Are supplemental appraisal/reimbursement processes needed for rare disease treatments? An international comparison of country approaches

Elena Nicod (elena.nicod@unibocconi.it)
SDA Bocconi Scuola di Direzione Aziendale
Amanda Whittal
SDA Bocconi Scuola di Direzione Aziendale
Mike Drummond
University of York
Karen Facey
The University of Edinburgh

Research

Keywords: Rare disease treatment, Orphan medicine, Ultra-orphan medicine, Appraisal, Reimbursement, Access to treatments, Supplemental processes, Health technology assessment

Posted Date: April 6th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-20907/v1

Version of Record: A version of this preprint was published on July 20th, 2020. See the published version at https://doi.org/10.1186/s13023-020-01462-0.

Abstract

BACKGROUND There is increasing recognition that conventional appraisal approaches may be unsuitable for assessing the value for money of rare disease treatments (RDTs). This research examines whether supplemental appraisal processes for RDTs are needed, and if so, what form should these take. A qualitative research design was used that included (1) documentation of country appraisal/reimbursement processes for RDTs via questionnaires, desk research and iterative interactions with country experts to produce country vignettes, and (2) a cross-country analysis of these processes to identify and characterise countries with supplemental processes for RDTs, and compare them to countries without supplemental processes.

RESULTS Thirty-two of the 37 invited countries participated in this research. Forty-one percent (13/32) use supplemental processes for RDTs. Their level of integration within standard processes ranged from low to high, characterised by whether they are separate or partially separate from the standard process, adapted or accelerated standard processes, or standard processes that account for rarity. They are characterised by features implemented throughout the appraisal process. These features are mechanisms that allow application of different standards to assess the value of the medicine, support to the appraisal/decision-making process, overcome the issues of lack of cost-effectiveness, or exempt from part of/the full HTA process. They apply to ultra-RDTs and/or RDTs, and are often combined. They increase the likelihood of reimbursement by adjusting and/or foregoing part of the assessment process, or accepting to pay more for the same added benefit as for common conditions, which is likely to lead to accepting high prices. A large proportion of countries with standard processes include one or more of these features (formally or informally) or are discussing potential changes in their systems.

CONCLUSIONS Results suggest revealed preferences to treat RDTs differently than conventional medicines. Some of the challenges around uncertainty and high price remain, but supplemental process features allow for more adapted and consistent decision-making. Many of these processes are new and countries continue to adjust as they gain experience. These results do not outline what an ideal process for RDTs looks like, but identify some key features that can be implemented to facilitate this process.

Background

Health systems are increasingly challenged to fund new and often high-cost medicines in a timely manner [1]. These include medicines to treat rare diseases affecting small patient numbers, which are often severe (life-threatening and/or causing significant disability), genetically acquired and have an onset of symptoms in childhood. In many parts of the world, financial and procedural incentives to facilitate research, development and marketing authorisation have been implemented for rare disease treatments (RDTs) to reduce the high unmet need for disease modifying treatments. In Europe, these incentives are provided by the European Medicines Agency (EMA) through the EU Regulation on Orphan Medicinal Products (OMPs), which was implemented in 2000 targeting medicines treating less than 5 in 10,000 people [2]. These measures are considered to have been successful, with the development of 1,670 products designated as OMPs, of which 171 have been authorised by the EMA [2].

Decisions relating to reimbursement, pricing and availability of treatments in health systems are often informed by health technology assessment (HTA), which is based on international evidence that is then deliberatively appraised by a committee of experts to determine the added clinical benefit and/or cost-effectiveness of new technologies in a specific health system. The two common challenges in HTA appraisal of RDTs are the uncertainties apparent in the evidence and the high price of the products [3]. The deliberation by the appraisal committee is particularly important for RDTs given the uncertainties resulting from the small and heterogeneous patient populations, lack of information about the natural history of the disease, and the direct and indirect burden of these conditions [4–7]. These uncertainties, combined with the high prices of these medicines (to recoup R&D costs from small patient populations), often lead to cost-effectiveness estimates, such as Cost/Quality Adjusted Life-Year (Cost/QALY), that are much higher than traditional willingness-to-pay (WTP)

thresholds [4,8]. In such circumstances, it may be doubly difficult to justify reimbursement. These aspects have led to increasing recognition that it may be difficult to subject RDTs to conventional HTA processes, particularly in those diseases that require highly specialised care and that are very rare or for so-called "ultra-OMPs" [3,4,9–11].

One way to overcome this issue would be to exempt RDTs from HTA altogether, as was the case initially within Germany's Act on the Reform of the Market for Medicinal Products (AMNOG) system, or pay more for the same added benefit for a patient with a rare disease compared to one with a common condition, as is the case in England's Highly Specialised Technology (HST) programme [8,12,13]. A lower level of scrutiny or a greater willingness to pay could also be seen as acceptable, given the smaller population (and associated budget impact) [11]. However, this has been criticised in the past by some analysts, on the grounds that all health care expenditure deserves thorough scrutiny, or that paying more for health benefit in RDTs could have a high opportunity cost, in terms of the services that other patients with common conditions may have to forego [12]. Another way to deal with these issues is to adapt conventional HTA processes to facilitate the appraisal of RDTs. For example, some HTA bodies have stated that the QALY may not capture all elements of value, have adopted a broader decision-making framework and implemented processes to incorporate wider considerations from clinical and patient experts [4,13]. Other HTA bodies are implementing managed entry agreements (MEAs) to collect outcomes to inform individual treatment decisions, to generate additional evidence for later re-appraisal or to accelerate access to these treatments [14]. Other countries have expedited processes for RDTs that allow patients to get access to these medicines sooner.

As pharmaceutical expenditure is shifting from treatments for more prevalent conditions to medicines that fall within the OMP legislation, the challenges relating to conventional appraisal processes will be faced more frequently [15]. However, the growing number of OMPs are not all for rare, genetic, previously untreatable conditions. Some may be for specific forms of a more prevalent condition, allowing stratified or personalised treatment within a clear patient pathway, whereas others may be very rare conditions where there is no country expertise.

Therefore, the key question is whether supplemental appraisal processes are needed that would deal better with the specificities of RDTs, and if so, what form these should take? This research aimed to address this question by examining how countries are appraising RDTs, with a special focus on those that have implemented supplemental processes that are specifically for RDTs. This work is part of a Work Package 10 within the EC H2020 funded IMPACT-HTA project; it feeds into the overarching objective of the Work Package to develop guidance on novel approaches to appraising medicines to treat rare diseases to support robust, accountable decision-making across Europe on high-cost products.

Methods

A mixed-methods design was used that included (1) documentation of country appraisal/reimbursement processes for RDTs via questionnaires, desk research and iterative interactions with country experts to produce vignettes for each country, and (2) a qualitative review of these processes to identify and characterise appraisal processes for RDTs and identify the features used in these "supplemental" processes.

The study countries comprised all European Member States and countries from the European Economic Area (Iceland, Liechtenstein, Norway, and Switzerland). Australia, Canada and New Zealand were also included to learn from these jurisdictions with more mature HTA processes. Experts involved in the HTA appraisal/reimbursement processes for RDTs were identified for each country using the authors' networks or via internet searches. Exchanges were often with just one expert per country, since he/she was often the person with the right competence to provide this information. In a few cases where the responsibility for health care provision is regional (Canada, Spain), several experts for one country were contacted. Experts were invited to participate in this research by email. In case of non-response after numerous follow-up emails, other experts with the appropriate expertise were contacted until appropriate input was received.

A questionnaire with open-ended questions was designed to collect information about country HTA appraisal/reimbursement processes for RDTs, associated challenges, impact and expected policy changes [Appendix 1 - Questionnaire]. The questionnaire was reviewed by co-authors (KF, MD) and project partners, and piloted with two institutional partners (National Institute for Health and Clinical Excellence (NICE) in England and the Dental and Pharmaceutical Benefits Board (TLV) in Sweden). Adjustments were made based on the feedback received to ensure the questionnaire was clear and enabled the information of interest to be collected. The questionnaire and accompanying documentation (information sheet and informed consent form) were sent to all country experts by email.

Country vignettes summarising individual country appraisal/reimbursement processes for RDTs were created. If one country had several jurisdictions, these were all included in the same country vignette. Additional desk research was also conducted to confirm and complement some of the information. The country vignette was created and reviewed in an alternating approach by two of the co-authors (AW, EN). Country experts were sent the draft vignettes by email with follow-up questions and opportunity to comment, and for their review and validation on two (or more) occasions, respectively. For some of the countries with RDT supplemental processes, the first validation round was conducted via 1-1 discussions on Skype to allow a more detailed understanding of the features of these supplemental processes to be obtained. The process of creating the vignettes was undertaken from January 2019 until March 2020.

Country definitions of rare and ultra-rare disease treatments were used. In Europe, RDTs were defined by the OMP legislation, but as there is no legislation about ultra-RDTs, this definition differed across countries. In this study, RDT are defined as all medicines that would fulfil the EMA's OMP prevalence criteria (medicines to treat less than 5 in 10,000 people), and the term OMP is used when reference is made specifically to those with an orphan designation from the EMA. A process was defined as supplemental if it only included rare and/or ultra-rare disease treatments and related to routine use for a defined patient population within a health service. These would not apply to, for example, named patient programs in which reimbursement is sought for individuals.

The analysis focused on characterising these supplemental processes in terms of (1) level of integration within standard appraisal/reimbursement processes, and (2) their features (unique and/or different) to standard processes. These features were grouped according to their occurrence in the HTA process: (a) categories of *evidence* required, (b) *assessment* of the evidence (including evidentiary standards), (c) *appraisal or deliberative process for decision-making*, and (d) recommendations for *pricing, reimbursement of use of the RDT*. Countries without supplemental processes were then examined to determine whether there were other features within their processes that could be applied to support appraisal of RDTs.

Results

Thirty-two of 37 countries (86%) were included in the study. Vignettes for each of these were created [16]. The five non-respondent countries excluded from the study were: Australia, Croatia, Cyprus, Luxembourg, and Wales. Responses were provided by 33 country experts (two experts for the different jurisdictions in Canada) (Figure 1). Eighty percent of experts work within, or close to, HTA/reimbursement processes in the public sector, with the remaining being from academia, health care providers or private sector. Their positions are directorship-level involved in the pricing and reimbursement processes (45%), HTA scientific experts (30%), appraisal committee members (6%), academics or clinical experts (18%), or consultants (3%).

The next section provides an overview of the countries with supplemental processes, explores their key features according to the typology, and examines countries without RDT supplemental processes.

Supplemental processes for rare disease treatments

Forty one percent (13/32) of countries include supplemental processes specifically targeting rare and/or ultra-RDTs (Figure 2). Integration levels of these supplemental processes within standard processes were categorised as low, medium and high. Processes with low integration are either completely (2/15) or partially separate (2/15) from the standard process. The main distinction between separate supplemental and standard processes are the different evidence submission requirements and appraisal committees. This is the case for the HST programme in England and the ultra-RDTs pathway in Lithuania, both targeting ultra-RDTs. They also include different features intended to better adapt to the specificities of RDTs. Both recognise the challenges for evidence generation and tend to be more lenient with its interpretation. The HST programme in England has an explicit decision-making framework that allows for broader consideration of treatment value (nature of the condition, clinical effectiveness, value for money, impact beyond direct health benefits) and greater WTP, whereas the ultra-RDT pathway in Lithuania has different appraisal rules (therapeutic value not graded), a special reimbursement list with no waiting list, and special pricing rules.

Partially integrated supplemental processes include the ultra-RDT pathway in Scotland (where the wider decision-making framework implemented in 2016 was changed to an ultra-RDT pathway in 2019) and the OMP pathway in Germany. In Scotland, once a product is designated as an ultra-RDT by the Scottish Medicines Consortium (SMC), it is submitted for initial assessment to SMC using a special submission form and it is then made available in Scotland for three years with a data collection plan and re-assessment after three years. In Germany, the assessment and appraisal are conducted by the Federal Joint Committee (G-BA) instead of the independent Institute for Quality and Efficiency in Health Care (IQWiG). RDTs are also subject to more simplified evidentiary requirements (e.g. no need for comparative data), and their additional benefit is considered automatically proven. There is also an option for conditional approval.

Countries were defined as having *adapted* processes for RDTs when they include adjustments to their standard process that allow better management of the challenges with RDTs. This is the case for Norway, Sweden and Slovakia, in which the adapted process targets ultra-RDTs, and in Scotland for OMPs. The main process features common to all the countries relate to a greater understanding of the challenges to produce high quality evidence for RDTs, and more favourable reimbursement through a higher WTP. Slovakia also includes an exemption from presenting an economic evaluation. In Scotland, being an OMP has been seen as a “modifier” to the appraisal process for many years, providing more flexibility in the decision-making process [17]. Recently, there is also the possibility to hold a patient and clinician engagement (PACE) meeting for OMPs.

Five of the 13 countries with supplemental processes for RDTs have a high level of integration with standard processes. These are either *expedited* processes or processes where *rarity is weighted*. The three countries with expedited processes allow for an earlier start of the assessment process (and subsequently earlier access for patients to these treatments). The other two countries have points systems to determine reimbursement status (e.g. Romania) and WTP (e.g. Slovakia), where OMPs get extra points.

Two of the 13 countries with supplemental processes use alternative routes to reimburse subgroups of RDTs, through *HTA exemptions*. These include the separate state-reimbursement budget for children living with rare diseases in Latvia and a list of rare diseases for which medicines are automatically reimbursed in Bulgaria.

Distinction of rare versus ultra-rare disease treatments within supplemental processes

All processes with a medium to low level of integration within standard processes target ultra-RDTs, with the exception of the orphan medicines pathway in Germany and the Patient and Clinical Engagement (PACE) programme and SMC modifiers in Scotland intended for OMPs (Table 1). The ultra-RDT definitions are defined using prevalence criteria ranging from less than 1 in 50,000 (Scotland, Slovakia) to less than 1 in 200,000 patients (Lithuania, Bulgaria), or are not defined (Sweden, likely to be less than 1 or 2 in 200,000 patients). Additionally, most countries limit these special processes to

ultra-RDTs with specific characteristics, such as treating a severe condition with high unmet need, to potentially effective and/or high cost treatments, requiring highly specialised management. Regarding the more integrated supplemental processes, eligible medicines are those with an OMP designation.

Key process features for appraisal of rare disease treatments

The distinctions between supplemental and standard processes have been characterised as features occurring throughout the HTA process, and are discussed in this section (Figure 3).

Evidence submissions

The countries with separate or partially separate processes have different clinical and/or economic evidence submission requirements. This is done through use of different submission forms as seen for the HST in England and ultra-RDT pathways in Lithuania and Scotland, or with the possibility of presenting a simplified version of the standard submission in Germany (exempt from presenting comparative data). In all other countries, evidentiary requirements are the same as for standard processes with the exception of Lithuania, Slovakia and Belgium, which don't require economic models for ultra-RDTs.

Assessment

The inclusion of disease-specific input is being achieved by involving patient and clinical experts in different ways across the HTA process, starting from the assessment phase. First, through the stand-alone PACE process in Scotland, where the SMC assessors discuss the added benefit of the treatment not captured within conventional clinical and cost-effectiveness assessments with those who have experience of the disease and/or treatment being assessed. This meeting can be requested by the manufacturer if a negative opinion is initially given by the assessment committee. A PACE statement is then drafted and becomes part of the evidence submitted to the appraisal committee. Second, the process may allow for patient and/or clinical experts to provide input about clinical issues. This is done in both countries with and without supplemental processes, and informs the assessment phase. Third, some countries have established committees with rare disease experts that support decision-making around pricing, reimbursement and use of the medicine. This is the case in Bulgaria with their rare disease expert committee that decides on inclusion of diseases on the special positive formulary (for which all treatments are reimbursed); in New Zealand with their clinical advisory committee; and in Ireland with their Rare Diseases Technology Review Committee enabling clinicians and other stakeholders to provide input in the post-HTA phase, and review MEA proposals.

Additionally, some processes may allow for an earlier start in the assessment process to guarantee more timely access to RDTs. This is seen in Belgium, Italy and New Zealand in their expedited processes targeting RDTs, which allow for the assessment process to start before marketing authorisation is granted.

Appraisal

The greatest number of features implemented in the supplemental processes relate to the appraisal phase. The main distinction seen within separate supplemental processes for ultra-RDTs is the existence of different appraisal committees, which provides a standing group with rare disease expertise who only assess RDTs. One of the main distinctions seen in England is in membership composition with the inclusion of rare disease clinical specialists (adult and paediatric), ethicists, geneticists, and expert centre representatives.

Broader consideration of value is another feature adopted in England's and Scotland's supplemental processes for ultra-RDTs (within their ultra-RDT decision frameworks), where context and specification of issues specific to rare diseases are considered as evidence. This is done by more detailed consideration about the nature of the condition (including consideration of severity, unmet need and existence of alternative treatments), and accounting for indirect costs and benefits on patients, carers and health system.

The most common feature in supplemental processes relates to allowing more leniency in the quality of the evidence. This is done through less stringent requirements for demonstrating added benefit (e.g. acceptance of non-comparative data), and/or willingness to accept surrogate endpoints or non-randomised controlled trials (RCTs). Generally, this is done on a case-by-case basis, if appropriate justification is provided or if the evidence is considered to be of best possible quality. Greater leniency may also be more acceptable for medicines with a high level of unmet need or those that have a high media profile.

In those countries where cost-effectiveness needs to be proven (e.g. where an economic submission is required), there may be more flexibility in the interpretation of the economic evidence. This is done by accepting natural outcome measures instead of QALYs or cost-consequence analyses, and including sensitivity analyses that reflect wider costs and benefits (Scotland) [18].

Some of the features included in supplemental processes allow for different decision rules. The first relates to different WTP, where a higher ICER than would be admissible in common conditions (Scotland, Norway, Sweden), or a higher adjusted WTP that increases with magnitude of benefit and QALY gained (England) would be accepted, or through a points-system calculation of the WTP threshold where OMPs get extra points (Slovakia). The second relates to alternative reimbursement rules, where the therapeutic benefit of the medicine would be considered proven (Germany), or would not be graded (Lithuania). In Romania, reimbursement status is based on a points system, where OMPs get extra default points. Third, the process features also include decision modifiers in the appraisal framework, which impact deliberation about WTP or reimbursement status. While most processes, including the standard ones, are mainly interested in severity, unmet need and existence of treatment alternatives, some of the processes explicitly account for rarity or other criteria that may favour appraisal of RDTs (e.g. children, equality or the innovative nature of treatment [19]). Rarity is accounted for in Scotland (as part of its decision modifiers) and Netherlands, where greater uncertainty or unfavourable cost-effectiveness may be more acceptable. Other criteria that may influence the decisions are equality (England, New Zealand, Netherland), children (Germany, Netherlands), ethical considerations (Netherlands, Slovenia, Bulgaria, Latvia, Finland), or innovative nature of treatment (England, Italy, Greece). These appraisal criteria are considered both in supplemental and standard processes.

Pricing and reimbursement

Many countries include different forms of conditional approval agreements or MEAs, aiming to collect additional data to facilitate later re-assessment of added benefit or cost-effectiveness. This is the case for England's HST programme, Scotland's ultra-RDT pathway, Germany, Norway, Slovakia, and Belgium.

A few countries also include alternative routes to pricing and reimbursement for a group of RDTs, where they would be exempt from HTA as a whole. This is the case in Bulgaria, where all medicines used to treat conditions included on a special list of rare diseases would be automatically reimbursed, and in Latvia, with their separate state-budget for children with rare diseases.

Impact and proposed changes

Country experts were asked to state the impacts of their supplemental processes for RDTs. Increased acceptance rate was the most common response, resulting in the reimbursement of medicines that otherwise would not be reimbursed. The

assumption of proven added benefit was considered to ensure a stronger negotiating position for the manufacturer and more flexibility in pricing. Some countries stated that these processes are more adapted to dealing with specificities in appraisal of RDTs. These processes allow special approaches to be taken for reimbursement of RDTs with clinical and/or budgetary issues in a consistent way, rather than on a case-by-case basis, supporting fairness in the decision-making system.

Changes in four of the 13 countries with supplemental processes are also being discussed, including refinement of processes (Sweden), potential legislative changes (Romania), implementation of a separate budget for adult rare disease patients (Latvia) and establishment of a therapy monitoring process (Bulgaria).

What are countries with standard processes doing?

In total, 19 countries (out of 32) do not have supplemental processes targeting RDTs, but may have features enshrined within their processes that might facilitate appraisal of RDTs. The most common feature included is granting more leniency around quality of clinical evidence (Austria, Canada, France, Estonia, Hungary, Poland, Portugal, Czech Republic, and Netherlands). The other features included acceptance of non-local language evidence submissions in Estonia; inclusion of disease-specific experts to input into the assessment phase in several countries; greater flexibility in the interpretation of the economic model or different WTP in Estonia (if consideration of cost/QALY is recognised as not possible, price would be set similar to other ultra-RDTs); ability to implement conditional approvals (Austria, Canada, Ireland, Italy, Czech Republic, Netherlands); or separate budgets (separate fund for innovative and cancer medicines in Italy, specific funds for political solutions in Austria). Finally, as stated earlier, some countries include criteria in their value assessment frameworks that may favour RDTs.

Two countries have processes that may be applicable to RDTs. In the Czech Republic, highly innovative medicines are eligible for conditional reimbursement, and do not need to prove cost-effectiveness. In France, their expedited processes target medicines with high unmet need. In addition to the expedited process for OMPs, Italy includes innovativeness criteria in their standard process, for which those medicines considered fully innovative will be automatically included in the regional formulary as part of a conditional approval.

Eleven of the 19 countries without supplemental processes are engaged in ongoing discussions about implementing changes in their processes for RDTs. Discussions revolve around general process changes in the standard pathway, or process changes for orphan medicines, including implementing exemptions for economic models or including bespoke patient involvement processes.

Discussion

This research contributes to a better understanding of how countries' reimbursement/appraisal processes are dealing with RDTs. The distinctive contribution is in the primary nature of the data collected from experts closely involved within these processes, which allow the first comprehensive and detailed review of the supplemental processes targeting RDTs in Europe and beyond. This issue has been previously explored through systematic reviews or case studies, however, these earlier findings, target a narrow sample of countries (with scarce information on Eastern European countries [6]), and focus on their evaluation criteria [6,20–22], and/or on governance structures for pricing and reimbursement [22]. This study additionally identified and characterised the process features that facilitate appraisal of RDTs.

Forty-one percent (13/32) of countries include supplemental processes for RDTs characterised by (add-on or adjusted) process features. This section discusses how these features help deal with uncertainty and price, and, on this basis, whether supplemental processes are needed for RDTs in all appraisal systems.

The (add-on or adjusted) features adopted allow for different standards to demonstrate the value of RDTs. This is reflected in the different submission requirements, the different value assessment frameworks, the different standards in assessing the quality of the evidence, or the different decision rules around determination of value. Including different submission requirements may be a way to overcome the issue of uncertain clinical evidence and/or lack of cost-effectiveness by bypassing it or seeking additional evidence about other aspects such as the nature of the condition, natural history etc. This is seen in Germany where a simplified submission without comparative data is permissible for OMPs as added benefit is automatically assumed. However, those drugs for which no comparative data is presented are likely to be categorised as "non-quantifiable" added benefit, which may prove to be more challenging when it comes to negotiations around price [23,24].

England and Scotland's pathways for ultra-RDTs consider different value frameworks informing a wider perspective of the treatment's value. The main contrasts with their standard appraisal frameworks relate to the information collected about nature of the condition, patient and carer benefit and indirect costs and benefits of the treatment. Accounting for these additional criteria may help overcome some of the limitations in assessing RDT value from traditional clinical and economic evidence based on QALYs [7], which are considered to be less sensitive in some disease areas [25]. This may be even more important for the rarer conditions considering the burden of these conditions on patients, their carers and the healthcare system in these often severe (e.g. life-threatening, disabling) and complex conditions (e.g. often affecting multiple organs, making it more difficult to treat) [25], for which evidence is likely to be even more uncertain [26]. A structured appraisal framework should include these additional criteria, as well as guidance on how to account for these criteria in determining added benefit during decision-making. This is particularly important to clarify for the qualitative considerations of evidence (e.g. value of hope, value of innovation), which includes non-quantified (e.g. where data may be lacking) or non-quantifiable considerations (e.g. where no appropriate measure exists to quantify a criterion), as they tend to be given less weight in appraisal compared to quantified evidence [11].

Different standards for demonstrating the value of RDTs can also be applied, by more leniency when interpreting the (uncertain) evidence. This is achieved in the majority of countries with (69%) and without (47%) supplemental processes by, for example, having less stringent requirements to demonstrate added benefit, and accepting surrogate endpoints or other sources of evidence. This may be particularly important in the case of ultra-RDTs, which have been shown to have poorer study designs (from non-randomised uncontrolled trials without comparator) compared to RDTs (with active and/or placebo control arms and double-blinding) [26].

The different decision rules around determination of value include considering therapeutic benefit as proven or not accounted for, or increasing the greater likelihood of reimbursement by giving extra points to RDTs in a reimbursement points-based system (mainly driven by therapeutic benefit). These measures can be considered as foregoing part of the HTA process around determination of the medicine's added benefit.

The features used in supplemental processes help resolve uncertainties in the interpretation of clinical (and related economic) evidence. Some processes allow for disease-specific input to inform the appraisal by gathering additional information about burden of illness and impact of treatment not included in the original submission (e.g. PACE meeting in Scotland), by receiving input on clinical issues (e.g. plausibility of clinical claims, relevance of outcomes and meaningfulness of improvement [13]), or by having special rare disease committees to support pricing, reimbursement and treatment use decisions. Two countries also have specific appraisal committees composed of decision-makers with experience in dealing with the common issues in rare diseases, which allows for more consistency in decision-making across similar conditions (England and Lithuania). Most countries (with and without supplemental processes) recognise the challenges to generate robust evidence for RDTs and are willing to be more flexible in its interpretation by, for example, assessing if it is the best quality evidence based on the feasibility of conducting RCTs and comparisons.

The features included in supplemental processes help overcome the issue of lack of cost-effectiveness. Overcoming the issues of lack of cost-effectiveness can be done by accepting different WTP or not considering cost-effectiveness. This also suggests that those who implemented these measures recognise the unsuitability of conventional cost-effectiveness approaches for the appraisal of RDTs. Different WTP for RDTs would consist of accepting higher thresholds and/or giving weight to rarity when calculating the threshold. This is a way to accept paying more for the same level of added benefit compared to common conditions. Implications are that those medicines undergoing these processes will have a greater likelihood of reimbursement, as well as higher prices compared with standard processes. Some countries, however, are still faced with cost effectiveness estimates above the revised WTP threshold.

Another approach to dealing with this issue is by granting more flexibility in the use of the economic model, accepting other types of models such as cost-consequence, recognising that it is not always possible to populate economic models, using alternative pricing approaches, or giving less weight to the economic model in appraisal.

Some countries allow exemptions from submitting an economic model, coupled with other measures. In Slovakia, no economic models are required for ultra-RDTs. Conditional approval with re-assessment in 24 months is mandatory if the expected reimbursement is greater than €1,500,000 for 12 months. In Belgium, within its expedited process, the exemption applies to OMPs having the highest added therapeutic value (class 1). In the Czech Republic, the exemption applies to the highly innovative medicines under a conditional approval programme (after which it would be re-assessed). These measures that forego cost-effectiveness target the rarer conditions or more effective treatments, and can also manage risk by granting a conditional approval (in certain cases when expenditure level is high). This exemption was also considered by the Institute for Clinical and Economic Review in the US within their modified Value Assessment Framework for ultra-rare conditions. The decision to keep the cost-effectiveness criterion was made due to its usefulness in decision-making, but it is noted that consideration is also be given to other relevant information not captured within the model [27]. The main issue is how these additional elements, which are often difficult to quantify or non-quantifiable, may influence decision-making, particularly when cost effectiveness is not shown even in adapted processes.

The features included in supplemental processes aim to accelerate the HTA process to guarantee more timely access to patients to RDTs. Delays and variability in access to OMPs across Member States is one of the key issues in Europe [28,29]. Different mechanisms to grant earlier access to patients are being adopted. First, expedited processes allow a more rapid decision by starting before marketing authorisation is granted, which then secures earlier access to treatment for patients (Belgium, Italy, New Zealand for RDTs, and France for drugs with high unmet need). Second, many countries have implemented conditional approvals, where the medicine is provided while collecting additional data for a later re-assessment to demonstrate added benefit or cost-effectiveness. This allows reimbursement of RDTs with important uncertainties that can be resolved by data collection. Third, some countries forego the HTA process by granting access via separate budgets (separate-state budget for children with rare diseases in Latvia), or rare disease positive lists (Bulgaria). However, separate routes, such as ear-marked budgets, heavily rely on political support and risk being revised or discontinued [10], particularly in a time when the proportion of pharmaceutical expenditure is likely to increase for RDTs and other high cost medicines [30].

In summary, the features implemented within supplemental processes aim to manage the specificities of RDTs fairly and consistently. They allow for different standards to demonstrate the value of RDTs, support the interpretation of limited clinical (and related economic) evidence, help overcome the issues of lack of cost-effectiveness, and aim to accelerate the HTA process to guarantee more timely access to RDTs for patients. Their impact increases the likelihood of reimbursement by adjusting and/or foregoing some part of the assessment process, and by being willing to pay more for the same added benefit as for common conditions, which is also likely to lead to accepting high prices. These elements can allow for more consistent decision-making and accountability for reasonableness [31].

Do we need supplemental processes for RDTs?

These results do not outline what an ideal process for RDTs looks like, but identify some of the key features that can be implemented to facilitate this process. Our results indicate revealed preferences to treat RDTs differently in many jurisdictions. Forty-one percent (13/32) of countries studied have implemented supplemental process (add-on or adjusted) features for the appraisal of RDTs. These features include the application of different standards to assess the value of the medicine, support the appraisal/decision-making process, overcoming the issues of lack of cost-effectiveness (e.g. pay more for the same added benefit as for normal conditions), or partial or full exemption from the HTA process. They apply to ultra-RDTs and/or RDTs, and are often applied in combination. Having supplemental processes does not mean that all issues are being dealt with. The challenges around uncertainty and high price remain, but these process features allow for more adapted, transparent and consistent decision-making. Many of these processes are new and countries continue to adjust them as they gain more experience in their use.

Even many of the remaining 19 countries without supplemental processes considered it important to adapt their standard processes in order to accommodate RDTs; 10 adopt one or more of these features in terms of granting more leniency around quality of evidence (9/19), more flexibility in input of economic model in decision-making (2/19), different WTP (1/19), or implementing conditional approval schemes (6/19). Of the 19 countries with standard processes, another 2 also account for appraisal criteria likely to favour RDTs. In total, 78% of countries are dealing with RDTs differently: 41% (13/32) of countries have supplemental processes for RDTs, 31% (10/32) of countries with standard processes adopt special features facilitating appraisal of RDTs, and additionally 6% (2/32) of countries with standard processes that did not adopt special features account for appraisal criteria likely to favour RDTs.

Of those 7 countries remaining (e.g. without supplemental processes, process features adopted in standard processes that could facilitate appraisal of RDTs, or appraisal criteria that could favour RDTs), 4 are planning changes in their systems. The high number of countries with standard processes that are applying some of the features facilitating appraisal of RDTs or that are planning changes in their systems suggests that these countries are adopting similar approaches to supplemental processes, but in a less systematic and more ad hoc manner. The advantage of implementing such measures is to ensure all drugs are treatment in a structured and consistent manner.

Limitations

A number of challenges arose when compiling the vignettes and analysing the data collected. Responses to questionnaires may have included an insufficient level of detail and/or absence of links or documentation, making it difficult to grasp the full context and complexity of the systems in different countries. In order to minimise the risk of missing relevant information, desk research, feedback from institutional partners, and several rounds of validation with country experts were conducted. Also, the focus of this research was to characterise the process features commonly used across countries in appraisal for RDTs. It does not extend to the examination of methodological approaches to better deal with RDTs (e.g. inclusion of scenario sensitivity analyses). Another challenge was that despite repeated efforts to contact different experts, for five out of 37 it was not possible to create a robust vignette. However, based on public knowledge these countries do not include supplemental processes. Furthermore, the less formal aspects of the appraisal processes that are implicit or not documented may not have been captured. For example, some countries stated they do not allow for flexibility in evidence quality, but in practice they may do so. Processes are also evolving rapidly; since the creation of the vignettes there have already been some updates (which are captured in this paper), but these may not capture the most recent changes. An update of these vignettes at the end of 2020 to capture any recent developments is planned. Issues related to implementation of stated appraisal processes vs. actual appraisal processes are studied in another part of WP10 and will be reported in the future.

Conclusions

This comprehensive overview developed with the support of country experts has explored the use of supplemental HTA appraisal processes for RDTs in Europe, Canada and New Zealand. A wide variety of approaches have been identified that permit leniency in standard HTA processes, or in a few cases bespoke processes that involve rare disease experts. The supplemental approaches used build on the ethos of the HTA process within each particular country and may require different evidence submissions, additional assessment inputs, broader considerations in appraisal or special considerations for pricing and reimbursement. The processes provide consistency in decision-making within that country and are being adapted as a result of legislative direction or stakeholder feedback. It is important that as more RDTs come to market, there is transparency in national appraisal processes not just to ensure fair and consistent decisions within countries, but to determine if a common appraisal framework could be developed for RDTs or ultra-RDTs across Europe.

List Of Abbreviations

Abbreviation	Full name
ACT	Anatomical therapeutic chemical classification
EEA	European Economic Area
EMA	European Medicines Agency
G-BA	Joint Federal Committee
HST	Highly Specialised Technology
HTA	Health Technology Assessment
ICER	Incremental Cost-effectiveness Ratio
IQWIG	Institute for Quality and Efficiency in Health Care
MS	Member States
NICE	National Institute for Health and Care Excellence
OMP	Orphan Medicinal Product
PACE	Patient and Clinical Engagement Programme
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
RDT	Rare Disease Treatment
SMC	Scottish Medicines Consortium
TLV	Dental and Pharmaceutical Benefits Board
ultra-RDT	Ultra-rare Disease Treatment
WTP	Willingness-to-pay

Declarations

Ethics approval and consent to participate

The primary data was collected from country experts via a questionnaire, and follow-up and validation questions either via email or Skype. Ethics approval was required for this. An information sheet and an informed consent form were developed according to the Bocconi ethics guidance. Ethics approval was received by the Bocconi Ethics Committee on May 9th 2018,

after which additional modifications were implemented to be in line with the General Data Protection Regulation end of May.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analysed during the current study are available on the IMPACT-HTA website: https://www.impact-hta.eu/country-vignettes

Competing interests

EN is part time employed and AW is contracted on a project base by Dolon Ltd. They do not have any competing interests with this work. MD and KF do not have any conflict of interests to declare.

Funding

This research was funded by the European Commission's Horizon 2020 research and innovation programme and was undertaken under the auspices of IMPACT-HTA (Grant number 779312). The results presented here reflect the authors' views and not the views of the European Commission. The European Commission is not liable for any use of the information communicated.

Authors' contributions

EN, AW, MD, KF contributed to the conception and design of the work; EN, AW collected the data; MD, KF reviewed the data collected; EN, AW, MD, KF contributed to the data analysis; EN, AW, MD, KF have drafted the work or substantively revised it. EN, AW, MD, KF have approved the submitted version; EN, AW, MD, KF have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Acknowledgements

We would like to thank all country experts for their time and valuable contribution in providing the information used to create the country vignettes and validate this vignette. Specifically: Claudia Wild, Inneke van Vijver, Tatyana Benisheva, Brendan McIntosh, Sylvie Bouchard, Erki Laimae, Piia Rannanhaimo, Carine Busin, Anne d'Andon, Gergo Meresz, Sveinbjorn Hognason, Panos Kanavos, Entela Xoxi, Diana Araja, Stefan Tomaselli, Andrius Vagoras, Andrej Janžič, Antonia Formosa, Angel Link, Ben Campbell Macdonald, Ana Zaremba, Aneta Lipinska, Claudia Santo, Ileana Mardare, Elena Marusakova, Thomas Fankhauser, and Jan Jones. A special thanks also to the IMPACT-HTA team for their input throughout the creation of the vignettes, specifically to Sheela Upadhyaya, and Jaime Espin.

References

1. Godman B, Malmstrom R, Diogene E, Gray A, Jayathissa S, Timoney A, et al. Are new models needed to optimize the utilization of new medicines to sustain healthcare systems? Expert Rev Clin Pharmacol. 2015;8:77–94.
2. European Union. Orphan medicinal products [Internet]. [cited 2020 Jan 20]. Available from: https://ec.europa.eu/health/human-use/orphan-medicines_en
3. UK GA. Action for Access: a report from Genetic Alliance UK for the All Party Parliamentary Group on Rare, Genetic and Undiagnosed Conditions. 2019.

4. Nicod E, Annemans L, Bucsics A, Lee A, Upadhyaya S, Facey K. HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries. Health Policy (New York). 2019;123:140–51.
5. Nestler-Parr S, Korchagina D, Toumi M, Pashos CL, Blanchette C, Molsen E, et al. Challenges in Research and Health Technology Assessment of Rare Disease Technologies: Report of the ISPOR Rare Disease Special Interest Group. Value Heal. 2018;21:493–500.
6. Zelei T, Molnár MJ, Szegedi M, Kaló Z. Systematic review on the evaluation criteria of orphan medicines in Central and Eastern European countries. Orphanet J Rare Dis. 2016;11:72.
7. Pearson I, Rothwell B, Olaye A, Knight C. Economic Modeling Considerations for Rare Diseases. Value Heal. 2018;21:515–24.
8. Drummond M, Towse A. Orphan drugs policies: A suitable case for treatment. Eur J Heal Econ. 2014;15:335–40.
9. Henderson N, Errea M, Skedgel C, Jofre-Bonet M. Ethical and economic issues in the appraisal of medicines for ultra-rare conditions. OHE Consulting Report [Internet]. London; 2020. Available from: https://www.ohe.org/publications/ethical-and-economic-issues-appraisal-medicines-ultra-rare-conditions-0#
10. Annemans L, Aymé S, Le Cam Y, Facey K, Gunther P, Nicod E, et al. Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL). Orphanet J Rare Dis. 2017;12:50.
11. Ollendorf D, Chapman R, Pearson S. Assessing the effectiveness and value of drugs for rare conditions [Internet]. 2017. Available from: https://icer-review.org/wp-content/uploads/2017/02/ICER_Assessing-the-Value-of-Drugs-for-Rare-Conditions_051017.pdf
12. McCabe C, Stafinski T, Menon D. Is it time to revisit orphan drug policies? BMJ. 2010;341:c4777.
13. Ollendorf DA, Chapman RH, Pearson SD. Evaluating and valuing drugs for rare conditions: no easy answers. Value Heal. 2018;21:547–52.
14. Ferrario A, Kanavos P. Dealing with uncertainty and high prices of new medicines: A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. Soc Sci Med. 2015;124:39–47.
15. Mestre-Ferrandiz J, Palaska C, Kelly T, Hutchings A, Parnaby A. An analysis of orphan medicine expediture in Europe: is it sustainable? Orphanet J Rare Dis. 2019;14:287.
16. Nicod E, Whittal A, Drummond M, Facey K. Country vignettes on HTA appraisal/reimbursement processes for rare disease treatments [Internet]. 2020 [cited 2020 Feb 26]. Available from: https://www.impact-hta.eu/country-vignettes
17. SMC modifiers used in appraising new medicines [Internet]. 2012. Available from: https://www.scottishmedicines.org.uk/media/3565/modifiers.pdf
18. Guidance to submitting companies for completion of new product assessment form (NPAF). Supplement for medicines for extremely rare conditions (ultra-orphan medicines) [Internet]. Glasgow; 2019. Available from: https://www.scottishmedicines.org.uk/media/4990/guidance-supplement-ultra-orphan-updated-011119.pdf
19. Nicod E, Kanavos P. Scientific and social value judgments for orphan drugs in health technology assessment. Int J Technol Assess Health Care. 2016;32:218–32.
20. Degtiar I. A review of international coverage and pricing strategies for personalized medicine and orphan drugs. Health Policy (New York). 2017;121:1240–8.
21. Rosenberg-Yunger ZR, Daar AS, Thorsteinsdottir H, Martin DK. Priority setting for orphan drugs: An international comparison. Health Policy (New York). 2011;100:25–34.
22. Denis A, Mergaert L, Fostier C, Cleemput I, Simoens S. A comparative study of European rare disease and orphan drug markets. Health Policy (New York). 2010;97:173–9.
23. Bouslouk M. G-BA benefit assessment of new orphan drugs in Germany: The first five years. Expert Opin Orphan Drugs. 2016;116:147–53.

24. Kirchmann T, Ewald A, Schönermark M. Orphan drugs in Germany - Lessons learned from AMNOG, best and worst practices and strategic implications. Value Heal. 2018;21:S200.
25. Towse A, Garau M. Appraising ultra-orphan drugs: is cost-per-QALY appropriate? A review of the evidence [Internet]. 2018. Available from: https://www.ohe.org/publications/appraising-ultra-orphan-drugs-cost-qaly-appropriate-review-evidence
26. Richter T, Janoudi G, Amegatse W, Nester-Parr S. Characteristics of drugs for ultra-rare diseases versus drugs for other rare diseases in HTA submissions made to the CADTH CDR. Orphanet J Rare Dis. 2018;13:15.
27. Modifications to the ICER value assessment framework for treatments for ultra-rare diseases [Internet]. 2017. Available from: http://icer-review.org/wp-content/uploads/2020/01/ICER_URD_Framework_Adapt_013120.pdf
28. Zamora B, Maignen F, O'Neill P, Mestre-Ferrandiz J, Garau M. Comparing access to orphan medicinal products in Europe. Orphanet J Rare Dis. 2019;14:95.
29. Eurordis. Breaking the Access Deadlock to Leave No One Behind [Internet]. 2018. Available from: http://download2.eurordis.org.s3.amazonaws.com/positionpapers/eurordis_access_position_paper_final_4122017.pdf
30. Drummond MF. Challenges in the economic evaluation of orphan drugs. Eurohealth (Lond). 2008;14.
31. Daniels N, Sabin JE. Accountability for reasonableness: an update. BMJ. 2008;337:a1850.

Table 1

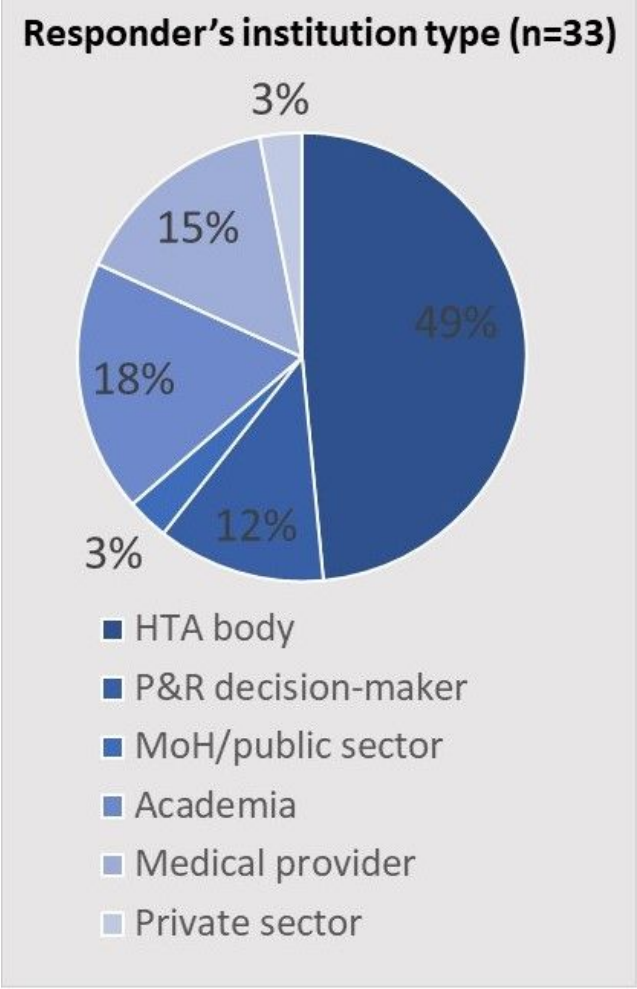
Table 1. Country definitions for rare and ultra-rare disease treatments, and their use as eligibility criteria within supplemental processes for rare disease treatments

PROCESS TYPE	COUNTRY	PROCESS DESCRIPTION	ELIGIBILITY	DEFINITION	
				Rare disease	Ultra-rare disease
Separate	**England** Highly Specialised Technology Programme (HST)	Main differences with standard process: willingness to pay threshold, specialised appraisal committee, more holistic perspective of value, managed access agreements possible	High cost technologies for ultra-rare conditions - see HST prioritisation criteria	-	No prevalence criteria, based on HST eligibility criteria
	Lithuania Ultra-rare disease treatment pathway	Very rare disease committee: special appraisal committee decides on inclusion in special list. Main differences with standard process: therapeutic value not graded, no waiting list in case of positive decision, special pricing rules. Decision can be individual-case (yearly revised fixed budget) or generalised-case approach (general budget)	(1) ultra-rare, (2) life-threatening or significant disability, (3) subject to effective aetiology or pathogenic treatment, (4) effective treatment (increases survival or reduces disability)	-	<1:200,000
Partially separate	**Scotland** Ultra-rare disease treatment pathway	Assessment based on ultra-orphan drug decision-making criteria, routine use for 3 years after which re-assessment. Option for Patient and clinician engagement programme (PACE). Disease-specific experts describe treatment benefit not captured within original assessment	URDT: (1) ultra-rare, (2) chronic and severely disabling condition, (3) highly specialised management PACE: OMPs (and end of life treatments) not considered cost-effective - after NDC decision (after 3-year monitoring)	-	<1:50,000
	Germany	Different reimbursement status: additional benefit guaranteed, strong negotiation power and reasonable reimbursement. Assessment by G-BA (instead of IQWIG), different evidence requirements	(1) OMP, (2) revenues from statutory health insurance < 50 million/last 12 months	OMP	-
Adapted	**Norway**	Greater willingness to pay	(1) ultra-rare, (2) effective treatment (>2 QALY gain), (3) severe condition (>30 QALYs lost)	-	<1:100,000
	Slovakia	Exempt from economic evaluation	Ultra-rare	-	<1:50,000
	Sweden	Greater willingness to pay	(1) ultra-rare, (2) good potential for effective drug, (3) very severe condition	-	no fixed limit ~<1-2:100,000
	Scotland Standard pathway with PACE and modifiers	PACE: disease-specific experts describe treatment benefit not captured within original assessment. Modifiers: standard assessment for OMPs, but SMC recognises limitation in evidence generation and will accept greater uncertainty in the economic case	PACE: OMPs (end of life treatments) not cost-effective, manufacturer can request a PACE to get additional insights Modifiers: OMPs, life-threatening, substantial increase in quality of life/life expectancy, can reverse the condition, bridges gap to a definitive therapy.	OMP	-
Expedited	**Belgium**	Earlier pricing: after positive CHMP opinion, before marketing authorisation. Exemption from economic model	OMP	OMP	-
	Italy	Earlier pricing and reimbursement: after positive CHMP opinion, before marketing authorisation	OMP (and hospital or exceptionally therapeutic and social medicinal products)	OMP	-
	New	Earlier reimbursement: before marketing	Rare disease (as per	Cum	-

	Zealand	authorisation	country definition)	prevalence <1:50,000	
Rarity weighted	Romania	Reimbursement status based on points cumulated (unconditional, conditional reimbursement etc.): OMPs get extra points	OMP	OMP	-
	Slovakia	Willingness to pay threshold based on points system: OMPs get extra points	OMP	OMP	-
Exempt from HTA	Bulgaria	All drugs to treat those rare diseases included in special list of rare diseases are 100% reimbursed	Drugs with indication included on special list of rare diseases	OMP	-
	Latvia	Separate state-reimbursement budget for children with rare diseases	OMP for use in children	OMP	-

Legend: HTA: Health technology assessment; OMP: orphan medicinal product (refers to drugs with an orphan designation from the European Medicines Agency); RDT: rare disease treatment; HST: Highly Specialised Technology programme; SMC: Scottish Medicines Consortium; PACE: Patient and Clinical Engagement programme; G-BA: Federal Joint Committee; IQWIG: Institute for Quality and Efficiency in Health Care; CHMP: Committee for Medicinal Products for Human Use of the European Medicines Agency; NDC: New Drugs Committee; QALY: Quality of Life Adjusted Life Years

Figures



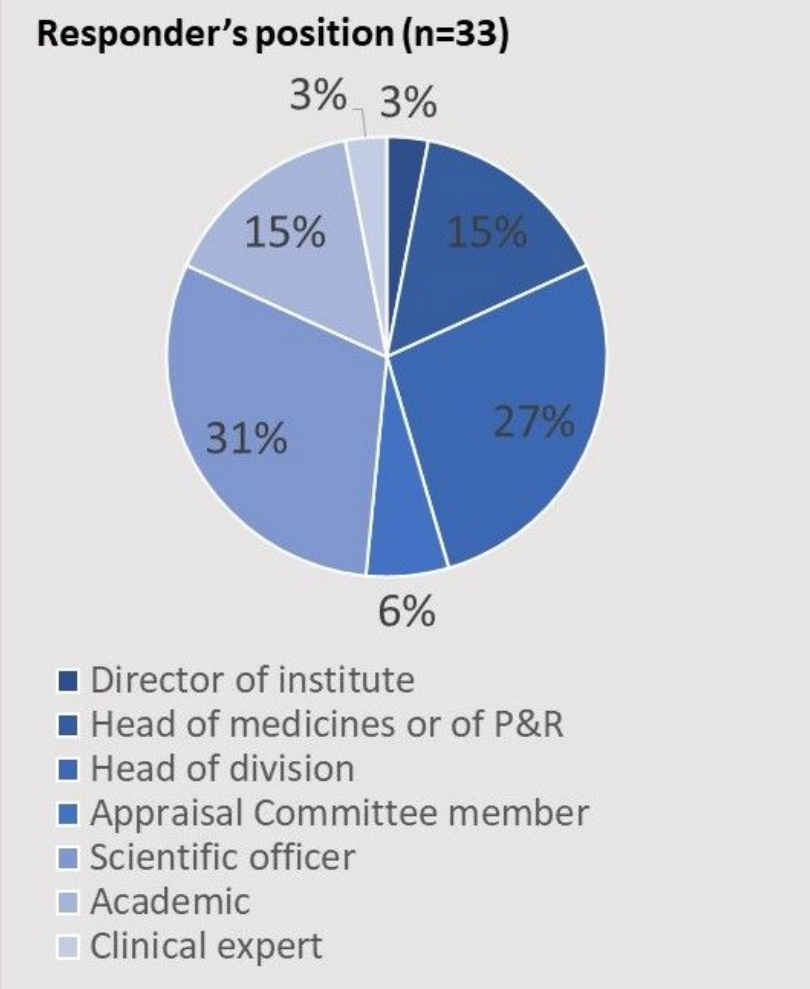


Figure 1

Responder characteristics (n=33)

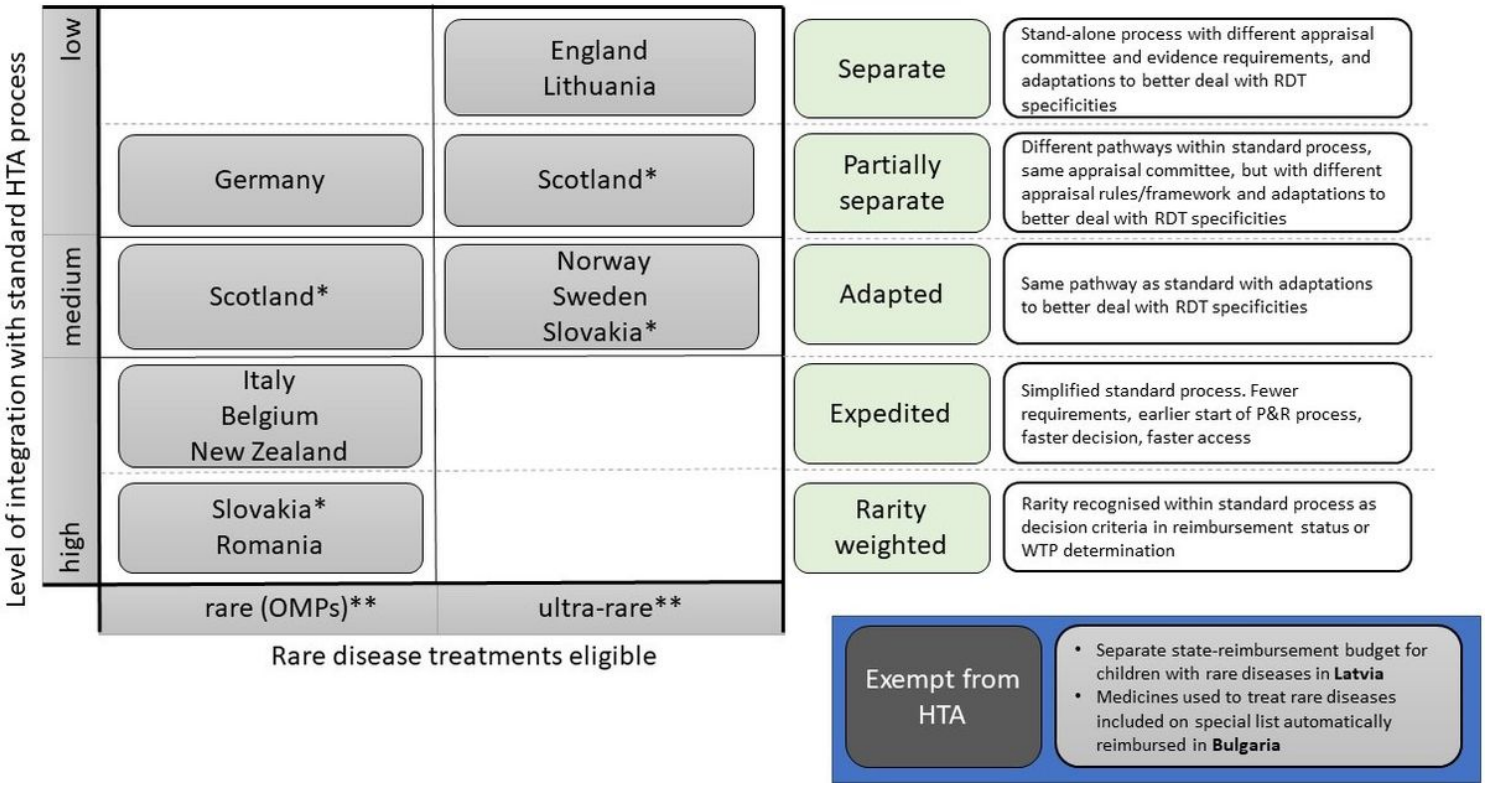


Figure 2

Classification of supplemental processes by level of integration and applicability to rare versus ultra-rare Legend: This figure provides an overview of the study countries that have supplemental processes for the routine use of rare and/or ultra-rare disease treatments in a defined patient population within a health service * Scotland and Slovakia have two different supplemental pathways for rare and ultra-rare disease treatments respectively, which are differentiated here. ** Rare disease treatment with orphan designation from European Medicines Agency (“Orphan Medicinal Product”, OMP); ultra-rare disease treatment defined by individual country definitions, often alongside other criteria RDT: rare disease treatment; OMP: orphan medicinal product; P&R: pricing and reimbursement process

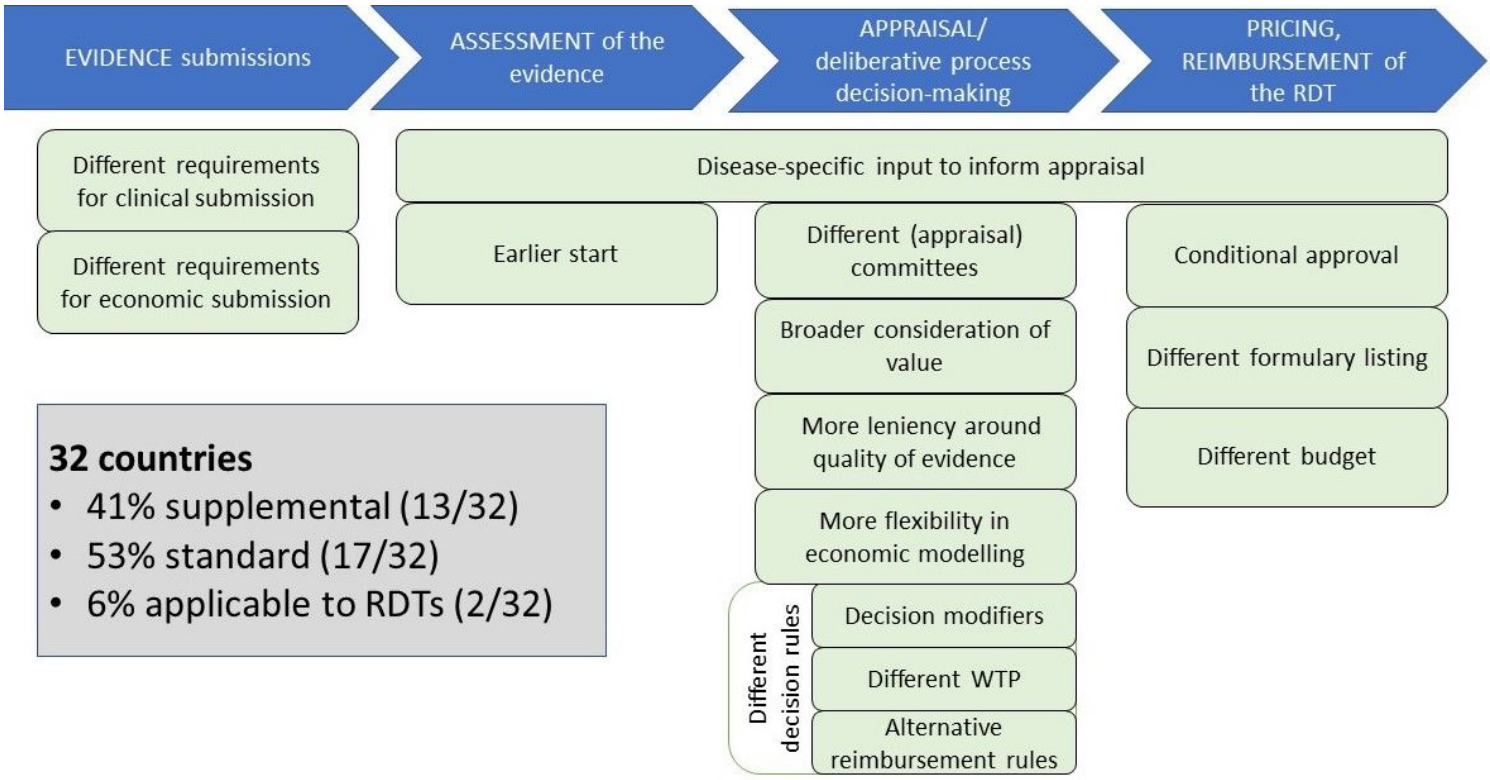


Figure 3

Features included in supplemental processes for rare diseases across the HTA process Legend: Figure 3 illustrates the (unique and/or different) features of supplemental processes to standard ones. They have been categorised according to their occurrence throughout the HTA process. RDT: rare disease treatment; WTP: willingness-to-pay