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Key considerations for early access schemes for single-administration (one-time) therapies

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Executive Summary

Background to early access schemes

The regulatory process for medicines evaluates whether products are safe, have efficacy and their benefit/risk, i.e. the potential benefit to patients outweighs the risk. Early access schemes (EASs) can enable access to products prior to completion of this regulatory process for patients with serious conditions and no satisfactory alternative therapy. EASs allow national regulators to issue an initial positive assessment of the balance between benefits and risks for groups of patients on the basis of early clinical trial data. The main aim is to meet the needs of patients facing exceptional challenges, i.e., those with seriously debilitating or life-threatening diseases and no satisfactory treatment alternative.

Challenge of early access for single-administration therapies

Single-administration (one-time) therapies present a challenge for EASs due to their one-off nature. In existing EASs, manufacturers are often required to provide the product free, with the expectation that if or when a positive reimbursement decision is made, the manufacturer can charge for any subsequent treatment for that patient. For single-administration (one-time) therapies, where treatment is completed within the timeframe of the EAS, there is no prospect of reimbursement at that time or in the future for that patient. Hence, models of early access without reimbursement may not be financially sustainable for manufacturers of single-administration therapies, reducing investment into finding subsequent single-administration therapies.

Expert roundtable

A literature review of EASs was undertaken to develop a background paper to inform an expert roundtable. The background paper generated four key topics in relation to the development of EASs for single-administration therapies for deliberation at the roundtable: timing of early access, patient involvement, reimbursement, and data collection.

The purpose of the expert roundtable was to elicit expert opinion on these topics, leading to the development of 'key considerations' for the design of EASs for single administration therapies. The roundtable was attended by 11 experts, including current and former payers, regulators, health technology assessment (HTA) body representatives, industry body representative, politicians, ethicists, government representatives and patient advisory groups. The experts included people with expertise at the EU level as well as national level experts from Spain, France, UK, Poland, Italy and Germany.

The key considerations set out in Chapter 4 of this paper were developed during the roundtable, though the wording has been refined. In formulating the wording of each key consideration, the viewpoints of each representative stakeholder were taken into account. Whilst the key considerations reflect the discussions and conclusions of the roundtable, they should not be interpreted as consensus or to accurately reflect the viewpoint of any single stakeholder group.

Key considerations

The key considerations for EASs for single-administration therapies are as follows:

A clear rationale for initiation and termination of an early access scheme

Patients should be able to access qualifying therapies through an EAS as soon as it can be presumed by the relevant regulatory authority that the likely benefit outweighs the risk. The EAS should continue to make the treatment available to eligible patients until it is routinely available through the health system. Currently, in many countries, treatments only become available following HTA and/or the conclusion of pricing and reimbursement negotiations.

Patients and physicians should be consulted early during the design of an early access scheme.

The views of patients and physicians must be taken into account at an early stage in the design of an EAS. It is noted that, where EASs are implemented, this is not routinely the case.

When reimbursement is appropriate, the price should reflect value.

The decision of whether or not to reimburse should be a national level decision, influenced by contextual factors. When reimbursement is deemed appropriate, it will likely raise issues around value and affordability. Given that the price used during the EAS may become a benchmark price when the drug is approved, attempts should be made to establish a value-based price for products supplied during an EAS. The value-based price can either be assessed prospectively at the start of the EAS or retrospectively. A retrospective mechanism would align the early access price with the final price resulting from the conclusion of pricing and reimbursement negotiations.

Data collection should be an integral part of an early access scheme and be designed to inform future assessment.

EASs should be used to generate information, including clinical effectiveness and safety data, that will be used by regulators for benefit/risk assessment and by HTA bodies for value assessment.

Conclusions

Early access is a vital mechanism for patients with exceptional need to access therapies that do not have a marketing authorisation and are not yet available through the health system. However, existing EASs are not suitable for single-administration therapies, in part due to commercial concerns around a lack of reimbursement. The key considerations presented here are intended to guide policymakers, payers, regulators, patient groups, physicians and manufacturers on important factors for the design of EASs for single-administration therapies. These considerations should be leveraged to improve patient access to single-administration therapies through appropriately designed EASs.

The design and implementation of any EAS will be influenced by the different national contexts and therefore barriers will also vary depending on the structure of the health care system, the processes for value assessment and pricing and reimbursement, and legal frameworks. Further research and discussion are needed to understand how these broad key considerations can be incorporated in the implementation of specific schemes. Barriers to implementation must be identified, and strategies to overcome these put in place. A review of the infrastructure needed to enable early access, both at the national and EU level – such as data collection and management systems that can be shared by different schemes and potentially linked to reimbursement – would also be useful.

1 Introduction

Early access schemes (EASs) enable patients to access new and investigational therapies that do not yet have marketing authorisation (NICE, 2020; European Medicines Agency, 2018b) or are otherwise not yet available through the health system (e.g. due to ongoing pricing and reimbursement negotiations). Early access addresses an ethical issue created by regulatory and decision-making pathways whereby patients can suffer debilitating disease or die while they wait for a medicine that current evidence indicates is likely to be beneficial to them (Houÿez et al., 2017). The main aim of EASs is thus to meet the needs of patients facing exceptional challenges, i.e., those with life-threatening or debilitating diseases or conditions with no satisfactory therapeutic options.

There is often great desire from patients in need to obtain early access to investigational treatments. Through social media and readily available information on the internet, patients, particularly for rare diseases, are increasingly aware of products in clinical development (Eytan et al., 2011) and are often well networked through online forums and patient representative groups (Houÿez et al., 2017).

However, there is great variation between countries in access to treatments through EASs. The variation between EASs has led patient groups to call for more consistency between countries to reduce inequality in access to important therapies (Houÿez et al., 2017). In addition, the rise of medical crowdfunding campaigns is an indication that the current processes for enabling early access often do not meet the expectations of patients.

Products that are intended to be given via single-administration create further challenges in the context of early access. Single-administration (one-time) therapies – such as advanced therapy medicinal products (ATMPs) like gene therapies – aim to treat the root cause of disease. They offer the potential for long-lasting, even life-long, treatment effects and transformative benefits for patients from a one-time or short-term treatment regimen. Their one-time nature presents a particular challenge because most EASs require treatment to be offered for free. Without reimbursement, the manufacturer cannot recoup any costs for that particular patient. This is of greatest concern for manufacturers when the patient pool is very small and incidence is very low, i.e. for rare disease therapies that are often targeted by single-administration therapies. Given the higher upfront cost of many single-administration therapies, and uncertainty in the long-term durability of the treatment effect, pricing and reimbursement negotiations could be prolonged, increasing patient demand for early access through EASs that cover not only the period to regulatory approval, but also to routine access through the health system. As a consequence, entering into an EAS is risky for a manufacturer and may lead to some treatments not being financially sustainable, reducing investment into finding subsequent single-administration therapies.

Policymakers, manufacturers, regulators and payers must consider how the design of EASs can be improved to ensure they are fit for purpose for single-administration therapies. It is vital to allow patients in exceptional need to access these transformative therapies through EASs while ensuring single-administration therapies remain viable investments for manufacturers.

In this paper, we explore the frameworks for early access focussing on the processes in Europe. We then present four key considerations for stakeholders developing EASs for single-administration therapies developed through a multi-stakeholder roundtable.

2 Methods

2.1 Development of the background paper

We conducted a selective literature review to understand the design and implementation of EASs in different countries and the benefits of different design features. The review was pragmatic rather than systematic as the aim was to build upon our existing knowledge of EASs rather than identify all the literature on this topic.

We searched PubMed and Google for academic and grey literature on EASs with general terms such as "early access scheme", "compassionate use", "expanded access", and specific search terms for known EASs such as "ATU" and "EAMS". We stopped searching once relevant papers were no longer highlighting new issues.

The literature review was used to develop a background paper for dissemination ahead of the expert roundtable (see 2.2) and formed the basis of Chapter 3 of this report. The paper gave an overview of existing EASs (included here as an Appendix), the issues for their application to single-administration therapies and suggested five areas for discussion developed following OHE analysis of the literature. The discussion areas were: patient involvement, data collection, the timing of early access, legal considerations and reimbursement.

2.2 Expert roundtable

OHE, in partnership with Novartis Gene Therapies, The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), The International Patient Organisation for Primary Immunodeficiencies (IPOPI), and Portland Communications, organised a virtual roundtable to bring together experts from different stakeholder groups to develop the thinking on EASs, with a particular focus on single-administration (one-time) therapies. The workshop was attended by 11 experts, including current and former: payers, regulators, Health Technology Assessment (HTA) body representatives, industry body representative, politicians, ethicists, government representatives and patient advocacy groups. These included people with expertise at the EU level, as well as national level experts from Spain, France, UK, Poland, Italy and Germany. The roundtable was held in March 2021.

The agenda for the roundtable reflected the key factors presented in the background paper, with the exception of 'legal considerations', which was judged to both cut across the other factors and too country-specific to discuss in a multi-national roundtable. Therefore, the first four themes (patient involvement, data collection, timing of early access and reimbursement) were discussed by the experts during the roundtable, and the OHE project team drafted key considerations in real-time. At the end of each discussion, the key considerations were shared back to the experts for refinement.

The key considerations set out in Chapter 4 of this paper were developed during the roundtable, though the wording has been refined. Key discussion points from the roundtable are presented as rationale. Attendees were also given the chance to provide comments on a draft of this paper following the roundtable event. Whilst the key considerations reflect the discussions and conclusions of the roundtable, they should not be interpreted as consensus or to accurately reflect the viewpoint of any single stakeholder group.

3 Background of early access schemes

3.1 Terminology and legal frameworks for early access

The terminology and supporting legislation for EASs varies and countries and stakeholders may use the same term with a different meaning (Iudicello et al., 2016; Hogan Lovells, 2020). In this paper, we use the term early access to describe the potential mechanisms to enable access before pricing and reimbursement negotiations have concluded, including access that is granted before marketing authorisation. Most EASs begin before marketing approval has been granted, and legal frameworks protect patients who access therapies before marketing authorisation, outside of a clinical trial. In Europe, early access is overseen by Regulation (EC) 726/2004. The three main legal frameworks for early access are described below.

Compassionate Use
This mechanism allows medicines to be made available to patients before marketing authorisation where there is significant unmet medical need. According to the EMA, products are only eligible if they treat 'patients with life-threatening, long-lasting or seriously debilitating illnesses, which cannot be treated satisfactorily with any currently authorised medicine' (European Medicines Agency, 2018a). There is EU legislation and EMA guidance on compassionate use, but individual countries implement the programmes and therefore set their own rules and procedures (European Medicines Agency, 2018a). Under EU legislation, a manufacturer can only apply for a compassionate use programme run by a member state if it has applied for marketing authorisation or clinical trials are ongoing. Manufacturers must also ensure that patients involved in the programme are able to continue to access the product between marketing authorisation and the market launch of the product in that country.

Expanded access
Expanded access is the form of early access that is most similar to an extension of a clinical trial and is regulated like a clinical trial. Expanded access can be for patients who have been involved in clinical trials or who would benefit from the drug while the clinical trial is ongoing but who cannot be included in the clinical trial. This mechanism is used across Europe but is also used in the US where it is the main route of early access and is overseen by the FDA. The conditions of unmet need required for compassionate use must still apply in these cases.

Named patient access
Legislation in many countries allows the distribution of unauthorised medicinal products to a named patient if there is a legitimate request from a physician and the medicine is not being used in a wider compassionate use programme.

The EU compassionate use legislation (i.e. Regulation (EC) 726/2004) is implemented differently across member states. Most European member states have national legislation governing the implementation of EASs following the criteria set out in the EU legislation (i.e. for a serious condition, with no satisfactory treatment alternative, where treatment cannot be delayed) (Balasubramanian et al., 2016). The Early Access to Medicines Schemes (EAMS) in the UK, the French early access schemes (formerly the ATU scheme) and the various Italian early access pathways are examples of specific schemes in Europe. An overview of these selected schemes, as well as a description of Expanded Access in the US, are included in the Appendix.

3.2 Positioning early access in the regulatory and approval pathway

EASs are designed to grant access to a product for a limited patient population, usually for a period between the clinical trial phase and the granting of marketing authorisation. In many countries, marketing authorisation is followed by delay in access as value assessment or HTA and pricing and reimbursement negotiations take place. This pathway is shown in Figure 1.

Whilst some EASs allow new patients to access therapies across the breadth of this timeline, others use regulatory approval as a cut-off. Manufacturers are obliged to continue supplying products to patients already being treated within an EAS after marketing authorisation, but EASs vary as to whether they allow new patients to access therapies during the HTA and pricing and reimbursement stages of the pathway. EAMS in the UK does not allow new patients to be treated after marketing authorisation. However, the French early access scheme does allow new patients to access treatment after marketing authorisation (see Appendix). Difference in provision at this point is a source of variation in access between countries (represented by the '?' in Figure 1). The differences in how EASs are delivered has been raised as a concern from a patient perspective as the consequential difference in access across member states can be up to three years (Houÿez et al., 2017).

FIGURE 1 SCHEMATIC OF THE REGULATORY AND APPROVAL PATHWAY HIGHLIGHTING WHERE EARLY ACCESS SCHEMES ARE USED

3.3 Stakeholder context for early access schemes

Early access is principally managed by regulators, with increasing involvement of HTA bodies in EASs within Europe. There are also benefits and risks of EASs for a wider group of stakeholders including patients, payers, physicians and manufacturers. The balance of benefits and risks for each stakeholder depends on how the scheme is implemented and the characteristics of the product itself. The perceived benefits and risks for each stakeholder are outlined in Table 1 below.

Stakeholder	Perceived benefits of early access	Perceived risks of early access
Patients	• A chance to access an effective treatment offering the hope of benefit when all other satisfactory options have been exhausted and inclusion in a clinical trial is not possible (Houÿez et al., 2017).	• There is a risk that therapy is not effective (Borysowski and Górski, 2020). • Any benefit obtained may be outweighed by long term harms. • In the case that marketing authorisation is rejected, patients who benefited can no longer access the treatment. Unfairness is introduced as other patients who may still want to have access cannot.
Physicians	• Able to offer a treatment for a patient with very high unmet needs and no satisfactory alternatives. • Gain early experience of a new therapy outside of clinical trial settings.	• Patient harm and/or lack of benefit. • Pressured by patients into using unapproved medicines that may cause harm or be ineffective for their patients. • Pressure to enrol ineligible patients.
Regulators	• Patients with high unmet needs can access promising treatments without unnecessary delay. • Safety data in a broader patient population than that included in clinical trials. • Potential to improve understanding of the product through use outside of clinical trials and real-world data collection (PwC, 2016; Houÿez et al., 2017).	• They may be criticised if their decision to grant access under an early access scheme results in patient harm. • Patients may be reluctant to be randomised into a clinical trial when an early access scheme is available, resulting in less robust clinical data to form the basis of the regulatory decision. • Risk setting precedent of authorising products based on limited data that may condition future decisions.
Payers/HTA	• If the therapy is effective, payers realise the benefits sooner. • If data collected increased understanding of a product in a local setting, that could inform assessment and reimbursement.	• Paying for a product with unproven value. • Granting access early may increase pressures on payers if they subsequently wish to restrict use. • Risk paying for treatment in a population that will not be included in the reimbursement population. • Pressure on payers if marketing authorisation is not granted and access removed. • Risk value assessment and pricing and reimbursement processes will be undermined or circumvented.
Manufacturer	• Able to give physicians experience of using the product outside of clinical trial settings before marketing authorisation which is thought to influence future prescribing practices (Jones, Greenfield and Bradley, 2001) (Patil, 2016). • Can generate additional data pre-launch to support the regulatory assessment (Patil, 2016; Houÿez et al., 2017; Degrassat-Théas et al., 2013). • In schemes that reimburse for products used within the scheme, there is a commercial benefit. • Reputational benefit with patient groups who may criticise the manufacturer if no access is possible.	• Unanticipated adverse events – the risk of which may be increased in a population group that may have more serious disease than the average patient for that product. This could impact the reputation of the product. • In schemes without reimbursement, manufacturers carry the cost of the product for an unspecified time period. • Less urgency to conclude approval and/or reimbursement. • There may be investment in data collection that is inconsistently used and is collected in an uncontrolled setting (Stein and Soni, 2018). • Demand could exceed supply which may have reputational impacts. • May jeopardise recruitment in clinical trials for rare diseases.

TABLE 1 SUMMARY OF PERCEIVED BENEFITS AND RISKS OF EARLY ACCESS SCHEMES FOR KEY STAKEHOLDERS

3.4 Data collection during early access schemes

EASs are an opportunity to gather valuable data on additional patients outside of clinical trial settings (Brett, Umeweni and McCracken, 2019). A number of EASs have mechanisms for data to be collected during the scheme that can be used for regulatory approval. For example, data collection protocols are established at the inception of both EAMS in the UK and the French early access scheme (see Appendix). However, real-world evidence generation is not a core aim of EASs, and for many reasons the data collected during this stage is often not used in subsequent appraisal beyond safety (Stein and Soni, 2018; Patil, 2016). The reasons include:

- Small patient populations in the schemes.
- Differences in use by physicians that are hard to observe may result in different treatment effects in uncontrolled contexts outside of clinical trials.
- Patient populations tend to be heterogeneous.
- Health Information Systems are often not adequate to collect standardised clinical endpoints outside of the context of a clinical trial.
- Early access is principally overseen by regulators and not HTA agencies or payers so there is little consideration as to what data would be most useful for HTA.

Data collection during an EAS is further complicated by a lack of guidance from regulators for industry on how data, beyond safety data, should be collected. For example, a case study of the collection of real-world evidence during EAMS in the UK found that because the collection of data on efficacy and quality of life is not common during early access, there was no formal guidance on how to collect this data effectively (Pang et al., 2019). In addition, data collected during an EAS can present a risk for manufacturers as it is collected in a less controlled environment than a clinical trial and may impact regulatory filing or subsequent value assessment (Darrow et al., 2015).

3.5 Supply of product before marketing authorisation

The supply of medicines during an EAS falls under the regulation of medicinal products used for clinical trials. This can present problems for the supply of products at a stage when supply is limited. At the time of early access, manufacturing is restricted to a small scale and is only scaled up following approval from regulators. EASs fall into a production 'grey-zone' where supply is still on a small scale, governed by clinical trial standards but demand is increased to cover a wider group of patients than those included in clinical trials. Particularly for named patient schemes (see 3.1), manufacturers also face uncertainty in demand at a national level as applications are made for individual patients by their physicians. This makes it difficult to determine the supply of a therapy across different EASs (Patil, 2016).

3.6 What is different about early access for single-administration (one-time) therapies?

The EASs in use today were designed for severe diseases treated with chronic therapies where the products, if successful, would be administered continuously to manage the symptoms of the disease. In contrast, single-administration (one-time) therapies-such as ATMPs – which include gene therapies – aim to treat the root cause of disease, resulting in the potential for long-lasting and even life-long treatment effects.

In most EASs, manufacturers are expected or required to provide the product for free to patients with high unmet need who meet specified criteria. There are some exceptions, for example, the French early access scheme and some pathways in the Italian early access pathways (see Appendix). For chronic therapies, manufacturers may be expected to continue to provide the product for free until payers make a reimbursement decision after the EAS has concluded. For single-administration (one-time) therapies, providing the product for free during early access may not be financially sustainable for manufacturers in some circumstances, as the full treatment duration will fall within the EAS, and thus there is no prospect of reimbursement for that patient. Without reimbursement, early access would result in a significant reduction in total revenue for the manufacturer over the lifetime of the product. This is particularly problematic given many of the diseases targeted by single-administration (one-time) therapies are rare or orphan diseases where the total patient population is small. An important consequence is likely to be reduced investment into finding subsequent single-administration therapies.

In addition, the upfront cost of single-administration therapies is higher than for chronic therapies that are paid for over time, and an inevitable uncertainty in long-term durability of the treatment effect at the time of launch. Therefore, there are likely to be delays in the pricing and reimbursement negotiations which can increase the demand for early access from patients.

4 Key considerations for Early Access Schemes for single-administration therapies

Based on the literature review and expert roundtable undertaken for this project, four areas of consideration for EASs for single-administration therapies are set out below. The considerations were developed with a particular focus on single-administration therapies reflecting the factors highlighted in the background paper. Whilst the points outlined below were not designed for EASs outside of the context of single-administration therapies, many of them are likely to also be beneficial for EASs more generally. Where relevant, we explore why early access for single-administration therapies are unique within each consideration discussed.

4.1 A clear rationale for initiation and termination of an early access scheme.

There is an inconsistent approach between countries with regard to the implementation of EASs. When EASs start and finish within the regulatory, pricing and reimbursement pathway has implications for access and creates inequalities across countries.

Initiation of early access

Products should ideally be available through an EAS as soon as it can be presumed that the likelihood of benefit outweighs the risk for patients facing life-threatening or serious illness with unsatisfactory treatment options. Therefore, the beginning of the EAS should be based on unmet medical need in line with the EU legislation on compassionate use. This involves a consideration of the benefit/risk ratio.

Some schemes have flexibility by allowing early access to begin as early as phase 1, while others only allow EAS for products in phase 3. The optimum benefit/risk ratio (and therefore decision point from a patients' perspective) depends on the disease, with products for severe and rare diseases more likely to justify earlier availability.

Roundtable attendees noted that there should be definite intent from the manufacturer to launch the product in the country before they initiate an EAS, and that pricing and reimbursement processes are not circumvented by the existence of a scheme. This is particularly important in instances where products used in an EAS are reimbursed.

End of early access

EASs should be designed to ensure access is available for those in need up to the point where the therapy is available through the health system. Most EASs cover the period between phase 3 clinical trials and marketing authorisation being granted and do not allow new patients to access therapies after marketing authorisation. This creates an arbitrary cut off in access at the point of marketing authorisation as in many health systems widespread access is not achieved at this point. In many cases, HTA or some form of value assessment and/or centralised pricing negotiation is required before a product is made available within the health system. When designing an EAS, stakeholders

should consider whether any elements of the scheme (such as data collection or reimbursement) should differ between the pre- and post-marketing authorisation periods.

Amongst the EASs that cease to provide access to new patients after marketing authorisation, there is typically some provision to ensure that treatment is not withdrawn for those patients who commenced treatment prior to this point. In the case of single-administration therapies, no patients will have access to the therapy beyond this point.

Managing delays in decision making

EASs are not intended to compensate for delays in HTA or pricing negotiation processes. These stages can cause significant delays in access after marketing authorisation[1]. In principle, delays to access may be more likely for complex therapies like single-administration (one-time) therapies if there is high clinical uncertainty and higher upfront costs to consider during HTA and pricing negotiations.

EASs alone will not address the delays in access due to downstream processes. Regulatory approaches such as expedited review through the PRIME designation at the EU level, or national level mechanisms like the ILAP[2] in the UK, could reduce those delays for some products. However, EASs could be effective at mitigating the public health impact of those delays by allowing the patients with the greatest need to have access during any delays.

Relevant stakeholders

This consideration may be most relevant for national regulators, payers, and HTA bodies in the design of EASs.

4.2 Patients and physicians should be consulted early during the design of an early access scheme.

The main aim of early access is to give treatment options to patients in exceptional need. Therefore, it is vital that patients' views are considered when designing an EAS. The involvement of patients is important both for the design of the national scheme structure and for the implementation of the scheme structure for specific therapies. Roundtable attendees stressed that patient involvement should begin early in the design of the scheme, rather than taking the form of a consultation towards the end of development when most decisions have already been made. Patient input is also important for ensuring that the other key considerations are implemented in a way that is acceptable to the patients. Their involvement in defining data collection protocols was flagged by roundtable attendees as particularly important.

[1] *The French EAS that is being reformed in 2021 (see Appendix), the ATU, highlights this delay. The ATU runs up to marketing authorisation and the post-ATU runs after marketing authorisation until pricing and reimbursement negotiations have concluded. Comparing the ATU and post-ATU periods highlights the delay for appraisal and pricing processes: the average length of the post-ATU period between 2014 and 2019 was 630 days (Cosset et al., 2020) which is longer than the average time included within the ATU itself of between 304 and 365 days (PwC, 2016).*

[2] *The Innovative Licensing and Access Pathway (ILAP) aims to facilitate early engagement with regulators and HTA bodies for innovative products* (GOV.UK, 2020a).

Coordinating patient representation

Patient representative organisations have an important role in advocating for the needs of specific groups of patients. However, there is variation in the level of influence that patient representative organisations have depending on the disease and the country. This variation could result in an unfair decision-making process if patient consultation for the design of EASs is mediated entirely through patient representative organisations. It is therefore important that any efforts to include patients in the design of EAS account for the different levels of influence of the relevant patient representative organisations across diseases and across countries.

Managing allocation where treatment supply is limited

The perceived fairness in the allocation of limited supplies of a product facing high demand is an important consideration for EASs. The inclusion of patient views in the allocation process is particularly important. There is a reputational risk to all stakeholders if schemes fail to meet the expectations of patients (Houÿez et al., 2017).

Manufacturers currently have control over the allocation of products under early access, which may not be transparent or fair from the perspective of patients (Raus, 2016). There is no industry-wide best practice for managing allocation. One suggestion is that priority should be given to patients with a higher probability of benefit and where no unacceptable harms are anticipated (Borysowski and Górski, 2020). Elsewhere, some schemes have used waiting lists or random allocation to try to overcome this challenge with mixed responses from patients. This underlines the importance of patient inclusion in the design of EASs.

Independent processes involving patients are particularly important for many severe, rare or genetic diseases where it may be difficult to establish clinically and ethically acceptable criteria to decide which subset of the patient population is eligible for an EAS. A pilot scheme run by Janssen in collaboration with New York University School of Medicine Division of Medical Ethics used an independent committee including physicians, academics and patient representatives to assess global applications for an expanded access programme (Caplan et al., 2018). Consulting patients and physicians and including them in the decision-making process could help to improve allocation.

Relevant stakeholders

This consideration is relevant for all stakeholders involved in the design of EASs and those managing allocation, specifically patients/patient representative organisations, physicians, regulators, HTA bodies, payers and manufacturers. Some stakeholder groups, e.g. industry and HTA bodies, already have experience working closely with patients, although improvements can be made. Specifically, this consideration highlights that involvement should commence early in the design process, which does not always happen currently.

4.3 When reimbursement is appropriate, the price should reflect value.

Roundtable attendees considered that the decision of whether or not to reimburse should be a national level decision, influenced by contextual factors. Therefore, rather than state whether reimbursement should take place, a key consideration should be to ensure that a value-based price is utilised when appropriate.

Commercial viability

Many EASs do not reimburse the manufacturer for the product supplied during the EAS. There are a small number of exceptions, including the French EAS (formerly ATU) and some pathways in the Italian scheme (see Appendix). For single-administration therapies, a lack of reimbursement may mean involvement in the EAS is seen by the manufacturer as too high risk and may not be financially sustainable. This is particularly relevant for the large number of single-product companies or small- and medium-sized enterprises (SMEs) developing ATMPs.

For single-administration therapies, other drivers such as altruistic concern, pressure from patient groups or other indirect commercial benefits (such as increasing physicians' experience of using a new product) may not be sufficient to outweigh the commercial impact from a lack of reimbursement. Therefore, when designing an EAS for single-administration therapies, stakeholders should be aware that a lack of reimbursement may impact manufacturers' willingness to participate in schemes and thus reduce patient access.

Pricing and valuation

Where reimbursement is deemed appropriate, it may raise issues around value and affordability. Mechanisms for reimbursement during EASs need to be financially sustainable for health systems as well as for manufacturers. This is particularly relevant in the case of therapies with higher upfront costs like single-administration therapies. There is also a concern amongst both payers and manufacturers that the price used during the access scheme may become a benchmark price when the drug is approved (Pontes et al., 2020).

It is therefore important to attempt to establish a value-based price for the product supplied during the EAS. Value assessment could either be carried out prospectively or applied retrospectively to the products supplied during the EAS with a clawback mechanism (through which repayment is made if the price paid during early access exceeds the final or negotiated price). The retrospective value assessment mechanism with clawbacks is used within the French EAS (see Appendix). It is important that the mechanism to reconcile the price used within the EAS with the price agreed through pricing and reimbursement negotiations is robust, as experience from the French scheme suggests it may be administratively complex to apply clawbacks in practice. It is also important that the process for price-setting and the relation between the early access price and the price agreed following value assessment is clear. This is to ensure the price charged within the EAS does not commit payers to a price that was set before the value assessment was carried out.

Payment mechanisms

The short-term budget impact of reimbursing high-cost, single-administration therapies within the early access period could be offset by splitting the payment into instalments. The potential mechanisms for addressing the short-term affordability issues of single-administration therapies are well established in the literature, but are not consistently used in practice (Schaffer et al., 2018), partly due to administrative hurdles. Given the small numbers of patients treated through early access and the need for data collection during this phase, outcomes-based payments in the early access scenario are likely to have lower administrative barriers than when they are used on more widely following pricing and reimbursement negotiations.

This said, care must be taken to ensure that a sole reliance on outcomes-based payments does not remove the commercial incentive for manufacturers to participate in an EAS. This is important in the context of EASs as they often provide access for patients who are very sick and may therefore be less likely to meet the outcomes required for manufacturer reimbursement. In addition, there is complexity in agreeing on a meaningful outcome that can be measured for the duration of the EAS.

Once again, a transparent multi-stakeholder process to manage allocation decision-making (i.e. who gets access to a limited supply for a treatment), including patient representatives, is necessary to manage these complexities. Finally, when designing an EAS with reimbursement, stakeholders should also consider whether the payment mechanism and the process for value assessment should differ in the pre- and post-market authorisation periods, for example, due to differences in data availability and uncertainty around value between these two periods.

Relevant stakeholders

This consideration may be most relevant for payers and HTA bodies in the design of EASs. Manufacturers will be significantly impacted by the decision on whether to reimburse and by any requirement for additional HTA. Patient engagement should inform both HTA and the design of any payment mechanisms which incorporate outcome-based payments.

4.4 Data collection should be an integral part of an early access scheme and inform future assessment.

EASs are an opportunity to generate important data on single-administration therapies. EASs should be used to generate information, including clinical efficacy and safety data, that is useful for regulators and HTA bodies for value assessment.

It was stressed during the roundtable that while data collection was important, it should not jeopardise clinical trial recruitment or the delivery of the EAS. Some argue that the primary objective of an EAS should be the treatment of the patient and that when data collection is set as a primary – not a secondary – objective, the study should be classed as a clinical trial (Borysowski and Górski, 2020; Bunnik and Aarts, 2019). There is a balance that needs to be reached through cross-stakeholder collaboration to develop accepted standards to enable data collection to be leveraged without becoming a burdensome obligation that circumvents clinical trial recruitment or delays access. Guidance on data collection during an EAS is particularly vital for single-administration therapies that are often administered in a small number of specialised centres. This presents challenges to routine follow up of patients treated under an EAS as it may not be realistic for patients to travel regularly to centres for data gathering that is for the EAS rather than their clinical care.

Once again, the data collection mechanisms and requirements may need to differ between the pre- and post-marketing authorisation periods to reflect different levels of data availability and different potential uses for additional data at each stage.

Relevant stakeholders

For the data collected during EASs to be useful to patients, physicians, regulators, HTA bodies, payers and manufacturers, collaboration is required between all stakeholders early in the process to define which data would be useful and feasible to generate, and practical ways to collect it. Collaboration between the regulator, the HTA body, patients and the manufacturer to define relevant outcomes to support decision making was raised in the roundtable as particularly important.

4.5 The balance of responsibility between national and European levels

As part of the deliberations for several of the key considerations presented in this paper, roundtable attendees discussed where the balance of responsibility should lie between national and European bodies. Attendees felt that the design and implementation of an EAS is the responsibility of national bodies. EASs need to be shaped to the specific health system and within existing approval and appraisal pathways that take place at the national level. The importance of national decision making was stressed particularly in the context of reimbursement during the EAS.

However, there is value in European level policy and infrastructure. For example, such guidance and collaboration could be important for platforms for patient involvement or data collection networks. This is particularly relevant for single-administration therapies that are currently administered at just a few sites in Europe within specialist centres. In the future, specialised centres for the delivery of therapies may not be set up in all countries. This would require patients to cross borders to be treated. In addition, collaboration on standards for data collection would mean greater data availability for subsequent value assessment/HTA processes if it can be gathered at the European level. Therefore, whilst the design of EASs should ultimately be a national responsibility, EU level policy could promote the collaboration and infrastructure required to support member states in better designing and implementing EASs.

5 Conclusion

Early access is a vital mechanism for patients with exceptional need to access therapies that are not yet available through the health system. Single-administration treatments often target rare and serious diseases for which satisfactory treatment alternatives are not available and thus may be prime candidates for EASs. However, single-administration therapies do not fit well within existing early access frameworks, largely due to commercial concerns around a lack of reimbursement. To ensure the appropriate design of EAS for single-administration therapies, national regulators, HTA bodies, and payers must work with industry, patients/patient groups, and physicians to design EASs that are fit for purpose for single-administration therapies. Engagement with policymakers and politicians will also be needed, particularly where legal or infrastructural barriers to implementing EAS exist.

In this paper, we have presented key considerations for the design of EASs for single-administration (one-time) therapies. The key considerations focus on four areas: patient involvement, timing and rationale, reimbursement, and data collection. They were developed through a review of the literature, OHE analysis, and expert consultation via a multi-stakeholder expert roundtable. The key considerations are intended to guide policymakers, payers, regulators, patient groups, and industry on the important factors for the design of EASs. It is hoped that the considerations presented here will be leveraged to improve patient access to single-administration therapies through appropriately designed EASs.

Discussions at the expert roundtable highlighted that stakeholders have varying incentives for engaging in an EAS. Manufacturers may be less willing to risk putting forward single-administration products for early access where there is no prospect for reimbursement for those patients, and hence patients in urgent need may be denied access. On the other hand, payers will be concerned that a payment could set a precedent for future price, whilst regulators may be concerned that the EAS will result in pressure to approve the drug for all patients covered under the EAS. These risks can be mitigated to some extent with robust data collection, value assessment, and mechanisms for spreading payments and linking them to outcomes.

Further research is needed to understand how the broad themes covered by the key considerations outlined in this paper can be implemented in different national contexts and embedded within the design of specific schemes. Barriers to implementation must be identified and strategies to overcome these put in place. Finally, a review of the infrastructure needed to enable early access, both at national and EU level, such as data collection and management systems that can be shared by different schemes and potentially linked to reimbursement, would also be useful.

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Appendix

EARLY ACCESS IN FRANCE (ATU AND PLFSS 2021)

The French ATU was established in 1994 and reformed in January 2021 under the Social Security Funding Bill (PLFSS).

Aims
ATU:
The aim of the ATU scheme was to ensure quicker patient access to drugs not yet covered by a marketing authorisation in France when there is unmet medical need (ANSM, 2015). The ATU scheme included a named patient scheme (the nominative ATU) and a compassionate use programme for groups of patients (the cohort ATU). The ATU has been recommended as a model for other countries to follow (Houÿez et al., 2017).

An ATU was approved for 1-year and in general, medicines were involved in the ATU for 10 to 12 months pre-marketing authorization (PwC, 2016). A second phase of funding called the post-ATU enabled patients to access products while HTA and pricing negotiations were completed. The post-ATU phase will also be incorporated into the new pathways.

The new early access pathway incorporates features of the ATU, but the changes under the 2021 Social Security Law (PLFSS 2021) aim to make the scheme more transparent and sustainable as the cost of the ATU scheme grew to €1 billion a year (Das and Marrazza, 2020). The numbers of patients treated within the nominative and cohort ATU are outlined below.

Changes under PLFSS:
The detail of the changes from the ATU have not been finalised at the date of publication of this paper. Under the 2021 changes, there are now two arms of the scheme: Early Access (EAP), which covers products that are awaiting marketing authorisation, and Compassionate Access (CAP) for the off-label use of products for which there is no intention to submit a marketing authorisation for that indication(Matthews, Stefani and Urruticoechea, 2021). The rest of this discussion will focus on the Early Access arm as this most closely resembles the early access schemes model relevant to this paper.

The 2021 legislation centres around two key changes to the ATU. Firstly, the inclusion of HAS, the HTA body, into the decision-making process which was previously the sole responsibility of the regulator ANSM under the ATU. Secondly, the 2021 legislation reforms the pricing mechanism and increases the control that HAS and ANSM have on the price set during Early Access. Other features of the ATU are carried over.

A key reason for reforming the ATU was the increasing cost of treating patients within the nominative arm which accounted for the majority of the patients and budget for the ATU (Cosset et al., 2020) (ANSM, 2019). The data for 2014- 2018 is presented in Table 2 and Table 3 below. The preference for the nominative ATU was likely because the evidence requirements were lower than for the cohort ATU. The nominative ATU required manufacturers to demonstrate only that safety and efficacy were 'presumed' to be favourable. The PLFSS 2021 has made the evidence requirements consistent such that that efficacy and safety have to be 'strongly presumed' for the inclusion in Early Access (Das and Marrazza, 2020; Allen and Bernardini, 2020).

Year	2014	2015	2016	2017	2018
Number of products in nominative ATU	208	219	205	253	217
Newly included patients in a nominative ATU	25,521	24,791	27,095	22,295	21,633
Average patients per product	122	113	132	88	99

TABLE 2 NUMBER OF PATIENTS AND PRODUCTS IN THE COHORT ATU FROM 2014 TO 2018 (SOURCE: SCHLEICH ET AL., 2019)

Year	2014	2015	2016	2017	2018
Number of products in cohort ATU	25	13	10	11	20
Newly included patients in a cohort ATU	12,111	10,216	11,909	8,250	5,642
Average patients per product	484	785	1191	750	282

TABLE 3 NUMBER OF PATIENTS AND PRODUCTS IN THE NOMINATIVE ATU FROM 2014 TO 2018 (SOURCE: SCHLEICH ET AL., 2019)

The data collection requirements have increased within the PLFSS. Under the ATU the data collected could be used to inform HTA, however it was rarely used for that purpose and if ATU data was used, it would only be for safety data (Cosset et al., 2020). The PLFSS2021 states that the manufacturer must collect the data defined by HAS and ANSM as a condition of inclusion in the scheme. The data collected should include information on efficacy, adverse events, conditions of use and the characteristics of the patients (Assemblée Nationale, 2020). The cost of data collection will fall on the manufacturer (Allen and Bernardini, 2020).

Eligibility

Eligibility for the EAS under PLFSS2021 is based on unmet medical need in line with EU legislation on compassionate use. Products are eligible if they are to treat serious, rare or disabling conditions that also meet the following criteria (Eversana, 2020):

- There is no appropriate treatment;
- Treatment cannot be postponed;
- Efficacy and safety are strongly presumed based on the results of clinical trials; and
- The product is innovative with respect to a relevant comparator.

The criteria mirror the previous cohort ATU criteria apart from the addition of a new requirement to demonstrate the product is innovative which reflects the inclusion of HAS (the HTA body) in decision making under PLFSS2021 and a desire to limit the EAS to medicines for unmet need.

Reimbursement

The French EAS is one of few where the manufacturer is reimbursed for products supplied through the scheme. The price within the EAS is set by the manufacturer. However, there are two clawback mechanisms. One based on the total revenue and one based on the final agreed price of the product. Manufacturers have to pay rebates if total revenue is higher than a set threshold or if the price of the product applied retrospectively is higher than the final price set for reimbursement in France (Allen and Bernardini, 2020). There are concerns from experts that the clawbacks are difficult to implement in practice.

A new addition of PLFSS2021 is that there may also be further reductions in the reimbursed price if the reimbursement negotiations with CEPS following the scheme last more than 6 months. The manufacturer must also inform ANSM of the number of eligible patients and the number of patients expected to be included in each year of treatment. The price within the EAS is also considered the upper limit for the reimbursement price in France and has been the case throughout the ATU (Allen and Bernardini, 2020).

EARLY ACCESS PATHWAYS IN ITALY

To obtain early access in Italy, there are four different pathways available: compassionate use, law 648, the AIFA national fund (5% fund) under Law 326 and the non-repetitive use of advanced therapies (Schleich et al., 2019).

Aims

All four pathways aim to give access to patients with significant unmet need where there is a serious or life-threatening condition and no satisfactory treatment alternatives. The scheme under law 648 is the only one of the pathways to give access to cohorts of patients where there is no marketing authorisation or satisfactory therapeutic alternatives. The expanded access scheme is to fast-track patient access to drugs that are currently in clinical trials or are approved outside of Italy that treat serious or rare diseases or pathological conditions that can be life-threatening.

The 5% fund under law 326 is specifically for the reimbursement of orphan and lifesaving drugs that are awaiting marketing authorisation (Schleich et al., 2019). The non-repetitive (i.e. single-administration) use of advanced therapies provision is regulated under the EU Hospital Exemption (HE) legislation and aims to allow hospitals to manufacture ATMPs that do not yet have marketing authorisation and are not subject to specific clinical trials in Italy.

Reimbursement

The level of reimbursement differs between the pathways. Through law 648, if a medicine is eligible and accepted by the Italian Medicines Agency- Agenzia Italiana del Farmaco (AIFA)- it is placed on a specialist list. Products on this list can be fully reimbursed. Local institutions purchase the product, and the procurement costs are reimbursed by the NHS. In contrast, the compassionate use scheme, which is more closely linked to clinical trials, requires the sponsor of the trial to provide the product for free (Hogan Lovells, 2020).

The 5% fund is supported by 50% of the contributions that pharmaceutical manufacturers pay to AIFA annually, which is 5% of their promotional expenses in Italy. It is intended that half of the fund be used to provide access to orphan drugs before marketing authorisation, and half should be used to promote independent research of those drugs (Prada et al., 2015). If an application is approved, the cost of the treatment is reimbursed to the hospital by AIFA (MAP BioPharma, 2019).

Eligibility

To qualify for access through law 648, a product must meet one of the following criteria:

- The product must have promising results from clinical trials of at least phase 2 and not be authorised in any country.
- The product has been authorised in a different country but not in Italy.
- The product has authorisation for a different therapeutic indication and positive results of clinical trials are available for the proposed off-label use.
- On economic grounds relative to alternative treatment options.

To be eligible for through compassionate use, a product must jointly meet the following criteria:

- The treatment must be for a serious or rare disease or a pathological condition that can be life-threatening and there must be no valid therapeutic alternative.
- Phase 3 clinical trials are ongoing, or phase 2 or phase 3 clinical trials have been concluded.

In some circumstances, such as for rare diseases, an application for expanded access can be accepted based on results from a phase 1 trial (Hogan Lovells, 2020). Once a product is supplied through law 648 and compassionate use, the product must be supplied until it becomes commercially available.

To access reimbursement through the 5% fund, a product must be an orphan drug and have no therapeutic alternative. Applications are made on a named patient basis, and once approved must be provided until the end of the patient's treatment (Schleich et al., 2019)(AIFA, 2021a). In the case of the non-repetitive use of advanced therapies pathway, the product must be an ATMP, with no valid therapeutic alternative and used in the case of emergency when a patient's life is in danger or there is a risk of serious damage to health. Furthermore, the product must comply with the definition of "preparation on a non-repetitive basis" i.e. is intended for a single-administration (AIFA, 2021b).

For all of the pathways, the physician applies on behalf of individual patients or small groups of patients in the case of law 648, therefore manufacturers have little influence on the application for early access.

EARLY ACCESS TO MEDICINES SCHEME IN THE UK

Aims

EAMS was established in 2014 to enable access to promising new medication for patients suffering with life-threatening or seriously debilitating conditions access (GOV.UK, 2016). Between April 2014 and November 2020, the UK national regulatory authority, the MHRA, received 50 applications[3], 36 were approved for inclusion in EAMS (72%) and 3 were refused (6%). The rest were either withdrawn or are pending (GOV.UK, 2020b)

The MHRA encourages data collection during the scheme for use in subsequent HTA subject to a minimum set of outcomes being collected (Kiff et al., 2018). EAMS is currently the only scheme that has clear guidelines for the collection of real-world data (Stein and Soni, 2018). The MHRA offers support to manufacturers to generate better data during EAMS, but despite these guidelines, data collected during EAMS is rarely used in appraisals (MHRA, 2015).

The Innovative Licensing and Access Pathway (ILAP) began in England from the beginning of 2021 and aims to facilitate early engagement with regulators and HTA bodies for innovative products. Under ILAP EAMS remains unchanged, but products will be eligible for advice through ILAP earlier in the pathway than is currently possible with EAMS (GOV.UK, 2020a).

Reimbursement

The legal framework which exempts EAMS from the prohibition of the supply of unauthorised medicinal products requires medicines be provided free of charge (Hogan Lovells, 2020). An independent review conducted by PwC suggested that the lack of reimbursement in EAMS has been a challenge of EAMS (PwC, 2016). Manufacturers have suggested that a price could be set during the EAMS in recognition of their commitment to early patient access, but would not need to reflect the expected price of the drug post-MA (PwC, 2016). Other methods of commercial recognition have also been suggested, for example the contribution to EAMS to be considered during later price

[3] Applications here refers to applications for MHRA scientific opinion, the second step in a two-step process to apply to EAMS which is explained in full in the 'Eligibility' section.

negotiations with NHS England following a NICE HTA assessment. EAMS does trigger the NICE appraisal timeline as we discuss below.

Eligibility
Approval for EAMS follows a two-step process usually for products that have completed phase 3 trials. A manufacturer must first apply for promising innovative medicine (PIM) designation from the MHRA which assesses whether a product meets the unmet need criteria for compassionate use, i.e. that the product:

- treats a life-threatening or seriously debilitating condition;
- treats a condition that currently does not have alternative treatments or for which existing treatments are known to have serious limitations; and
- the potential adverse events of the product are likely to be outweighed by the benefits.

Following the PIM designation, the manufacturer must submit an application for a scientific opinion which if positive the scientific opinion initiates the EAS.

Duration
EAMS runs for 12-18 months with 3 monthly periodic reviews by the MHRA. The scheme is designed so that NICE begins the technology appraisal process as the early access period begins and NICE submits its recommendation at the end of the period, to be implemented immediately by NHS England. At the scientific opinion meeting, the manufacturer must also agree the exit strategy with NICE and NHS England in the case that market authorisation is not granted and/or if the HTA guidance is negative (GOV.UK, 2016). New patients cannot access drugs through EAMS after marketing authorisation is granted but patients already being treated can continue treatment through EAMS after marketing authorisation.

Expanded Access Programmes in the US.

Aims
The expanded access programmes in the US are designed to extend access to a medicine beyond its use in a clinical trial based on unmet need. As with the other schemes, expanded access is based on serious unmet need which may justify continuation of treatment for patients within a clinical trial, or the extension of the clinical trial to populations not included within the main trial. Applications for expanded access are made through an Investigational New Drug (IND) application to the FDA made by the treating physician while a medicine is undergoing large-scale clinical trials (FDA, 2020b).

Data collection during an expanded access programme is not a priority within expanded access. Data collected from the pre-approval period on any adverse events that occur must be reported to the FDA (Darrow et al., 2015). However, manufacturers are said to be concerned that data collected from the early access programmes may negatively affect the regulatory review for the drug, particularly when use is monitored less closely than in a clinical trial and inappropriate use of drugs by physicians could lead to adverse effects (Expanded Access Program Report, 2018; Patil, 2016).

Reimbursement
Manufacturers may charge patients or insurers the direct costs. However, most manufacturers do not charge for their products for reputational reasons relating to price differences in the expanded access period compared to the post-market launch period (Darrow et al., 2015). Patients benefiting may still face financial uncertainty as, although the drug is typically provided at no cost by the manufacturer, additional costs, such as appointments for monitoring clinical efficacy and adverse events, may not be covered by a patient's health insurance plan (Expanded Access Program Report, 2018).

Eligibility

There are three types of expanded access: expanded access for individual patients, for intermediate-size patient groups (10s to 100s of patients) and for widespread treatment use, usually following the conclusion of a successful clinical trial but before FDA approval (Darrow et al., 2015). A key criterion for making an investigational drug available through an expanded access programme is the risk-benefit assessment and whether there is sufficient evidence of safety and effectiveness, which changes depending on the size of the scheme (FDA, 2020a). Between 2013, the FDA approved 2472 individual cases, 66 intermediate-size requests and 41 widespread treatment schemes (Darrow et al., 2015).

Right-To-Try in the US

The 2018 Right to Try legislation enables patients with a life-threatening condition who have no alternative treatment options to bypass the FDA to demand access to drugs that are currently being investigated within a clinical trial outside of the trial (Hogan Lovells, 2020). Access through Right-To-Try is hard to follow and data is not available on numbers of patients who have secured treatment through the law. To encourage manufacturers to participate the legislation takes away liability for everyone involved and adverse events do not need to be reported (Morrison, 2018). Right-To-Try is led by the patient as opposed to the physician as is the case with Expanded Access.

About us
Founded in 1962 by the Association of the British Pharmaceutical Society, the Office of Health Economics (OHE) is not only the world's oldest health economics research group, but also one of the most prestigious and influential.

OHE provides market-leading insights and in-depth analyses into health economics & health policy. Our pioneering work informs health care and pharmaceutical decision-making across the globe, enabling clients to think differently and to find alternative solutions to the industry's most complex problems.

Our mission is to guide and inform the healthcare industry through today's era of unprecedented change and evolution. We are dedicated to helping policy makers and the pharmaceutical industry make better decisions that ultimately benefit patients, the industry and society as a whole.

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- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
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