AN EU HTA FIT FOR RARE DISEASES

Part 2: Stakeholder involvement in joint clinical assessments

Copenhagen Economics

European Expert Group on Orphan Drug Incentives
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European Expert Group on OD Incentives

Established in 2020, the European Expert Group on Orphan Drug Incentives (OD Expert Group) brings together representatives of the broad rare disease community, including researchers, academia, patient representatives, members of the investor community, rare disease companies and trade associations.

The group aims to become the source of ground-breaking ideas and potential solutions that will provide input to the Orphan Medical Products (OMP) Regulation evaluation. The initiative is led by a steering group composed of the European Organisation for Rare Diseases (EURORDIS), the Voice of Rare Disease Patients in Europe, and the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), representing several companies focused on finding new therapies for rare diseases.

The group is co-chaired by Professor Maurizio Scarpa, Coordinator of the European Reference Network for Hereditary Metabolic Disorders (MetabERN). The following EUCOPE member companies sponsor and provide expertise to the initiative: Alexion, Biogen, Bristol Myers Squibb, Chiesi, Novo Nordisk, PTC Therapeutics, and Takeda.

Source: https://od-expertgroup.eu

The OD Expert Group worked together with Copenhagen Economics in a series of workshops and interviews to investigate how the current framework for EU health technology assessment (HTA) needs to be adjusted to fit the needs of orphan medicines.
In this report, the OD Expert Group makes a set of recommendations that will improve the upcoming EU HTA for the needs of orphan development and will allow handling stakeholder involvement in joint clinical assessments (JCA) concerning conflicts of interest.

This is the third report produced by the OD Expert Group since 2020. The group's further work includes

- Orphan Medicine Incentives. How to address the unmet needs of rare disease patients by transforming the European OMP landscape – Link
- An operational framework for the modulation of orphan medicine incentives – Link

Enable stakeholder involvement in JCA by implementing three initiatives, including declaration and categorisation of interests.

HTA bodies seek input from external experts to assess health technologies

To make well-informed decisions in JCA, HTA bodies rely on input from experts from outside their own organisations with subject matter expertise or experience. 'Stakeholders' means individuals providing input to HTA bodies that will not be contributing to the final decision-making. For instance, stakeholders comprise health care professionals (HCP) with expertise in the condition the health technology aims to treat or patients suffering from the condition the HTA is indicated for.

Rare diseases are categorised by few subject matter experts and small patient populations

OMP indicated for rare diseases often differ from other health technologies in the sense that there are few subject matter experts and small patient populations, drastically confining the pool of relevant stakeholders in a position to provide useful input to JCA.

The few experts are likely to have experience that could constitute interests

In rare diseases in general, and increasingly as we turn to even less prevalent rare diseases, relevant experts are likely to have engagements that constitute an interest in the assessment. For instance, relevant experts might be engaged either as patients, participants enrolled in the clinical trials, as HCP, developers of the OMP, or a combination of the above. In other words, compared to other health technologies, OMP tend to feature a few experts who can provide relevant input to JCA, and therefore those available are more likely to be engaged in ways that may constitute an interest in the outcome of the assessment. This problem is recognised by the EUnetHTA.

Today, declared interests may lead to the exclusion of stakeholders' input

In the current practice of European HTA, experts may be excluded from providing input to clinical assessments if certain engagements are deemed a conflict of interests by the HTA body, for example, where the expert has a financial interest and could financially benefit from the outcome of the assessment.

A Declaration of Interest form is available on the EUnetHTA website.[1] We find that the form suffices to ensure transparency concerning stakeholders declaring their interests in the context of assessments of OMP.

Interests should be handled and mitigated through three initiatives rather than exclusion

We recommend that interests and even conflicts of interest are handled through transparency and declarations of interest rather than exclusion when assessing OMP.

Our recommendation is aligned with the procedure guidance of both the National Institute for Health and Care Excellence[2] (NICE) and EUnetHTA[3] for exceptional circumstances in which input from an expert with a conflict of interest is accepted. An example is an area where the number of relevant experts is very small and there has been close collaboration between a clinical speciality and the industry[3] in developing the new health technologies under assessment.

However, we recommend flipping the approach when assessing OMP by including input from all relevant stakeholders by default rather than exceptionally. To ensure an unbiased decision at the HTA body despite potentially biased input, we recommend implementing three initiatives to handle and mitigate the interests of stakeholders:

1. Categorise interests according to the potential biases they may give rise to.
2. Reduce bias by aligning expectations with stakeholders, asking concrete questions and scoring replies immediately.
3. Invite stakeholders with expertise in other disease areas to deliver generic input.

On the next three pages, we elaborate on each of these initiatives. All three go beyond current practice at, for example, NICE and EUnetHTA. We find that the initiatives can contribute to reducing potential bias in the outcome of assessments of OMP in which stakeholders with a conflict of interest are already asked for input under exceptional circumstances.

We focus solely on the potential bias in outcomes arising from interests among experts providing input to HTA bodies, rather than interests or conflicts of interest within HTA bodies.

Sources: 1) EUnetHTA's Declaration of Interest (DOI) form, see link / 2) National Institute for Health and Care Excellence (2022) Policy on declaring and managing interests for NICE advisory committees - Also includes witnesses, expert commentators and other contributors / 3) EUnetHTA (2022) Handling declaration of interest (DOI) and EUnetHTA 21 Confidentiality agreement (ECA) forms

First, categorise interests according to the potential biases they may give rise to.

For greater transparency, we suggest categorising the interests of stakeholders providing input to JCA of OMP and adding the potential biases as disclaimers to stakeholders' answers. See Figure 1 below.

Categorise interests according to the potential biases they may give rise to.
We have identified several interests giving rise to potential stakeholder bias. These are listed on the left-hand side of Figure 1. The list is non-exhaustive. Hence, additional interests or subdivisions of those already listed may be useful to include in a final version of the list.

Match potential biases with input from individual stakeholders.
In the table on the right-hand side of Figure 1, stakeholders providing input and their answers are matched with the list of potential biases. The potential biases are meant as disclaimers to help the HTA body have its guard up when listening to or reading answers from stakeholders. For instance, if a stakeholder is potentially biased due to financial interests in a positive outcome of the assessment, answers indicating a relatively high clinical efficacy of the OMP would be incentive-compatible with the potential bias.

Moreover, the potential bias labels will help HTA bodies analyse whether answers from stakeholders with certain potential biases systematically deviate from other stakeholders' answers, indicating that the potential biases have materialised.

Figure 1. List of interests leading to potential bias and match of potential biases with input from individual stakeholders

Please note that input provided by the stakeholders is potentially biased due to the following:

- The stakeholder is diagnosed with the rare disease in question.
- The stakeholder is an HCP treating patients with the rare disease in question.
- The stakeholder has taken part in conducting the clinical studies of the OMP under assessment.
- The stakeholder is closely related to a person diagnosed with the rare disease in question.
- The stakeholder has financial interests in the outcome of the assessment, e.g., due to paid employment with the developer.
- …
- The stakeholder is potentially biased for other reasons than those stated above. Please provide elaboration.
- The stakeholder contributed considerably to the design of a study aimed at evaluating a comparator technology.

Question by the HTA body to stakeholders: *"How do you find the clinical efficacy of the OMP under assessment relative to the comparator that is the current standard of care?"*

Stakeholder	Potential biases	Answer
Stakeholder 1	🔴 🟠 🟡	*"Answer by Stakeholder 1"*
Stakeholder 2	-	*"Answer by Stakeholder 2"*
Stakeholder 3	🟢 ⚫	*"Answer by Stakeholder 3"*
Stakeholder 4	🟡 🔵	*"Answer by Stakeholder 4"*
…		…

Note: The list of sources of stakeholder interests is non-exhaustive.
Source: Copenhagen Economics; EUnetHTA21, Procedure guidance, Handling declaration of interest (DOIi) and EUnetHTA 21 confidentiality agreement (ECA) forms

Second, reduce bias by aligning expectations with stakeholders, asking concrete questions and scoring replies immediately.

We suggest implementing three behaviours to reduce the potential bias of input from stakeholders in JCA or mitigate the effects of potential bias. The first behaviour is based on a simple alignment of expectations and the two latter initiatives are inspired by results from the field of human resources (HR).

1. Ensure alignment of expectations with stakeholders providing input.
We recommend that HTA bodies are diligent in uncovering exactly what questions they rely on input from stakeholders to answer. By asking stakeholders concrete and narrow questions rather than only questions for broader input, the scope for biased input is reduced. This is because the stakeholder's potential bias may materialise only within certain topics in which they are not necessarily asked questions.

If the experts are expected to share their input verbally at a meeting, the list of questions should be circulated to the experts well in advance, allowing them to develop answers. Moreover, we recommend that the HTA body drafts and shares a process description outlining what is expected from the experts and how their input will feed into the decision of the HTA body.

We believe that unnecessary stress and incorrect expectations could be avoided if HTA bodies made questions and processes clear to experts up front. For instance, it has happened that patient representatives thought their task was to convince an HTA body to grant access to the treatment in question and that the quality of their input would be decisive for the outcome of the assessment.

Handling biases based on inspiration from human resources
We find that two other research-based conclusions from the field of HR can contribute to behaviours decreasing the potential biases materialising from stakeholder involvement in JCA.

In HR, it is acknowledged that everyone is biased in some way; it is part of being human. Background and experiences shape the way people see the world. Sometimes people realise this and sometimes they do not, but they are often driven to make decisions based on their biases. This includes HTA bodies and stakeholders providing input. While one cannot fully eliminate unconscious biases, it is crucial to become aware of them and actively work to keep them out of decision-making.[1] Unconscious biases have a critical and problematic effect on judgement as they cause people to make decisions in favour of one person or group to the detriment of others.

The field of HR has developed sophisticated methodologies for handling and mitigating biases in decision-making, which in this context allows the inclusion of input from experts with interests and potential biases. We find that these methodologies can serve well as inspiration for how biases among those providing input to JCA could be handled.

2. Minimise bias by standardising questions to stakeholders providing input.
We recommend that HTA bodies standardise questions to stakeholders providing input to JCAs and stay in control of the topics being discussed. By steering the discussion through predefined topics and questions, HTA bodies will receive more targeted and standardised input, which can be compared across stakeholders with different interests and potential biases. Research in HR shows that unstructured interviews, which lack defined questions and whereby a candidate's experience and expertise are meant to unfold organically through conversation, are often unreliable for predicting job success.[2] In contrast, structured interviews, whereby each candidate is asked the same set of defined questions, standardise the interview process and minimise bias by allowing employers to focus on the factors that have a direct impact on performance. We suggest using an interview scorecard that grades candidates' responses to each question on a predetermined scale.[2]

According to the research, companies should rely on a structured interview that standardises the process among candidates, eliminating much subjectivity. These interviews pose the same set of questions in the same order to all candidates, allowing clearer comparisons.

3. Minimise the variety of biases by scoring stakeholders' replies immediately after they are provided.
We recommend that HTA bodies score stakeholders' replies immediately after they are provided to minimise the variety of biases: For example, we are more likely to remember answers with vivid examples and answers that are most recent. This means that a stakeholder who has input at the same level of quality and relevance as other stakeholders but who masters high-quality storytelling may remain better in the memories of the HTA body's representatives. In HR, evaluators who wait until the end of the interview to rate answers risk forgetting early or less-vivid but high-quality answers or favouring candidates whose speaking style favours storytelling.[3]

Sources: 1) Forbes Human Resources Council (2018) Nine Strategies To Keep Unconscious Bias Out Of Your HR Department, see link / 2) Rebecca Knight (2017) 7 Practical Ways to Reduce Bias in Your Hiring Process, see link / 3) Iris Bohnet (2016) How to Take the Bias Out of Interviews, see link

Third, invite stakeholders with expertise in other disease areas to deliver generic input.

Stakeholders with expertise in other disease areas may be able to provide useful input in several instances.
If an HTA body is concerned about its ability to make an informed and unbiased JCA decision based on inputs from stakeholders and other available sources, we recommend the HTA body supplements its evidence by inviting stakeholders with expertise from other disease areas to deliver generic input to fill knowledge gaps or add perspectives. Stakeholders with expertise in other disease areas are less likely to have any interests in the OMP under assessment and hence less of an incentive to provide biased input.

Table 4 shows three examples of when it can be relevant to invite stakeholders with expertise in other disease areas to deliver generic input.

If more stakeholders deliver input, the weight of an individual stakeholder's potentially biased input is reduced.
An extra benefit of inviting additional stakeholders to provide JCA input is that potential bias from an individual stakeholder will be diluted. However, biases can be expected to be diluted only if the group of stakeholders providing input is sufficiently diverse not to share the particular bias. Hence, it is important to either critically assess the input of stakeholders or ensure sufficient diversification of the stakeholders providing input.

Table 4. Examples of when it can be relevant to invite stakeholders with expertise in other disease areas to deliver generic input

Input to OMP-specific challenges, for example, evaluating clinical trials without randomised controlled trial (RCT) data	HTA bodies can decrease the risk of biased input stemming from OMP-specific challenges such as the evaluation of non-RCT data by inviting stakeholders with expertise in handling non-RCT data in other rare disease areas. OMP tend to lack RCT data when entering into JCA. This poses a number of methodological questions, but as the questions are not necessarily specific to the rare disease or OMP under assessment, stakeholders with expertise in other disease areas may be able to provide valuable input.
Input to tools, for example, quality of life instrument expertise	HTA bodies can decrease the risk of biased input from stakeholders with interests in the JCA outcome by inviting stakeholders with expertise in certain tools used across multiple disease areas, such as quality-of-life instruments. In other words, if the parameters of a quality-of-life instrument are discussed and are pivotal for the JCA outcome, the evidence base could be supplemented by input from a relevant expert with quality-of-life instrument expertise rather than a disease-specific expert.
Input to disease characteristics, for example, attack-based diseases	HTA bodies can decrease the risk of biased input from stakeholders by looking across disease areas with specific similarities. In a JCA of an OMP indicated for an attack-based rare disease, it may be of value to assess the effect of the disease on patients' quality of life between attacks. To deliver input to this assessment, it may be useful to look for stakeholders with expertise in another attack-based disease to investigate whether the parallels are sufficiently strong for results to be extrapolated across disease areas.

Source: Copenhagen Economics

Hard facts. Clear stories.

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