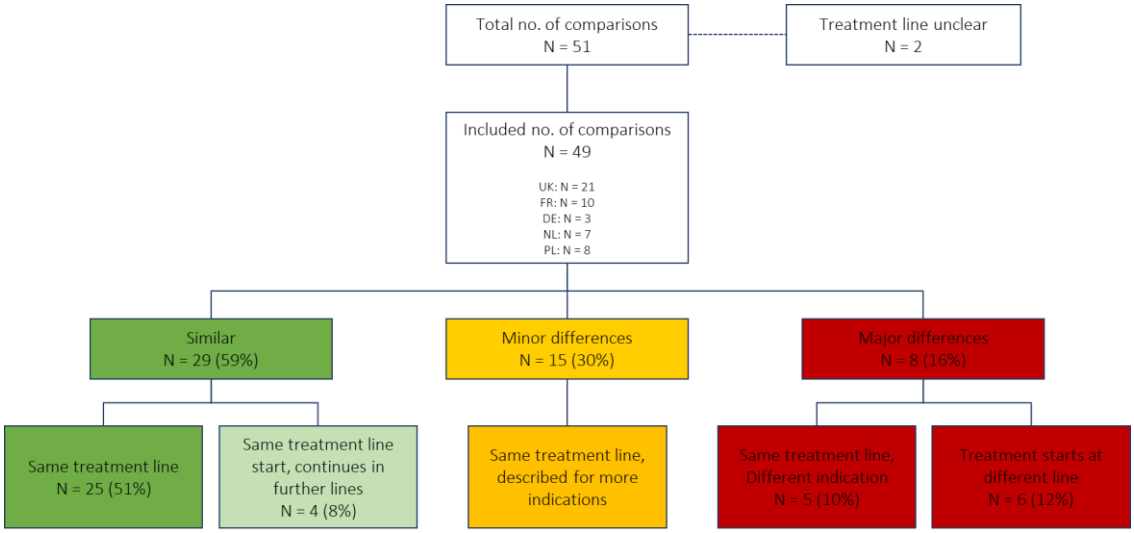

Figure 6: Comparison of recommended treatment lines for the various MS pharmaceuticals as made by HTA organisations and clinical guidelines.

In Germany, all treatment lines were the same in the HTA reports and CGs. However, IQWIG concluded with a negative recommendation for the assessed treatment line, whereas the CG was positive for the same treatment in this position. This discrepancy, however, can be explained because the G-Ba decided positive on these treatments with this treatment line. These cases are shown as ‘same treatment line’ in Figure 6. Generally, there was no trend visible where one stakeholder was more cautious in recommending treatments in its recommendations than the other.

Discussion

Our results give insight into the alignment and discrepancies between published HTA reports and CGs for MS in five European countries. Discrepancies were identified in the process, indicated by time lags between publication or updates of documents and the lack of (early) consultations between the two parties in more than half of the cases. The content of the documents are generally more aligned. Final recommendations made by both parties were usually similar and were considered during the development of the documents. Diving into the details of the recommendations did highlight some differences. Subtle differences were created by extension of a recommendation to a wider population or to earlier or later treatment lines. Only in a few cases the recommendations entailed a completely different population or treatment position..

The relation between HTA and clinical guidelines

Only half of the HTA reports referred to the use of CGs during assessment, or to consultation of clinicians. NICE is the only HTA organisation that clearly describes the procedure for involvement of physician experts and guideline developers on their website. National professional organisations are allowed to participate in the appraisal by submitting evidence and respond to consultations as well as to appeal against the final appraisal determination (FAD). They can nominate clinical specialists to represent views to the appraisal committee. The nominated experts have the opportunity to comment on the appraisal consultation document (ACD) separately from the organisations that nominated them, but do not have the right to appeal against the FAD. Among others, the national collaborating centre, commissioned by NICE to develop clinical guidelines and the British National Formulary are asked to comment. They engage in the appraisal process by responding to consultations and do not have the right of appeal against the FAD(34).

The delays between publication of HTA reports and subsequent CG updates that were visible in our results can at least partly be explained by the way the current system is structured. For instance, in the Netherlands, assessment siponimod were completed by ZIN just before publication of the updated guideline from the NVN. Updating guidelines requires funding, which may not always be granted for the update of a single treatment, it may require sufficient reasons. Both awaiting a sufficient number of arguments legitimizing an update and the more extensive updating process necessary for multiple treatments take time and thus delay any updates. This may be one hurdle despite the potential existing willingness among involved clinicians to maintain a ‘living’ CG document.

Whilst the final recommendations on whether or not to reimburse or to include a treatment in the treatment algorithm were usually aligned with one another, details of these recommendations show some discrepancies. A reason for some of the discrepancies in the recommended eligible patient populations is the ongoing discussion on the definition and diagnosis of specific subpopulations within MS(35,36). Some argue that relapsing and progressive forms of MS are two distinct types of the diseases(35). This is supported by clinical trials showing better results of specific disease modifying treatments for either the relapsing or the progressive types of MS, as the in- and exclusion criteria become stricter and narrower. Others argue that the manifestation

of MS evolves over time rather than consist of distinct subtypes(36). This is supported by an analysis of data from multiple clinical trials that showed that age is an important predictor for the way MS is manifested, as age modulates the frequencies of relapse and thus phenotype presentation. Even though most CGs and HTA reports seemed to follow the McDonald criteria for diagnosis of MS(37), this difference in definition may have caused any discrepancies in the description of eligible patient population among documents versus which patient characteristics are actually considered eligible in clinical practice.

A second discrepancy, in recommended treatment lines, could be explained by the different definitions of treatment line used among parties. The ABN guideline, for example, divides all treatments into two groups: moderate and high efficacy treatments, representing first and second line treatments(19). This deviation leaves room for treatment choice within each line, that fits best for the patient. Fingolimod was characterized this way as a 'moderate', thus first line, treatment. NICE concludes on a second line treatment in this case, because other first line options, e.g. interferons or glatiramer acetate are considered favourable due to their safety profile. HAS uses a different way of describing treatment lines, by adding when treatments are preferred(24). Glatiramer acetate is considered a first line treatment if interferons are contra-indicated, as well as a second line treatment if interferons cannot be continued. In the Netherlands this difference occurred for alemtuzumab where ZIN considered alemtuzumab a second line treatment for RRMS, in case of a very active form of RRMS it was allowed as first use. The NVN guideline describes the same populations, only classifies the treatment line as 'third' due to safety concerns, which is in line with a later EMA restriction(29,30,38). The presentation of our results was therefore based on both the described treatment line and the positions in the described population, to find actual differences.

MAGIC (making GRADE the irresistible choice') is a non-profit foundation with a new approach for producing and disseminating CGs. Their aim is to '*increase value and reduce waste in healthcare through a digital and trustworthy evidence ecosystem*'. It is one of the first examples of the trend towards 'living' guidelines, i.e. dynamically updated CGs to provide real-time information to the health care provider at the point of care(39). This trend would facilitate solving the issue of time gaps between the events in the process of a treatment towards patient access, but would require closer collaboration with HTA.

HTA and clinical guidelines in relation to the broader patient access process

In addition to this study, an extensive review was performed in the HTx project on the synergies between regulators and HTA organisations, combining literature with survey data(40). This review concluded that four organizational interventions could promote improved synergies between regulators and HTA: tripartite early dialogue, post-authorisation data generation, parallel reviews and adaptive licensing pathways. These four interventions circle around the most important issue for alignment, which is the alignment of evidentiary requirements among the parties. Certainly, this entails methodological issues to overcome, such as agreement on trial designs, considered endpoints, appropriate comparators and the optimal eligible patient population. Nevertheless, discussions in literature indicated that safety and clinical outcomes are at least two requirements for common ground.

This common ground is shared with clinicians developing CGs, as described by Woolf and colleagues in a series of papers on methods to develop guidelines(41). The *tripartite dialogue* is a facilitator for alignment of evidentiary requirements, by increasing understanding among involved parties on the divergence of needs. In a few jurisdictions, tripartite dialogues already exist to provide parallel advice to the manufacturers in an early stage. Australia, Canada, the US, the UK, Sweden and the Netherlands know similar initiatives, however as the name *'tripartite'* indicates, these are limited to only three parties: manufacturers, regulators and HTA organisations. Extension of these dialogues into a quadripartite, giving clinical guideline developers a formal role in these dialogues, could help further alignment of the process including the step from reimbursement to update in CGs. Initiatives such as 'Ronde Tafels' that include clinicians do already exist at ZIN, for some indications including MS(42).

Early dialogue, as also suggested by Vreman and colleagues, would go hand in hand with the second proposed strategy, post-authorization data generation(43). Often, the data available at time of first assessment are insufficient for robust decision-making for either regulators or HTA organisations. Increased certainty on the treatment's risk/benefit profile is desired. Early dialogue, in addition to beneficial financial prospects, would facilitate a so called 'post-approval evidence generation plan' entailing value-based pricing reimbursement schemes with the acquired generated data as a basis. At the same time this would prevent delays in access. The HTx review suggested for regulatory bodies and HTA organizations to cooperate on the guidance on post approval study designs that matches both stakeholder's needs for supplementing efficacy data with effectiveness data, i.e. in real-world setting. Clinical guideline developers are just like the two institutions in need of this data for decision making, and vastly contribute to the gathering of this data. As proposed for the earlier two solutions, this strategy could also be extended by involving clinicians in the guidance for post-approval study designs and other aspects related to data generation. Research among European HTA organizations showed that policies for the use of real-world data vary widely among originations in different countries(44). This means that, just like with the evidentiary requirements, discussion to reach consensus on these policies is necessary.

As a third strategy, parallel reviews were suggested as a solution to speed up the process, allowing for earlier patient access. This solution could as well be extended to a simultaneous review for uptake in CGs. This would facilitate the 'living' guideline with timely updates. This comes, as any solution, with drawbacks as demonstrated by Australian and US examples, such as the otiose work by HTA organizations if a treatment is not granted market approval. This would be similar with inclusion of reviews for CGs, as this work would be unnecessary if the treatment gets a negative reimbursement decision, or is not granted market authorization. A way to circumvent this ineffective work, is to make the applicant cover any costs. Such a penalty is in any case not ideal for developers, and might not find sufficient support, especially in the case of CG development. Where organizations deciding on market approval and reimbursement mostly have decisive power that act as a veto for a treatment's access to patients, uptake in clinical guidelines, on the contrary, acts as a more soft hurdle, which might not justify such a measure. Starting with the least labor-intensive work or a focus solely on the most promising treatments could be ways around this. One additional way, is the opportunity that a parallel review creates for cooperation and potential to find specific populations that do actually benefit from a new treatment, suiting the trend towards individualized and personalized treatment.

Strengths and limitations

Our results find strength in the rigorous and standardized method that was used to gather data via the data extraction tool. Still, the information in this data is limited to what was actually reported and published by HTA organisations and CG developers. Practice might differ from what was reported, or events might not be reported at all. Informal moments of contact between HTA organisations and CG developers might happen without documentation. This introduces a form of reporting bias that highlights the necessity to confirm our results with data from other sources, such as questionnaires or interviews.

Data were gathered from a large number of HTA reports which makes the results for the MS case strong. However, the results are not necessarily transferable to other indication areas. As for each indication there is a specialized guideline committee, the procedures might differ for some of these committees. Solitary initiatives exist, which would alter outcomes for those indication areas. For example, in the Netherlands, the treatment pathways for oncology products are coordinated by the BOM committee (Committee for Assessment of Oncology Products), which is closely cooperating with the Dutch National Health Care Institute (ZIN)(45). However, these results do show that at least for some indications synergies are not always optimal, and that there is room for improvement. MS was an appropriate example for this demonstration due to the clearly visible divergence in HTA recommendations, large number of expensive disease modifying treatments that rapidly entered the market over the last decade(4,5,12).

A diverse set of countries was considered in our study, including large and small, eastern, southern and western European countries. The data underlying our results showed distinct differences among the country's procedures. Reports from IQWiG consistently reported one single clinician to be involved and requested written feedback on a draft report at the end of the development process, whereas HAS usually did not report on consulting any clinician. The differences in procedures were clearly visible among countries, but were consistent over time. This indicates that our results are not automatically generalizable to other European countries. To acquire that type of information, the study should be expanded to additional countries. As we included countries with some of the frontier HTA organisations in this field, it is likely that our results create an image that is too positive when generalized to the whole of Europe.

Translation to future practice

MS is one of the case studies in the Horizon 2020 HTx project(14). It is used as the case for the development of a prediction model suitable as decision aid for use in real-time individual treatment decision making. At this point, CGs and decision-making aids are two distinguished tools as one describes general considerations and the other gives an individualized treatment advice. With the current landscape moving towards personalized or individualized treatments, the aims of these tools are likely to converge, which is also shown by initiatives such as the MAGIC project(39). The focus on individualized treatments is also an emerging challenge for HTA organizations(46–48). Without alignment of processes in both timing and evidentiary requirements, the recommendations of both parties would increasingly diverge from one another. To prevent misalignment and facilitate access to individualized treatments, both parties would need early insights in each other's needs and use the other's knowledge and experience.

More data is necessary to generalize results to other countries in Europe, in particular the eastern European countries or countries outside Europe, and to other disease areas. The results also require confirmation by other data sources such as stakeholder experiences and opinions, which would shed light on details that are necessary to provide any recommendations on improvements in the process.

These results are the start of more extensive data generation that is rendered necessary to inform on improvement of this process. These data will be supplemented by experiences of assessors at HTA organizations and clinicians involved in guideline development via a survey. Both these studies will inform the discussion among the three stakeholder groups, including regulators, in a workshop that is planned to be organized by the HTx consortium in 2021. The aim is to describe hands-on possibilities to create a more efficient process, which would result early patient access.

Conclusion

The organizational process from reimbursement to uptake in clinical treatment guidelines, is not so well-aligned in the case of MS based on published outcomes of assessments. It seems that not always the HTA organisations and clinicians systematically access each other's knowledge. Additionally, recommendations made by the one stakeholder do not always seem to trigger action by the other stakeholder, such as timely updates of guidelines. While these organisational aspects are not so well-aligned, the final recommendations on reimbursement and treatment position, on the other hand, were usually similar among the stakeholders. Differences do become visible when zooming into details of the recommendation. The synergies in recommendations that both parties make underline the possibilities to improve the process towards patient access. Early consultations or dialogue could facilitate this increased efficiency by highlighting the needs for both parties and exchanging knowledge.

More detailed knowledge on the development of HTA reports and CGs as well as the stakeholder's viewpoints on and experience in the process is necessary to determine how current synergies can be improved. Results from this study will feed into the discussion among stakeholders groups, including regulators, to identify these possibilities for improving the alignment of the process during a workshop that will be organized. Ultimately, this data combined with stakeholder input will lead to policy recommendations that would facilitate the improved synergies among the three stakeholder groups. Increased efficiency in the process would ensure earlier and more sustainable access to required treatments.

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Appendices

Appendix 1

Table 1: The tool used to systematically extract data

Document element	Description		
	HTA – REA	**HTA – CEA**	**Guideline**
Year published	Year	NA	Year
Reason for assessment / publication	New substance, reassessment, indication extension	NA	Aim guideline
Assessment initiated by	Ministry of Health, HTA organisation, manufacturer data submission, etc.	Requirement for type of analysis performed (budget impact, cost-effectiveness assessment, etc.)	Government, medical (specialist) association, other
Final recommendation	Reimbursed yes / no	NA	In treatment algorithm yes / no
Recommendation – therapeutic / economic	Not assessed/ more/ equally/ less effective	Not assessed/ Positive/ Negative/ Restricted	Yes/ No/ Yes, but not with a fixed position in the treatment algorithm
Positioning (applied for by manufacturer)	1, 2, 3rd line After X… Before Y… In combination with Z…	NA	1, 2, 3rd line After X… Before Y… In combination with Z…
Specified population (applied for by manufacturer)	Specified clinical or lab characteristics	NA	Specified clinical or lab characteristics
Comparator	Used comparator in recommendation	NA	NA
Main outcome (that was used for assessment)	Relapses, disease progression, quality of life, adverse events	NA	Relapses, disease progression, quality of life, adverse events
Referred trials (used for recommendation)	Trials used for recommendation	NA	Trials used for recommendation
Reference to clinical guideline / HTA report	Does document refer to any relevant guideline regards REA input	NA	Yes, REA Yes, CEA Yes, both No Indirectly / other reference to costs or cost-effectiveness
Guideline / report used for	Information gathered from guideline	Information gathered from guideline, specifically for economic assessment	Information gathered from HTA report
Reference to consulted CG developers (if not: physician (organisation) in general) or HTA representative	No reference to consult/ Consulted guideline developers/ Consulted clinicians in general	No reference to consult/ Consulted guideline developers/ Consulted clinicians in general	No reference to consult/ Consulted guideline developers
Consultation used for	Information gathered during consult	Information gathered during consult, specifically for economic assessment	Information gathered during consult
Main argument leading to PT / PE recommendation	Main described reason for recommendation in REA	Main described reason for recommendation in CEA	Main argument for in- or exclusion and positioning
Additional relevant information	…	…	…

Appendix 2

Table 1: Search terms HTA reports

Term	Dutch	English	German	French
Guideline	richtlijn, directief, guideline, klinisch	guideline, guidance, clinical	Richtlinie, Leitlinie	ligne directrice, ligne directive,
Organisation	vereniging, organisatie, genootschap, gezelschap, federatie	association, organization, consortium	Gesellschaft, Gesellschaft, Vereinigung, Föderation	Association, société, union, organisation, foundation, groupe
Treatment	therapie, behandeling, interventie	therapy, treatment, algorithm, intervention	Intervention, Therapie	Traitement, thérapie, algorithm, intervention
Guideline names (search for abbreviation)	NVN (Nederlandse vereniging neurologie), MSVN (MS vereniging nederland), Nationaal MS fonds FMS (Federatie medisch specialisten), ECTRIMS (European Committee for Treatment and Research in MS), EAN (European Academy of Neurology), EMSP (European MS Platform)	NHS (National Health Service), Neuroscience, CRG (Clinical Reference Group) ECTRIMS (European Committee for Treatment and Research in MS), EAN (European Academy of Neurology), EMSP (European MS Platform)	DGN (MS-Leitliniengruppe und dem ärztlichen Beirat der DMSG), KKNMS (Krankheitsbezogenen Kompetenznetzes Multiple Sklerose), MSTKG (Multiple Sklerose Therapie Konsensus Gruppe), ECTRIMS (European Committee for Treatment and Research in MS), EAN (European Academy of Neurology), EMSP (European MS Platform)	Fondation pour l'aide à la recherche sur la sclerose en plaques (ARSEP), Groupe de reflexion, sur la sclerose en plaques (GRESEP), ECTRIMS (European Committee for Treatment and Research in MS), EAN (European Academy of Neurology), EMSP (European MS Platform)
Clinician	neuroloog, arts, dokter, expert, specialist, clinicus, professional, adviseur, raadgever	phycisian, doctor, neurologist, expert specialist, clinician, professional, adviser	Arzt, Doktor, Experte, Fachlichen, Berater, Kliniker, Spezialist, Neurologe	Docteur, clinicien, expert, spécialiste, neurologue
Consulting	Raadplegen, consult, raad, input, aanbevelingen, aangeraden, advies Bijdrage, medisch	Consult, recommendation, input, advice, medical, contribution	Rat, Beitrag, Beratung, Konsultieren, Empfehlung, Medizinisch	Consulter, consultation, conseil, contribution, recommandations, médical
Communication	Consultatie, brief, gesprek, conversatie, discussie	Memo, message, conversation, discussion, letter	Brief, Buchstabe, Konversation, Gespräch, Diskussion, Beteiligung	Letter, conversation, discussion, message

Table 2: Search terms clinical guidelines

Term	Dutch	English	German	French
HTA	HTA, health technology assessment, ZIN, Zorginstituut Nederland, EUnetHTA	HTA, health technology assessment, NICE (National Institute for health and Care Excellence), EUnetHTA	HTA, health technology assessment, IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen), G-Ba (Gemeinsamer Bundesausschuss), EUnetHTA	HTA, health technology assessment, HAS, Haute Autorité de Santé, EUnetHTA
Costs	Kosten, kosten-effectief, budget, prijs, vergoeding, uitgaven, economie, economische evaluatie	Costs, cost-effectiveness, budget, price, reimbursement, refund, payment, spending, economic, economic evaluation	Kosten, Ausgabe, kosteneffizient, budget, Preis, Rückerstattung, Ersatz, Vergütung, Ersetzung, Zahlung, Leistung, Wirtschaft, wirtschaftliche Bewertung, economic, economic evaluation, costs, cost-effectiveness	Coûter, rentable, compensation, rembourser, budget, prix, édition, économie, évaluation, revue