

Rare insights

Examining the social values of
treating rare diseases



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Foreword



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Since the establishment of the National Institute for Health and Care Excellence (NICE) in 1999, the complexity and volume of the treatments it assesses for the NHS has changed dramatically. Advancements in science and technology have catalysed the development of transformative medicines in new therapy areas, including rare diseases, offering hope to under-served patient populations.

Recent data shows a growing pipeline for rare disease treatments, with products in development for rare diseases accounting for 30% of the overall treatment pipeline.¹

Ensuring that its ways of working keep pace with the evolving nature of healthcare is a central tenet on which NICE operates, and one that will be increasingly important as more of these treatments reach market. However, as explained in this report, it is equally important that NICE's methods and processes keep pace with the evolving aspirations, ethical principles and preferences of society.

The findings of this research indicate the need for a fresh assessment of social values associated with treating rare diseases that underpin the decision-making processes informing the NHS funding of treatments for rare diseases.

NICE has recently published its proposed approach for future updates to its methods for health technology evaluations, through 'modular updates'.² The BIA warmly welcomes the role that stakeholder engagement, including with industry and patients, will play through this approach and is encouraged to see that the NICE Listens programme will be a key vehicle for informing updates.

As NICE assesses and prioritises the topics for future modular updates, we hope that this research will be useful in demonstrating the need for further research into the social values associated with treating rare diseases, and the need for rarity to be prioritised as a modular update topic to address this. The BIA looks forward to continuing to engage with NICE and other relevant stakeholders as it implements this new approach.



Executive Summary



Between 2019 and 2022, NICE conducted a large-scale review of the methods and processes it uses to carry out assessments of a treatment's cost-effectiveness. During the review, the BIA argued that NICE should consider adopting specific measures to its methods to support improved patient access to innovative treatments for rare diseases. One such approach could have been the introduction of a modifier for rare diseases, however, NICE concluded that there was “no evidence that society values more highly health benefits in rare diseases” and that the information presented during the consultation did not provide sufficient evidence to support adding a modifier for rare diseases.³

Following the conclusion of the review, the BIA decided to conduct primary research to support NICE's requirement for more robust evidence on the social value associated with treating rare diseases. The aim of the research was to understand public opinion on how treatments for rare diseases should be funded and evaluated. The research was carried out using an established method of qualitative research to determine social value. Subsequent quantitative research was also used to test the findings among a broader sample size.

The research findings, set out in this report, demonstrate that the public believes that a distinctive and alternative approach should be adopted for making funding decisions about treatments for rare diseases, including the methods and processes in place to make these decisions. The findings also indicate a need for further research to determine the social value associated with rare diseases and how this should underpin its decision-making processes.

Recommendations

Based on the findings of this research, the BIA recommends the following actions:

- NICE should utilise its NICE Listens programme to undertake primary research on the social value associated with treating rare diseases
- NICE should undertake, as a priority, a modular update review with a specific focus on rarity
- As part of a modular update, NICE should reconsider the case for a rarity modifier, or consider a sliding scale of incremental cost-effectiveness ratio (ICER) thresholds within its single technology appraisal (STA) process
- NHS England, the Department of Health and Social Care, and HM Treasury should commit to working with NICE to support the implementation of any changes to its methods and processes that are necessary to reflect contemporary social value judgements on rare diseases.



Introduction and background



The National Institute for Health and Care Excellence (NICE) is responsible for developing guidance for the NHS and the wider public health community. As set out in its charter, part of this role includes deciding which treatments should be funded by the NHS and hereby made available to NHS patients. By the nature of its remit, decisions made by NICE have direct implications for the allocation and prioritisation of taxpayer resources for the provision of NHS care.

While NICE bases its guidance on the best available evidence, this evidence is rarely complete or of perfect quality, leaving a degree of uncertainty. NICE is therefore required to make judgements about priority setting and the fair and equitable distribution of scarce resources in the development of its guidance. In the absence of scientific evidence, NICE makes these judgements by taking into account the aspirations, ethical principles and preferences of society. Judgements informed by these aspects are referred to as social value judgements. This approach contributes to the clarity and transparency of decision making and is an important way in which NICE fulfils the NHS Constitution requirement to be accountable to the public.

To support the accurate and consistent application of social value judgments in producing guidance, in 2005 NICE developed a set of guidelines, known as the Social Value Judgement (SVJ) document⁴ (superseded in 2008⁵) that described the social value judgements that should be incorporated into the processes NICE uses to develop guidance and be applied when preparing individual items of guidance.

The approach used by NICE to determine the social value judgements which it should apply is called deliberative public engagement. This is a process that involves engaging with members of the public to debate and discuss moral and ethical issues from a societal perspective to determine their values, principles and preferences. The NICE SVJ document was informed by the findings of extensive deliberative public engagement undertaken on a range of issues prior to its publication.

The SVJ document has since been replaced by a set of principles that reflect NICE's broader remit.⁶ While these principles explain the morals, ethics and principles that underpin its recommendations, as they are universal to all NICE guidance and standards, they are necessarily broad in nature. As a result, the SVJ document continues to set out NICE's most recent determination of those social value judgements that have implications for priority setting and resource allocation.

As the health and social care landscape changes, so too do society's ethical principles and preferences. For NICE guidance to remain defensible and acceptable by the public, it is important that deliberative public engagement continues to play a central role in determining the social value judgements that should underpin NICE's decision making processes.

Rarity and NICE's methods and processes

Between 2019 and 2022, NICE undertook a large-scale review of the methods and processes it uses to carry out health technology assessments (HTAs), which resulted in some important changes. Despite the significant opportunity the review presented to modernise NICE methods and processes, the BIA believes that insufficient consideration was given to whether NICE methods and processes continue to be underpinned by judgements that are reflective of present-day social value associated with many issues.

One issue that the BIA believes was insufficiently explored during the review is rarity. Like all other new treatments, treatments for rare, and very rare, diseases must undergo a NICE HTA. Since 2013, NICE has had a process in place for the evaluation of treatments for very rare diseases. However, treatments for rare diseases often end up being evaluated by a process that was designed for evaluating medicines for more common diseases with larger eligible populations. Rare disease treatments are disadvantaged in this process, receiving worse outcomes with respect to positive recommendations than treatments assessed by the process designed for very rare diseases.⁷ The reasons why it has been deemed inappropriate for rare disease treatments to be assessed through this process have been explored in detail elsewhere previously, including by Genetic Alliance UK⁸, the Association of British Pharmaceutical Industry⁹ (ABPI), and in the BIA report *A rare chance for reform*¹⁰. Though adaptations to this process were made following the review to better accommodate rare disease treatments, the extent to which they will resolve the challenges remains to be seen.

The barrier to change

Rare disease treatments continue to be evaluated by a process designed for more common diseases, despite the well-documented challenges of this approach.

NICE's SVJ document provides one explanation for how NICE processes should contend with treatments for rare diseases. The document states that '*NICE considers that it should evaluate drugs to treat rare conditions, known as 'orphan drugs', in the same way as any other treatment*'.⁴ In this context, it appears that overall NICE's approach to evaluating rare disease treatments continues to be informed by social value judgements determined by the deliberative public engagement that took place prior to 2005.

According to NICE, one aspect that the review considered was the way to ensure that HTA methods are suitable for rare diseases.¹¹ During the review, however, NICE concluded that there was 'no evidence that society values more highly health benefits in rare diseases.'³ Subsequently, NICE discounted the need to introduce any targeted measures to support rare disease treatments, including a rarity modifier, although it did introduce a modifier for more severe conditions and recognised the need for more work to address the health inequalities often faced by people living with rarer conditions.

As part of the review consultation process, the BIA submitted the results of a YouGov survey it had commissioned, indicating that there is public support for the adoption of targeted measures to support improved access for people with rare diseases.¹² The BIA recommended that NICE carried out further research to clearly establish the societal value of health benefits in rare diseases and the overlap between severity and rarity and reconsider the case for the introduction of a rarity modifier. However, NICE determined that ‘the information provided in the consultation responses did not provide usable or robust evidence of societal preferences for placing additional value on health benefits in rare diseases’.³ NICE has also recognised that issues surrounding health outcomes associated with rare diseases were ‘beyond the scope’ of the review, and that the question of rarity ‘remains complex and challenging’.³

Modular updates

At the end of the review, NICE announced that it would be moving to a more flexible, ‘modular’ approach towards updating and revising its methods and processes. By adopting a topic-focused approach to reviewing and updating its processes, modular updates will enable NICE to comprehensively review and adapt without the need for further full-scale reviews. This approach will be particularly important for exploring NICE’s approach to a range of challenging issues, including rarity, and providing the opportunity for NICE to ensure that the social value judgements informing and underpinning its work remain accurate.

It is in this context that the BIA set out to undertake further research to support NICE’s requirement for more robust evidence of the social value associated with rare diseases and the health benefits provided by rare disease treatments. In generating this evidence, the BIA hopes to demonstrate the need for prioritising rarity as a future topic for modular updates and a reassessment of social value judgements associated with rarity that should be used by NICE. This report also seeks to secure system-wide support for NICE to implement the changes it deems necessary.



Exploring social value



In 2022, the BIA commissioned Synergy Healthcare Research to undertake primary research to explore the social value associated with rare diseases. In designing the overall approach and methodology, the research was informed by the deliberative public engagement approaches that have been used by NICE to understand public opinion social value issues, including the former NICE Citizens Council approach and the current NICE Listens approach.

NICE Citizens Council

The NICE Citizens Council was a formal committee created for the purpose of deliberative public engagement. The Council was comprised of 30 members of the public and reflected the age, sex, socioeconomic status and ethnicity of the population of England and Wales. It operated through ‘citizen’s jury’ meetings and was responsible for considering a range of issues about which NICE sought advice. The Council’s reports were used to justify NICE’s approach to challenging issues and informed NICE’s SVJ document and its subsequent Principles. The Council has been dormant since 2015.

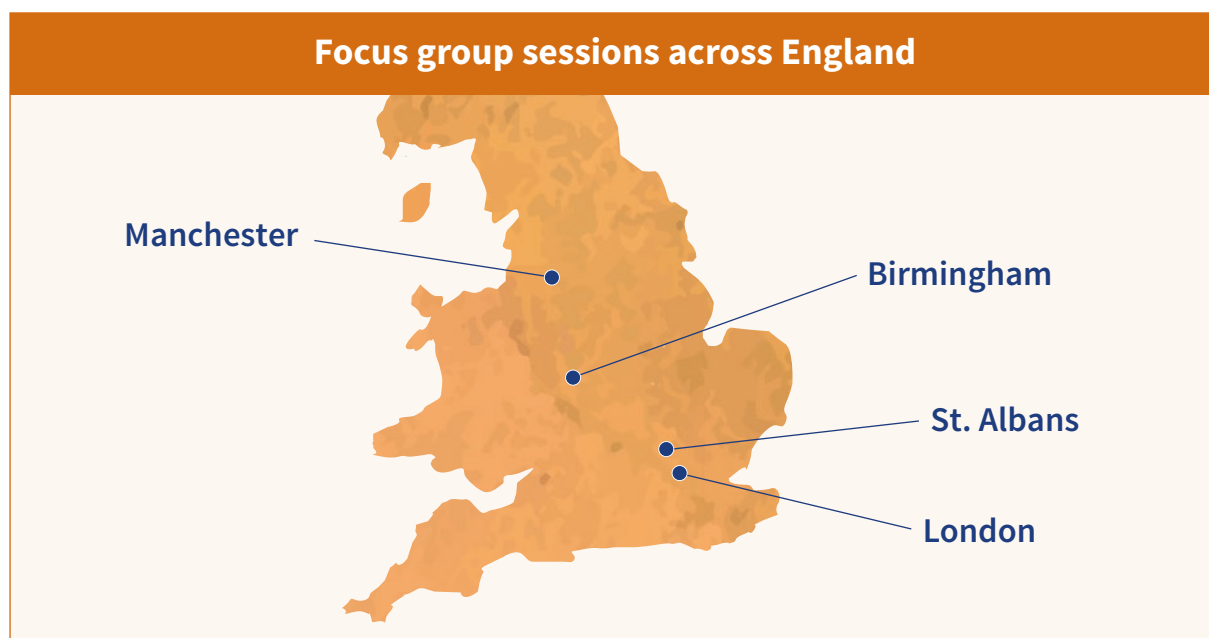
NICE Listens Programme

NICE Listens is a new programme for deliberative public engagement, used to provide an understanding of public opinion on challenging moral, ethical and social value issues. NICE Listens operates through workshops with members of the public and replaces the Citizens Council as the model of deliberative public engagement used by NICE. Like the Council, NICE Listens aims to help ensure its policies on complex and controversial issues reflect the values of members of the public.¹³

Focus groups

Drawing on the methodology of both approaches, focus groups were carried out to explore the social value associated with treating rare diseases. Like the ‘citizen’s jury’ model of the NICE Citizens Council, focus groups are a form of deliberative public engagement, involving discussion and debate among a socially representative group of people on a particular issue. With the use of informative materials to support a better understanding of the topic at hand, participants are given the opportunity to reflect on the information they are given before developing their own informed views through deliberation. Focus groups are a particularly useful tool for understanding the public’s views on complex issues, such as rare diseases, which require a minimum level of background information for people to be able to understand and meaningfully engage with.

Between 26 July and 15 August 2022, four sessions were conducted across England among a group of socially representative members of the public. During the focus group sessions, participants were presented with a range of informative materials to help them become familiar with the topic of rare diseases. The material included information drawn from a range of sources, including the 2004 NICE Citizens Council report on ultra-orphan drugs,¹⁴ NICE guidance,¹⁵ Genetic Alliance UK¹⁶ and the House of Commons Library.¹⁷



Participants were given the opportunity to ask questions about the information they were given, and their level of understanding was checked by the facilitator. Participants were then encouraged to share their views and discuss their reasoning with the group. Throughout the focus group sessions, a number of anonymous voting exercises were conducted, the results of which are explored later in this report. The full range of materials is set out in the methodology.

Online Survey

To ensure that the research was sufficiently robust, a quantitative stage, in the form of an online survey, was also built into the research design. Quantitative research methods, like surveys, have specific drawbacks when used to explore public opinion on complex issues of social value, as NICE itself has recognised.⁴ Not only are survey results very sensitive to the way in which questions are framed, but participants are not provided with the same benefit of deliberating the underlying issues first, as they are in a focus group, and may therefore have a less comprehensive understanding of the issue at hand. Acknowledging these drawbacks, the purpose of incorporating an online survey was to test whether the insights from the qualitative stage of the research were broadly replicated across a larger representative sample of the UK population.

Between October and November 2022, an online survey was conducted of 1,000 representative adults across the UK. To ensure that a consistent approach was taken in both stages of the research, the survey questionnaire was designed to incorporate, as far as possible, the information that was provided to participants during the focus groups. By including specific questions to ensure that participants were considering the information presented to them, it was possible to mitigate some of the drawbacks of quantitative approaches. Further detail on the online survey can be found in the methodology.

Defining rarity

During both stages of the research, participants were informed about the distinction between rare and very rare diseases. Clarifying the distinction between the two was an important step in ascertaining public opinions on the differences in how they are evaluated and funded.

A rare disease has been defined as a disease that occurs in fewer than 1 in 2,000 people, affecting between 1,100 – 25,000 people in England. This is the definition set out in the UK Rare Diseases Framework.¹⁸

A very rare disease has been defined as a disease that occurs in fewer than 1 in 50,000 people, affecting fewer than 1,100 people in England. This is consistent with the definition used by NICE for a very rare disease, as set out in routing criteria 1 for the Highly Specialised Technology Programme.¹⁹

A common disease has been defined as a disease that would not meet the criteria for being a rare disease. This includes any disease that affects more than 25,000 people in England.



Key findings



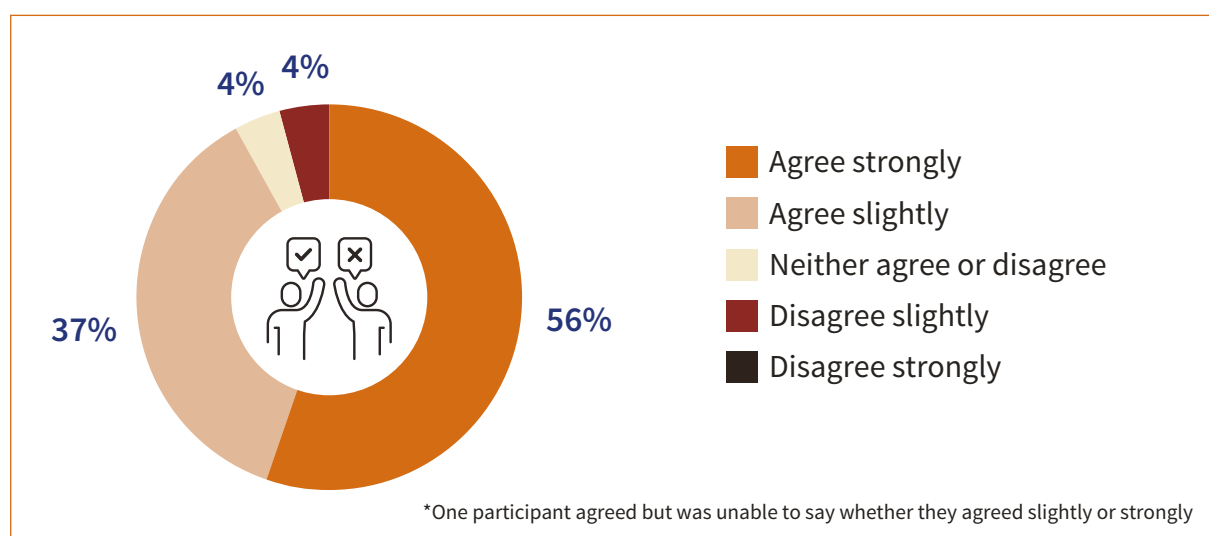
Providing equitable access to treatments

Our research found broad support among the general public for providing equitable access to treatments for people with rare diseases, even if it results in additional costs for the NHS. When participants were asked whether they agreed or disagreed that “people with rare diseases should have equitable access to treatments, even if this means additional costs for the NHS”, 93% of focus group participants and 80% of survey participants said that they agreed.

In the focus groups, a number of participants expanded on why they felt it was important for the NHS to be willing to pay more for treatments for rare diseases in order to provide equitable access to treatments. Many participants felt it would be unfair for people with rare diseases not to have equitable access to treatments, and that equitable access was a central tenet of the NHS. While a minority of participants expressed some concern regarding the additional costs leading to cuts being made elsewhere in the NHS, given limited budgets, 89% of focus group participants felt that if a treatment could demonstrate its ability to change patients’ lives significantly for the better, the NHS should pay more for patients with rare diseases than for patients with common diseases.

Fig 1: To what extent do you agree or disagree with the following statement:

People with rare diseases (affecting 1,100-25,000 people in England) should have equitable access to treatments, even if this means additional costs for the NHS



Rewarding the development of rare disease treatments

Participants also discussed the challenges often associated with developing treatments for rare and very-rare diseases, including a lack of pre-existing knowledge about the causes of the disease, and small patient populations resulting in a high level of uncertainty in clinical trial data. It was generally agreed that there was a need to encourage investment in developing treatments for rarer diseases due to the lack of existing treatments and the commercial environment potentially making it more attractive for drug companies to invest in treatments for common diseases than rare diseases.

Participants agreed that the additional challenges of drug development for rare diseases may result in higher development costs and therefore more expensive treatment. Most felt it was unfair that the additional development costs could result in barriers to access to treatments for rare diseases.

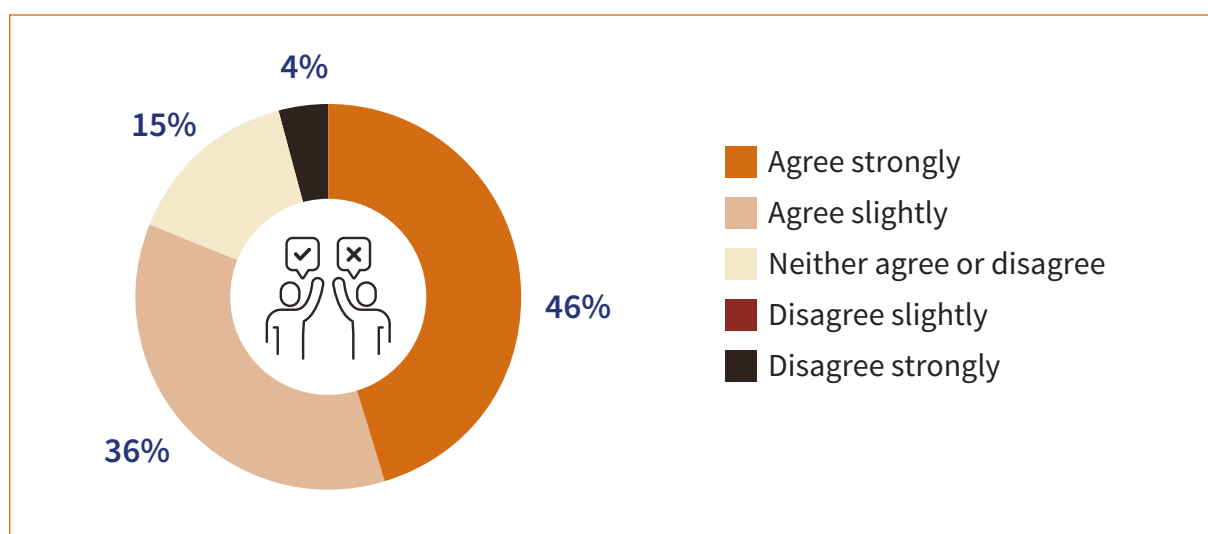
In the focus group, 82% of participants felt that NICE should evaluate the cost effectiveness of treatments for rare diseases differently than for more common diseases, taking into account the additional challenges in developing medicines for rare diseases.

There's less existing knowledge, and it's more difficult, and therefore more expensive, to do clinical trials [for rare diseases]. So it's not fair, it's not equitable... to keep the funding model exactly the same [as for common diseases]. And, if it has been the same up to now, you can see why 95% of these [rare diseases] have no treatment.

Female, 57, Ealing London

Fig 2: To what extent do you agree or disagree with the following statement:

NICE should evaluate the cost effectiveness of treatments for rare diseases (affecting 1,100-25,000 people in England) differently than for more common diseases, taking into account the additional challenges in developing medicines for rare diseases



NICE approach to very-rare diseases

In contrast to medicines for rare diseases, NICE evaluates those for very rare diseases via the Highly Specialised Technologies (HST) programme. Participants were presented with information about this different approach. It was highlighted that the HST programme uses a cost-effectiveness threshold of £100,000-£300,000 per quality-adjusted life year (QALY), compared to the £20,000-£30,000 per QALY threshold used in NICE's Standard Technology Appraisal process, and the rationale for this was explained.

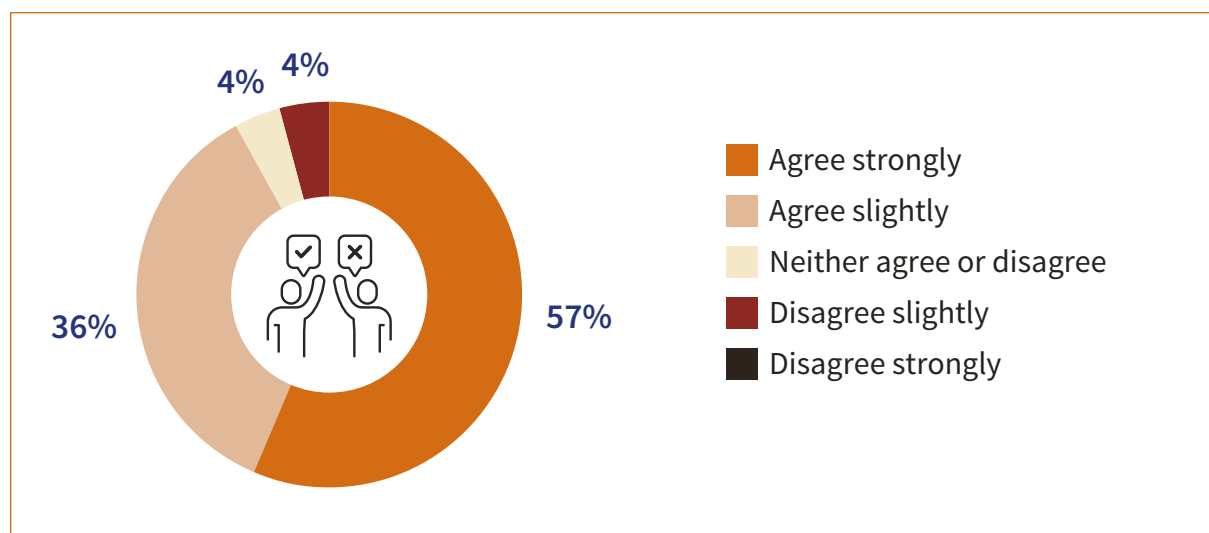
Our research found that members of the public agreed that NICE should have a higher cost-effectiveness threshold for evaluating medicines for very rare diseases, with 93% agreement in the qualitative research and 70% agreement in the survey.

I think that without the increased threshold, there wouldn't be the incentive to the drug companies to develop medications for very rare diseases.

Female, 41, Birmingham

Fig 3: To what extent do you agree or disagree with:

NICE's decision to evaluate new treatments for very rare diseases using a different process, with a higher cost-effectiveness threshold, compared to the evaluation of new treatments for more common diseases



NICE approach to rare diseases

Having discussed NICE's approach to evaluating treatments for very-rare diseases, focus group participants discussed the approach that NICE takes towards evaluating medicines for rare diseases. They felt that the recognition of the need for a higher cost-effectiveness threshold for evaluating medicines for very rare diseases demonstrated that medicines for rare diseases shouldn't be evaluated using the same threshold as that used for medicines for common diseases.

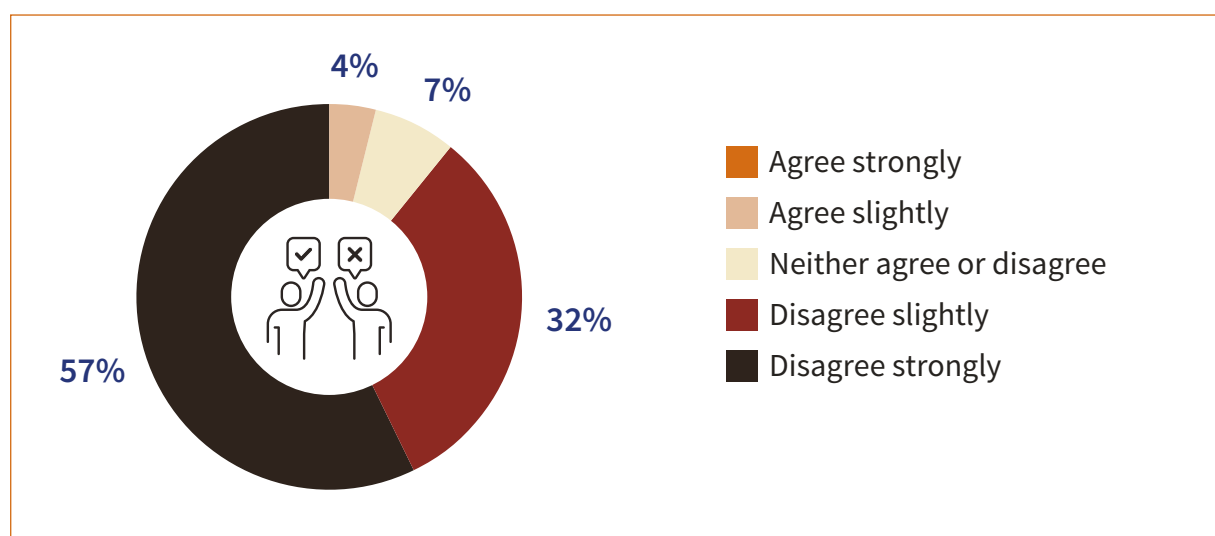
89% of the focus group participants *disagreed* that treatments for rare diseases should be evaluated at a cost-effectiveness threshold of £20,000-£30,000 per QALY, given the recognition that treatments for very rare diseases should be evaluated at a cost-effectiveness threshold of £100,000 - £300,000 per QALY. Participants felt that the approach to evaluating very rare disease treatments should be adapted and applied to the evaluation of rare disease treatments.

...given that these things (cost- effectiveness criteria) have been developed to treat very rare diseases equitably, then why not do the same for rare diseases... Well, not exactly the same extent, but why not flex the rules?

Female, 57, Ealing London

Fig 4: To what extent do you agree or disagree with the following statement:

Given the recognition by NICE that treatments for very rare diseases should be evaluated at a cost effectiveness threshold of £100,000 - £300,000 per QALY, to what extent do you agree or disagree that treatments for rare diseases should be evaluated at a cost-effectiveness threshold of £20- £30,000 per QALY, as for more common diseases



An alternative approach for rare diseases

After discussing NICE's approach to treatments for rare and very rare diseases, participants in the focus groups were shown a number of arguments both for and against reviewing NICE's approach to evaluating treatments for rare diseases. After discussing these arguments, participants were asked to complete a number of voting exercises to capture their opinion on how funding decisions *should* be made about treatments for rare diseases.

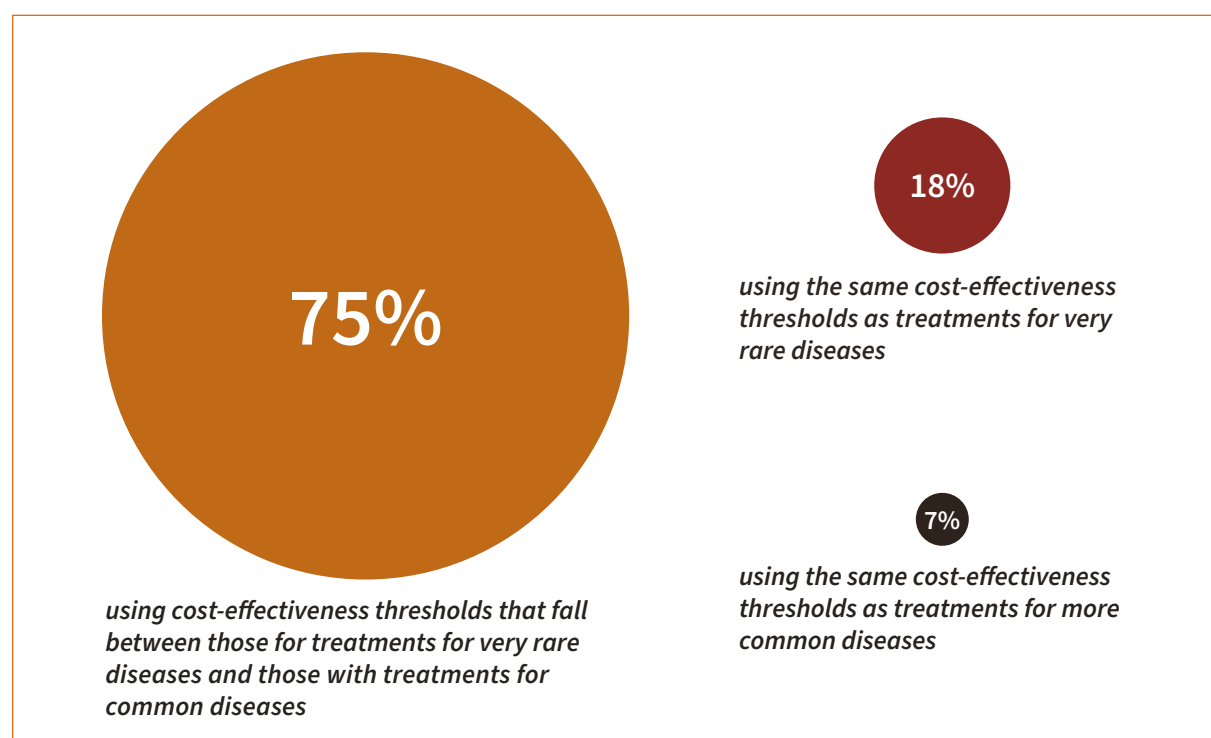
It was found that the majority (75%) of participants felt that the NHS should make funding decisions for medicines to treat patients with rare diseases using cost-effectiveness thresholds that fall between those for treatments for very rare diseases and those for treatments for more common diseases. Most participants felt that the additional challenges and associated costs for developing treatments for rare diseases fall somewhere between those for common diseases and very rare diseases, and therefore suggested the cost-effectiveness threshold for rare diseases should reflect this. In the survey, we also found that a majority of participants (56%) felt that cost-effectiveness thresholds used to evaluate treatments for rare diseases should fall between those used for treatments for very rare diseases and treatments for common diseases.

I think there's a moral question about what do we want to be as a society, so do we protect individuals, accepting that for a tiny number of those, that's going to be a very significant financial burden. But, actually, the benefit to us as a society is worth it.

Male, 56, Manchester

Fig 5: Which one of the following statements do you most agree with:

The NHS should make funding decisions for medicines to treat patients with rare diseases...

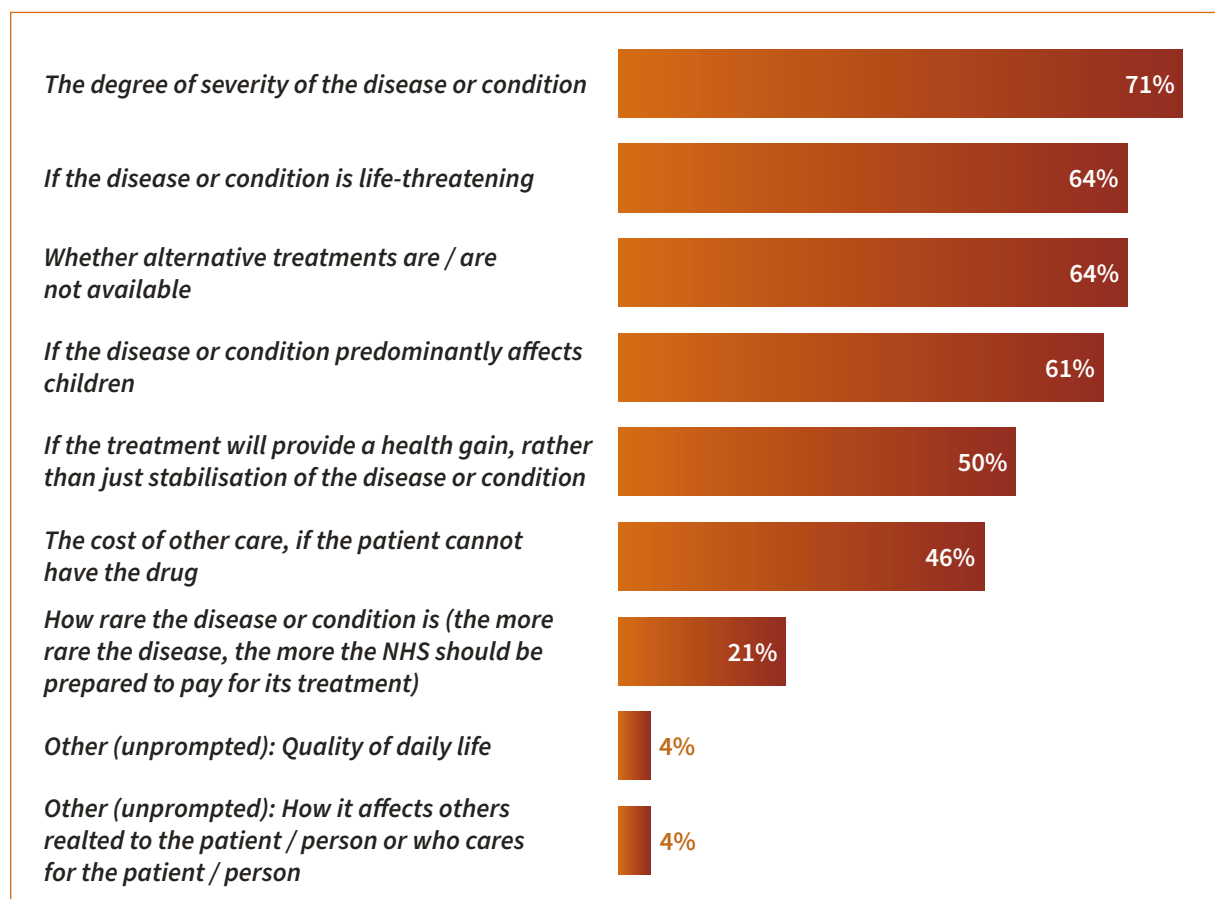


Other factors to consider

Participants in the focus groups then discussed whether additional factors should be taken into account when deciding how much the NHS should be willing to pay for drugs to treat patients with rare diseases. The majority (82%) of focus group participants agreed that additional factors should be taken into account, and these participants were then asked about which additional factors should be considered. The severity of the disease was considered an important factor by 71% of the focus group participants, who felt that the NHS should be willing to pay more for treatments for rare diseases that have a severe impact on people's lives. However, some participants felt that the current system of calculating cost effectiveness through cost per QALY should automatically prioritise treatments that were likely to be beneficial for more severe diseases. Other factors which a majority of participants said it was important to consider were if the disease is life-threatening (64%), whether alternative treatments are available (64%) and if the disease predominantly affects children (61%).

A minority of participants (17%) felt that NHS should be willing to pay more for the treatment of patients with rare diseases without considering additional factors. These people were concerned about additional criteria complicating the decision-making process and potentially creating barriers to the use of new treatment options that might offer benefits to people with rare diseases.

Fig 6: If you believe that the NHS should take additional factors into account when deciding how much it is willing to pay for treatments for rare diseases, please tick below which additional factors you feel should be considered in deciding whether to pay more for a treatment for a rare disease:





Conclusion



The findings of our research demonstrate that there is strong public support for ensuring that people living with rare diseases can access treatments on an equitable basis compared to other patients. Through deliberation, participants demonstrated an understanding of the limited NHS budget and the impact that assigning additional costs could have elsewhere in the system. The results indicate that the public would be willing for the NHS to spend more money to achieve equitable access for people with rare diseases.

The research findings also suggest that the social value judgment set out in NICE's SVJ document – that rare disease treatments should be evaluated in the same way as any other treatment – is not an accurate reflection of contemporary social values associated with rarity. On the contrary, participants in our research felt strongly that treatments for rare diseases should be evaluated differently than for more common diseases to account for the additional challenges in developing drugs for rare diseases. This position was further demonstrated through participants' disagreement that rare disease treatments should be evaluated at the same cost-effectiveness threshold as treatments for more common diseases.

When it came to how members of the public feel that funding decisions about rare disease treatments *should* be made, our research found that people think a different approach is required. In particular participants felt that the NHS should adopt a cost-effectiveness threshold for rare disease treatments that falls in between that used for very rare disease treatments and that used for treatments for more common diseases. The rationale driving this view was the recognition among participants that while the additional challenges and associated costs of developing treatments for rare diseases are not as acute as they are for very rare disease treatments, they are relatively greater than those involved in the development of treatments for common diseases.

This research also found that there is a range of factors that are often associated with rare diseases which the public deems to be important in deciding how much the NHS should be willing to pay for rare disease treatments. Factors that a majority of respondents felt to be important included the severity of the disease, whether the disease is life-threatening, whether alternative treatments are available, and whether the disease predominantly affects children. These findings indicate that the public view on how decisions are made about the funding of rare disease treatments is informed by a combination of individual and interrelated decision-making factors. It also suggests that no single decision-making factor can be used to accurately reflect social value associated with treating rare diseases, and that further research is required to understand the role that various decision-making factors play in creating social value.

Overall, this research sheds new light on the question of whether society values health benefits for rare diseases more highly and signals the need for further research to determine the contemporary social value judgements associated with rarity that should underpin NICE's evaluations. The findings indicate that there is a strong case for NICE to review as a priority, whether the methods and processes it has in place for making recommendations about the use of rare disease treatments in the NHS are reflective of these social value judgements, and the measures it can take to address this if not.



Recommendations



Based on the findings of this research, the BIA recommends:

- **NICE should utilise its NICE Listens programme to undertake primary research on the social value associated with treating rare diseases.**

As its primary tool for facilitating deliberative public engagement, the BIA recommends that NICE carries out a NICE Listens topic on rare diseases to inform the social value judgements associated with rarity that should underpin NICE decision-making processes

- **NICE should undertake, as a priority, a modular update review with a specific focus on rarity.**

Using the findings from a NICE Listens topic on rarity, NICE should undertake a review of the methods and processes in place for evaluating the cost-effectiveness of treatments for rare diseases to ensure that they are reflective of contemporary social value judgements associated with rarity

- **As part of a modular update, NICE should reconsider the case for a rarity modifier, or consider a sliding scale of incremental cost-effectiveness ratio (ICER) thresholds.**

These approaches would enable cost-effectiveness threshold for rare disease treatments that fall in between that used for very rare disease treatments and that used for treatments for more common diseases

- **NHS England, the Department of Health and Social Care, and HM Treasury should commit to working with NICE to support the implementation of any changes to its methods and processes that are necessary to reflect contemporary social value judgements on rare diseases.**

These stakeholders have responsibility for different parts of the system which determines the evaluation and funding of treatments in the NHS, and collaboration between these stakeholders is necessary to deliver system level change.



Methodology



Overview

The research was conducted by an independent market research agency, Synergy Healthcare Research, in accordance with the codes of conduct of the Market Research Society (MRS) and British Healthcare Business Intelligence Association (BHBIA) and in compliance with Data Protection legislation.

The research took place between July and November 2022 in two stages. The first stage of the research was qualitative in nature and consisted of focus groups. The second stage of the research was quantitative and consisted of an online survey. This section details the methodology that was employed during both stages of the research.

Focus groups

Between 26 July and 15 August 2022, four focus group sessions were conducted across England in London, Manchester, St Albans and Birmingham. A total of 30 members of the public were recruited to take part but 2 participants did not show up to their focus group session. As a result, a total of 28 members of the public participated in the focus groups, with 6-8 people in each session. Each session lasted up to three hours.

During the recruitment process, a screener was put in place to ensure that the sample would be representative of the UK population with regard to sex, age, ethnicity and socio-economic background. Individuals who have a rare disease, or have a family member with a rare disease, were excluded during the recruitment process to ensure the focus group discussion was not unfairly influenced by their views and experiences.

Each focus group session was facilitated by a member of the Synergy Healthcare Research team. The following discussion guide was used during all four focus group sessions.

Discussion guide

Thank you for taking part in this market research to explore views among members of the general public on how decisions are made regarding whether or not the NHS should pay for new treatments. Our discussion is going to focus specifically on your attitudes to the funding of new treatments for **rare diseases which affect fewer than 25,000 people in the England.**

Outputs of the research will be fed back to the NHS to help it understand what is important to members of the public when deciding how new treatments for rare diseases should be funded. During the session we will explain to you how decisions are currently made about funding, and then get your feedback on whether or not you feel this is how funding decisions for new treatments for rare diseases should be made.

The group discussion will last 3 hours and we have scheduled in some breaks for refreshments, but please do let us know if anyone needs to take an additional break at any point.

My name is ; I work for Synergy Healthcare Research, an independent market research agency specialising in researching attitudes to health-related issues for a wide range of different organisations. In the past we have carried our market research in collaboration with Myeloma UK, Psoriasis UK, The Royal College of Surgeons and a wide range of other organisations who want to understand people's views on a particular topic.

This project is being funded by an organisation which works in partnership with a number of patient charities, in order to understand the views of the general public on the funding of new treatment options for rare diseases. In order to avoid any risk of influencing responses, we will reveal the identity of the sponsoring organisation at the end of the group discussion.

All the research we do is carried out in accordance with the codes of conduct of the Market Research Society (MRS) and British Healthcare Business Intelligence Association (BHBIA) and complying with Data Protection legislation. This means we are not allowed to reveal the identity of research participants to anyone else, including the company sponsoring the research, and we are not allowed to seek to influence your views. You do not have to answer any questions you don't want to and you can withdraw from the research at any time. For more information about your rights, please see our privacy policy at www.synergyresearch.co.uk/privacy-policy

The discussion will be audio recorded for analysis purposes and the results from four group discussions being conducted across England will be collated and summarised in written feedback to the sponsoring organisation. The identity of participants will not be divulged, but we will with your permission include an appendix in the research outputs which lists the age, gender and occupation of research participants so that the research can be seen to have been carried out among a representative sample, but we will ensure nothing is included that you identify participants.

We need your consent in order for us to collect and use any information about you. Any personal data collected will be treated confidentially and only used for the purposes of market research. It will not be passed to any other organisation without your permission. Personal data relating to market research will be kept for up to 12 months following the end of this market research project, with one exception.

- The consent form you signed containing your name, the date, and the amount you received as an incentive will be kept indefinitely for accounting and audit purposes

These will have no impact on the confidentiality and anonymity associated with the interview itself. At any time you can ask to know what personal data are being held and for these to be amended or destroyed.

Are we all happy to proceed on this basis? **Respondents to sign written agreement confirming the above (appended)**

1. Introduction / warm up (10 mins)

Thank you again for coming. Before I ask everyone to introduce themselves I thought I'd outline in a little more detail what we are going to be discussing today.

SHOW AGENDA CHART:

- Introductions (10 minutes)
- NHS funding of new treatments for common diseases – discussion (10-15 minutes)
- What are rare diseases? NHS funding of new treatments for very rare diseases affecting fewer than 1,100 people in England – discussion and voting (20-30 minutes)
- Break (10 minutes)
- NHS funding of new treatments for rare diseases affecting 1,100- 25,000 people in England – discussion and voting (up to 2 hours, including a further break)

Our main focus will be exploring your views on funding new treatments for rare diseases. In order to provide a context for this discussion, we're going to start off by telling you about the way in which decisions are made for NHS funding of treatments for more common diseases and explore your reactions to this

We're then going to tell you about NHS funding of new treatments for what are called **very** rare diseases, which are those affecting fewer than 1,100 people in England and discuss your views on this.

We'll then move onto the main focus of this research, which is to explore your views on NHS funding of new treatments for rare diseases affecting 1,100- 25,000 people in England and whether these should be funded in the same way as new treatments for common diseases, the same way as new treatments for very rare diseases, or some different approach.

One of the main things I want to emphasise is that we want to get everyone's options on the main topic. It's ok to have different perspectives but we want everyone to feel they can share their views. There are no right or wrong answers to the questions we will be discussing as long as you share your genuine views on the topics we discuss. The key thing to bear in mind is that the feedback you provide will be fed back to people responsible for how new treatments are funded to inform their understanding of what the general public feels about this

Is that OK?

MODERATOR TO INVITE AND ANSWER ANY QUESTIONS TO ENSURE RESPONDENTS FEEL COMFORTABLE WITH THE PROCESS

So I'd like now to ask people to introduce themselves to the group in turn, with their name and in a couple of sentences a little bit about themselves - such as what you do for a living and what you enjoy doing in your spare time.

Moderator go first and then encourage participants to introduce themselves; write names

2. Introduction to developing new treatments for diseases (10-15 mins)

I'd like to start off by introducing you to some general information about the development of new drugs, many of which are developed for conditions which affect hundreds of thousands or millions of people in the UK.

MODERATOR TO SHOW / READ OUT SLIDE 2: Introduction – developing new treatments

Are there any questions on this chart?

MODERATOR SHOW/ READ OUT SLIDE 3: NHS funding of new treatments for common diseases

This chart describes how the NHS decides whether or not to fund new treatments for common diseases

Moderator to read through chart and check that all participants understand the concept of a QALY / cost per QALY and the threshold of £20,000 to £30,000 per QALY for reimbursing most new medicines for use in the NHS; encourage discussion and if necessary use back-up slides 25 and 26 to help participants assimilate this information

MODERATOR TO SHOW SLIDE 4 - What are your reactions to the current way in which NICE evaluates the cost effectiveness of new medicines for common diseases?

What are your reactions to the current way in which NICE evaluates the cost effectiveness of new medicines for common diseases? **Encourage all participants to comment on their views; emphasise if necessary that the remit of this research is not to suggest any changes to this approach to NICE and that this information is just being shown to provide a context for the later discussion**

3. Rare diseases (10 mins)

I would now like provide you with some information about rare diseases and impact of these on people's quality of life, before going on to provide you with some specific examples of these and describing how the NHS makes decisions on funding new treatments for rare diseases.

SHOW / READ OUT SLIDE 5 – Rare diseases

I'll show you some examples of rare disease shortly, but is this information clear?

SHOW /READ OUT SLIDE 6 – People with rare diseases face additional challenges

Genetic Alliance UK is an alliance of over 200 member organisations supporting people with genetic, rare and undiagnosed conditions in the UK (including the Brittle Bone Society, Haemophilia Society, British Heart Foundation, Childhood Tumour Trust, Cystic Fibrosis Trust, Muscular Dystrophy UK, Sarcoidosis UK, Sickle Cell Society, Thalidomide Society) and they have written a report that describes the challenges faced by people with rare disease.

Looking at the information here, to what extent would you agree or disagree that people with rare diseases face additional challenges to those with more common diseases? **Invite discussion around the challenges which are agreed to be most important; if necessary to help focus attention, invite respondents to underline the things that they feel are most important**

SHOW /READ OUT SLIDE 7 – Additional challenges in developing treatments for rare diseases

This chart summarises some potential additional challenges in the development of new treatments for rare diseases. What are your reactions to each of these points? **Generate discussion to identify level of agreement or otherwise with each suggested challenge**

SHOW /READ OUT SLIDE 8 – Rare diseases and quality of life

EQ5D is a scale that is used by NICE to assess the beneficial impact of treatments; you can see on the right side of this chart the things it covers. What are your reactions to the suggestion that this scale might not capture all the ways in which a rare disease might impact on people's quality of life? What do you feel it misses out?

4. NICE evaluation of new treatments for very rare diseases (20mins)

We've talked about the issues affecting people with rare diseases and affecting the development of treatments for these diseases. I now would like to share with you information about how NICE evaluates treatments for very rare diseases based on the issues we've discussed.

NICE has developed a different approach for evaluating whether or not the NHS should pay for new treatments for very rare diseases which affect fewer than 1,100 people in England. Treatments for diseases that affect more than 1,100 people are evaluated in the same way as the common disease that affect hundreds of thousands of people

SHOW /READ OUT SLIDE 9 – NICE evaluation of new treatments for very rare diseases

Moderator check participant understanding of distinction between rare and very rare diseases - write on flipchart:

- ***very rare diseases = fewer than 1,100 people in England***
- ***rare diseases = 1,100 - 25,000 people in England***
- ***more common diseases = more than 25,000 people in England***

SHOW /READ OUT SLIDE 10 – NICE evaluation of new treatments for very rare diseases

What are your reactions to the decision by NICE to accept a higher price for new treatments for very rare diseases which affect fewer than 1,100 people in England?

Generate discussion to allow both positive and negative reactions to this decision to be raised; write up reasons for positive reactions to this on one flipchart , and reasons for negative reactions to this decision on another flipchart for subsequent reference

After issues have been discussed, move on to explain voting exercise:

SHOW CHART 11: To what extent do you agree or disagree with NICE's decision to evaluate new treatments for very rare diseases using a different process, with a higher cost-effectiveness threshold, compared to the evaluation of new treatments for more common diseases

I would now like to conduct an individual voting exercise on whether people agree or disagree with the decision by NICE to accept a higher price for new treatments for very rare diseases which affect fewer than 1,100 people in England. I don't want anyone to feel under pressure to answer this in a certain way, so I'll ask people to do this individually and then fold up their voting forms before handing them in.

Before I do this, please can I check if everyone feels able to vote on this topic, or if there is anything else anyone would want to know or flag up before deciding how to vote? **CHECK UNDERSTANDING OF EXERCISE BEFORE HANDING OUT VOTING FORMS I**

HAND OUT VOTING FORMS BASED ON CHART 11 OF STIMULUS MATERIALS AS ABOVE

Once forms handed in ask: are people happy for me to look at these and write up on the flipchart how people voted? **Write up result on flipchart**

Is anyone happy to explain why they voted in the way that they did? **Probe reasons for responses but ensure that voting decisions of individuals who do not wish to be identified cannot be deduced**

If anyone has voted 'neither agree nor disagree' probe reasons for this:

- **to check if any information has not been provided to allow a participant to agree or disagree with the statement**
- **check if they would agree in some situations and disagree in other situations, probe for the additional factors that would result in agreement or disagreement**

5. 10 MINUTE BREAK

6. Funding new treatments for rare diseases (up to 2 hours)

We've talked about how NICE evaluates whether the NHS should fund treatments for most diseases (up to £20,000 to £30,000 per QALY), and we've discussed the different criteria it uses when evaluating new treatment for very rare diseases (up to £100,000 to £300,000 per QALY)

I would now like to move on to discussing the key question we are looking to ask in this research, which is how NICE should decide whether a new treatment for rare diseases that affect between 1,100 and 25,000 persons in England should be funded.

Before we ask this question, I wanted to give you some examples of diseases that are categorised as being rare diseases rather than being either common or very rare:

SHOW /READ OUT SLIDE 12 – What about other rare diseases?

Confirm understanding of how a rare disease is defined (as distinct from 'very rare' disease) ie affecting between 1,100 and 25,000 persons in England

To what extent do these examples of rare disease illustrate the need for new treatment options?

Just to remind you, the current approach taken by NICE for evaluating treatments for rare diseases affecting **between 1,100 and 25,000 persons in England is the same as for more common diseases ie £20,000 to £30,000 per QALY, as opposed to the approach for very rare disease which is £100,000 to £300,000 per QALY**

I'd like us to discuss both the arguments for and against changing this approach – what are your views on this? **Write spontaneously generated arguments for/ against changing funding criteria on 2 flipcharts (one for, one against)**

After issues generated say: I'd like to show you some further arguments for and against reviewing the current NICE criteria for funding new treatments for rare diseases to explore your views on these

SHOW /READ OUT SLIDE 13/14 – Rare diseases - arguments for reviewing NICE approach

What are your reactions to these arguments for suggesting the NICE approach used for evaluating new treatments for rare diseases should be reviewed. Which arguments are most convincing and why? Which are least convincing and why?

SHOW /READ OUT SLIDE 15 – Equality vs Equity

What are your reactions to this way of seeking to illustrate the need for more investment in treatments for rare disease to achieve the same outcomes in terms of access to treatments as for common diseases? **Probe fully to explore how participants articulate this concept in their own words**

SHOW /READ OUT SLIDE 16 – Arguments against increasing the cost per QALY threshold for new treatments for rare diseases

What are your reactions to these arguments against reviewing the NICE approach?

Probe fully any other arguments for / against reviewing NICE criteria

Having discussed the arguments for and against reviewing the criteria use for funding, I'd like to spend the last hour discussing and voting on some very specific questions I'd like you to consider. Again, I want to emphasise that we are keen to get your honest opinions, and nobody will be asked to reveal the way they voted unless they are happy to do so.

Show voting exercise 1

Q1a) People with rare diseases (affecting 1,100-25,000 people in England) should have equal access to treatments as those with more common diseases, even if this means additional costs for the NHS

Q1b) Should the NHS pay more for patients who have rare diseases than those with more common diseases, where a treatment that has been developed that demonstrates it can change patients lives significantly for the better?

Before people vote on this, please let's discuss your views on these specific questions. For each, what encourages you to agree? What encourages you to disagree? Is anyone finding it difficult to decide? Why?

- Probe reasons for anyone who is undecided to check they have fully understood the task and the issues involved; encourage discussion as appropriate
- Once discussed, ask participants to vote and collect in responses
- If time permits, put up voting numbers on flipchart and invite discussion

Show voting exercise 2

Q2a) NICE should evaluate the cost effectiveness of treatments for rare diseases (affecting 1,100-25,000 people in England) differently than for more common diseases, taking into account the additional challenges in developing medicines for rare diseases

Q2b) NICE should give a higher threshold (in terms of the cost per patient regarded as cost-effective) for the evaluation of treatments for rare diseases (affecting 1,100-25,000 people in England) than it does for treatments for more common diseases

Before people vote on this, please let's discuss your views on these specific questions. For each, what encourages you to agree? What encourages you to disagree? Is anyone finding it difficult to decide? Why?

- Probe reasons for anyone who is undecided to check they have fully understood the task and the issues involved; encourage discussion as appropriate
- Once discussed, ask participants to vote and collect in responses
- If time permits, put up voting numbers on flipchart and invite discussion

Show voting exercise 3

Q3. Given the recognition by NICE that treatments for very rare diseases should be evaluated at a cost effectiveness threshold of £100,000 - £300,000 per QALY, to what extent do you agree or disagree that treatments for rare diseases should be evaluated at a cost-effectiveness threshold of £20,000- £30,000 per QALY, as for more common diseases?

Before people vote on this, please let's discuss your views on this specific question. What encourages you to agree? What encourages you to disagree? Is anyone finding it difficult to decide? Why?

- Probe reasons for anyone who is undecided to check they have fully understood the task and the issues involved; encourage discussion as appropriate
- Once discussed, ask participants to vote and collect in responses
- If time permits, put up voting numbers on flipchart and invite discussion

Show voting exercise 4

Q4. Which one of the following statements do you most agree with:

- **The NHS should make funding decisions for medicines to treat patients with rare diseases using the same cost- effectiveness thresholds as treatments for more common diseases**
- **The NHS should make funding decisions for medicines to treat patients with rare diseases using cost-effectiveness thresholds that fall between those for treatments for very rare diseases and treatments for more common diseases**
- **The NHS should make funding decisions for medicines to treat patients with rare diseases using the same cost- effectiveness thresholds as treatments for very rare diseases**

Before people vote on this, please let's discuss your views on this specific question. What are your views?

- Probe reasons for anyone who is undecided to check they have fully understood the task and the issues involved; encourage discussion as appropriate
- Once discussed, ask participants to vote and collect in responses
- If time permits, put up voting numbers on flipchart and invite discussion

Show voting exercise 5

Q5. Which of the following statements do you most agree with:

- **The NHS should NOT pay more for the treatment of patients with rare diseases than those with common diseases**
- **The NHS should be willing to pay more for the treatment of patients with rare diseases than those with common diseases, without the need for additional factors to be considered**

- **The NHS should be willing to pay more for treatments for people with rare diseases than those with common diseases, but should take into account additional factors when deciding how much it is willing to pay**

Before people vote on this, please let's discuss your views on this specific question. What are your views?

- Probe reasons for anyone who is undecided to check they have fully understood the task and the issues involved; encourage discussion as appropriate
- Once discussed, ask participants to vote and collect in responses
- If time permits, put up voting numbers on flipchart and invite discussion

Show voting exercise 6

Q6. *To what extent do you agree or disagree that when assessing a treatment's cost-effectiveness, additional value should be given to treatments for diseases that have a severe impact on people's lives than those for less severe diseases (even if the improvement offered by a treatment is similar for both diseases).*

Before people vote on this, please let's discuss your views on this specific question. What are your views?

- Probe reasons for anyone who is undecided to check they have fully understood the task and the issues involved; encourage discussion as appropriate
- Once discussed, ask participants to vote and collect in responses
- If time permits, put up voting numbers on flipchart and invite discussion

Thank you very much for everybody's input into these topics. Finally, taking into account everything that we've discussed today, what do we think is the best way for NICE to evaluate new treatments for rare diseases and make decisions on whether or not they should be funded for use by the NHS?

THANK AND CLOSE

Confirm research has been sponsored by the UK Bioindustry Association, the trade association for innovative life sciences and biotech industry in the UK, counting over 460 companies including biotechnology companies, universities and research centres among its members.

Stimulus material

In order to equip participants to develop informed views on the rare diseases and the issues explored, a range of informative materials was developed to stimulate discussion and understanding.

The materials were designed to inform participants about the following:

- The process for developing new treatments
- The role that NICE plays in deciding which treatments should be funded by the NHS, including how NICE determines the cost-effectiveness of new treatments.

Introduction – developing new treatments

The discovery, development and manufacture of medicines is largely carried out by the pharmaceutical industry. Some potential new pharmaceutical products are initially discovered as a result of research in universities, research institutes or small venture capital companies. Their subsequent development and manufacture, is invariably undertaken by, or in partnership with, established pharmaceutical companies.

The discovery and development of a new drug is now estimated to cost in excess of £500 million and may take more than 12 years to complete.

The expertise required to fulfil the requirements of national drug regulatory authorities, for the licensing a new medicine, is beyond the capacity of any university or healthcare system in the world.

In Great Britain, the Medicines and Healthcare products Regulatory Agency (MHRA) reviews the safety and efficacy of medicines that have been tested in clinical trials and provide a licence for it to be prescribed.

Certain diseases or conditions are very common in the UK; many of these have a wide variety of treatment options available to treat them

Disease or condition	People affected in the UK	Treatment options available
High blood pressure	16 million people	Over 100 treatment options
Depression	6 million people	Over 25 treatment options
Asthma	5.4 million people	Over 30 treatment options
Diabetes	4.9 million people	Over 40 treatment options
Angina	2 million people	Over 10 treatment options
Rheumatoid arthritis	400,000 people	Over 20 treatment options

Source: BNF, MIMS

NHS funding of new treatments for common diseases

- Once a new medicine has been approved as safe and efficacious to use on the basis of clinical trials, the National Institute for Health and Care Excellence (NICE) will evaluate it further, to determine whether it is value for money. It then makes a recommendation on whether it can or cannot be used to treat patients by the NHS, looking at:
 - Evidence from research showing how well a treatment works, including its impact on mortality and quality of life (such as pain or disability)
 - How much it will cost the NHS (in the context of how great the benefits of the new treatment are over existing treatments)
- The benefit of a new treatment is measured by NICE in terms of the number of additional quality-adjusted life years (QALYs) that it offers. For example:
 - A treatment that increases life by 1 year in perfect health would offer 1 QALY
 - A treatment that did not improve survival but improved quality of life for 1 year might offer 0.5 QALYs (dependent on how much quality of life was improved)
- The cost effectiveness of new medicines is usually measured in terms of the cost per additional QALY that a medicine offers. For example:
 - A treatment costing £10,000 that improved survival for 100% of patients in perfect health for an extra 12 months would be calculated to cost £10,000 per QALY
 - A treatment costing £10,000 that improved survival for 100% of patients in perfect health for an extra 6 months would be calculated to cost £20,000 per QALY
 - A treatment costing £10,000 that improved survival for 100% of patients in perfect health for an extra 3 months would be calculated to cost £40,000 per QALY
- Cost per QALY refers to how much the NHS is willing to pay for each extra year of life and/or a level of improved health. NICE currently uses a cost-effectiveness threshold in the range of £20,000 to £30,000 per QALY for reimbursing most new medicines in the National Health Service – ie most medicines which cost more than £20,000-£30,000 per QALY are not recommended for funding by the NHS
- NICE also assesses affordability – assessing the likely financial impact of a medicine over the first 3 years of its use in the NHS. Where a medicine's costs are expected to exceed £20 million per year in any of the first three years of its use in the NHS, it is generally considered unaffordable to the NHS.

Rare diseases

A rare disease is one which occurs in fewer than 1 in 2,000 of the population, affecting fewer than 25,000 people in England

- Overall, rare diseases affect in 1 in 17 people in the UK, and around 3.5 million people will be affected by a rare disease at some point in their lifetime.^{1,2}
- The term 'rare disease' encompasses a wide range of diseases spanning multiple therapeutic areas; there are over 7,000 known rare diseases.
- However, only 5% of rare diseases have licensed treatments. For those that do have a licensed treatment, funding by the NHS is not guaranteed.
- As a result, many people with rare diseases die prematurely or live with debilitating symptoms which place huge burdens on caregivers, families and society.³

Disease or condition	People affected in the UK
High blood pressure	16 million people
Depression	6 million people
Asthma	5.4 million people
Diabetes	4.9 million people

Rare disease or condition	People affected in the UK
Cystic Fibrosis	Around 11,000 people
Motor Neuron Disease	Around 5,000 people
Spinal Muscular Atrophy	Between 670 and 1340 people
Sickle Cell Disorder	Around 15,000 people



1. Genetic Alliance UK. The hidden costs of rare disease. A feasibility study. 2016

2. Genetic Alliance. Action For Access 2019 <https://actionforaccess.geneticalliance.org.uk/>

3. PhRMA. A Decade of Innovation in Rare Diseases 2015 <http://phrma-docs.phrma.org/files/dmfile/PhRMA-Decade-of-Innovation-Rare-Diseases4.pdf>

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People with rare diseases face additional challenges

- Poorly coordinated care is a major issue for patients and families affected by rare conditions (*Rare Disease UK, 2010; 2013; 2015*); there is huge variation in the way that services are organised including excessive and uncoordinated appointment scheduling; lack of communication between providers; and a lack of resources within services
- Patients and families face significant ('hidden') costs (both financial and psychosocial) associated with the way that their care is managed related to both medical appointments and wider condition management costs including impact on time in the absence of efficiently coordinated services.
 - Families described the financial costs associated with attending medical appointments including trips to see the GP, outpatient appointments, clinical research and inpatient hospital stays
 - Travel costs were particularly high for those travelling to specialist centres, which were often a long distance away from home.
 - Not only did patients and parents report taking days off work (and school) for appointments, many had made the decision to leave employment altogether
 - The impact on siblings of patients was noted by parents

Costs for patients and family members of managing a rare condition

Financial	Other
Costs associated with appointments: Time off work and reduced income; childcare; travel including petrol, public transport and taxis; parking; food and refreshments; accommodation; sundries; accessible vehicles and transport options.	Time: Time off work; time spent coordinating ('project managing') care and the various agencies and appointments involved; time spent fighting to access care and support.
Other financial costs associated with wider condition management: Private healthcare; childcare and respite; specialist activities and equipment; IT, internet and telephone costs (including paper and printing cost); prescriptions; fees for informal helpers and carers; disruption to employment and income.	Psychosocial, health and well-being: Disruption to schooling, employment and personal time; impact on relationships and social life; isolation; impact on identity and sense of self; living with uncertainty; mental health; fatigue; confidence and self esteem; anxiety and stress associated with appointments.
Wider family: Costs identified above related to patients, parents and grandparents; siblings and wider support networks.	

Costs to the NHS (and wider society) of uncoordinated care

Wider societal costs: Patients/parents out of work; benefits; implications for social care budgets
NHS costs: Duplication of efforts and unnecessary appointments (healthcare professional and secretarial time, tests and interventions, administration (e.g. appointment letters)); missed appointments (Did Not Attend (DNA) rates) and non-compliance with medication; higher rates of hospital admissions; poor patient outcomes.

Source: Genetic Alliance UK. The hidden costs of rare diseases. A feasibility study. 2016 page 36



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Additional challenges in developing treatments for rare diseases

1. 95% of rare diseases have no licensed treatment. This means that there is often a lack of pre-existing knowledge about the causes of rare disease, which means that researchers need to invest additional resources in identifying how to develop new treatment options, compared to more common diseases which are more well understood.
2. Some rare disease treatments are conventional therapies that aim to manage symptoms. Others, like cell and gene therapies, work by targeting the underlying causes of a disease and can be potentially curative in effect. Cell and gene therapies often have higher upfront development and delivery costs than conventional therapies, but can provide immediate and long-lasting benefits, often from a single dose. This makes demonstrating cost-effectiveness to NICE more challenging.
3. Rare diseases often have small patient populations. Consequently, there is often a high level of uncertainty in clinical trial data due to small sample sizes.
4. The costs of developing a new treatment for a common condition are divided between a large number of patients, which brings down the cost of treatment per patient. In contrast, the development costs for a rare disease will be borne by a much smaller number of patients and will therefore be more costly per patient.

Rare diseases and quality of life

- To determine the quality of life benefit of a new treatment, NICE uses standard measurements of health-related quality of life (such as EQ5D) to make a comparison against the current standard of care.
- Demonstrating quality of life gains using existing measurements is extremely challenging for rare genetic disorders which affect patients from birth. This is because patients often score themselves highly in terms of their quality of life on the current standard of care treatments because they are used to living with their condition and have no comparison.
- This makes it challenging for a new treatment to significantly improve quality of life score and means that direct quality of life gains from new treatments are not captured. This will ultimately impact how cost-effective NICE deems a new treatment to be.

'Standard of care' refers to the best currently available treatment

EQ5D scale

MOBILITY	
I have no problems in walking about	<input type="checkbox"/>
I have slight problems in walking about	<input type="checkbox"/>
I have moderate problems in walking about	<input type="checkbox"/>
I have severe problems in walking about	<input type="checkbox"/>
I am unable to walk about	<input type="checkbox"/>
SELF-CARE	
I have no problems washing or dressing myself	<input type="checkbox"/>
I have slight problems washing or dressing myself	<input type="checkbox"/>
I have moderate problems washing or dressing myself	<input type="checkbox"/>
I have severe problems washing or dressing myself	<input type="checkbox"/>
I am unable to wash or dress myself	<input type="checkbox"/>
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems doing my usual activities	<input type="checkbox"/>
I have slight problems doing my usual activities	<input type="checkbox"/>
I have moderate problems doing my usual activities	<input type="checkbox"/>
I have severe problems doing my usual activities	<input type="checkbox"/>
I am unable to do my usual activities	<input type="checkbox"/>
PAIN / DISCOMFORT	
I have no pain or discomfort	<input type="checkbox"/>
I have slight pain or discomfort	<input type="checkbox"/>
I have moderate pain or discomfort	<input type="checkbox"/>
I have severe pain or discomfort	<input type="checkbox"/>
I have extreme pain or discomfort	<input type="checkbox"/>
ANXIETY / DEPRESSION	
I am not anxious or depressed	<input type="checkbox"/>
I am slightly anxious or depressed	<input type="checkbox"/>
I am moderately anxious or depressed	<input type="checkbox"/>
I am severely anxious or depressed	<input type="checkbox"/>
I am extremely anxious or depressed	<input type="checkbox"/>

NICE evaluation of new treatments for very rare diseases

- As discussed, a rare disease is one which occurs in fewer than 1 in 2,000 of the population, affecting fewer than 25,000 persons in England
- A 'very rare' disease is one which is even more rare, occurring in less than 1 in 50,000 people and affecting fewer than 1,100 persons in England
- Treatments for very rare diseases are evaluated by NICE under its highly specialised technology (HST) programme. This acknowledges that, given the very small numbers of patients living with these very rare conditions, establishing value for money is not straightforward. In particular, the HST guidance recognises the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and need to encourage investment by manufacturers in developing new treatments for very rare diseases given the very small populations treated.
- Examples of treatments that have been recommended through the HST programme include:
 - Soliris (eculizumab) is a treatment for atypical haemolytic uraemic syndrome (aHUS) affecting 20-30 new patients each year in England. aHUS causes the formation of blood clots in small blood vessels throughout the body; within a year of diagnosis, up to 70% of patients progress to end-stage renal failure and need dialysis or die.¹
 - Luxturna (voretigene neparvovec) is a gene therapy treatment for RPE65-mediated inherited retinal dystrophies. RPE65-mediated retinal dystrophies are a group of rare genetic eye diseases which cause progressive vision loss, ultimately leading to near-total blindness. It is estimated that 86 people in England would be eligible.²
 - Translarna (ataluren) is a treatment for 10-15% of the 2,500 boys living with Duchenne muscular dystrophy (DMD) in the UK who have a specific mutation. The main symptom of DMD is motor dysfunction but the gastrointestinal tract and vital organs such as the heart are affected. After the age of 12, most children need to use a wheelchair. As the disease progresses, people with DMD lose the ability to breathe unaided with subsequent respiratory and cardiac failure that leads to death, usually before age 30 years.^{3,4,5}

NICE evaluation of new treatments for very rare diseases

- Treatments for very rare diseases are evaluated by the NICE highly specialised technology (HST) programme. To qualify for this assessment route, medicines must meet the following criteria:
 - 1 – the disease is 'very rare', defined as occurring in no more than 1 in 50,000 / no more than 1,100 people in England
 - 2 – normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications
 - 3 – the very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life
 - 4 – there are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options
- NICE has accepted that for very rare diseases, society is prepared to pay more for those benefits because it is very difficult to develop new treatments for small patient populations: **NICE has set a maximum additional threshold of £100,000 to £300,000 per QALY for these treatments, under which they will be approved for NHS use**
- 20 treatments for very rare disease treatments have been evaluated via NICE's HST programme since 2015. In the same time period, NICE evaluated 447 products via the standard technology appraisal programme, which is used for the majority of new treatments.

What about other rare diseases?

Although NICE has developed a different process for the evaluation of treatments for **very rare** diseases (fewer than 1,100 persons in England, fewer than 500 eligible for treatment), at present treatments for **rare** diseases (affecting between 1,100 and 25,000 persons in England) are often evaluated in the same way as those for more common diseases, which may affect millions of patients

- A rare disease (as opposed to a **very rare** disease) is one which occurs in fewer than 1 in 2,000 of the population - affecting between 1,100 and 25,000 persons in England

Examples of rare diseases (as opposed to very rare diseases) include the following:

- **Cystic Fibrosis (CF)** is a genetic condition affecting more than 10,800 people in the UK. In CF, a faulty gene disrupts the movement of salt and water in the body's cells causing the body to produce thick mucus. The build-up of this mucus in the lungs can cause long term lung infections and progressive lung damage. CF can also cause problems with the digestive system and the liver. People born in the UK with CF today are likely to die before they are 48. The daily impact of treatment is significant. It can take four or more hours involving nebulisers, physiotherapy and up to 70 tablets a day.
- **Motor Neuron Disease (MND)** affects up to 5,000 people in the UK; it affects adults of any age but is more likely to affect people over 50. With MND, the nerves in the brain and spinal cord responsible for telling muscles what to do are damaged, and their ability to send messages hindered. This can lead the muscles to weaken, stiffen and waste and can affect walking, talking, eating, drinking and breathing. MND cannot be stopped or reversed but therapies, equipment and medication can help to manage symptoms
- **Spinal muscular atrophy (SMA)** is a genetically inherited condition affecting between 670 and 1340 people in the UK. There are different forms of SMA and a wide spectrum of how severely children and adults are affected, with the most severe types affecting babies and young children. SMA causes progressive muscle weakness and muscle wasting which may affect crawling and walking ability, arm, hand, head and neck movement, breathing and swallowing.
- **Sickle Cell Disorder** affects approximately 15,000 people in the UK. It can affect anyone, although it most commonly affects people from African and Caribbean backgrounds. Sickle Cell is a disorder of haemoglobin - the substance in red blood cells responsible for carrying oxygen around the body. Sickle cell disorder causes anaemia and episodes of severe pain known as a sickle cell crisis. Over time, people with sickle cell can experience damage to the liver, kidney, lungs, heart and spleen.



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Rare diseases arguments for reviewing NICE approach

- There are 7,000 rare diseases and 95% of these have no licensed treatment
- Only 20 medicines have been evaluated by NICE under the HST system for **very rare** diseases in the seven years since it was created, with the bulk of treatments for rare diseases being reviewed using the same process as for more common diseases
- The challenges faced the development of treatments for very rare diseases (those affecting less than 1,100 patients in England) have been recognised and responded to by NICE by the development of an assessment process with a higher threshold for funding (£100,000 - £300,000 per quality adjusted life year)
- However, NICE still evaluates treatments for rare diseases (affecting between 1,100 and 25,000 persons in England) in the same way as those for more common conditions – although the development of treatments for rare diseases faces the same challenges as for very rare diseases, as follows:
 1. Compared to more common diseases, there is a much smaller pool of preexisting knowledge about the condition that a new drug is being developed to treat from which to begin work. As no pre-existing treatments exists for most rare diseases, the task of identifying a disease target must often be started from scratch; companies have to develop specialist expertise; a lack of knowledge on the history of the disease makes it difficult to design clinical trials
 2. Small and geographically dispersed patient populations present challenges for clinical trial recruitment and make it harder to generate sufficient data to demonstrate the medicine's effectiveness
 3. Around half of rare disease patients are children, making trials more difficult and creating ethical challenges in the recruitment process
 4. These challenges mean that treatments for rare disease can have high upfront costs and have high levels of clinical uncertainty which can make it difficult to demonstrate cost effectiveness
 5. The costs of developing a new treatment for a common condition are divided between a large number of patients, whereas the development costs for a rare disease will be borne by a much smaller number of patients
- All these factors impact on the costs of drug development and may discourage investment in seeking new treatments for rare diseases, as the opportunities to recoup the cost of developing a new treatment become more challenging



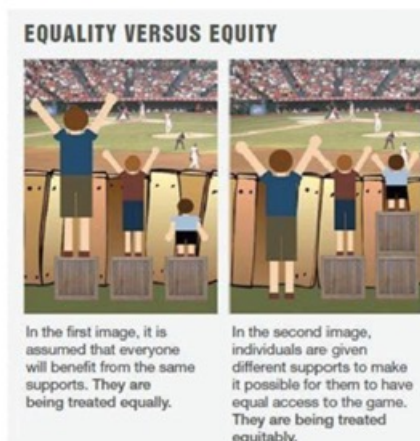
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Rare diseases arguments for reviewing NICE approach

- A number of further arguments could be made for reviewing NICE's approach to evaluating treatments for rare conditions:
 - The rarity of the condition may often mean there are fewer (or no) existing effective treatment options; many treatments for rare conditions are the first effective treatment options available;
 - Innovations in treating rare diseases may be cutting -edge, such as with cell and gene therapies, which are potentially curative; by encouraging innovation in a small field, science is able to advance in ways that over time could benefit more and more people;
 - Many rare conditions are inherited or genetic conditions which people have from birth or which manifest in childhood;
 - Many rare conditions are life -threatening, greatly reduce life expectancy and/or seriously impede the patient's quality of life and ability to lead a normal life, as well as their families and carers;
 - Increased productivity if patients are returned to health
 - With time, the price may fall as competitors enter the market.
 - The creation of an evaluation system that is capable of accommodating rare disease treatments will encourage the development of potentially life -changing and curative treatments for rare diseases.

Rare diseases - arguments for reviewing NICE approach

The following image illustrates the situation faced by people with a rare disease. The short child represents a patient with a rare disease, who needs more support in order to achieve equity of treatment with the tall child, who represents a patient who has a more common condition which is more likely to be approved by NICE



Investing more in treating people with rare conditions helps these under-served patients achieve a greater degree of equity with the rest of the population

Arguments against increasing the cost per QALY threshold for new treatments for rare diseases

A number of arguments could be made for NOT increasing the threshold for NICE permitting the use of new treatments for rare diseases:

- It's unfair to treat rare diseases differently from common diseases
- Providing more expensive care to a small proportion of the population could reduce funding available to treat other diseases; resources could be limited for more common diseases
- Whilst the total sum spent in one rare disease may be relatively small this will inevitably grow:
 - Patients given these treatments will survive, instead of dying; and their number will grow as more children with these genetic defects are born.
 - The number of drugs available to treat rare diseases is likely to increase in future
- Impact on overall government expenditure on medicines and thus taxes/borrowing

Online survey

Between October and November 2022, an online survey was conducted among a representative sample of 1,000 adults in England. Respondents were excluded from taking part if they or a member of their household or immediate family worked in the pharmaceutical industry or for a charity representing patient groups. Unlike the focus groups, individuals with rare diseases were included.

The survey took roughly 20 minutes to complete, and information was presented to participants throughout the survey to support their ability to provide an informed response to the questions asked. To ensure that participants were reading the information provided to them additional questions were included in the survey requiring participants to indicate their awareness or understanding of the information presented to them.

As with the focus groups, most questions included in the survey required participants to indicate the extent of their agreement or disagreement with various positions. The response options for these questions ranged from 'Agree strongly' to 'Disagree strongly' with a neutral option included.

About BIA



The BioIndustry Association (BIA) is the voice of the innovative life sciences and biotech industry, enabling and connecting the UK ecosystem so that businesses can start, grow and deliver world-changing innovation. We are an award-winning trade association representing more than 500 member companies including:

- Start-ups, biotechnology and innovative life science companies
- Pharmaceutical and technological companies
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Learn more about RDIG at bioindustry.org/RDIG

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