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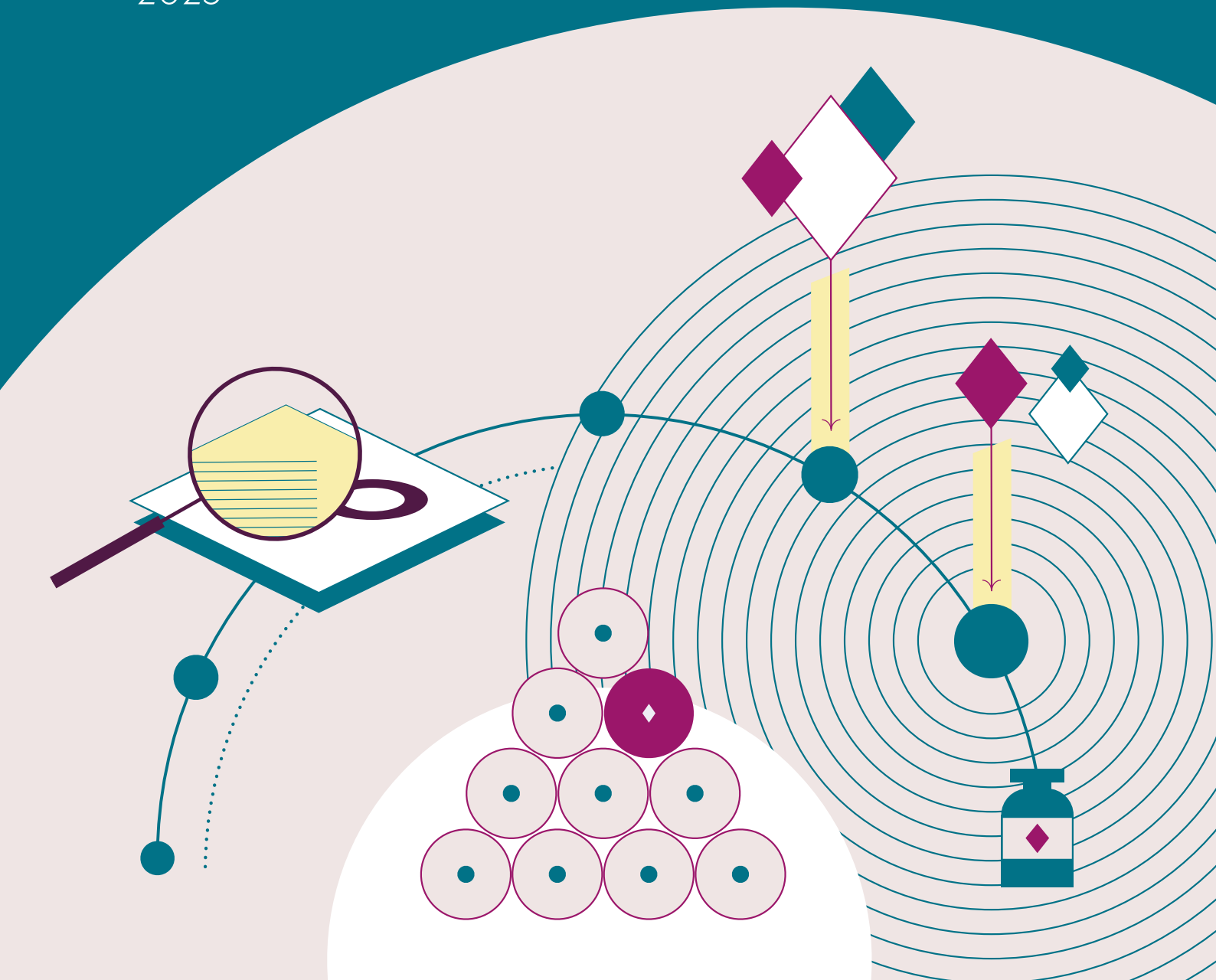
MAXIMISING THE VALUE OF EXPERT JUDGEMENT IN RARE DISEASES

Discovering how and when expert judgement is currently being applied in rare diseases, and identifying areas of untapped potential

2023



Foreword

- Rare diseases are often associated with limited evidence and a high degree of uncertainty regarding treatment outcomes, which can make it challenging to develop and evaluate therapies
- In the absence of suitable data, industry, regulators and payers may rely on the opinion of experts to inform decisions throughout the development of an orphan or ultra-orphan product
- In particular, expert judgement can play a critical and influential role during health technology assessment (HTA), with a reference protocol now available for structured expert elicitation (SEE) in health-care decision-making[1]
- Despite extensive opportunities for the application of expert judgement in rare diseases, there remains a limited number of published examples of high-quality best practice. The extent to which expert judgement is being used in rare diseases, the challenges stakeholders are facing, and the opportunities to increase use and improve methodologies remain unclear
- **This overview provides a summary of the current state-of-play and discusses some potential barriers to the application of expert judgement methods in rare diseases**

- Based on these findings, we have put forward a number of key questions which remain outstanding in this field
- A survey was conducted in August–September 2023, and collected international perspectives from a wide range of stakeholders within the rare diseases community, on the application of expert judgement
- Findings from this survey will inform a multi-stakeholder roundtable event, with the intention of developing rare disease-specific best practice recommendations for the application of expert judgement

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Plain Language Summary

What is expert judgement and why is it important for rare diseases?

There is often limited information available on rare diseases. Because of this, it can be difficult to develop and judge the importance of new treatments. Insights from experts can provide useful context, to help patients access new rare disease treatments. This is known as applying 'expert judgement'. Experts might include doctors, researchers, patients and their carers. These experts could be asked for their experience on many different topics, such as how rare diseases should be diagnosed, how well treatments work, or what the effect of a rare disease is on patients and their families. However, it is important that the way in which expert judgement is collected is clear and fair.

When is expert judgement used?

We carried out a review of studies collecting and applying expert judgement in the context of rare diseases. Our review found that most of the studies asked experts for their input on how diseases should be diagnosed or treated. However, there are many other opportunities when expert input could be used. Other opportunities might include when designing clinical trials, or when developing recommendations for best practice in patient care. We also found that it was often unclear how expert judgement was collected.

Can use of expert judgement be improved?

Some guidance already exists on how to apply expert judgement to support the approval of new treatments in healthcare. However, there is a need for more specific guidance on how to apply expert judgement to support the approval of new rare disease treatments. This could better support access to rare disease treatments in the future.

Introduction

Rare diseases are often associated with limited evidence and a high degree of uncertainty regarding treatment outcomes, which can make it challenging to develop and evaluate therapies.[2,3] In cases where robust data is unavailable, developers of treatments and organisations making regulatory and reimbursement decisions often rely on insights from experts. These experts may include clinicians, academics, patients and/or their representatives who are able to make judgements based on their expertise and experience. These judgements can inform evidence gaps throughout therapy development, including but not limited to, how the rare disease progresses in the absence of treatment, long-term clinical and safety outcomes of treatments, as well as the impact that the disease and any treatments have on the everyday lives of patients, caregivers and family members.

Although the use of terminology can vary, expert judgement can be used to describe all types of insights provided by experts. More specifically, expert opinion refers to qualitative information (e.g. asking an expert to define the most common symptoms of a disease). Contrastingly, expert elicitation is a process through which quantitative information is obtained from an expert (e.g. estimates of the number of general practice [GP] appointments a person with the disease

might have each year and how much this estimate may vary).[4] Additionally, the methods applied can range from a formal, structured approach, to a more flexible and unstructured format, depending on the nature of the questions asked and the opportunity to provide open-ended answers.

In recent years, recommendations for the collection and application of expert judgement in healthcare have emerged, covering topics such as how to select experts, how to incorporate patient perspectives, and how to apply expert judgement to support reimburement for new therapies.[4–6] These publications have been developed by authors based in the United Kingdom (UK) and United States (US), and therefore are not necessarily applicable globally.[4–6] Notably, last year, a reference protocol for structured expert elicitation (SEE) for reimbursement decision-making was published.[1] This protocol recommends reference methods across eight elements of the SEE process: experts, quantities elicited, approach to elicitation, method, aggregation, delivery, training and piloting, and rationales and documentation. The protocol, however, is limited to UK reimbursement decision-making and notes some issues associated with rare diseases, such as limited access to sufficient experts; the authors emphasise that there is a need for additional reference protocols that reflect more complex settings, including reimbursement for rare diseases therapies.

When Could Expert Judgement be Applied in Rare Diseases?

Despite best efforts by all stakeholder groups, it is common within rare diseases to face evidence generation challenges. These often relate to: the small number of patients able to take part in studies, the heterogeneity of rare conditions, a lack of validated patient-relevant endpoints, and limited awareness of rare conditions. As a result, opportunities for the application of expert judgement in order to address evidence gaps are extensive. These opportunities arise from early Phase I study design through to post-marketing surveillance, and include both disease and therapy-related topics **(Figure 1)**.

Disease-related topics include developing understanding of the disease background. For example, for more recently recognised rare diseases, there may be limited published literature on the incidence or prevalence of a disease. In this case, clinicians could provide input by commenting on the number of patients they have encountered in their clinics.

Expert judgement can also be sought on the diagnosis and treatment pathway, including the diagnostic criteria, referral and management of a disease. For example, in the absence of established treatment guidelines for a particular rare disease, a group of clinical experts could provide insight into how diagnosis and referral pathways could be improved to streamline patient pathways. Additionally, clinicians may be able to comment on which treatments are most effective when managing certain symptoms or conditions, based on their experience.

Lived experience from patients and caregivers can help inform understanding of the impact a disease can have on quality of life. Patients and caregivers may be able to provide valuable insights on how the disease affects their ability to carry out day-to-day activities, as well as identifying challenges with current treatments and barriers to accessing care.

Expert judgement can also play a valuable role in improving understanding of therapy-related topics. These can include input on clinical trial design or the relevance and validity of clinical trial endpoints, as well as inputs for health economic models, long-term treatment effects and quality

of life data. When designing clinical trials, both patients and clinicians can provide insights into the outcomes that are most important within a particular disease area, therefore ensuring that the most relevant endpoints are being investigated for a new treatment. Similarly, input from experts can guide the development of health economic models, which are used by decision-makers to understand what the cost-effectiveness of a treatment is. In cases where limited prior economic evidence is available for a specific disease area, clinical experts can provide quantitative estimates of economic costs to inform model inputs, so as to reflect the disease and its management in real life.

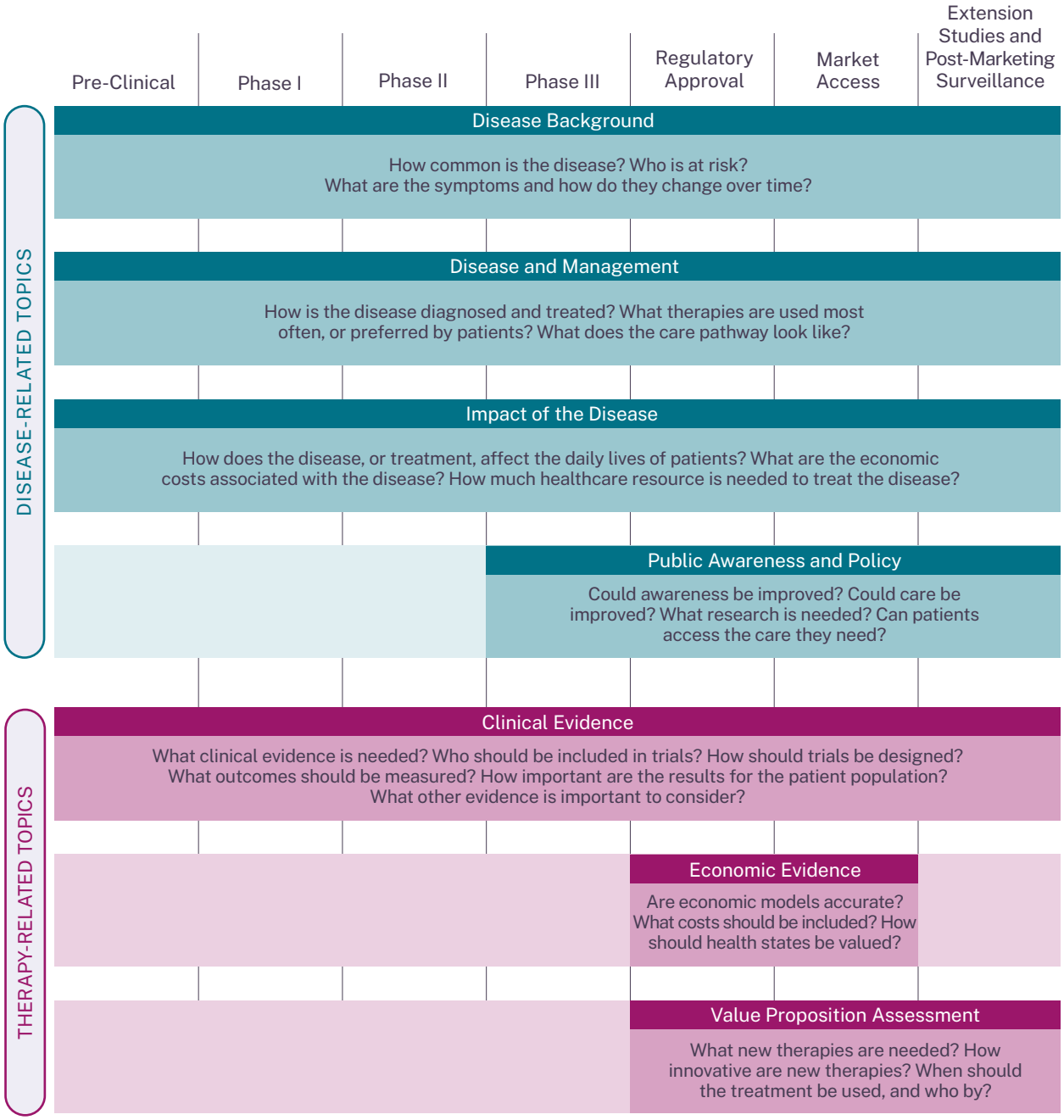

Figure 1. Opportunities to Apply Expert Judgement in Rare Diseases

When is Expert Judgement Currently Being Applied in Rare Diseases?

Targeted and time-limited searches of the literature were performed to identify publications reporting on the application of expert judgement, specifically within the context of rare diseases. Searches were designed to target six representative countries: UK, France, Germany, Canada, Brazil and Thailand. A summary of the findings is presented in **Figure 2A and 2B**.

Based on the identified literature, very few studies reported the use of expert judgement to improve understanding of disease background (e.g. causes, symptoms, who is affected).[7–10] However, expert judgement is frequently used to develop clinical guidelines on how to diagnose, treat and monitor individuals with rare diseases, making up the majority of the identified publications. Very few records used expert judgement to explore the impact that specific rare diseases have on the daily lives of patients and their caregivers.[11,12] Only two papers were identified providing expert recommendations to inform policy or improve awareness of rare diseases amongst healthcare professionals and other key stakeholders.[13,14]

For therapy-related topics, the use of expert judgement to support clinical evidence generation is also limited, although two identified papers sought expert consensus on appropriate endpoints and inclusion criteria for rare disease patient registries.[15,16] There are some examples where expert judgement methods, including SEE, have been used to inform health economic

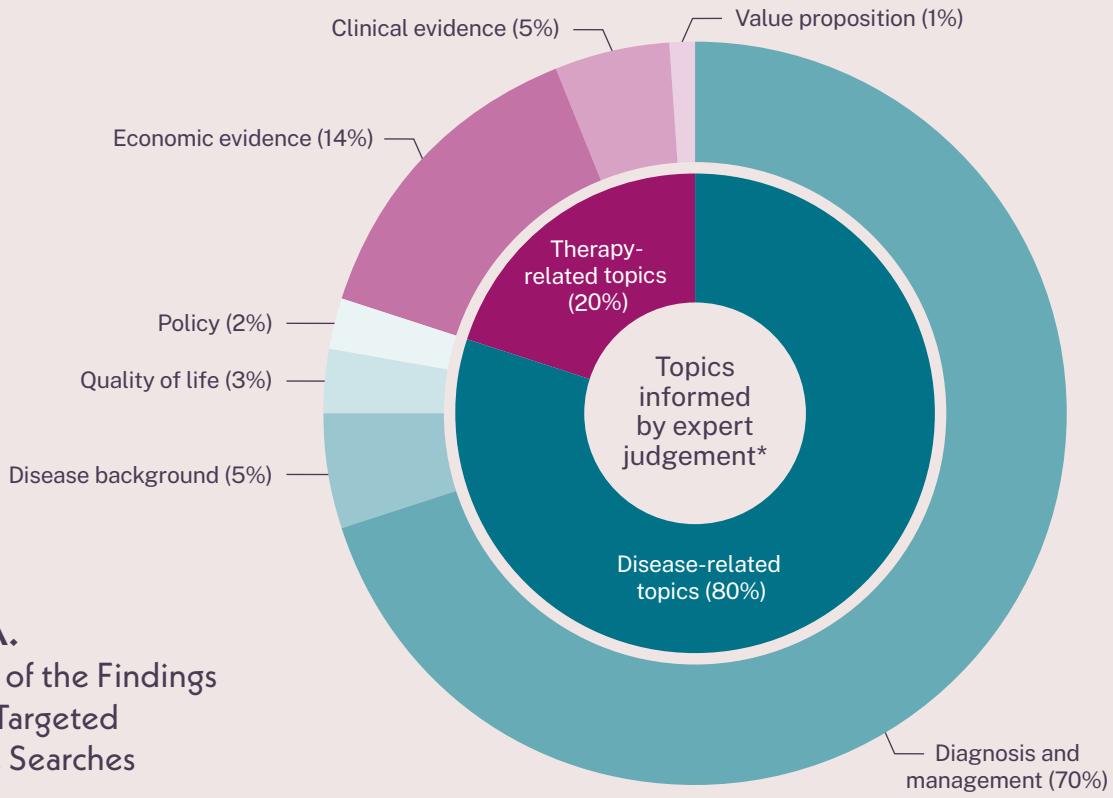

Figure 2A.
Summary of the Findings from the Targeted Literature Searches

*From the 100 relevant papers extracted across 81 rare diseases

Which type of expert judgement methods were reported?*

Figure 2B. Summary of the Findings from the Targeted Literature Searches

*From the 100 relevant papers extracted across 81 rare diseases.
SEE: Structure expert elicitation.

models, by providing insight on how a new treatment would influence disease progression and quality of life, as well as how resource use may change with the introduction of a new treatment (e.g. how many hospital visits a patient would require and the associated costs).[17,18] Furthermore, one study specifically explored expert input to provide recommendations on reimbursement processes and the pricing of therapies for rare diseases.[19] As the second most reported use of expert input, reporting of expert judgement to inform rare disease economic models may reflect the positive influence of existing guidelines of the collection of expert input to inform rare disease economic models may reflect the positive influence of existing guidelines on the use of expert judgement, particularly SEE, to inform reimbursement decision-making.[1]

It should be noted that in all cases identified in the literature, detailed reporting of expert judgement methods was lacking, with very few studies providing details of how experts were recruited, how insights were collected, or whether the results were assessed for validity. Of the studies that did report the methods used to gather expert input, modified Delphi panels and structured surveys were the most common. Only two identified studies used the SEE process to gather expert input, and in both cases this was used to inform economic evidence.[20,21]

The disparity between the large number of areas where expert judgement could be applied and what is currently observed in the literature, suggests that there are challenges associated with the collection and/or application of expert judgement in rare diseases. Some challenges have been recognised in the literature; for example the time commitment required from experts for SEE processes typically ranges from 3–9 months to allow for preliminary training, responding to questions and other touchpoints.[22] Furthermore, there is often a shortage of local experts in rare diseases, which can make it more challenging to ensure bias is minimised.[6,23] Finally, there is a lack of clarity on how expert judgement and the methods used may be valued by the organisations making regulatory and reimbursement decisions. In the absence of specific or consistent guidance from decision-makers, developers of rare disease therapies may be less willing and able to dedicate time and money to collecting and using expert judgement.

Outstanding Questions

The role of expert judgement in healthcare decision-making is evolving, with formal methods increasingly being reflected in the published literature. There is now an opportunity for rare disease stakeholders to reflect on developments to date and challenges faced so far, with a view to making collective improvements that maximise the value expert judgement can bring to rare diseases.

To address this, we conducted a survey in August–September 2023, which put forward a number of key questions which we believe remain outstanding in this field:

- **To what extent does published literature reflect the current application of expert judgement methods in rare diseases?**
- **Considering the current reported use of expert judgement, are there any other areas in the drug development process where stakeholders think expert judgement could add value?**
- **If so, what challenges do stakeholders face when trying to apply these methods and how can they be overcome?**

Findings from the survey will inform a multi-stakeholder roundtable event. Our intention is to develop rare disease-specific best practice recommendations for the application of expert judgement, that can be applied by stakeholders globally to support access to rare disease therapies.

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Annabel Griffiths, Isabelle Newell, Noa Chapman and Chloe Zentai are members of the Rare Diseases and Health Policy divisions and employees at Costello Medical. The views/opinions expressed are their own and do not necessarily reflect those of Costello Medical's clients/affiliated partners. If you would like any further information on the themes presented above, please do not hesitate to contact:

Annabel Griffiths,
Global Head of Rare Diseases
annabel.griffiths@costellomedical.com

Isabelle Newell,
Consultant, Rare Diseases
isabelle.newell@costellomedical.com

Glossary

Bias
A tendency to prefer or favour a person, thing or viewpoint to another

Expert Elicitation
A process through which quantitative information is obtained from an expert (e.g. estimates of the number of GP appointments a person with the disease might have each year and how much this estimate may vary)

Expert Opinion
Qualitative (non-numerical) information (e.g. asking an expert to define the most common symptoms of a disease)

Health Economic Model
A tool that gathers inputs on the costs and benefits associated with a new therapy to predict its clinical and cost impact, and therefore its cost-effectiveness

Health Technology Assessment (HTA)
The process by which the clinical, economic and ethical value of a new therapy is evaluated. This assessment is carried out by a national governing body

Modified Delphi Panel
A technique for gathering consensus from a group of experts, where experts respond to a number of statements to reach an agreement'

Patient Registry
A system where data are collected from patients with a shared disease (e.g. background, symptoms, medications and treatment outcomes)

Qualitative
Relating to the nature or standard of something, rather than its quantity (i.e. non-numerical information)

Quantitative
Relating an amount that can be measured (i.e. numerical information)

Reference Protocol
A formal guidance document that can be used to direct how a certain activity should be carried out

Regulatory Decision
The action of concluding whether a therapy is safe and effective

Reimbursement
In the context of healthcare systems, the cost of a new therapy is covered to make it available freely (or at a discounted price) to patients. This decision is made by the relevant payer (e.g. the national governing body or insurer, depending on the healthcare system)

Resource use
The use of time from healthcare professionals, facilities or consumables (e.g. medicines)

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