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## HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries

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### ABSTRACT

**Background:** Challenges commonly encountered in HTA of orphan medicinal products (OMPs) were identified in Advance-HTA. Since then, new initiatives have been developed to specifically address issues related to HTA of OMPs.

**Objective and methods:** This study aimed to understand why these new HTA initiatives in England, Scotland and at European-level were established and whether they resolve the challenges of OMPs. The work of Advance-HTA was updated with a literature review and a conceptual framework of clinical, regulatory and economic challenges for OMPs was developed. The new HTA programmes were critiqued against the conceptual framework and outstanding challenges identified.

**Results:** The new programmes in England and Scotland recognise the challenges identified in demonstrating the value of ultra-OMPs (and OMPs) and that they require a different process to standard HTA approaches. Wider considerations of disease and treatment experiences from a multi-stakeholder standpoint are needed, combined with other measures to deal with uncertainty (e.g. managed entry agreements). While approaches to assessing this new view of value of OMPs, extending beyond cost/QALY frameworks, differ, their criteria are similar. These are complemented by a European initiative that fosters multi-stakeholder dialogue and consensus about value determinants throughout the life-cycle of an OMP.

**Conclusion:** New HTA programmes specific to OMPs have been developed but questions remain about whether they sufficiently capture value and manage uncertainty in clinical practice.

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## 1. Introduction

At local and national levels, Health Technology Assessment (HTA) is increasingly being used to inform drug coverage decisions to ensure that rational, evidence-based choices are made within a limited budget [1]. OMPs generally undergo the same HTA processes as drugs for more prevalent diseases [2,3], even if an orphan designation distinction is previously made at regulatory level. Is this approach fair, or should different approaches be used?

Rare diseases affect small patient numbers (with a prevalence of less than five in 10,000 in Europe), and are life-threatening, debilitating and frequently genetically acquired [4]. An estimated number of 5000 to 8000 rare diseases exist, affecting 6–8% of the population in Europe. Based on the principle of equity [5], where “patients suffering from rare conditions should be entitled to the same quality of treatment as other patients” [6], incentives were implemented in medicines regulation processes in the EU and other countries to stimulate research and development for rare disease treatments [7]. Medicinal products treating a rare disease are eligible to receive an orphan designation by regulators. Upon receiving this designation, they are referred to as Orphan Medicinal Products (OMPs), and benefit from incentives that allow expedited authorisation with more limited evidence than other medicinal products. However, this does not give patients automatic access to the treatments, as their reimbursement often depends on HTA.

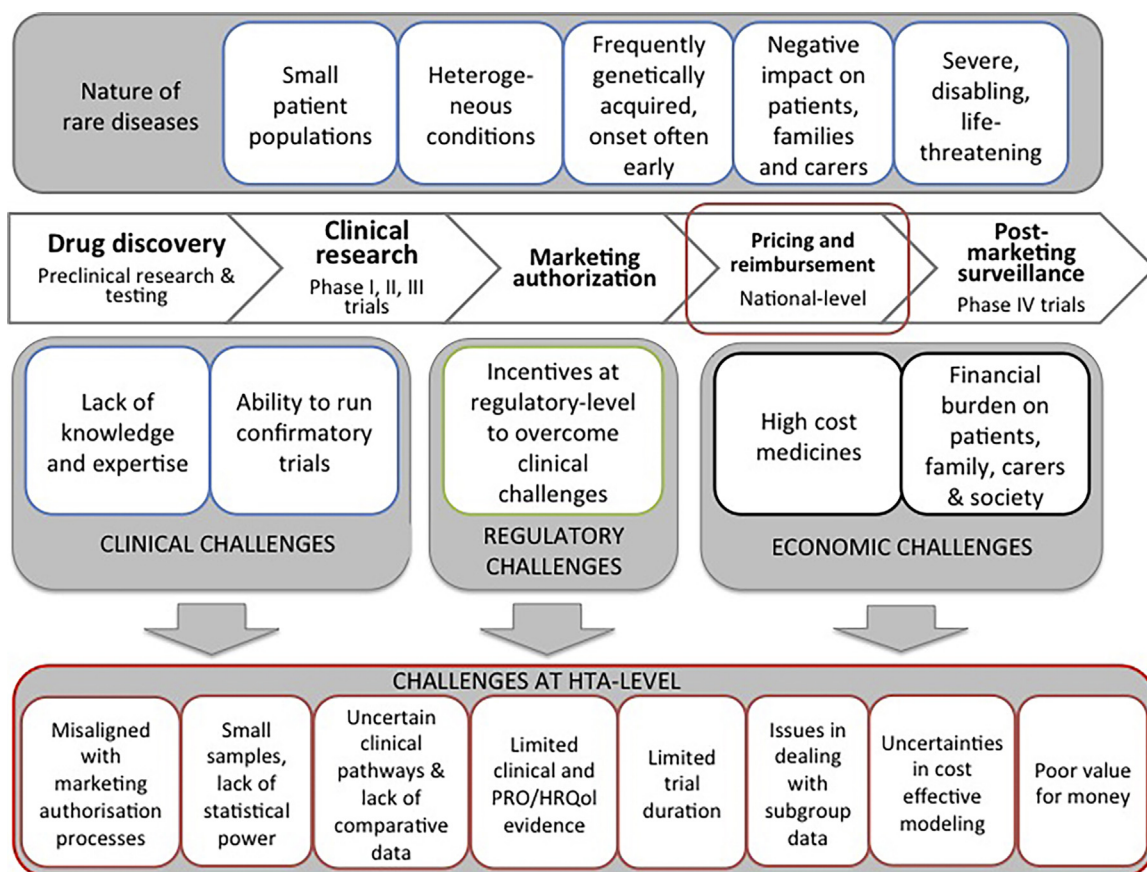
A Work Package in the Advance-HTA project systematically investigated HTA decision processes for a sample of ten OMPs between October 2007 and December 2012 in four European countries (England, Scotland, Sweden and France). It identified a number of issues that HTA bodies faced when making these difficult coverage decisions [8]. Although these issues are also encountered for drugs treating more prevalent diseases, they are more challenging for OMPs [9]. When economic evaluation is used in HTA, OMPs often fail to meet standard cost-effectiveness criteria due to their high acquisition costs and the uncertain evidence-based produced, and so would generally not be recommended for coverage [5,10–12]. Despite the common problems with OMPs, there were different approaches to dealing with them in the four countries, with different issues raised as most important and different judgments about the acceptable levels of uncertainty. This included, for example, accepting greater uncertainty when considering the orphan status or conditional licensing of the medicine, imposing future reassessments, or improving the incremental cost-effectiveness ratio (ICER) with a patient access scheme [8]. This raised the question as to whether we [society] are willing to pay more for rare disease patients [13]. A number of surveys aiming to elucidate this question found little support when resources are taken from more prevalent diseases, but a positive response if it is for more serious conditions with no treatment alternatives [10,11,14–17]. This emphasizes the recognized need for more suitable approaches to appraising orphan drugs, particularly with regards to the challenges encountered during the assessments.

Since the Advance-HTA project, new HTA programmes specific for OMPs or ultra-OMPs (treating less than one in 50,000) have recently been developed and/or implemented within Europe (e.g. the Patient and Clinician Engagement (PACE) meeting and ultra-OMP decision-making programmes at the Scottish Medicines Consortium (SMC); the Highly Specialised Technology (HST) programme at the National Institute for Health and Care Excellence (NICE) in England; or the Mechanism of Coordinated Access (MoCA) to OMPs, a European initiative initiated during the Belgian EU Presidency [18]). This research updated the literature search undertaken for the Advance-HTA project to identify challenges in assessing OMPs. It then developed a conceptual framework to explain these issues. The rationale for new HTA programmes for OMPs was then reviewed and compared with the HTA-level issues identified in the framework. The outputs of the new programmes were explored to examine their impact.

## 2. Materials and methods

Previous findings from the Advance-HTA project were used to summarise the types of challenges faced when dealing with OMPs in four countries [8,19]. This was based on a document analysis of HTA reports issued by four HTA bodies in four countries (NICE in England, SMC in Scotland, the Dental and Pharmaceutical Benefits Board (TLV) in Sweden, and the Haute Autorité de Santé (HAS) in France). This summary was generated by the lead author, and received two rounds of comments by non-institutional co-authors (KF, LA), to ensure their clarity and completeness. A review of the literature was conducted to understand how issues relating to the assessment of treatments for rare diseases are reflected at HTA-level. The databases Web of Science and Medline were searched using the following MeSH heading: (“orphan drug” OR “rare disease” OR “rare condition” OR “rare disorder”) AND (“uncertainty” OR “health technology assessment”). The abstracts were reviewed and selected if they referred to issues encountered with OMPs at HTA-level or to the type of uncertainty encountered with OMPs. We also cross-checked the references included in the papers identified of interest, and searched the grey literature, including websites from key institutions or initiatives in the rare disease field (e.g. Eurordis, European Commission). On this basis, a conceptual framework was built summarising the challenges that arise due to the nature of OMPs in terms of drug development and their implications for HTA (Fig. 1).

Representatives leading new HTA programmes for OMPs and/or ultra-OMPs were invited to participate in this research. These included the HST programme at NICE, the PACE programme and ultra-OMP decision-making programme at SMC, and the MoCA project. SMC is the HTA body in Scotland that undertakes HTA for all medicinal products. Within this remit, new processes have been created for certain types of medicines (e.g. OMPs and ultra-OMPs), these have been referred to as “programmes” in this paper. A questionnaire developed by some of the authors (EN, KF, LA) was sent by email to these representatives. It included open-ended questions about: (a) their definition of an OMP and ultra-OMP; (b) the reasons for establishing these



**Fig. 1.** Conceptual framework of OMP development and assessment challenges.

Fig. 1 illustrates the conceptual framework built summarising the challenges commonly encountered for OMPs, how they relate to the nature of OMPs throughout the drug development pathway and their implications for HTA.

Legend: PRO: Patient-reported Outcomes; HRQoL: Health-related Quality of life.

new programmes; (c) a brief description of their processes and how it differed from standard HTA approaches; (d) whether the issues pertaining to OMPs previously identified are commonly encountered in their setting; and (e) whether they can summarise the impact of their new programmes. Responses were compiled and organized to highlight the key characteristics for each question and contrasts across countries. Follow-up questions were sent when necessary. All co-authors reviewed and commented on versions of the manuscript. The responses and feedback were received from representatives participating in these new programmes, and reflect their views and not those of the organisations they represent.

### 3. Results

#### 3.1. Issues with OMPs

OMPs often exceed cost-effectiveness thresholds in HTA due to lack of evidence about clinical benefit and high acquisition costs. Moreover, evidence on their cost-effectiveness is typically characterised by greater uncertainty. This can lead to rejection through the routine approval process, or funding restricted to subgroups

of patients where their use is considered most effective or cost-effective [5,11,20–23].

These challenges emerge from the clinical, regulatory and economic obstacles encountered throughout the OMP development process (Fig. 1). Clinical challenges relate to the scarce scientific literature and number of clinical experts available [24], where often little is known about the diseases' epidemiology, natural history or best treatment pathways [25,26]. This affects the ability to run confirmatory trials in terms of design, e.g. lack of agreement on relevant endpoints [22], treatment pathways or appropriate trial durations [22], lack of active comparator [27], lack of validated patient reported outcome instruments [28] and conduct (e.g. recruitment [25], diagnosis [24], multiple clinical trial sites due to the few patient numbers [24]). The small patient numbers and relatively short duration of these clinical trials often imply that intermediate outcomes such as biomarkers or the six-minute walk test are studied rather than longer-term clinical outcomes [22]. These, in addition to the regulatory incentives for expedited approval based on phase II trials, may result in lower quality evidence generation for OMPs [29,30]. The statistical power to detect clinically meaningful outcomes from these often small-scale trials is limited [31]. Given the severity,

chronicity, life-threatening and disabling nature of these rarer diseases, the economic, psychological, and quality of life burden is also frequently high for patients, their families and carers, the healthcare system and society [25,27,32].

These challenges were reflected in the types of issues highlighted by the HTA bodies across the OMPs previously analysed in the Advance-HTA project (Fig. 1, eAppendix A) [8]. Misalignments with marketing authorisation incentives were seen, where some of the assessments relied on phase II trials following early marketing authorisation under exceptional circumstances or with conditional approval [8]. Other issues relating to the nature of these rare diseases included those around sample size and statistical power, clinical pathways, comparators, clinical, health-related quality of life or patient reported outcomes endpoints, trial duration, or subgroup data. The base case ICER estimates of NICE and SMC's assessment were generally high (> £30,000/QALY in 60–70% of cases) and sensitivity analyses showed high levels of uncertainty. This was a consequence of high acquisition costs, marginal benefits and uncertain evidence (Fig. 1, sAppendix A) [8]. These are in line with the issues seen for OMPs highlighted by Menon and colleagues [9].

### 3.2. New programmes for OMPs and ultra-OMPs

#### 3.2.1. Rationales

It was generally recognized that OMPs do not usually prove to be cost-effective based on conventional HTA methods designed for common diseases. Over several years HTA bodies have been criticized about their evaluation processes for OMPs and ultra-OMPs [33,34], where there may have been more leniency when dealing with them. As a result, HTA bodies have been facing political pressures to change their processes and be more transparent. At the same time, research has been conducted to identify the types of issues HTA bodies faced for OMPs within these conventional processes. The aim of this paper was to compare how the new programmes being implemented are tackling the findings from this research.

In England, NICE has been responsible for assessing selected ultra-OMPs since 2013 and established the new HST programme to do this [35]. HST's remit is to evaluate the benefits and costs of a technology within its marketing authorization for the treatment of a specific disease for national commissioning by NHS England using a specific decision-making framework. About three ultra-OMPs undergo the HST process each year. The products are chosen in the same manner as other technologies through a topic prioritization process led by the Department of Health. Ultra-OMPs not selected for the HST programme undergo the usual commissioning process via NHS England. OMPs can undergo the same process as non-OMPs at NICE (e.g. single or multiple technology appraisal process) or be part of the commissioning process at NHS England. The Department of Health mandates NICE to issue a coverage decision, which should be enacted within 90 days.

In Scotland, SMC assesses all new medicinal products and new indications for existing products. Manufacturers make evidence submissions and SMC recommends routine, restricted, or not recommended use in NHS Scotland. If a

manufacturer does not make a submission for a product, then it is not recommended for routine use. In 2013, three petitions were brought to the attention of the Scottish Parliament Health and Sport Committee about lack of access to ultra-OMPs due to not recommended advice from SMC. The Committee report to the Scottish Government prompted a major review of processes with all stakeholders, and led SMC to develop new, more flexible programmes for OMPs and ultra-OMPs (and end-of-life treatments) in order to increase patient access. These new approaches include the PACE meeting and the new decision-making framework for ultra-OMPs [36].

At European-level, the challenges and discrepancies in access to OMPs across Member States triggered the implementation of the MoCA project [37]. The MoCA provides a mechanism for European countries to collaborate on access for patients with rare diseases to OMPs via a voluntary, dialogue-based approach, with flexible interactions between key stakeholders to agree on the value of OMPs [38]. This approach aims to facilitate a quicker and broader access to OMPs, to allow for greater equity in access to OMPs across Member States, and to better coordinate the collection of patient-reported outcomes and real-life experiences. Payers should benefit from a better documentation of the treatment's added value, more precise budget estimates and efficient price negotiations, while manufacturers gain a better predictability, rapid uptake of their products, and understanding of payers' expectations. Participation is initiated upon the manufacturer's expression of interest. MoCA is currently being piloted, and focuses on the early dialogue phase about evidence generation and how to provide access to these OMPs.

#### 3.2.2. New processes

The HST evaluation process is similar to NICE's conventional technology appraisal processes, with the main difference being the criteria accounted for defined by HST's value framework [39]. When evaluating costs, the committee also considers the cost to the NHS and personal social services. It takes into account the total budget for specialised services and its allocation, as well as the scale of investment in comparable areas of medicine. The committee assesses what could be considered a reasonable cost for the medicine in the context of recouping manufacturing, research and development costs from sales to a limited number of patients. Interim methods for the HST programme are currently under review.

In SMC's process, the New Drugs Committee drafts the HTA advice according to the standard clinical and cost-effectiveness framework. The manufacturer may request that SMC convenes a PACE meeting if the draft advice issued is to not recommend the use of the medicine [40]. Patients, clinicians and the pharmaceutical company then submit a written report to the PACE meeting, with patient and clinician representatives contributing to further discussions in person, leading to a joint PACE statement that is circulated in full to the SMC members, summarized in the Detailed Advice Document and highlighted in a verbal report by the PACE Chair during the SMC meeting. Additionally for OMPs, SMC will account for additional criteria defined in their framework of explicit decision-making criteria for ultra-

OMPs [36]. This adds about one to three months to the standard 18-week SMC process. At this point in the process, the company also has the option to offer a new or revised Patient Access Scheme (confidential discount) to improve value for money.

By contrast, the MoCA is not a standard HTA programme but a collaborative process that involves a sustained dialogue between the OMP developer, a group of payers and other stakeholders from various European countries [37]. Participants consist of companies with new products, EURORDIS, an umbrella patient organization, which also ensures the participation of relevant patient groups, and volunteers from the Medicine Evaluation Committee (MEDEV). The main difference with the parallel scientific advice at the European Medicines Agency (EMA) is that participation from the stakeholders is voluntary and not initiated by the applicant, allowing for participation in the dialogue of smaller countries. It also differs from the early dialogue with HTA bodies in that it focuses on practical, pragmatic, legal and economic aspects of reimbursement decision-making, and integrates the HTA-relevant questions into this context.

### 3.2.3. Appraisal criteria

HST's decision-making criteria include considerations around the nature of the condition, impact of the new technology, including its impact beyond direct health benefits and on the delivery of specialised services, costs to the NHS and Personal Social Services, and value for money [39]. For each criterion, a sub list of criteria is provided (Table 1). The methods guidelines give freedom in the form of the health economic evaluation that can be used, e.g. cost-consequence, cost-utility. To date, all companies have chosen to submit a cost-utility analysis.

The SMC first considers the traditional HTA measures, e.g. ICER, while PACE assesses where these did not capture certain aspects of the disease or conditions by giving patients and clinicians the opportunity to comment on their experiences. This includes clinical, psychological and social issues, such as the added value of the medicine for the patients, their families and carers. Participants are asked to focus on quality of life issues, which could be improved by taking the medicine such as the ability to continue work or education, treatment convenience, ability to improve symptom management (e.g. pain, extreme tiredness), relieve psychological distress, enable self-care or maintain independence and dignity. In addition to a PACE meeting, the assessment of an ultra-OMP is based on a dedicated framework of explicit decision-making criteria, which include the same criteria as for the HST programme, setting out the higher level criteria only (Table 1) [36]. A cost-utility analysis is requested as part of the company submission to assess value for money. Other forms of economic evaluations, including cost-consequence analysis, are accepted if the submitting company believes an evaluation using QALYs is not feasible.

By contrast, the MoCA aims to facilitate a dialogue amongst key stakeholders throughout the OMP's development life cycle. Dialogue may start at any point during the lifecycle of an OMP and results in a final report containing learnings and recommendations, which is confidential and

non-binding, unless otherwise agreed. Companies as well as payers are free to opt out at any time (until a contract is signed) and the process is currently free of charge.

### 3.3. Dealing with uncertainty commonly encountered with OMPs

All programmes agreed that the challenges highlighted in Fig. 1 (eAppendix A) are in line with those commonly encountered for both OMP and ultra-OMPs. The common characteristic of NICE and SMC's programmes is to account for a broader range of criteria and include patient and clinician input to help address uncertainty and better understand the value of a product. The decision then relies on the Committee's judgment as to whether this evidence is sufficient to overcome greater uncertainty. This may be combined with other measures helping deal with uncertainty such as the ability to implement a Managed Access Agreement (MAA) (which is a type of outcomes based managed entry agreement) at HST, or Patient Access Schemes (PAS) (e.g. simple discounts) at HST and SMC (Table 2).

A MAA scheme facilitates access to ultra-OMPs, whilst generating valuable evidence in collecting 'real-world' data. All stakeholders agree on a set of criteria and conditions that need to be fulfilled by patients, clinicians and industry. These include conditions and criteria for patient eligibility, start and stop criteria, data collection and monitoring (e.g. implementation of registries, data collected and assessments to be made), appeal process, ownership of data, or exit strategy [41]. There may be some additional financial arrangements between payers and the relevant pharmaceutical company. At the end of the MAA period, the product is re-evaluated via the HST process. If no benefit is gained, the ultra-OMP will no longer be available to any patient via the NHS. These drugs are usually dispensed within specialised services, which allows for patients to receive expert care and infrastructure to manage patients with the condition in question.

MoCA aims to address these issues in advance through the conversations among stakeholders about how to best generate evidence for HTA and payers with reasonable resources, defining patient-relevant outcomes, demonstrating cost-effectiveness, and designing pathways for equitable and sustainable financing. This involves discussions about the design and implementation of registries, the feasibility of managed entry agreements, and delivery pathways (e.g. how to establish or designate treatment centers for very rare diseases with cross-border access, where it is not feasible to establish one or more centers per Member State – a particularly relevant issue for advanced therapy medicinal products).

### 3.4. Challenges encountered with these new programmes

The HST programme is challenged by the number of new products needing an evaluation and its capacity to undertake only three evaluations per year. Other challenges include the ability to assess and manage the uncertainty in the evidence submitted. With limited natural history data, short and small-scale trials, careful consideration of the evidence in line with the company value proposition

**Table 1**  
**Assessment criteria accounted for during the HST and PACE processes.**

Criterion to assess ultra-OMPs	NICE HST Value Framework	SMC ultra-OMP Framework	SMC PACE group(non-exhaustive)
<b>Nature of the condition</b>	✓	✓	
Patient clinical disability with current standard care	✓		
Impact of the disease on family/carers' quality of life	✓		
Extent and nature of current treatment options	✓		
Unmet need			✓
Severity of the condition			✓
<b>Impact of the new technology</b>	✓	✓	✓
Clinical effectiveness	✓		
Overall magnitude of health benefits to patients, and where relevant, their families/carers	✓		✓
Heterogeneity of health benefits within the population	✓		
Robustness of the current evidence base and anticipated contribution the guidance may make to strengthen in	✓		
Treatment continuation rules (if applicable)	✓		
<b>Cost to the NHS and Personal Social Services (PSS)</b>	✓	✓	
Budget impact of technology in the NHS and PSS	✓		
Robustness of costing and budget impact information	✓		
Patient access schemes	✓		
<b>Value for money</b>	✓	✓	
Incremental benefit of the new technology compared with current treatment options (technical efficiency)	✓		
Nature and extent of other resources needed to enable the technology to be used (productive efficiency)	✓		
Impact of the new technology on the budget available for specialised commissioning (allocative efficiency)	✓		
Opportunity cost of the technology (effect of investing in this technology rather than in another specialised service)	✓		
<b>Impact of the technology beyond direct health benefits</b>	✓	✓	
Significant benefits other than health	✓		
Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and PSS	✓		
Potential for long-term benefits to the NHS and society of research and innovation	✓		
<b>Impact of the technology on the delivery of the specialised service</b>	✓	✓	
Staffing and infrastructure requirements	✓		
Training requirements and need to plan for expertise	✓		
Best clinical practice in delivering the service	✓		
Service/infrastructure changes/benefits as a result of using the medicine			✓
<b>Impact of the new technology on quality of life</b>			✓
The ability to continue to work or education			✓
The management of symptoms such as pain and extreme tiredness			✓
Helping relieve psychological distress			✓
Convenience of how and where the treatment is received			✓
The ability to self-care or maintain independence and dignity			✓
Time for accompanied visits for treatment			✓
Requirement for assisting the patient with personal care and support			✓
Out of pocket expenses			✓
Impact on family life			✓
Impact on the carer's ability to go to work			✓
<b>Clinical issues</b>			✓
Specific patient groups that may benefit more from use of the medicine			✓
Place in the patient pathway			✓

Legend: NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium; TLV: Dental and Pharmaceutical Benefits Board; HAS: Haute Autorité de Santé; HST: Highly Specialised Technology; PACE: Patient and Clinician Engagement; OMP: Orphan Medicinal Product.

is needed. New approaches are also needed to allow better management of the risk burden relating to the uncertain evidence that the NHS is willing to bear.

The SMC ultra-OMP framework allows companies to make a submission that emphasizes the wider benefits of medicines that may not be easily captured in the QALY. Although the Committee now has more flexibility to accept medicines with a higher ICER than would conventionally have been accepted, the extremely high acquisition

costs of many of these medicines, coupled with very significant uncertainty about the magnitude and duration of clinical benefits, means that the most plausible ICER may be £500,000 or more, which is well above the perceived willingness-to-pay threshold (Table 2).

The MoCA project's main challenge is that there is no single payer voice. Each country has different health care systems, laws, economies, and priorities. It is not always possible to find "one-size-fits-all" solutions – ultimately,

**Table 2**  
Products assessed by SMC ultra-orphan process and informed by PACE (May 2014–September 2016).

Medicine	Indication	Recommendation	Economic evaluation*	SMC modifiers for ultra-OMPs
<b>Indications other than cancer</b>				
Ataluren	Duchenne muscular dystrophy	Not recommended	£793,498/QALY versus BSC (Public ICER, ICER including PAS confidential).	– absence of other treatments of proven benefit.
Eculizumab	Paroxysmal nocturnal haemoglobinuria	Not recommended	Cost-consequence analysis: estimated incremental QALY gain of 11.96 with eculizumab compared to BSC and a life year gain of 9.23 (lifetime incremental costs remained in confidence).	– substantial improvement in quality of life, – absence of other treatments of proven benefit.
Eculizumab	Atypical haemolytic uraemic syndrome	Not recommended	Cost-consequence analysis: Estimated lifetime QALY gain of 15.3 with eculizumab compared to BSC and a life year gain of 14 (lifetime incremental costs remained in confidence).	– substantial improvement in quality of life, – potential to bridge to a definitive therapy, – absence of other treatments of proven benefit.
Elosufase alfa	Mucopolysaccharidosis type IVa	Not recommended	£829,870/QALY versus standard medical care, including a PAS (simple discount) and a 3.5% discount rate applied to costs and benefits. £822,265/QALY using a societal perspective.	– absence of other treatments of proven benefit.
Ivacaftor	Cystic fibrosis with certain genetic mutations	Not recommended	Early ivacaftor versus: – late ivacaftor: £484,386/QALY – standard of care: £609,316/QALY (Public ICER, ICER including PAS confidential).	– absence of other treatments of proven benefit.
Pasireotide	Acromegaly where surgery is not an option and are inadequately controlled on other treatments	Accepted	£5855/QALY versus monthly somatostatin analogues.	– potential to bridge to a definitive therapy.
<b>Cancer indications</b>				
Bevacizumab (in combination)	Persistent, recurrent or metastatic cervical cancer	Accepted	£43,624/QALY for bevacizumab + cisplatin + paclitaxel versus carboplatin + paclitaxel, including a PAS (confidential discount as a rebate on the list price of bevacizumab).	– substantial improvement in life expectancy.
Bevacizumab (in combination)	Platinum resistant, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer	Restricted	£50,538/QALY versus chemotherapy alone.	– absence of other treatments of proven benefit.
Blinatumomab	Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia	Accepted	£52,201/QALY versus standard care (multi-drug chemotherapy), including a PAS.	– absence of other treatments of proven benefit, – potential to bridge to a definitive therapy.
Bosutinib (resubmission)	Previously treatment Philadelphia chromosome positive chronic myelogenous leukaemia	Accepted	£39,119–£62,619/QALY depending on the model and disease phase (Public ICER, ICER including PAS (simple discount) confidential).	– substantial improvement in quality of life, – absence of other treatments of proven benefit.



Table 2 (Continued)

Medicine	Indication	Recommendation	Economic evaluation*	SMC modifiers for ultra-OMPs
Brentuximab vedotin	Relapsed or refractory CD30+ Hodgkin lymphoma	Restricted	£43,731/QALY in both subgroups considered.	<ul style="list-style-type: none"> <li>– substantial improvement in life expectancy,</li> <li>– substantial improvement in quality of life,</li> <li>– the potential to bridge to a definitive therapy,</li> <li>– absence of other treatments of proven benefit.</li> </ul>
Cabozantinib	Progressive, unresectable locally advanced or metastatic medullary thyroid cancer	Not recommended	£93,141/QALY versus BSC.	<ul style="list-style-type: none"> <li>– absence of other treatments of proven benefit.</li> </ul>
Ceritinib	Previously treated anaplastic lymphoma kinase positive advance non-small lung cancer	Accepted	£50,908/QALY versus BSC, including a PAS (simple discount).	<ul style="list-style-type: none"> <li>– substantial improvement in life expectancy.</li> </ul>
Crizotinib	First-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer	Accepted	£48,355/QALY versus pemetrexed plus cisplatin or carboplatin, including a PAS (simple discount).	<ul style="list-style-type: none"> <li>– substantial improvement in quality of life.</li> </ul>
Ibrutinib	Relapsed or refractory mantle cell lymphoma	Accepted	£41,798/QALY versus physician's choice of treatment, including a PAS (discount)	
Idelalisib	Refractory follicular lymphoma	Accepted	£62,653/QALY versus standard care (Public ICER, ICER including PAS confidential).	
Lenvatinib	Adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine	Accepted	£49,525/QALY versus sorafenib, including a PAS (simple discount).	
Olaparib	Maintenance treatment of platinum sensitive relapsed BCRA mutated high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer	Not recommended	£49,236/QALY versus watch and wait, including a PAS.	<ul style="list-style-type: none"> <li>– absence of other treatments of proven benefit.</li> </ul>
Regorafenib	Unresectable or metastatic gastrointestinal stroma tumours	Accepted	£31,200/QALY versus BSC, including a PAS (confidential discount).	<ul style="list-style-type: none"> <li>– substantial improvement in quality of life,</li> <li>– absence of other treatments of proven benefit.</li> </ul>
Trametinib	In combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation	Restricted	£35,134/QALY versus dabrafenib, including a PAS (discount); and £39,956/QALY versus vemurafenib, including a PAS (discount)	<ul style="list-style-type: none"> <li>– substantial improvement in life expectancy,</li> <li>– substantial improvement in quality of life.</li> </ul>
Trastuzumab (in combination) (2nd resubmission)	HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction	Restricted	£41,347/QALY versus epirubicin, oxaliplatin and capecitabine.	<ul style="list-style-type: none"> <li>– substantial improvement in life expectancy,</li> <li>– absence of other treatments of proven benefit.</li> </ul>

\*ICER as used for decision-making unless confidential PAS applied. Sensitivity analyses were performed, and various ICERs presented, but this is the ICER that appears to have been accounted for in the decision. Legend: SMC: Scottish Medicines Consortium; QALY: Quality-adjusted Life Years; PAS: Patient Access Scheme; ICER: Incremental Cost-effectiveness Ratio; BSC: Best Supportive Care

each national authority will have to make a decision, but this may be expedited through the previous discussions. There are also challenges in designing appropriate registries, which can accommodate the needs of regulators, HTA bodies and payers, and are workable across borders. Moreover, at many payer institutions resources for this type of activity are scarce.

### 3.5. Impact of new programmes

To date, three ultra-OMPs have undergone the HST process and were approved, three are in the process. Two of the three were approved under an MAA. For example, elosulfase alfa in the treatment of mucopolysaccharidosis type IVa in adults and children was approved under the condition of a MAA achieved through a working partnership between NHS England, NICE, a patient organization, the manufacturer and a clinical expert. The MAA was designed to assess patient response to treatment based on pre-defined criteria monitoring clinical data and quality of life. The outcomes covered include a combination of registry data and condition-specific outcome measures. The MAA also included confidential negotiated commercial terms and a stopping clause for those patients not meeting treatment targets [41].

Since the introduction of the PACE programme (May 2014–September 2016), the acceptance rate for eligible medicines has increased by 58% compared to the 2011–2013 period, from 48% to 76%, and the number of non-submissions has reduced by around a third. The PACE programme has proven helpful to facilitate joint dialogue between patient groups, clinicians and HTA staff to highlight the impact of a condition on patients and their personal experience together with the expected wider benefits and disadvantages of a new medicine. The PACE statement is expected to be a significant factor in the SMC decision. For example, the output of the PACE meeting assessing ruxolitinib in the treatment of disease-related splenomegaly in adults clearly illustrated the symptom burden in primary myelofibrosis and its devastating effect on the quality of life for patients and their families. The benefits from treatment response were also highlighted in terms of the ability to return to a virtually normal life and in some cases to work, the improvement of family relationships following a reduced dependency on carers, the easing of the psychological burden on patients, and their ability to regain their personal dignity and independence. Patients were also less likely to need inpatient or outpatient care. The utility values for treatment were derived using a relatively new condition-specific HRQoL measure, the MF-8D. The novelty of this measure, together with the relatively high utility values from responding patients, was one of several key uncertainties in the economic case. The knowledge of the patient experience derived from the PACE process provided some reassurance to decision-makers in this context. At this stage, a Patient Access Scheme improving the cost-effectiveness of the medicine was also submitted by the company. For elosulfase alfa, previously discussed within the HST context, a number of considerations about the condition's severity and treatment benefit were also accounted for during the PACE

meeting and within the ultra-OMP decision-framework. These were not sufficient, and a negative recommendation was issued because of weaknesses in the economic case and the high ICER (>£800,000/QALY), where the medicine was unlikely to provide value for money.

To date, no product discussions within the MoCA framework have advanced to the point of specific agreements on managed entry. Companies participating in the discussions have termed them as very useful to gain insights into the problems payers face, and into the outcomes that matter to patients and payers. This is especially important for smaller and newer companies, which are those most likely to find the MoCA process useful [42]. Payers get an earlier opportunity to plan for introducing the new therapies and developing new models for access.

## 4. Discussion

While the challenges in dealing with orphan drugs are generally recognized, the approaches to tackle these varied. Differences were seen in the technologies selected to undergo these new programmes. The same ultra-OMPs do not necessarily undergo NICE's HST and SMC's ultra-OMPs evaluation programmes despite their common definition. Those not selected by the Department of Health for NICE's HST programme proceed through the usual commissioning process, where NHS England makes their own decision on how to provide access. OMPs undergo conventional HTA processes at NICE and SMC. In the latter case, additional considerations are accounted for via the PACE programme for those drugs that were not recommended during the initial standard HTA assessment by the New Drugs Committee.

The main commonality across these new programmes at NICE and SMC is the recognition that the QALY may not capture all elements of value and that wider considerations are needed from a multi-stakeholder standpoint. These considerations are accounted for during the deliberative process and contribute to accepting greater uncertainty and high ICERs. This is one way forward to recognising other sources of evidence through greater patient, clinician and public participation (patient experiences, care pathways) [43], as well as the value of qualitative evidence [2,43].

When comparing the criteria across these programmes, the information requested is similar (Table 1). These criteria are accounted for through NICE's consultee submissions or SMC's PACE statements and ultra-OMP explicit decision-making framework, and discussed during the appraisal committees' deliberations. While NICE has a committee dedicated to the HST programme, the same Committee evaluates all drugs at SMC. Additionally, NICE's patient and clinician submission templates provide more detailed guidance about the type of evidence to be provided compared to SMC's PACE submission template [35,44]. It is not clear whether this influences the level of detail provided during these processes. Our examples also showed that these additional criteria may not be sufficient to accept poor value for money (e.g. SMC for elosulfase alfa). One of the main issues highlighted by SMC, but not by NICE, are the extremely high ICERs encountered. This suggests that

despite accounting for similar criteria (Table 1), differences may be seen in their consideration.

While one of the main criticisms of traditional cost-effectiveness models is the failure to capture multiple attributes of the value of an OMP, a number of studies have tried to define these [societal preferences]. We have seen earlier that rarity does not justify a special status, but other attributes may. One recent study identified some of these societal preferences, which included disease severity, the rule of rescue (priority to the more urgent conditions), other patient attributes (e.g. age, parent and caregiver status), and (non) smokers [24]. Paulden and colleagues (2015) have performed a scoping review of the social value arguments put forward and against the reimbursement of orphan drugs [42]. They propose a value framework with the factors that should be considered in the decision, which include value-bearing factors (e.g. disease-, treatment-, population-, and socio-economic-related factors), opportunity cost-determining factors (e.g. cost of treatment, budget impact), and other factors (e.g. feasibility of diagnosis and of treatment). They also consider the patient, physician and societal preferences, as well as the rule of rescue, the equity principle and the rights based approach. Most of these are captured in the ultra-OMP frameworks, either through their eligibility criteria (e.g. prevalence), their process (e.g. accounting for stakeholder input), or in the criteria considered. The following, however, were not captured: the identifiability of the treatment beneficiaries (tendency to give preference to visible individuals, e.g. rule of rescue), the treatment's innovative nature [45], the feasibility of diagnosing the disease and providing the treatment, industrial and commercial policy, legal considerations, or certain patient attributes. Similar criteria were also accounted in the ultra-OMP frameworks to those defined as the normative universal criteria included in the EVIDEM framework, which aims "to evaluate interventions and facilitate their prioritization using a comprehensive set of decision criteria" based on the criteria rooted in different ethical positions" [46]. These examples suggest that the criteria included in the ultra-OMP frameworks correspond to those highlighted as relevant for both OMPs and non-OMP, despite in some instances, a lack of consensus in the literature as to whether these should be considered.

Whether the ICER is still relevant for ultra-OMPs is obviously a key question. For example, since 2002, a distinction has been made in Belgium between the reimbursement criteria for OMPs and other drugs. Cost-effectiveness is not mandatory for OMPs. An OMP is reimbursed if there is a high medical need, a clinically significant effect and an acceptable budget impact. Interestingly NICE and SMC do review budget impact, but it has not been a part of decision-making. This is an important consideration for ultra-OMPs. NICE utilises a national risk-sharing scheme to support implementation via the HST programme. There is currently no comparable scheme in NHS Scotland. The SMC remit excludes affordability.

However, as we see increasingly high prices for orphans and ultra-OMPs, some mechanism is needed to ensure fairness for all those in the health system including the opportunity costs these high cost OMPs will bring. While both NICE and SMC's programmes recognise the need to

go beyond cost/QALY estimates, one important consideration is how these new programmes are being implemented and whether they ensure accountability for reasonableness and consistency in the way the criteria are accounted for. Their explicit consideration during the deliberative process is already one step forward to making sure they are examined, but more could be done to gain international multi-stakeholder agreement on the wider elements of value and to ensure that deliberative processes document how these new elements have contributed to the decision. New approaches such as multiple criteria decision analysis (MCDA) not only ensure consideration of these elements, but also give them an explicit weight that can be derived through stakeholder participation [47]. MoCA takes account of this. Additionally, other features encountered with orphan drugs include issues such as salami-slicing, drug repurposing or the making of excessive profits [10]. The current systems fail to account for multiple indications and whether excessive profits are being made or to distinguish between products developed de novo and "repurposed" drugs, with much lower development costs. These would not be accounted for explicitly when assessing their value, but should be regarded by the decision-makers during the deliberative process.

While such innovative approaches and greater stakeholder participation and inclusion of other forms of evidence may help go beyond the ICER, uncertainty will still be present. This could be managed by additional evidence generation after HTA approval to allow reassessment, e.g. via MAA/PAS, registries and real world data to collect natural history and longer term outcomes [2]. This was seen in our illustrative examples, and allowed to better deal with uncertainty or high costs, sharing the associated risks with the manufacturer, or accepting uncertainty until additional evidence is available.

Both the HST and SMC programmes for OMP and ultra-OMPs are at early stages and currently under review [48]. This is also the case for MoCA. There are still a number of open questions about their application, and the ongoing issue of having to deal with extremely high ICERs and uncertain evidence. The question therefore arises as to whether these processes are still sufficient or whether there is a need to look at new ways to assessing value. The potential added value of the MoCA project is of key importance within this context, in fostering a multi-stakeholder dialogue in view of reaching greater consensus when discussing the determinants of a product's value at earlier stages and throughout the drug development process. This early and continuous dialogue will contribute to improving the efficiency (and effectiveness) of drug development [49]. The importance of this approach is highlighted by the Adaptive Pathways initiative of the EMA, which does not specifically address OMPs, but does include them [50]. In a context where a number of new value frameworks for prescription drugs and OMPs are being developed [51,52], MoCA has the potential to bring together these new models and gain more experience in order to find out how best to integrate these processes and reduce the complexities encountered from these multiple systems.

## 5. Conclusions

Two HTA bodies in the UK have recognized that OMPs or ultra-OMP operate in a context of greater uncertainty due to clinical, regulatory and economic challenges and responded to this by creating new bespoke programmes for these products. These encourage alternative economic models to the standard cost-utility approaches and managed entry agreements in the form of patient access schemes and managed access agreements to collect real world data. In addition, the HTA appraisal decision-making criteria is extended beyond the cost/QALY, to consider a more holistic framework that considers disease and treatment experiences and uncertainty from a range of stakeholders. The question arises as to whether these new programmes and decision-making frameworks will be successful in capturing value and dealing with uncertainty. What is needed are trials that answer the question that payers and HTA bodies will pose. Payers have recognized this issue and MoCA is seeking to foster multi-national and multi-stakeholder dialogue and reach consensus about the determinants of a product's value throughout the drug development process. Although discussions around specific products are confidential, the process needs to be evaluated and the challenges and issues faced in all these programmes need to be shared widely.

## Conflict of interest statement

KF has received fees from Sanofi, Genzyme and UCB for consulting in relation to rare diseases. KF has undertaken a range of other consultancy with other pharmaceutical companies but not related to rare diseases. EN has received fees from Contingo and Redmond Consulting, the latter not being related to rare diseases. No other conflicts of interest arise.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.healthpol.2017.03.009>.

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