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The European Journal of Health Economics

Consideration of quality of life in the health technology assessments of rare disease treatments

--Manuscript Draft--

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| Full Title: | Consideration of quality of life in the health technology assessments of rare disease treatments | |
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| Keywords: | patient-reported outcome; rare disease; orphan medicinal products; health-state utility value; Health technology assessment; reimbursement | |
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| | | |
| Abstract: | <p>Objectives: Challenges with patient-reported outcome (PRO) evidence and health state utility values (HSUVs) in rare diseases exist due to small, heterogeneous populations, lack of disease knowledge and early onset. To better incorporate quality of life (QoL) into Health Technology Assessment, a clearer understanding of these challenges is needed.</p> <p>Methods: NICE appraisals of non-oncology treatments with an EMA orphan designation (n=24), and corresponding appraisals in the Netherlands, France, and Germany were included. Document analysis of appraisal reports investigated how PROs/HSUVs influenced decision-making and was representative of QoL impact of condition and treatment.</p> <p>Results: PRO evidence was not included in 6/24 NICE appraisals. When included, it either failed to demonstrate change, capture domains important for patients, or was uncertain. In the other countries, little information was reported and evidence largely did not demonstrate change. In NICE appraisals, HSUVs were derived through the collection of EQ-5D data (7/24 cases), mapping (6/24), vignettes (5/24), and published literature or other techniques (6/24). The majority did not use data collected alongside clinical trials. Few measures demonstrated significant change due to lack of sensitivity</p> | |

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| | <p>or face validity, short-term data, or implausible health states. In 8/24 NICE appraisals, patient surveys or input during appraisal committee meetings supported the interpretation of uncertainty or provided evidence about QoL.</p> <p>Conclusions: This study sheds light on the nature of PRO evidence in rare diseases and associated challenges. Results emphasise the need for improved development and use of PRO/HSUVs. Other forms of evidence and expert input are crucial to support better appraisal of uncertain or missing evidence.</p> |
| Response to Reviewers: | <p>Dear Editor and Reviewers,</p> <p>Thank you for providing your suggestions and opportunity to improve the quality of this manuscript. We have revised it in accordance with the suggestions as detailed in the point-by-point response included in the submission. We've also included two versions of the manuscript: one with all changes tracked for your reference, and another clean version.</p> <p>We are happy to make any further amendments should they be required.</p> <p>Many thanks again. Best wishes, Elena Nicod</p> |

Point-by-point response

Submission ID: EJHE-D-21-00236

Consideration of quality of life in the health technology assessments of rare disease treatments

Dear Editor and Reviewers,

Thank you for providing your suggestions and opportunity to improve the quality of this manuscript. We have revised it in accordance with the suggestions as detailed in the point-by-point response below. We are happy to make any further amendments should they be required.

Reviewer #1

Very well written and important paper that I highly recommend getting published. Minor comments to address.

| Reviewer's comment | Author's response |
|--|--|
| 1) where "lack of knowledge" is mentioned in the abstract and text, change to "lack of knowledge of natural history" for clarity | Thank you for spotting this. We have changed this to "lack of disease knowledge", which would be broader than natural history (e.g. patient population, treatment pathways, etc). We hope this is ok |
| 2) pg 2 line 8- sentence starting with Quality of Life...is not true across the board. Rephrase to say Quality of Life of patients living with a rare disease is often poor due to the disease impacting multiple aspects of functioning". | Changed as suggested, thank you |
| 3) Next sentence- issues with diagnosis are mainly diagnosis delays (add delays); | Changed as suggested |
| 4) og 2, line 49- drop "more nuanced" that isn't needed | Changed as suggested |
| 5) pg 5 line 11- the symptoms, not "they symptoms" (typo) | Thank you for spotting |

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| 6) Figure 2 is really hard to understand what it's trying to convey and another type of figure (or table) should be considered | We've changed the figures to tables to make them more easier to understand |
| 7) The table 2 is great but very lengthy for a manuscript and the organization wasn't clear/ could be improved to show some type of pattern | We feel that Table 2 is important to include as it gives the "data" that is the basis for our analysis, so it is more for reference than detailed review. The text and new preceding summary table draws out the key elements. |
| 8) in the discussion more solutions could be mentioned including early scientific advice with the EU agencies, and working with disease registries early on to get natural history data | Thank you for this suggestion. We have included in the discussion, under how QoL information should be better used for HTA, the following paragraph: "This could be achieved through greater involvement in early multi-stakeholder dialogues and early scientific advice to better align across HTA bodies and agree on what QoL evidence would be accepted, and a greater acceptance of registry data to leverage early on data on natural history on the disease." |

Reviewer #2

The concept of the study is interesting, and the authors have clearly undertaken a huge amount of work in analysing so many appraisals. However, with so much information presented (in the results and discussion particularly), it is difficult for me to understand exactly what the authors did, what they found and what the implications are. I believe that part of my difficulty stems from the methods used – I am not overly familiar with thematic analyses and suggest that more detail in this section would be beneficial. I would also suggest that the authors reconsider the presentation of the results as neither the text, tables, not figures are particularly intuitive.

I have provided comments on specific sections below, but overwhelmingly feel that the paper needs substantial revisions and restructuring to make what should be a useful and thought-provoking analysis much more accessible to readers.

We have provided responses, point by point, below.

| Reviewer's comment | Author's response |
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| I believe that part of my difficulty stems from the methods used – I am not overly familiar with thematic analyses and suggest that | We have provided more clarifications on what was done, how and have referenced a key resource on thematic analysis + a source on the methodological framework |

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| more detail in this section would be beneficial. | previously developed and used as a basis to structure the data collection and analysis – see methods section |
| I would also suggest that the authors reconsider the presentation of the results as neither the text, tables, nor figures are particularly intuitive. | The figures have been redrawn (Figure 1) and new tables developed to ease interpretation (Tables 1, 3 and 5) |
| Introduction line 5 – should be referenced to EMA or similar, not reference 1 (is ref 1 the 2020 publication in cost effectiveness and resource allocation)? | Thank you for spotting this – the reference was not correct. We now referenced this to the webpages from the EC on orphan medicinal product and EURORDIS on what is a rare disease |
| Intro line 43 – HSUVs can be lower than 0 | We've added the worse than dead state as negative HSUV values |
| Intro line 24 – please change to active voice rather than passive (throughout) | The choice of active or passive voice is a stylistic matter. If the journal has a strong preference for the active voice, we can make the change. Meanwhile, we have proof read the paper but have not explicitly changed the voice |
| The objective is not entirely clear...to understand challenges, how QoL was appraised, and whether aligned with expected disease impact? What does this actually mean? | We have now made the objectives more specific: "To better incorporate QoL evidence into HTA decision-making, a clearer understanding of the challenges encountered when using PRO evidence and HSUVs in rare diseases is needed. Hence this research explored how QoL evidence has been used in appraisal of non-oncology rare disease treatments in a selection of countries using different HTA approaches." |
| Methods – why not other countries (e.g. Australia, Canada, Sweden)? | We selected two countries per HTA approach (e.g. use of cost-effectiveness estimates, or use of added clinical benefit). EU countries were preferred over non-EU as this work was conducted as part of an EU project. We have added the following clarification in the "study sample" section in the methods: "Considering the depth of the analysis conducted, the inclusion of four countries was considered sufficient to understand the nuances between one HTA approach and another, and the differences within each approach." |

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| <p>Methods – data collection and analysis. How were these criteria chosen? Are they established elsewhere? They could appear fairly arbitrary otherwise.</p> <p>Why would being heterogenous indicate a higher burden of disease? Why would the administration mode affect QoL?</p> | <p>We have provided references and clarifications in the methods section. This work leveraged an existing methodological framework developed, that allows for a structured collection and analysis of decision-making processes. Further explanation about thematic analysis and how this was done have also been added (and referenced). We hope this is sufficient.</p> <p>We have swapped the order of what has been collected – and linked the data collected to how it was analysed. Hopefully it is more clear now.</p> |
| <p>Methods – what does thematic analysis entail? What published techniques were used?</p> | <p>This has been better explained in the methods section and references have been provided</p> |
| <p>Methods – data collection and analysis line 23. Latter means last of two, replace with last.</p> | <p>Changed as suggested</p> |
| <p>Really this is a study of NICE appraisals with a couple of paragraphs about other HTA bodies. Is it valuable to include these other HTA bodies – what do they add with the level of information available? Is there a useful comparison to NICE here?</p> | <p>The intention was to compare all countries equally but little information was found from other countries. Hence it is this that hampered the review. This is now explained more clearly in the text. Some elements of interest can be drawn from the other countries, particularly France and Germany that consider added benefit and we would not wish to miss the opportunity to share those findings.</p> |
| <p>In NICE appraisals, how are you differentiating between company and ERG work and the committee’s preferred assumptions?</p> | <p>The focus has been on the appraisal process, meaning the interpretation of the evidence by the Committee. The ERG’s model/assumptions/results on HSUVs are included when discussed by the Committee and accounted for in the decision – this is described in Table 4 under the HSUV technique column, and last column on the decision and reasons for decision does specify when ERG’s assumptions have been preferred. This is explained in the methods</p> |

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| <p>What is meant by “patient-based evidence” and how is this different from PROs/HSUVs?</p> | <p>We now refer to all other evidence relating to QoL as patient evidence – this is now defined in the methods.</p> |
| <p>Is patient-based evidence really a separate category that is comparable to PROs and HSUVs? Surely preferences on administration mode are very different to patient information being used to derive HSUVs?</p> | <p>We have clarified in the text that we mean evidence related to QoL that does not arise from PROs or HSUVs. This could include feedback from patient focus groups, or patients’ contributions to the discussions during the Committee discussions.</p> |
| <p>I’m confused about the numbers for patient submissions – there are 5 appraisals cited where patient surveys were used, but only four sources (two company submissions and two patient submissions). What was the source of the patient and clinician input for the other 4 appraisals?</p> | <p>Thank you for spotting that, we have double checked all the data and updated the results accordingly – see results section</p> <p>The sources are the appraisal reports, where the interpretation of this evidence was commented on. In the methods section, we reference the appraisal reports and mention that we refer to these appraisal reports when discussing the NICE appraisals of the individual drugs in the text</p> |
| <p>Would it be useful to distinguish between PROs in addition to HSUVs? Otherwise it doesn’t make sense to say that PRO wasn’t reported, or PROMs and results weren’t discussed.</p> | <p>In the PRO analysis, we distinguished when the PRO data were used to derive HSUVs used to inform the decision, versus when the PRO data were discussed separately or in addition to the HSUVs and had an influence on the decision. This distinction highlights cases when, in cost-effectiveness approaches, the interpretation of the HSUV data was complemented by the PRO data. Hopefully, this is now clear in the paper</p> |
| <p>Conclusion – is patient-based evidence preferable to PROMs/HSUV data though? Were they preferred by committees to the HSUV/PROM data from studies? I can see that they might be used to supplement this, but I disagree with the “most importantly” conclusion</p> | <p>We now clarify that patient evidence is additional information, which can be discussed in the absence of, or additional to, HSUV or PROM data.</p> <p>We have changed ‘Most importantly’ to ‘Additionally’</p> |
| <p>The paper needs a comparison to non-rare diseases. I’m not expecting the authors to do the same analysis for all NICE appraisals</p> | <p>The objective of our study was to explore the issues with interpreting and using quality of life data in rare diseases. It was</p> |

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| <p>that aren't in rare diseases, but is there something published that they could refer to? Otherwise how will readers know that these results and conclusions are specific to rare diseases?</p> | <p>our prior view that this could be particularly problematic, for the reasons we give.</p> <p>Although it was not in our remit to undertake a comparison, it is possible that some of the same problems could exist in the HTA of treatments for common diseases, even given the increased likelihood of having validated PROMs and HSUVs in the literature.</p> <p>We are not aware of an equivalent study in common diseases that we could refer to.</p> <p>Therefore, we now mention this in the limitations, and highlight that a comparison with non-rare diseases could be an area for further research.</p> <p>“Finally, this study highlights some of the nuances in considering QoL evidence in rare diseases. It is possible that some of the same issues could arise in the HTA of more common diseases, Further research would be needed, comparing the results from this analysis with those from a similar analysis of HTAs for common non-cancer treatments.”</p> |
| <p>Figure 1 – please replace with a grouped bar chart. Centring at zero (as per a tornado diagram) seems strange.</p> | <p>We have changed the chart as suggested – hopefully more clear now.</p> |
| <p>Figure 2 – there are circles for PRO evidence reported and PRO evidence not reported.</p> <p>Some appraisals don't have either circle in different areas – how are we to interpret these? It seems like they neither had PRO evidence reported nor didn't have PRO evidence reported. This figure suggest that some of the appraisals not have any QoL evidence at all (eg Holoclax, strimvelis), but in the text it says other QoL were considered for 2 studies – what about the other 4 (obethocholic acid, strimvelus, burosumab, pifrenidone)?</p> | <p>We have now changed Figures 2-3 to Tables 1 and 3, respectively.</p> <p>In Table 1, the legend explains the “not reported” cases, which relate to PRO results not being reported in the appraisal report, but mentioned as having been collected. We assumed these had no influence on the decision.</p> <p>Indeed there are a number of cases that did not consider any PRO data – in the table, there is no sign corresponding to any of the PROMs. These included: strimvelis, burosumab, obeticholic acid, holoclax,</p> |

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| | <p>pirfenidone, elosulfase alfa. In the second paragraph of the results section, under “use and influence of PRO evidence in NICE appraisals”, it states that 6/24 didn’t consider any PRO data and explains why it was the case for the 6 drugs. For the remaining 4, no PROM evidence was considered and HSUV were derived based on other data / using other techniques, e.g. strimvelis - published literature, burosumab/vignettes, obeticholic acid/published literature. No information on the quality of life data accounted for pirfenidone was a re-assessment and no new QoL was provided (this is specified in the paragraph).</p> <p>We have added the following clarification in the paragraph: “QoL evidence for the remaining drugs without PRO data was based on HSUVs derived from vignettes or published evidence (Table 3, discussed in the next section on HSUVs).”</p> <p>In the table we added the following clarifications:</p> <p>*No PRO data was provided, but patient evidence or PRO data from the literature was used instead (Elosulfase alfa, Holoclar)</p> <p>** No PRO data was provided, QoL evidence was derived from HSUVs from vignettes or published literature (Strimvelis, Burosumab, Obeticholic acid, Holoclar)</p> <p>*** No PRO data was provided as this is a re-assessment and no new QoL evidence was presented (Pirfenidone)</p> <p>We hope that it is now more clear</p> |
| <p>Similar, in figure 3 – did some appraisals not use HSUVs?</p> | <p>Figure 3 is now Table 3 and hopefully more clear.</p> <p>All drugs apart from Pirfenidone considered HSUVs. We have added that clarification in the footnotes: “No HSUV results were considered as this is a re-assessment and no new QoL evidence was provided“</p> |

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| <p>The circle size suggests that the influence was the same between HSUVs and other evidence – this is clearly not true when HUSVs are used to generate ICERs.</p> | <p>Figures changed to Tables, signs used and explained in legend</p> |
| <p>Conclusion – is patient-based evidence preferable to PROMs/HSUV data though? Were they preferred by committees to the HSUV/PROM data from studies? I can see that they might be used to supplement this, but I disagree with the “most importantly” conclusion</p> | <p>Repeat of question above</p> |

Reviewer #3

Results are worth being published as they raise an important and often neglected aspect of HTA.

| Reviewer’s comment | Author’s response |
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| <p>The paper can benefit from a review of the text to make it less wordy and bring up the key results.</p> | <p>Text has been cut, particularly in the intro and methods and new tables developed to succinctly present the results</p> |
| <p>The text also needs to explain some key distinctions (PROs vs HSUVs) and why HTA such as NICE focus on the latter.</p> | <p>This has now been clarified in the text</p> |
| <p>Finally, there is a need to point out that the issues identified might be relevant also in more common diseases, particularly in NICE appraisals where the focus is on cost per QALY.</p> | <p>We have not added this as we only have data for rare diseases. In the “Limitations’ section we mention that a similar study should be undertaken of HTAs for common diseases.</p> |
| <p>Line 8-9 page 2: the article quoted refers to more prevalent chronic conditions not only more prevalent. Please check the reference and adjust the wording accordingly.</p> | <p>We have changed this based on reviewer #1’s comment to read “QoL is poor in rare disease patients due to multiple aspects affecting functioning” – and took away the comparison with common conditions</p> |
| <p>Line 10-11 page 2: Is the HSUV that is not sufficiently sensitive? Is it not an issue with the descriptive measure, the PRO, rather than the utilities?</p> | <p>Thank you for spotting this. In the referenced paper by Pearson et al, they refer to QALY’s not being sensitive to disease severity of the population. We’ve also added some references.</p> |

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| <p>Overall, the introduction on page 1 and 2 can be shortened, particularly around the details of the HTA approach. If it is assumed that the audience knows about them, the text of the section can be reduced. There are some word repetitions that can be edited to improve readability.</p> <p>What it would be useful to know is the difference between PROs and HSUV, which currently is not explained very clearly (patient completing the questionnaire vs eliciting public preferences on the health states).</p> <p>Finally is HSUV used at all in added benefits countries?</p> | <p>The intro has been shortened and we've clarified the difference between PRO and HSUVs</p> <p>In added benefit countries, HSUVs are not being used – e.g. in the IQWiG methods guidelines, there is a provision for something akin to disease-specific QALYs, but they have never been used (to our knowledge). We have not added anything in the manuscript, to keep the two approaches distinct and avoid confusion</p> |
| <p>Line 57 page 3: the reasons for excluding cancer treatments are not explained "above" as stated in the text.</p> | <p>We've added the explanation:</p> <p>"...because added benefit often relies on survival gains, and many rare cancers are subsets of more common cancers for which a validated PRO often exists"</p> |
| <p>Line 44: it is administration of EQ5D (in the trial?) AND use of the UK value set.</p> | <p>We have specified how the EQ5D data to derive HSUVs was collected: "within a trial (4/7) or from a registry or cohort study (3/7)"</p> |
| <p>How HSUV is derived from EQ5D is not clear from the paper. Most readers should know but given that it is the focus of the paper it should be explained</p> | <p>A brief description of how HSUVs are derived from EQ-5D has been added in the introduction.</p> |
| <p>Line 50 page 7: unclear what HSUVs for adverse events or administration mode is?</p> | <p>We've clarified this in the text: "... to determine the HSUV estimated to measure the impact of adverse events on QoL included in the submission"</p> <p>We've also clarified that these were derived and considered alongside the HSUVs</p> |
| <p>In figure 3, what is patient-based evidence? How can you use patient evidence to obtain utilities (usually based on societal values)?</p> | <p>Thanks for pointing this out, we've changed it to patient evidence and clarified in the text that we mean evidence related to QoL that does not arise from PROs or HSUVs. This could include feedback from patient focus</p> |

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| | groups, or patients' contributions to the discussions during the Committee discussions. |
| Table 2 page 8: the information in table 2 is far too detailed for a paper. In addition, no reference to the decision outcome and the cost per QALY is made in the text and it is not stated how this information was extracted. I suggest excluding the table or presenting a much reduced version of it. | <p>We feel that Table 2 is important to include as it gives the "data" that is the basis for our analysis, so it is more for reference than detailed review. The text and new preceding summary table draws out the key elements.</p> <p>One option could be to make the table supplementary material, but we would prefer not to as we would lose this level of detail which is important. We would also prefer to include the cost/QALY information, even if it is not explicitly discussed, the table does highlight when the PRO evidence made a difference in accepting (or not) a cost/QALY on the higher end.</p> <p>However, we would accept the Editor-in-Chief's guidance on whether Table 2 should be moved to the supplementary material</p> <p>We've included the appraisal report references for each of the drugs</p> |
| Line 29 page 9: I can only see table 1 and 2. Table 3 is missing from the text. | Table 4 should have been Table 3 – apologies, now changed in the manuscript. Table 5 also now included (it hadn't been uploaded in the initial submission – apologies!) |
| Line 34 page 10. Is the sentence misleading? It sounds like in all cases improvement in QoL was the main objective of the treatment and so presumably included as primary endpoints. Is this the case? Line 16 to 23 on page 5 can help in explaining this. | This sentence has been re-worded as follows, and is hopefully more clear: "For all of the treatments investigated, their added benefit was also considered to improve QoL." |
| Line 47 to 55 page 10: I tend to agree with the missed opportunity to consider rich PRO data in HTA. However, is this only an issue in rare diseases? I believe this happens for common disease too because the remit of HTA bodies, in particular NICE. The key decision criterion is cost effectiveness and hence committee will primarily consider HSUVs via the incremental cost effectiveness ratio. The paragraph at the | We agree it is worth emphasising the distinction depending on the approach used. We have added the following sentences: "Results illustrate that different QoL evidence would be considered depending on the HTA approach. For cost-effectiveness oriented approaches, HSUVs are considered within the incremental cost-effectiveness ratio and are derived from |

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| <p>end of page 10 partially explained this. In countries focusing on added benefits, HSUVs will not be considered (and this should be stated explicitly in the paper).</p> <p>Another point that should be raised is around the reasons for not considering PROs in added benefits countries: are they all related to the quality of the data provided (as explained on page 9) rather than the intention of not considering the data?</p> | <p>PRO data using indirect techniques (e.g. generic preference-based instruments, mapping), or measured directly from patient responses using direct preference-based techniques (e.g. time-trade-off) [18]. In countries with an added benefit assessment approach, the PRO data would be considered and interpreted as is without being derived into a numerical HSUV. To help with the comparability and interpretation of the PRO data, generic PROMs are often preferred.”</p> <p>We also specified that “It was not clear from the appraisal reports why this evidence was not reported or accounted for.”</p> |
| <p>Line 37 to 49 page 13: the sentence about the role of patients and clinical input might not need to be reported in the conclusion. The sentence starting "patients should be better informed" should be deleted as it is unclear how the authors can draw these conclusions and it seems to be in contrast with the previous one. Further research are not very clear and informative so they either need to be expanded in the discussion section or be deleted.</p> | <p>We have clarified how patient evidence and patient / clinical input can help in the process, and deleted the point about patients needing to be better informed about what type of evidence and input can be meaningful. We’ve also deleted the last sentence on further research, which is more focused on methodological aspects of HSUV techniques</p> |
| <p>References do not include the NICE appraisals consulted.</p> | <p>References now included</p> |

Consideration of quality of life in the health technology assessments of rare disease treatments

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Declarations:

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Conflicts of interest: Michael Drummond and Karen Facey have received funding and consultancy fees from manufacturers of treatments for rare diseases outside of this work. Elena Nicod and Amanda Whittal are part-time employed by Dolon Ltd and have no conflicts with this work.

Availability of data and material (data transparency): Data was extracted from publicly available reports and literature

Authors' contributions: All authors made substantial contributions to the design of the work; EN and AW collected the data, EN conducted the data analysis and drafted the work; all authors revised it

critically at several occasions for important intellectual content; all authors approved the version being submitted; all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Key words: patient-reported outcome, rare disease, orphan medicinal products, health-state utility value, health technology assessment, reimbursement

Acknowledgments: We would like to thank Dr. Andrew Lloyd for his time and feedback on the results.

ABSTRACT

Objectives: Challenges with patient-reported outcome (PRO) evidence and health state utility values (HSUVs) in rare diseases exist due to small, heterogeneous populations, lack of disease knowledge and early onset. To better incorporate quality of life (QoL) into Health Technology Assessment, a clearer understanding of these challenges is needed.

Methods: NICE appraisals of non-oncology treatments with an EMA orphan designation (n=24), and corresponding appraisals in the Netherlands, France, and Germany were included. Document analysis of appraisal reports investigated how PROs/HSUVs influenced decision-making and was representative of QoL impact of condition and treatment.

Results: PRO evidence was not included in 6/24 NICE appraisals. When included, it either failed to demonstrate change, capture domains important for patients, or was uncertain. In the other countries, little information was reported and evidence largely did not demonstrate change. In NICE appraisals, HSUVs were derived through the collection of EQ-5D data (7/24 cases), mapping (6/24), vignettes (5/24), and published literature or other techniques (6/24). The majority did not use data collected alongside clinical trials. Few measures demonstrated significant change due to lack of sensitivity or face validity, short-term data, or implausible health states. In 8/24 NICE appraisals, patient surveys or input during appraisal committee meetings supported the interpretation of uncertainty or provided evidence about QoL.

Conclusions: This study sheds light on the nature of PRO evidence in rare diseases and associated challenges. Results emphasise the need for improved development and use of PRO/HSUVs. Other forms of evidence and expert input are crucial to support better appraisal of uncertain or missing evidence.

Consideration of quality of life in the health technology assessments of rare disease treatments

ABSTRACT

Objectives: Challenges with patient-reported outcome (PRO) evidence and health state utility values (HSUVs) in rare diseases exist due to small, heterogeneous populations, lack of disease knowledge and early onset. To better incorporate quality of life (QoL) into Health Technology Assessment, a clearer understanding of these challenges is needed.

Methods: NICE appraisals of non-oncology treatments with an EMA orphan designation (n=24), and corresponding appraisals in the Netherlands, France, and Germany were included. Document analysis of appraisal reports investigated how PROs/HSUVs influenced decision-making and was representative of QoL impact of condition and treatment.

Results: PRO evidence was not included in 6/24 NICE appraisals. When included, it either failed to demonstrate change, capture domains important for patients, or was uncertain. In the other countries, little information was reported and evidence largely did not demonstrate change. In NICE appraisals, HSUVs were derived through the collection of EQ-5D data (7/24 cases), mapping (6/24), vignettes (5/24), and published literature or other techniques (6/24). The majority did not use data collected alongside clinical trials. Few measures demonstrated significant change due to lack of sensitivity or face validity, short-term data, or implausible health states. In 8/24 NICE appraisals, patient surveys or input during appraisal committee meetings supported the interpretation of uncertainty or provided evidence about QoL.

Conclusions: This study sheds light on the nature of PRO evidence in rare diseases and associated challenges. Results emphasise the need for improved development and use of PRO/HSUVs. Other forms of evidence and expert input are crucial to support better appraisal of uncertain or missing evidence.

Introduction

Rare diseases are conditions affecting a small number of patients (e.g. less than 1/2,000 people in Europe), which are life-threatening and/or chronically debilitating, frequently genetic and with an early onset [1, 2]. Quality of life (QoL) of patients living with a rare disease is often poor due to multiple aspects affecting functioning [3]. This is partly explained by issues around diagnostic delays, and/or a lack of knowledge about the disease, its treatment pathways or treatment options [3]. Given the severity of these conditions and paucity of curative treatments, understanding their impact on QoL is crucial, particularly when assessing the benefit of a new treatment.

Health Technology Assessment (HTA) aims to assess the value of a treatment to inform decisions on whether it should be provided routinely to the relevant patient population. The assessment generally relies on clinical and patient-reported outcome (PRO) endpoints, which provide evidence about health outcomes and impact on patients' wellbeing [4]. In the latter case, PRO evidence is collected directly from patients or proxies using patient-reported outcome measures (PROMs) [5]. PROMs are intended to capture aspects that matter most to patients about the impact of disease and treatment on symptoms, QoL or health status [6].

HTA relies on the critical assessment of added benefit or cost-effectiveness of a treatment. This is then appraised by a Committee, taking account of other relevant factors, who decide on reimbursement (and pricing in some cases). Added benefit is assessed by considering the magnitude and certainty of treatment benefit over existing therapies based on the clinical and PRO evidence presented. The level of benefit is then generally ranked into categories as, for example, in France, where the added benefit (ASMR) is ranked between I and V. In cost-effectiveness assessments, an economic evaluation is conducted that models the progression through health states along the care pathway, with and without the new treatment under review. In order to assist cost-effectiveness assessments, techniques have been developed to translate PRO evidence into numerical values called health state utility values (HSUVs). HSUVs represent individual preferences for given health states measured on a scale between 0, representing dead and 1, full health (with negative values implying states considered to be worse than dead). These are then merged with survival data (e.g., length of life) into a composite measure called quality-adjusted life-year (QALY). HSUVs represent the utility value associated with the different models' health states, for both treatment and comparator arms [7]. The most common way of deriving HSUVs is currently using indirect techniques, e.g. preference-based instruments such as EQ-5D that are accompanied by an algorithm (or a set of tariffs) providing HSUVs. Tariffs are pre-determined at individual country level by a sample of the general population that uses direct techniques (e.g. time trade-off) to express preferences for a subset of health states derived from the combination of instrument's dimensions and levels.

Challenges exist when developing and using PRO evidence and HSUVs for HTAs of rare diseases treatments due to the small and heterogeneous nature of the patient populations, and frequent lack of knowledge about the disease [8, 9]. Additionally, patients are often children or infants who cannot

1 self-report and who may be cognitively impaired or unable to communicate. There may also be
2 distinct challenges around capturing meaningful outcomes, including: difficulty achieving concept
3 validity through concept saturation, use of methods that may not capture aspects important for
4 patients, or selecting the appropriate PROM when natural history is poorly understood. There are also
5 few validated disease-specific PROMs for rare diseases, probably due to the amount of time and
6 resources needed to develop these instruments, which are further complicated by the nature of these
7 diseases [10].
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10 Additional challenges frequently encountered when deriving and using HSUVs for rare diseases
11 include the need for a large number of respondents to minimise random measurement errors (e.g.
12 person-trade-off, development of mapping algorithms), identification of appropriate values
13 corresponding to the model's health states from the existing literature, and QALYs being insufficiently
14 sensitive to disease severity or changes that are important for patients [11–14].
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18 Although these challenges in measuring QoL are common to all rare disease treatments, they are
19 most important in treatments of non-oncological diseases, since in cancer the main value of treatment
20 is often increased survival, and many rare disease treatments in cancer are for sub-populations of a
21 more common cancer for which validated QoL measures may be available.
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25 To better incorporate QoL evidence into HTA decision-making, a clearer understanding of the
26 challenges encountered when using PRO evidence and HSUVs in rare diseases is needed. Hence
27 this research explored how QoL evidence has been used in appraisal of non-oncology rare disease
28 treatments in a selection of countries using different HTA approaches.
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32 33 34 35 **Methods**

36 37 **Study sample**

38 For this EU Horizon2020 project, European countries were selected to represent those that make
39 decisions based on added clinical benefit and those that focus on cost-effectiveness, and who have
40 publicly available reports. Those selected were England (National Institute for Health and Care
41 Excellence, NICE) and the Netherlands (National Health Care Institute, ZIN) as users of the cost-
42 effectiveness approach, and France (Haute Autorité de Santé, HAS) and Germany (Federal Joint
43 Committee, G-BA) as users of the added benefit approach. Considering the depth of the analysis
44 conducted, the inclusion of four countries was considered sufficient to understand the nuances
45 between one HTA approach and another, and the types of contrasts within one approach. As only the
46 reports from NICE presented detailed information about the committee deliberations of the QoL
47 evidence, the analysis focused on the NICE appraisals, and other countries' appraisals were used as
48 a contrast to highlight any different approaches.
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53 All treatments with a European Medicines Agency (EMA) orphan medicinal product designation and
54 appraised by NICE within its Technology Appraisal (TA) or Highly Specialised Technologies (HST)
55 programmes before 1 June 2020 were selected (n=50). Cancer treatments (26) were excluded
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1 because added benefit often relies on survival gains, and many rare cancers are subsets of more
2 common cancers for which a validated PRO often exists [4, 15]. This left 24 rare disease treatments
3 (12 TA and 12 HST) for analysis [16, 17, 26–35, 18, 36–39, 19–25] In the results section, the
4 information reported for the individual NICE sample was extracted from these reports.
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6 7 **Data collection and analysis**

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9 Information about QoL, PROs, HSUVs and other evidence from patients about their QoL (such as
10 patient group submissions and patient expert input) was extracted from NICE’s appraisal reports.
11 These were sufficiently detailed to enable documentation of the source of the evidence, results,
12 issues highlighted by the appraisal committee and the influence on the decision. If needed, supporting
13 documentation such as manufacturer submissions and Evidence Review Group (ERG) reports were
14 reviewed. A published framework was used to extract these key aspects of the appraisal in a
15 structured way [40]. PRO evidence was categorised on the basis of the type of PROM used (generic,
16 disease-group (developed for a range of conditions), disease-specific or symptom-specific). HSUVs
17 were categorised on the basis of the technique used to derive them (e.g. collection using an
18 instrument such as EQ-5D, or mapping from other PROMs).
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25 Thematic analysis was undertaken to identify issues arising in appraisals and their influence on
26 decision-making based on the researchers’ interpretation of the discussion reported in the published
27 documents. The identification of themes was done iteratively and was continuously refined while the
28 researchers familiarised themselves with the data and grouped the data in a logical way to allow for a
29 better understanding of the decision process [41]. Once the themes were identified and categorised,
30 the researchers assessed the level of influence of PRO evidence or patient evidence on decisions.
31 This was categorised as “influence” when the Committee explicitly recognised and accounted for a
32 change in QoL in their decisions, “possible influence” when PRO evidence or patient evidence was
33 explicitly reported but considered limited by the Committee and it was therefore unclear whether it
34 influenced the decision, and “no influence” when PRO evidence or patient evidence was reported, but
35 inconclusive or failed to demonstrate change and did not influence the Committee’s decision. HSUVs
36 were considered in all cases to have influence on the decision, since the Committee always took note
37 of the incremental cost per QALY ratio. The interpretation of the HSUV evidence was distinguished as
38 “accepted” when the Committee recognised the evidence presented was acceptable, “not
39 commented” when no issues were raised with the HSUVs presented and therefore there was a high
40 likelihood that it was accepted, and “uncertain” when a number of issues around the HSUV were
41 highlighted, which rendered their interpretation challenging.
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51 The second set of extracted information related to the burden of disease and treatment impact:
52 infant/childhood onset; progressive; heterogeneous; multi-systemic; debilitating; life-threatening;
53 supportive care; and regarding the impact of treatment on QoL: length of life improved, QoL improved
54 from reduced symptoms, daily living, families/carers, compared to current treatment, administration
55 mode. The burden of disease and intended impact of the treatments reported in the HST and TA
56 programmes, respectively, were extracted and compared.
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1 The analysis aimed to understand how QoL was appraised, and the extent to which PRO evidence
2 and/or HSUVs were considered appropriate. The possible influence of the nature of the rare diseases
3 on PRO evidence and HSUV estimates was also explored to generate a better understanding of what
4 was feasible in the different contexts. In the cross-country analysis, the information reported by the
5 other countries was scarce. The focus was therefore on the PRO evidence and HSUVs considered
6 and their influence on the decision.
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10 Results

11 Impact of disease and treatment on quality of life

12 Most of the diseases undergoing the TA and HST processes were life-threatening and/or debilitating
13 (Figure 1). The burden of disease, however, was greater in the diseases undergoing the HST
14 programme compared with the TA in that these diseases affect children, have a heterogeneous and
15 progressive nature, or affect multiple organs. With the exception of the prophylaxis treatment
16 letermovir, the symptoms of all of the diseases analysed affect patients' daily living and QoL. No
17 previous treatments were available for 58% (7/12) and 17% (2/12) of those undergoing the HST and
18 TA processes, respectively.
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26 In terms of the intended effects of treatment, 67% (8/12) of HST and 83% (10/12) of TA treatments
27 aim to improve length of life, while all improve patients' daily living and QoL by reducing symptoms
28 (with the exception of letermovir). Six of these aim solely to improve QoL. Furthermore, all of the HST
29 and 83% (10/12) of the TA treatments aim to improve patients' daily living and QoL over standard of
30 care. In 50% of all cases (12/24), QoL improvement is linked to a different administration mode.
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34 All conditions appraised by HST and half of those by TA were considered to affect carer QoL. In all
35 cases, with the exception of letermovir, the treatment intends to improve their QoL.
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38 The estimated yearly number of patients to be treated in England ranged between 1-50 for 10 of the
39 12 HST treatments [1-7 patients for 3 treatments, 20-35 for 2 treatments, 50-100 for 3 treatments, and
40 140-150 for 2 treatments]. No details about patient numbers were provided in all other cases.
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45 <Figure 1. Proportion of appraisals for which various items of burden of disease and treatment impact
46 are relevant in NICE Highly Specialised Technology and Technology Appraisal programmes (n=24)>
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51 Use and influence of PRO evidence in NICE appraisals

52 In NICE appraisals, PROMs can have an influence either through being considered directly and/or
53 through their use in generating HSUVs. Across the 24 treatments appraised by NICE, 28 different
54 PROMs were reported. This included 10 generic PROMs considered across 14 treatments, seven
55 disease-group PROMs across seven treatments, three disease-specific PROMs across five
56 treatments, and eight symptom-specific PROMs across seven treatments (Table 1). Several PROMs
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could be considered for the same treatments. Examples of disease-group PROMs include the Paediatric Outcomes Data Collection Instrument (PDOCI) measuring functional outcomes in paediatric orthopedics [42], and the St George's Respiratory Questionnaire (SGRQ) measuring overall health, daily life, and perceived well-being in patients with obstructive airways disease [43]. The three disease-specific PROMs considered were for cystic fibrosis (Cystic Fibrosis Questionnaire Revised questionnaire, CFQ-R), recurrent angioedema (Angioedema Quality of Life questionnaire, AE-QoL), and neuronal ceroid lipofuscinosis type 2 (Neuronal Ceroid Lipofuscinosis Type 2 Quality of Life Instrument, CLN2-QoL). The seven symptom-specific PROMs related to pain, gastro-intestinal symptoms, diabetic neuropathy, fatigue, asthma, and anxiety and depression (Table 2).

Forty-two percent (10/24) of submissions did not include any generic PRO, and 25% (6/24) no PRO evidence at all. Reasons for the latter included PRO evidence not collected in trials (elosulfase alfa, obetocholic acid, holoclar), collected but limited (strimvelis), being collected and not reported (burosumab), or not presented given it was a re-assessment based on new clinical evidence (pirfenidone). In two of the cases without PRO evidence, other QoL evidence was considered, such as observational studies and cross-sectional surveys involving patients and families (elosulfase alfa), and visual acuity data from the literature used to derive HSUVs (holoclar) (Table 1). QoL evidence for the remaining drugs without PRO data was based on HSUVs derived from vignettes or published evidence (Table 3, discussed in the next section on HSUVs).

<Table 1. Types and influence of PRO evidence considered in NICE TA and HST appraisals of non-oncology rare disease treatments (n=24)>

<Table 2. Use and influence of PRO evidence in NICE TA and HST appraisals of non-oncology rare disease treatments (n=24)>

Further exploration of the influence of PRO evidence on NICE decisions suggested that beyond those used to derive HSUVs, few of them had any influence on the decisions (Tables 1 and 2).

Of the 14 appraisals considering generic PRO evidence, eight were used to derive HSUVs and the remaining six had unclear or no influence on the decisions. For asfotase alpha, the EQ-5D data collected in a patient survey may have been considered by clinicians when developing the vignette's health states, but it is not discussed in the report. For cerliponase, it was inconclusive due to the lack of correspondence between EQ-5D and the model's health states, and short trial duration for the Pediatric Quality of Life Inventory (PedsQL). For ataluren, no significant improvements in the PedsQL were shown, despite the positive trend in the functioning subscale. For the remaining treatments (migalastat, letermovir, lanadelumab), the SF36 and EQ-5D collected did not show any significant improvements and were not considered.

With the exception of one disease-group PROM used to derive the economic model's HSUVs, their inclusion had limited influence. This was the case for mepolizumab, where SGRQ data, suggesting improved QoL due to fewer exacerbations and improved symptom control and lung function, was

1 mapped to EQ-5D to obtain HSUVs. In the other cases, the PODCI data collected for ataluren
2 showed improvements on two dimensions, but was considered uncertain due to the short trial
3 duration. In all other cases (letermovir, asfotase alfa, voretigene, darvadstrocel and nintedanib), the
4 disease-group PROMs, Functional Assessment of Cancer Therapy - Bone Marrow Transplantation
5 (FACT-BMT), PODCI, Visual Function Questionnaire (VFQ), perianal disease activity index (PDAI),
6 SGRQ or Shortness of Breath Questionnaire (SOBQ) either did not show a significant improvement or
7 were not reported.
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10 A similar situation was seen for the disease-specific PROMs. For only one case, colistimethate
11 sodium and tobramycin DPI, the CFQ-R was mapped to HSUVs and used for the decision. However,
12 it did not show any improvement in QoL relating to administration mode (dry powders for inhalation
13 versus nebuliser) given a non-inferiority trial design was adopted. For three treatments, the PRO
14 evidence was uncertain and thus the influence on the decision was unclear. The data collection
15 period of CLN2-QoL for cerliponase was considered too short, and the CFQ-R data collected for
16 mannitol dry and lumacaftor-ivacaftor did not show a statistically significant improvement. Results
17 from the AE-QoL data collected for lanadelumab were not commented on in the appraisal report.
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20 Of the six treatments that considered symptom-specific PROMs, one of them influenced and another
21 possibly influenced the decision. For patisiran, the Neuropathy Impairment Score (NIS) and Norfolk
22 Quality of Life Questionnaire - Diabetic Neuropathy (Norfolk QoL-DN) data collected was statistically
23 improved and contributed to recognising treatment effectiveness. For eliglustat, no significant
24 improvements were demonstrated for the Fatigue Severity Scale (FSS) and Brief Pain Inventory
25 (BPI), and it was unclear whether they were used to determine the HSUV estimated to measure the
26 impact of adverse events on QoL included in the submission. In the remaining cases, there was either
27 no demonstration of change with BPI and Gastrointestinal Symptoms Rating Scale (GSRS) for
28 migalastat and with Norfolk QoL-DN for inotersen, or results were not reported (Cough and Sputum
29 Assessment Questionnaire, CASA-Q for nintedanib, Asthma Control Questionnaire, ASQ for
30 mepolizumab and Hospital Anxiety Depression Scale, HADS for lanadelumab).
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33 For eight of these drugs, determination of QoL impact was influenced by patient evidence (Table 2).
34 First, patient surveys provided information about impact of QoL on patients and carers (eculizumab,
35 ataluren), preferences for administration mode (eliglustat, colistimethate sodium and tobramycin DPI),
36 or whether it was used to derive HSUVs (elosulfase alfa). Respondents were patients and in one case
37 also family members, three formed part of the company submissions and the other two, patient
38 submissions. Second, patients and clinicians provided input about the dimensions not captured in the
39 model (patisiran), about impact on QoL (letermovir), effect on tolerability (nintedanib), and
40 administration mode (migalastat, eliglustat, colistimethate sodium and tobramycin DPI).
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43 **Use and influence of HSUV estimates in NICE appraisals**

44 The most frequently used technique to derive HSUVs in NICE appraisals was through EQ-5D data
45 (7/23) collected within a trial (4/7) or from a registry or cohort study (3/7), followed by mapping (6/23),
46 vignettes (5/23), published literature (3/23), Health Utility Index Mark 2 (HUI2) (1/23) and other (1/23)
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1 (Table 3). No HSUVs were reported for one treatment (pirfenidone) given it was a re-assessment;
2 therefore, it was excluded from this analysis, which focused on the 23 remaining treatments. The
3 mapping technique was more frequently used in the TA, and vignettes in the HST process. Additional
4 HSUVs were derived to measure the impact on QoL of adverse events (9/23), of the administration
5 mode (4/23), of carer burden (7/23) or other (7/23) and considered alongside the HSUV derived.
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10 < Table 3. Techniques used to derive HSUVs in NICE TA and HST appraisals of non-oncology rare
11 disease treatments (n=23) >
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13 The detail and summary of the individual appraisals are summarised in Table 4. Seven treatments
14 used EQ-5D, two of which collected EQ-5D 3L in trials and the remaining collected EQ-5D 5L
15 (mapped to 3L) or foreign EQ-5D datasets converted using the UK tariff. In one case, the HSUVs
16 included in the model were considered acceptable by the TA Committee (lanadelumab). For mannitol,
17 the generic Health Utility Index Mark 2 (HUI2) was used to derive HSUV estimates. Even if EQ-5D
18 would have been preferred, the HUI2 was accepted by the relevant committee. For all remaining
19 cases, a number of issues were raised by the relevant committees, which included benefits
20 (eculizumab, migalastat) or long-term effects not captured (leteirmovir), measure insensitive to change
21 (nintedanib), uncertain duration (patisiran), or possible implausible health states (inotersen).
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30 <Table 4. Use and influence of HSUVs in NICE TA and HST appraisals of non-oncology rare disease
31 treatments (n=23) >
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36 Mapping was used in six cases, in one of which (lumacaftor-ivacaftor) the applicant developed a new
37 algorithm, while in the others published functions were used. Source measures included lung function
38 and pulmonary exacerbation (lumacaftor-ivacaftor), SF36 (eliglustat), PedsQL (nursinersen), CFQ-R
39 (colistimethate sodium and tobramycin DPI), SGRQ (mepolizumab) and visual acuity (holoclax); all
40 were converted to EQ-5D-3L. The results were considered acceptable in only one case
41 (mepolizumab), or not commented on (likely acceptable) in two cases (eliglustat, holoclax). The issues
42 raised regarding the remaining cases included: ceiling effects and little change captured even though
43 it was collected in the largest existing cystic fibrosis trial (lumacaftor-ivacaftor), limited face validity
44 resulting in expert elicitation being used to estimate the HSUVs (nursinersen), or limited
45 methodological approach (colistimethate sodium and tobramycin DPI).
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51 Vignettes were used in five cases. Reasons for their use over more conventional approaches included
52 a lack of correspondence between QoL data collected in the clinical trial and model health states
53 (cerliponase), lack of negative values when deriving the PedsQL being considered unrealistic
54 considering the condition's severity (cerliponase), or QoL data not collected in trial (darvadstrocel,
55 burosumab, voretigene). The health states were developed by patient and clinical experts
56 (voretigene), or only clinicians (cerliponase, asfotase alpha, burosumab). Respondents included
57 clinicians (voretigene, cerliponase, asfotase alpha, burosumab), or patients and public
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1 (darvadstrocel). The QoL measure included was EQ-5D-5L (cerliponase, asfotase alpha, burosumab),
2 and HUI2 and EQ-5D (voretigene).

3 A number of issues were raised about the vignettes. For voretigene, poor convergent validity between
4 EQ-5D and HUI2 and preference for EQ-5D (considered to better capture overall QoL over HUI2)
5 were highlighted. For alfotase alfa, trial data would have been preferred over vignettes by the
6 appraisal committee; however, QoL results from the vignette were compared to results from a patient
7 survey and considered aligned. Additionally, given the health states were based on the surrogate
8 outcome "six-minute walking test" (6MWT), all of the relevant symptoms that would produce lower
9 HSUVs in the more severe states may not have been captured (likely underestimate). The HST
10 Committee was also concerned with clinicians responding to the vignettes instead of patients
11 (burosumab). Furthermore, there was concern about the uncertain robustness of the vignettes given
12 an unclear association of other elements (e.g., pain) to health states (cerliponase).

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Published literature was used in three cases. This was because QoL was not measured in the trials
(strimvelis, obeticholic acid) or the available mapping algorithm was conducted on a healthy
population and thus unsuitable (ataluren). No detail on the published literature was provided for
strimvelis and ataluren, whereas for obeticholic acid, values from an analogue disease (Hep C) were
used.

In one case (elosulfase alfa), HSUVs were derived by converting improvement in 6MWT and forced
vital capacity (FVC) collected in natural history studies and combining these with the correlation
observed between 6MWT, FVC and QoL from the patient and families survey. For each additional
benefit reported by patients not captured in 6MWT or FVC, an HSUV increment was derived from the
literature. The HST Committee highlighted that the data were not collected within a trial but
recognised the challenges in collecting QoL data from children alongside the lack of validated
PROMs.

Use and influence of PRO evidence and HSUV estimates in HAS, G-BA and ZIN appraisals

Comparing the appraisal of PRO evidence by NICE with those by ZIN, G-BA and HAS, a number of
observations arose (Table 5). First, a proportion of the appraisal reports did not include any detail
about QoL evidence (38% for ZIN, 61% for HAS, and 16% for G-BA). Second, a vast majority of those
that did report QoL data were deemed inconclusive. The main reasons were the lack of statistical
significance (ZIN, HAS, G-BA), the exploratory nature of the evidence, e.g. secondary endpoint
(HAS), the non-inclusion of a hierarchical test (HAS), the lack of validated or non-clinically relevant
endpoint (G-BA). Third, in the few cases when QoL was considered to be improved by treatment in
one country, a different outcome was determined in the other countries. Only one treatment appraised
by HAS (inotersen) was considered to provide a moderate improvement in QoL, as it was one of the
trial's co-primary endpoints; whereas no meaningful clinically relevant change was recognised by
NICE and G-BA. Two treatments appraised by G-BA, patisiran and lanadelumab, were considered to
provide some benefit as they were both validated and clinically relevant endpoints. For ZIN, it was

1 unclear whether the PRO evidence had any influence on the decisions and the HSUVs appraised for
2 three treatments were considered very uncertain.
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5 <Table 5. Use and influence of PRO evidence in HAS, G-BA and ZIN appraisals of non-oncology rare
6 disease treatments>
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10 11 12 **Impact on carers**

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14 Eighteen of the treatments were considered to have an impact on carers (Table 1), whereas evidence
15 on carer impact was considered for only nine of these by NICE (8 HST and 1 TA). Impact of disease
16 and treatment on carers was considered either qualitatively or quantitatively through HSUVs. In the
17 former case, the relevant committees discussed the burden on carers during the deliberative process
18 (mepolizumab, strimvelis, asfotase alfa), and in other cases, considered evidence from patient/carers
19 surveys (eculizumab, elosulfase alfa). In the latter cases, HSUVs were derived from various sources
20 (e.g. published literature, number of carers affected, report on challenges from living and caring for a
21 sick child, or cross-sectional surveys). Some of the HSUVs submitted were changed so as to better
22 align with previous appraisals (patisiran), to only include HSUVs for children (voretigene), to reflect a
23 shorter timeframe (cerliponase), or to reflect a different number of carers (ataluren). In four of these
24 cases, carer disutility was uncertain (also in the decision). Carer QoL was not reported in the other
25 countries.
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36 **Discussion**

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38 This study explored the appraisal of QoL in all the non-oncology rare disease treatments considered
39 by NICE. It is the first study of this type, which furthers our understanding of the nature of QoL
40 evidence and the nuances of its use in HTA of rare disease treatments.
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43 **Our results primarily enable a better understanding of whether the QoL evidence was actually**
44 **considered.** The vast majority of conditions investigated, particularly in NICE's HST programme, are
45 life-threatening and/or debilitating. For all of the treatments investigated, their added benefit was also
46 considered to improve QoL. Measuring their impact on QoL is therefore critical in determining their
47 added benefit, particularly for those treatments aiming solely to improve QoL. This, however, is not
48 reflected in our results. PRO evidence was not reported for a large number of treatments across all of
49 the study countries, and when reported, most of the PROMs and results were not discussed (and
50 therefore we assume not accounted for). In the other study countries, no PRO evidence was reported
51 in 16%, 38% and 61% respectively in Germany, the Netherlands and France. It was not clear from the
52 appraisal reports why this evidence was not reported nor accounted for. When PRO evidence was
53 reported, it was limited to one or two PROMs (versus more in the NICE reports).
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1 Overall, a large amount of QoL data was collected, but these data were barely reported or referred to
2 in the appraisal reports across the different study countries. However, the 28 different PROMs
3 identified and collected in the trials are most likely covering concepts important for patients [5]. Their
4 lack of use points either to a loss of valuable information on the patient perspective, issues in
5 capturing meaningful change in rare diseases, or issues in accounting for all of these PROMs within
6 the HTA approach adopted. Results illustrate that different QoL evidence would be considered
7 depending on the HTA approach. For cost-effectiveness oriented approaches, HSUVs are
8 considered within the incremental cost-effectiveness ratio and are derived from PRO data using
9 indirect techniques (e.g. generic preference-based instruments, mapping), or measured directly from
10 patient responses using direct techniques (e.g. time-trade-off) [44]. In countries with an added clinical
11 benefit assessment approach, the PRO data would be considered and interpreted as is without being
12 derived into a numerical HSUV. To help with the comparability and interpretation of the PRO data,
13 generic PROMs are often preferred. Consideration should therefore be given to how this information
14 could be better used in HTA. This could be achieved through greater involvement in early multi-
15 stakeholder dialogues and early scientific advice to better align across HTA bodies and agree on what
16 QoL evidence would be accepted, and a greater acceptance of registry data to leverage early on data
17 on natural history on the disease.

26 **Second, our results enable a better understanding of whether the QoL evidence actually**
27 **considered was impactful.** Results point to a limited influence of PRO evidence in general. In the
28 NICE appraisals, this was because QoL is mainly measured by HSUVs used in the economic models.
29 PRO evidence was considered to support the interpretation of HSUVs included in the model in one
30 case, and potentially in a few other cases; but overall, its influence was fairly limited. Just over 1/3 of
31 the HSUVs were accepted, even if, in some cases, they were recognised as not ideal. In the
32 remaining cases, the HSUVs were highly uncertain and in most cases the relevant committee
33 recognised that all benefits were not captured. In these cases, interpretation was informed by
34 information from patient and clinicians in four cases, and a patient survey in one case.

40 Only three disease-specific PROMs were reported, but their consideration had a limited influence on
41 the decision and in only one case, it was mapped to derive HSUVs. This confirms the issue of a lack
42 of validated disease-specific preference-based PROMs and their conversion into HSUVs through
43 mapping [8, 45, 46]. Disease-group PROMs were more frequently used and may constitute a suitable
44 alternative for rare diseases; however, their influence was also limited. A similar situation was seen
45 around the use of symptom-specific PROMs. By contrast, there were a number of cases where the
46 relevant committees recognised that the QoL evidence did not capture the full range of dimensions
47 important to patients. These related to improvements in QoL, such as the ability to return to work, to
48 perform daily activities, to have a social life, to maintain independence and dignity, improving in
49 walking, better tolerability profile, reduced dosing frequency, or improved patient choice, as well as
50 decrements in QoL, such as the impact from relying on wheelchairs, or adverse events not captured.
51 However, considering that many of these domains are typically covered in PROMs, the issue may be
52 more around the lack of sensitivity of these measures rather than domains not being captured.

1 In Germany and France, most of the PRO evidence was considered inconclusive due to the frequent
2 lack of a statistically significant improvement and/or they did not meet the country-specific evidentiary
3 requirements. In Germany, PROMs need to be validated and PRO evidence clinically relevant (based
4 on a minimally important difference (MID)). However, a treatment failing to meet the MID criterion
5 does not imply lack of improvement across all patients, where there may be some patients improving
6 above the MID and others under [47]. This may be more frequent in heterogeneous and small patient
7 populations [48]. In France, the PRO endpoint should be a significant one (e.g. primary endpoint). In
8 only one case in France and two cases in Germany was QoL considered improved, and this
9 concerned different treatments. Similarly in the Netherlands, the PRO evidence was generally
10 inconclusive and the HSUVs reported in three cases were considered very uncertain.

11 Overall, findings suggest that a big proportion of the PRO evidence and HSUVs appraised are either
12 not considered or provide inconclusive uncertain outcomes. The main contrast between NICE and the
13 other countries is their willingness to account for other forms of evidence, such as patient surveys or
14 expert input to provide additional and complementary information on QoL impact. They also appear to
15 be more flexible when interpreting QoL evidence, e.g. in recognising that all benefits are not captured
16 by the measures used, and account for that when making their decisions.

17 **We then tried to understand whether the issues highlighted by the relevant committees related**
18 **to nature of rare disease treatments.** One main distinction seen in NICE's HST Programme is a
19 greater likelihood of treatments targeting children/infants or treating heterogeneous and/or multi-
20 systemic conditions. In the 15 NICE appraisals affecting children, only three considered children-
21 specific PROMs (PedsQL) and none considered any proxy-reported PRO evidence. This confirms the
22 frequent lack of validated measures in children [10], but does not reflect the common reliance on
23 proxy-reported data [9]. In only one case was the PedsQL mapped to EQ-5D, but results were limited
24 and the challenges in collecting data from children recognised (together with another case).

25 The extent to which it may be more difficult to capture meaningful and generalisable outcomes in
26 heterogeneous populations and conditions affecting multiple organs [9, 10, 49] was not entirely clear
27 from the results. There were, however, cases where evidence on QoL was lacking to estimate the
28 HSUVs required by the model (ataluren), to capture all relevant symptoms (asfotase alfa), or to deal
29 with multiple co-morbidities (mannitol).

30 Patient numbers for three HST treatments were small (an incidence of 1-7 patients/year in England),
31 possibly resulting in uncertain aggregated results [9]. In one case (cerliponase), the HST Committee
32 recognised an initial improvement in QoL based on PRO evidence. However, vignettes were used to
33 derive HSUVs due to the lack of correspondence of PRO evidence with health states. The other two
34 cases either did not report (asfotase alfa), nor collect (strimvelis) any PRO evidence, and published
35 literature was used to derive HSUVs.

36 No existing treatments were available for almost 60% of the 12 HST and 17% of the 12 TA treatments
37 (in total, 9 of 24 treatments). Current standards of care for these diseases require multi-disciplinary
38 specialised services and are considered burdensome for patients and their carers. They generally
39 entail monitoring of disease, management of symptoms, complications or disability, and/or supportive
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1 care (e.g. counselling, occupational therapy, physiotherapy, social care, palliative care, etc.). This
2 may create additional challenges in identifying the relevant domains of QoL to measure in the
3 comparative arm [50].

4
5 Three quarters of the conditions appraised affect QoL of families and carers, and the treatments were
6 considered to improve their QoL. None of the PRO evidence collected and reported related to carer
7 burden. However, the NICE Committees did account for the impact on carers either qualitatively or in
8 cases where impact on carer's QoL was collected within a patient and carer survey (eculizumab). On
9 the other hand, carer HSUVs were estimated in only eight cases for which more than half the data
10 were uncertain or inconclusive. This further emphasises the tendency for inconsistent inclusion of
11 carer HSUVs and the variety of approaches used for their measurement [51]. There is a need for
12 methodological guidance on when and how to include carer HSUVs in QALY and non-QALY
13 approaches to HTA [52]. Considering that 80% of rare diseases affect children, and are often severe
14 and disabling, including carer QoL is crucial in determining the added benefit of a new treatment.
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22 **Limitations**

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24 This study is not without limitations. First, it relies on information from a small number of appraisals,
25 which is unavoidable given the small number of RDTs (excluding oncology treatments) considered
26 each year. Secondly, it relies on official reports, which may not comprehensively depict the full
27 appraisal process. This was more pronounced for some study countries that do not provide detail of
28 their appraisal of the evidence. Based on expectations around transparency, we considered that the
29 items documented in the HTA reports included the most important determinants of decisions. Further,
30 there may have been some limitations relating to language barriers given the use of google translator
31 for some of the countries. However, no inconsistencies across countries were identified that could
32 indicate missing or misinterpreted information. Additionally, our document analysis was qualitative
33 and as a result, we may have missed or misinterpreted some aspects leading to the decision. Given
34 the complexity of some of these appraisals, it was challenging to identify explanations for some of the
35 limitations highlighted, and how they related to the nature of rare diseases. However, we attempted to
36 identify some possible explanations and examples on some of the implications. Finally, this study
37 highlights some of the nuances in considering QoL evidence in rare diseases. It is possible that some
38 of the same issues could arise in the HTA of more common diseases. Further research would be
39 needed to compare the results from this analysis with those from a similar analysis of HTAs for
40 common non-cancer treatments.
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52 **Conclusions**

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54 This study highlights some of the limitations and challenges in appraising PRO evidence and HSUVs
55 to understand the impacts of a rare condition and treatments on QoL, and the influence of these
56 aspects on determination of value. In many cases, PRO evidence did not have a major influence in
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HTA decisions, as it often did not demonstrate meaningful change or was inconclusive. The HSUVs were often very uncertain due to numerous reasons, such as being insensitive to change, ceiling effects, limited face validity, not capturing all domains important to patients, lack of long-term data or methodological issues. This emphasises the need for improved development, testing, use and reporting of PRO evidence, and use of HSUVs that are better adapted to rare disease specificities, such as small sample sizes. HTA bodies would also benefit from greater flexibility in accepting less conventional techniques to derive HSUVs, for example, using vignettes, but there is a need to develop methodologies that support their robust development and application. Additionally, patient evidence, including patient surveys, focus groups, interviews, and expert testimony, have shown to be crucial for providing information about the burden of illness, treatment benefits including outcomes that matter most, and in supporting the interpretation of uncertain aspects of the QoL evidence considered important for the decision.

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Consideration of quality of life in the health technology assessments of rare disease treatments

ABSTRACT

Objectives: Challenges with patient-reported outcome (PRO) evidence and health state utility values (HSUVs) in rare diseases exist due to small, heterogeneous populations, lack of [disease](#) knowledge [of disease](#) and early onset. To better incorporate quality of life (QoL) into Health Technology Assessment ~~(HTA)~~, a clearer understanding of these challenges is needed.

Methods: NICE appraisals of non-oncology treatments with an EMA orphan designation (n=24), and corresponding appraisals in the Netherlands, France, and Germany were included. Document analysis of appraisal reports investigated how PROs ~~and~~ HSUVs influenced decision-making and was representative of QoL impact of condition and treatment.

Results: PRO evidence was not included in 6/24 NICE appraisals. When included, it either failed to demonstrate change, capture domains important for patients, or was uncertain. In the other countries, little information was reported, and evidence largely did not demonstrate change. In NICE appraisals, HSUVs were derived [through the collection of using EQ-5D data](#) ~~(in 7/24 cases)~~, mapping ~~in~~ ~~(6/24)~~, vignettes ~~in~~ ~~(5/24)~~, and published literature or other techniques ~~(6/24)~~ ~~in the remainder~~. The majority did not use data collected alongside clinical trials. Few measures demonstrated significant change due to lack of sensitivity or face validity, short-term data, or implausible health states. In 8/24 NICE appraisals, patient surveys or input [during appraisal committee meetings](#) supported the interpretation of uncertainty or provided evidence about QoL.

Conclusions: This study sheds light on the nature of PRO evidence in rare diseases and associated challenges. Results emphasise the need for improved development and use of PRO/HSUVs. Other forms of evidence and expert input are crucial to support better appraisal of uncertain or missing evidence.

Introduction

Rare diseases are conditions affecting a small number of patients (e.g. less than 1/2,000 people in Europe), which are ~~most often~~ life-threatening and/or ~~severely chronically~~ debilitating, frequently genetic and with an early onset [1, 2]. Quality of life (QoL) of patients living with a rare disease is ~~often poorer than those living with more prevalent conditions due to multiple aspects affecting functioning~~ [3]. This is partly explained by issues around ~~diagnostic delays~~, and/or a lack of knowledge about the disease, its treatment pathways or treatment options [3]. Given the severity of these conditions and paucity of curative treatments, understanding their impact on QoL is crucial, particularly when assessing the benefit of a new treatment.

Health Technology Assessment (HTA) aims to assess the value of a treatment to inform decisions on whether it should be provided routinely to the relevant patient population. The assessment generally relies on clinical and patient-reported outcome (PRO) endpoints, which provide evidence about health outcomes and impact on patients' wellbeing [4]. In the latter case, PRO evidence is collected directly from patients or proxies using patient-reported outcome measures (PROMs) [5]. PROMs are intended to capture aspects that matter most to patients about the impact of disease and treatment on symptoms, QoL or health status [6].

HTA relies on the critical assessment of added benefit or cost-effectiveness of a treatment. This is then appraised by a Committee, taking account of other relevant factors, who decide on reimbursement (and pricing in some cases). ~~Added benefit is assessed throughby considering the magnitude and certainty of treatment benefit over existing therapies based on the clinical and PRO evidence presented. The level of benefit is then generally ranked into categories as, for example, in France, where the added benefit (ASMR) is ranked between I and V. In cost-effectiveness assessments, an economic evaluation is conducted that models the progression through possible health states along the care pathway, with and without the new treatment under review, e.g. decision tree. For each health state, treatment effect and probability of that health state occurring are estimated.~~ In order to assist cost-effectiveness assessments, techniques have been developed to translate PRO evidence into numerical values called health state utility values (HSUVs). HSUVs ~~represent individual preferences for given health states are values~~ measured on a scale between 0, representing dead ~~(or negative values when ranked as worse than dead),~~ and 1, full health ~~(with negative values implying states considered to be worse than dead)~~. These are then merged with survival data (e.g., length of life) into a composite measure called quality-adjusted life-year (QALY). HSUVs represent the utility value associated with the different models' health states, for both treatment and comparator arms [7]. ~~The most common way of deriving HSUVs is currently using indirect techniques, e.g. preference-based instruments such as EQ-5D that are accompanied by an algorithm (or a set of tariffs) providing HSUVs. Tariffs are pre-determined at individual country level by a sample of the general population that uses direct techniques (e.g. time trade-off) to express~~

1 [preferences for a subset of health states derived from the combination of instrument's dimensions and](#)
2 [levels.](#)

3 ~~More nuanced e~~Challenges exist when developing and using PRO evidence and HSUVs for HTAs of
4 rare diseases treatments due to the small and heterogeneous nature of the patient populations, and
5 frequent lack of knowledge about [natural history the disease](#) [8, 9]. ~~This leads to challenges around~~
6 ~~data collection, often requiring multi-country trials, which raise additional challenges to achieve~~
7 ~~psychometric validation.~~ Additionally, patients are often children or infants ~~who cannot self-report~~
8 ~~and,~~ who may ~~also~~ be cognitively impaired or unable to communicate. There may also be distinct
9 challenges around capturing meaningful outcomes, including: difficulty achieving concept validity
10 through concept saturation, use of methods that may not capture aspects important for patients, or
11 selecting the appropriate PROM when natural history is poorly understood. There are also few
12 validated disease-specific PROMs for rare diseases, probably due to the amount of time and
13 resources needed to develop these instruments, which are further complicated by the nature of these
14 diseases [10].

15 Additional challenges frequently encountered when deriving and using HSUVs for rare diseases
16 include the need for a large number of respondents to minimise random measurement errors (e.g.
17 person-trade-off, development of mapping algorithms), identification of appropriate values
18 corresponding to the model's health states from the existing literature, and ~~QALYHSUVs~~ being
19 insufficiently sensitive to disease severity or changes that are important for patients [11–14].

20 Although these challenges in measuring QoL are common to all rare disease treatments, they are
21 most important in treatments of non-oncological diseases, since in cancer the main value of treatment
22 is often increased survival, and many rare disease treatments in cancer are for sub-populations of a
23 more common cancer for which validated QoL measures may be available.

24 To better incorporate QoL evidence into HTA decision-making, a clearer understanding of the
25 challenges encountered when using PRO evidence and HSUVs in rare diseases is needed. ~~Hence~~
26 ~~The objective of this research explored is to better understand~~ how QoL ~~evidence has been used in~~
27 ~~appraisal~~ of non-oncology rare disease treatments ~~in is appraised across a selection of~~ countries
28 using different HTA approaches.

29 **Methods**

30 **Study sample**

31 ~~For this EU Horizon2020 project, European c~~Countries were selected to represent those that make
32 decisions based on added [clinical](#) benefit and those that focus on cost-effectiveness, ~~and who~~
33 ~~approaches in HTA with have~~ publicly available reports. ~~Those selected were:~~ England (~~NICE—~~
34 National Institute for Health and Care Excellence, [NICE](#)) and the Netherlands (~~ZIN—~~National Health
35 Care Institute, [ZIN](#)) ~~as users offer~~ the cost-effectiveness approach, ~~and~~ France (~~HAS—~~Haute Autorité
36 de Santé, [HAS](#)) and Germany (~~G-BA—~~Federal Joint Committee, [G-BA](#)) ~~as users of for~~ the added

benefit approach. Considering the depth of the analysis conducted, the inclusion of four countries was considered sufficient to understand the nuances between one HTA approach and another, and the types of contrasts within one approach. In Germany, the Institute for Quality and Efficiency in Health Care (IQWiG) conducts the assessment and G-BA the appraisal[15]. At HAS in France, the Transparency Committee conducts assessments of added benefit. In England, rare disease treatments can be considered either in NICE's general Technology Appraisal (TA) programme or its Highly Specialised Treatments (HST) programme. Due to the greater availability of detailed As only the reports from NICE presented detailed information about the committee deliberations of the QoL evidence, the analysis mainly focused on the NICE appraisals, and reflections were made on how these contrast with the other countries' appraisals were used as a contrast to highlight any different approaches.

All treatments with a European Medicines Agency (EMA) orphan medicinal product designation and appraised by NICE within its Technology Appraisal (TA) or Highly Specialised Technologies (HST) either programmes before 1 June 2020 were selected (n=50). Cancer treatments (26) were excluded for the reasons outlined above because added benefit often relies on survival gains, and many rare cancers are subsets of more common cancers for which a validated PRO often exists [4, 15]. This left Twenty-four 24 rare disease treatments were selected (12 TA and 12 HST) for analysis [16, 17, 26–35, 18, 36–39, 19–25]. In the results section, the information reported for the individual NICE sample was extracted from these reports.

Data collection and analysis

Data collection consisted of extracting all relevant information about QoL, PROs, HSUVs and other evidence from patients about their QoL (patient evidence, such as patient group submissions and patient expert input) etc) was extracted from NICE's appraisal reports. These were sufficiently detailed to enable documentation of the source of the evidence, results, issues highlighted by the appraisal committee and the influence on the decision, and, if needed, from the supporting documentation available on their website (e.g., such as committee papers, manufacturer submissions and Evidence Review Group (ERG) assessment group reports were reviewed. A published. Two sets of information about (1) the appraisal of QoL were extracted, and (2) the burden of disease and impact of treatment on QoL, and (2) the appraisal of QoL were extracted. The following information was collected regarding the burden of disease: infant/childhood onset; progressive; heterogeneous; multi-systemic; debilitating; life threatening; supportive care; and regarding the impact of treatment on QoL: length of life improved; QoL improved from reduced symptoms, daily living, families/careers, compared to current treatment, administration mode. The information extracted about the appraisal of QoL was based on an existing methodological framework was used to extract in a structured way these key aspects of the appraisal- in a structured way [40]. included: (1) PRO evidence, HSUVs or other patient-based evidence considered, (2) their source (e.g. trial, patient/clinical input), (3) their outcome (e.g. meaningful change), (4) the issues highlighted by the Committee, and (5) their influence on the decision PRO evidence was categorised on the basis of the type of PROM used

(generic, disease-group (developed for a range of conditions), disease-specific or symptom-specific), and HSUVs were categorised on the basis of the technique used to derive them (e.g., collection using an instrument such as EQ-5D, or mapping from other PROMs). Patient-based evidence was defined as any other evidence on patient QoL that is not PRO or HSUV evidence. This includes evidence from surveys (e.g. on patient and families QoL impact, or administration modes preferences), and patient or clinical input supporting the interpretation of the QoL evidence during the appraisal process.

Thematic analysis was undertaken to identify the latter two items (issues arising in appraisals and their influence on decision-making) based on the researchers' interpretation of the discussion reported in the published documents. This consisted in identifying the themes arising from the information extracted for each bucket outlined in the previous paragraph, and categorising these. The identification of themes was done iteratively and was continuously refined while the researchers familiarised themselves with the data and grouped the data in a logical way to allow for a better understanding of the decision process [41]. Once the themes were identified and categorised, the researchers assessed the level of influence of PRO evidence or patient evidence on decisions. This was categorised as "influence", when the Committee explicitly recognised and accounted for a change in QoL in their decisions, "possible influence", when PRO evidence or patient evidence was explicitly reported but considered limited by the Committee and it was therefore unclear whether it influenced the decision, and; "no influence", when PRO evidence or patient evidence was reported, but inconclusive or failing to demonstrate change and did not influence the Committee's decision. HSUVs were considered in all cases to have influence on the decision, since the Committee always took note of the incremental cost per QALY ratio. The interpretation of the HSUV evidence was distinguished as "accepted" when the Committee recognised the evidence presented was acceptable, "not commented" when no issues were raised with the HSUVs presented and therefore there is a high likelihood that it was accepted, and "uncertain" when a number of issues around the HSUV were highlighted, which rendered their interpretation challenging.

The second set of information extracted information related to the following information was collected regarding the burden of disease and treatment impact: infant/childhood onset; progressive; heterogeneous; multi-systemic; debilitating; life-threatening; supportive care; and regarding the impact of treatment on QoL: length of life improved; QoL improved from reduced symptoms, daily living, families/carers, compared to current treatment, administration mode.

The burden of disease and intended impact of the treatments reported in the HST and TA programmes, respectively, were extracted and compared.

The analysis aimed to understand how QoL was appraised, and the extent to which PRO evidence and/or HSUVs were considered appropriate. The possible influence of the nature of the rare diseases on PRO evidence and HSUV estimates was also explored to generate a better understanding of what is feasible in the different contexts. In the cross-country analysis, the information reported by the

1 other countries was scarce. The focus was therefore on the PRO evidence and HSUVs considered
2 and their influence on the decision.
3

4 Results

5 Impact of disease and treatment on quality of life

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8 Most of the diseases undergoing the TA and HST processes ~~are~~were life-threatening and/or
9 debilitating (Figure 1). The burden of disease, however, was greater in the diseases undergoing the
10 HST programme compared ~~with~~to the TA ~~in terms in that of~~ these diseases ~~affecting~~affect children,
11 ~~their have a heterogeneity~~heterogeneous and progressive nature, or ~~fact that they~~ affect multiple
12 organs. With the exception of the prophylaxis treatment letermovir, ~~they~~ symptoms of all of the
13 diseases analysed affect patients' daily living and QoL. No previous treatments were available for
14 58% (7/12) and 17% (2/12) of those undergoing the HST and TA processes, respectively.
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18 In terms of the intended effects of treatment, 67% (8/12) of HST and 83% (10/12) of TA treatments
19 aim to improve length of life, while all improve patients' daily living and QoL by reducing symptoms
20 (with the exception of letermovir). Six of these aim solely to improve QoL. Further~~more~~more, all of the HST
21 and 83% (10/12) of the TA treatments aim to improve patients' daily living and QoL over standard of
22 care. In 50% of all cases (12/24), QoL improvement is linked to a different administration mode.
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26 All conditions appraised by HST and half of those by TA were considered to affect carer QoL. In all
27 cases, with the exception of letermovir, the treatment intends to improve their QoL.
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31 The estimated yearly number of patients to be treated in England ranged between 1-50 for 10 of the
32 12 HST treatments [1-7 patients for 3 treatments, 20-35 for 2 treatments, 50-100 for 3 treatments, and
33 140-150 for 2 treatments]. No details ~~s~~ about patient numbers were provided in all other cases.
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39 <Figure 1. Proportion of appraisals for which various items of burden of disease and treatment impact
40 are relevant in NICE Highly Specialised Technology and Technology Appraisal programmes (n=24)>
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45 Use and ~~i~~influence of PRO evidence in NICE appraisals

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47 ~~In NICE appraisals, PROMs can have an~~and influence either through being considered directly, and/or
48 ~~through its~~their use in generating HSUVs. Across the 24 treatments appraised by NICE, 28 different
49 PROMs were reported. This included 10 generic PROMs considered across 14 treatments, seven
50 disease-group PROMs across seven treatments, three disease-specific PROMs across five
51 treatments, and eight symptom-specific PROMs across ~~six~~seven treatments (Table ~~Figure 21~~).
52 Several PROMs ~~may have been~~could considered for the same treatments. Examples of disease-
53 group PROMs include the Paediatric Outcomes Data Collection Instrument (PDOCI) measuring
54 functional outcomes in paediatric orthopedics [42], and the St George's Respiratory Questionnaire
55 (SGRQ) measuring overall health, daily life, and perceived well-being in patients with obstructive
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airways disease [43]. The three disease-specific PROMs considered were for cystic fibrosis (Cystic Fibrosis Questionnaire Revised questionnaire, CFQ-R), recurrent angioedema (Angioedema Quality of Life questionnaire, AE-QoL), and neuronal ceroid lipofuscinosis type 2 (Neuronal Ceroid Lipofuscinosis Type 2 Quality of Life Instrument, CLN2-QoL). The seven symptom-specific PROMs related to pain, gastro-intestinal symptoms, diabetic neuropathy, fatigue, asthma, and anxiety and depression (Table 24).

Forty-two percent (10/24) of submissions did not include any generic PRO, and 25% (6/24) no PRO evidence at all. Reasons for the latter included PRO evidence not collected in trials (elosulfase alfa, obetocholic acid, holoclar), collected but limited (strimvelis), being collected and not reported (burosumab), or not presented given it was a re-assessment based on new clinical evidence (pirfenidone). In two of the cases without PRO evidence, other QoL evidence ~~were~~ was considered, such as observational studies and cross-sectional surveys involving patients and families (elosulfase alfa), and visual acuity data from the literature used to derive HSUVs (holoclar) (Figure 2 Table 1). QoL evidence for the remaining drugs without PRO data was based on HSUVs derived from vignettes or published evidence (Table 3, discussed in the next section on HSUVs).

<Figure Table 12. Types and influence of PRO evidence considered in NICE TA and HST appraisals of non-oncology rare disease treatments (n=24)>

<Table 42. Use and influence of PRO evidence in NICE TA and HST appraisals of non-oncology rare disease treatments (n=24)>

Further exploration of the influence of ~~the~~ PRO evidence on NICE decisions ~~suggested~~ eds that beyond those used to derive HSUVs, few of them had any influence on the decisions (Tables 1 and 2 Figure 2, Table 4).

Of the 14 appraisals considering generic PRO evidence, eight were used to derive ~~the economic models'~~ HSUVs and the remaining six had unclear or no influence on the decisions. For asfotase alpha, the EQ-5D data collected in a patient survey may have been considered by clinicians when developing the vignette's health states, but it is not discussed in the report. For cerliponase, it was inconclusive due to the lack of correspondence between EQ-5D and the model's health states, and short trial duration for the Pediatric Quality of Life Inventory (PedsQL). For ataluren, no significant improvements in the PedsQL were shown, despite the positive trend in the functioning subscale. For the remaining treatments (migalastat, letermovir, lanadelumab), the SF36 and EQ-5D collected did not show any significant improvements and were not considered.

With the exception of one disease-group PROM used to derive the economic model's HSUVs, their inclusion had limited influence. This was the case for mepolizumab, where SGRQ data, suggesting improved QoL due to fewer exacerbations and improved symptom control and lung function, was mapped to EQ-5D to obtain HSUVs. In the other cases, the PODCI data collected for ataluren showed improvements ~~in-on~~ two dimensions, but ~~were~~ was considered uncertain due to the short trial

1 duration. In all other cases (letermovir, asfotase alfa, voretigene, darvadstrocel and nintedanib), the
2 disease-group PROMs, Functional Assessment of Cancer Therapy - Bone Marrow Transplantation
3 (FACT-BMT), PODCI, Visual Function Questionnaire (VFQ), perianal disease activity index (PDAI),
4 SGRQ or Shortness of Breath Questionnaire (SOBQ) either did not show a significant improvement or
5 were not reported.
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8 A similar situation was seen for the disease-specific PROMs. For only one case, colistimethate
9 sodium and tobramycin DPI, the CFQ-R was mapped to HSUVs and used for the decision. However,
10 it did not show any improvement in QoL relating to administration mode (dry powders for inhalation
11 versus nebuliser) given a non-inferiority trial design was adopted. For three treatments, the PRO
12 evidence were-was uncertain and thus their-the influence on the decision was unclear. The data
13 collection period of CLN2-QoL for cerliponase was considered too short, and the CFQ-R data
14 collected for mannitol dry and lumacaftor-ivacaftor was-not-statistically-improved-did-not-show-a
15 statistically significant improvement. Results from the AE-QoL data collected for lanadelumab were
16 not commented on in the appraisal report.
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19 Of the six treatments that considered symptom-specific PROMs, one of them influenced and another
20 possibly influenced the decision. For patisiran, the Neuropathy Impairment Score (NIS) and Norfolk
21 Quality of Life Questionnaire - Diabetic Neuropathy (Norfolk QoL-DN) data collected was statistically
22 improved and contributed to recognising treatment effectiveness. For eliglustat, no significant
23 improvements were demonstrated for the Fatigue Severity Scale (FSS) and Brief Pain Inventory
24 (BPI), and it was unclear whether they were used to determine the HSUV estimated to measure the
25 impact of on QoL of treatments for adverse events, on QoL included in the submission. In the
26 remaining cases, there was either no demonstration of change with BPI and Gastrointestinal
27 Symptoms Rating Scale (GSRS) for migalastat and with Norfolk QoL-DN for inotersen, or results were
28 not reported (Cough and Sputum Assessment Questionnaire, CASA-Q for nintedanib, Asthma Control
29 Questionnaire, ASQ for mepolizumab and Hospital Anxiety Depression Scale, HADS for
30 lanadelumab).
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33 For eight of these drugs, determination of QoL impact was influenced by patient-based evidence
34 (Table 2). First, patient surveys provided information about impact of QoL on patients and carers
35 (eculizumab, ataluren), preferences for administration mode (eliglustat, colistimethate sodium and
36 tobramycin DPI), or were-whether it was used to derive HSUVs (elosulfase alfa). Respondents were
37 patients and in one case also family members, threewe formed part of the company submissions and
38 the other two, patient submissions. Second, patients and clinicians provided input about the
39 dimensions not captured in the model (patisiran), about impact on QoL (letermovir), effect on
40 tolerability (nintedanib), and administration mode (migalastat, eliglustat, colistimethate sodium and
41 tobramycin DPI).
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43 Use and influence of HSUV estimates in NICE appraisals

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45 The most frequently used technique to derive HSUVs in NICE appraisals was through the the
46 administration of EQ-5D data (7/23) collected within a trial (4/7) or from a registry or cohort study
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(3/7), followed by mapping (6/23), vignettes (5/23), published literature (3/23), Health Utility Index Mark 2 (HUI2) (1/23) and other (1/23) (Figure-Table 3). No HSUVs were reported for one treatment (pifrenidone) given it was a re-assessment; therefore, it was excluded from this analysis, which focused on the 23 remaining treatments. The mapping technique was more frequently used in the TA, and vignettes in the HST process. Additional HSUVs were derived to measure the impact on QoL of relating to adverse events (9/23), of the administration mode (4/23), of carer burdens (7/23) or other (7/23) and were considered alongside the HSUV derived.

< Figure-Table 3. Techniques used to derive HSUVs in NICE TA and HST appraisals of non-oncology rare disease treatments (n=23) >

The detail and summary of the individual appraisals are summarised in Table 42. Seven treatments used EQ-5D, two of which collected EQ-5D 3L in trials and the remaining collected EQ-5D 5L (mapped to 3L) or foreign EQ-5D datasets converted using the UK tariff. In only one case, the HSUVs included in the model were considered acceptable by the TA Committee (lanadelumab). In only one other case, For mannitol, the generic Health Utility Index Mark 2 (HUI2) was used to derive HSUV estimates. Even if EQ-5D would have been preferred, the HUI2 was accepted by the relevant committee. For all remaining cases, a number of issues were raised by the relevant committees, which included benefits (eculizumab, migalastat) or long-term effects not captured (letermovir), measure insensitive to change (nintedanib), uncertain duration (patisiran), or possible implausible health states (inotersen). In only one other case, mannitol, the generic Health Utility Index Mark 2 (HUI2) was used to derive HSUV estimates. Even if EQ-5D would have been preferred, the HUI2 was accepted by the relevant committee.

<Table 42. Use and influence of HSUVs in NICE TA and HST appraisals of non-oncology rare disease treatments (n=23) >

Mapping was used in six cases, in one of which (lumacaftor-ivacaftor) the applicant developed a new algorithm, while in the others published functions were used. Source measures included lung function and pulmonary exacerbation (lumacaftor-ivacaftor), SF36 (eliglustat), PedsQL (nursinersen), CFQ-R (colistimethate sodium and tobramycin DPI), SGRQ (mepolizumab) and visual acuity (holoclax); all were converted to EQ-5D-3L. The results were considered acceptable in only one case (mepolizumab), or not commented on (likely acceptable) in two cases (eliglustat, holoclax). The issues raised regarding the remaining cases included: ceiling effects and little change captured even though it was collected in the largest existing cystic fibrosis trial (lumacaftor-ivacaftor), limited face validity resulting in expert elicitation being used to estimate the HSUVs (nursinersen), or limited methodological approach (colistimethate sodium and tobramycin DPI).

Vignettes were used in five cases. Reasons for their use over more conventional approaches included the a lack of correspondence between QoL data collected in the clinical trial and model health states

1 (cerliponase), lack of negative values when deriving the PedsQL being considered unrealistic
2 considering the condition's severity (cerliponase), or QoL data not collected in trial (darvadstrocel,
3 burosumab, voretigene). The health states were developed by patient and clinical experts
4 (voretigene), or only clinicians (cerliponase, asfotase alpha, burosumab). Respondents included
5 clinicians (voretigene, cerliponase, asfotase alpha, burosumab), or patients and public
6 (darvadstrocel). The QoL measure included was EQ-5D-5L (cerliponase, asfotase alpha,
7 burosumab), and HUI2 and EQ-5D (voretigene).
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10 A number of issues were raised about the vignettes. For voretigene, poor convergent validity between
11 EQ-5D and HUI2 and preference for EQ-5D (considered to better capture overall QoL over HUI2)
12 were highlighted. For alfotase alfa, trial data would have been preferred over vignettes by the
13 appraisal committee; however, QoL results from the vignette were compared to results from a patients
14 survey and considered aligned. Additionally, given the health states were based on the surrogate
15 outcome "six-minute walking test" (6MWT), all of the relevant symptoms that would produce lower
16 HSUVs in the more severe states may not have been captured (likely underestimate). The HST
17 Committee was also concerned with clinicians responding to the vignettes instead of patients
18 (burosumab). Furthermore, there was also concern about the uncertain robustness of the vignettes
19 given an unclear association of other elements (e.g., pain) to health states (cerliponase).
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23 Published literature was used in three cases. This was because QoL was not measured in the trials
24 (strimvelis, obeticholic acid) or the available mapping algorithm was conducted on a healthy
25 population and thus unsuitable (ataluren). No detail on the published literature was provided for
26 strimvelis and ataluren, whereas for obeticholic acid, values from an analogue disease (Hep C) were
27 used.
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34 In one case (elosulfase alfa), HSUVs were derived by converting improvement in 6MWT and forced
35 vital capacity (FVC) collected in natural history studies and combining these with the correlation
36 observed between 6MWT, FVC and QoL from the patient and families survey. For each additional
37 benefit reported by patients not captured in 6MWT or FVC, an HSUV increment was derived from the
38 literature. The HST Committee highlighted that the data were not collected within a trial, but
39 recognized the challenges in collecting QoL data from children alongside the lack of validated
40 PROMs.
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46 Use and influence of PRO evidence and HSUV estimates in HAS, G-BA and ZIN appraisals

47 Comparing the appraisal of PRO evidence by NICE with those by ZIN, G-BA and HAS, a number of
48 observations arose (Table 45). First, a proportion of the appraisal reports de-did not include any detail
49 about QoL evidence (38% for ZIN, 61% for HAS, and 16% for G-BA). Second, a vast majority of those
50 that did report QoL data were deemed inconclusive. The main reasons were the lack of statistical
51 significance (ZIN, HAS, G-BA), the exploratory nature of the evidence, e.g. secondary endpoint
52 (HAS), the non-inclusion of a hierarchical test (HAS), the lack of validated or non-clinically relevant
53 endpoint (G-BA). Third, in the few cases when QoL was considered to be improved by treatment in
54 one country, a different outcome was determined in the other countries. Only one treatment,
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1 inotersen, appraised by HAS ([inotersen](#)) was considered to provide a moderate improvement in QoL,
2 as it was one of the trial's co-primary endpoints; whereas no meaningful clinically relevant change
3 was recognized by NICE and G-BA. Two treatments, ~~patisiran and lanadelumab,~~ appraised by G-
4 BA, [patisiran and lanadelumab](#), were considered to provide some benefit as they were both validated
5 and clinically relevant endpoints. For ZIN, it was unclear whether the PRO evidence had any influence
6 on the decisions and the HSUVs appraised for three treatments were considered very uncertain.
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11 <Table 54. Use and influence of PRO evidence in HAS, G-BA and ZIN appraisals of non-oncology
12 rare disease treatments>
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15 16 17 18 Impact on carers

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20 Eighteen of the treatments were considered to have an impact on carers ([Table 1](#)), whereas evidence
21 on carer impact was considered for only nine of these by NICE (8 HST and 1 TA). Impact of disease
22 and treatment on carers was considered either qualitatively or quantitatively through HSUVs. In the
23 former case, the relevant committees discussed ~~during the deliberative process~~ the burden on carers
24 [during the deliberative process](#) (mepolizumab, strimvelis, asfotase alfa), and in other cases,
25 considered evidence from patient/carers surveys (eculizumab, elosulfase alfa). In the latter cases,
26 HSUVs were derived from various sources (e.g. published literature, number of carers affected, report
27 on challenges from living and caring for a sick child, or cross-sectional surveys). Some of the HSUVs
28 submitted were changes so as to better align with previous appraisals (patisiran), to ~~include~~ only
29 [include children](#)-HSUVs [for children](#) (voretigene), to reflect a shorter timeframe (cerliponase), or to
30 reflect a different number of carers (ataluren). In four of these cases, carer disutility was uncertain
31 (also in the decision). Carer QoL was not reported in the other countries.
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41 Discussion

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43 This study explored the appraisal of QoL ~~of in a sample of all the~~ non-oncology rare disease treatments
44 [considered by NICE](#). It is ~~at the~~ first study of this type, which furthers our understanding of the nature of
45 QoL evidence and ~~its~~ the nuances [of its use in for](#) HTA ~~in of~~ rare disease [treatments](#).
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49 **Our results primarily enable a better understanding of whether the [QoL](#) evidence was actually**
50 **considered.** The vast majority of conditions investigated, particularly in NICE's HST programme, are
51 life-threatening and/or debilitating. ~~For all of the treatments investigated, their added benefit was also~~
52 ~~considered to improve QoL. All of the treatments investigated aimed to improve QoL and, for 75% of~~
53 ~~these, also length of life.~~ Measuring their impact on QoL is therefore critical in determining their added
54 benefit, particularly for those treatments aiming solely to improve QoL. This, however, is not reflected
55 in our results. PRO evidence was not reported for a large number of treatments across all of the study
56 countries, and when reported, most of the PROMs and results were not discussed (and therefore we
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1 assume not accounted for). In the other study countries, no PRO evidence was reported in 16%, 38%
2 and 61% respectively in Germany, the Netherlands and France. It was not clear from the appraisal
3 reports why this evidence was not reported nor accounted for. When PRO evidence was reported, it
4 was limited to one or two PROMs (versus more in the NICE reports).
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6 Overall, a large amount of QoL data was collected, but these data were barely reported or referred to
7 in the appraisal reports across the different study countries. However, the 28 different PROMs
8 identified and being collected in the trials are most likely covering concepts important for patients [5].
9 Their lack of use points either to a loss of valuable information on the patient perspective, issues in
10 capturing meaningful change in rare diseases, or issues in accounting for all of these PROMs within
11 the HTA approach adopted. Results illustrate that different QoL evidence would be considered
12 depending on the HTA approach. For cost-effectiveness oriented approaches, HSUVs are
13 considered within the incremental cost-effectiveness ratio and are derived from PRO data using
14 indirect preference-based techniques (e.g., generic preference-based multi-attribute utility instruments,
15 mapping), or measured directly from patient responses using direct preference-based techniques
16 (e.g., time-trade-off, vignettes) [44]. In countries with an added clinical benefit assessment approach,
17 the PRO data would be considered and interpreted as is without being derived into a numerical
18 HSUV. To help with the comparability and interpretation of the PRO data, generic PROMs are often
19 preferred. Consideration should therefore be given to how this information could be better used in
20 HTA. This could be achieved through greater involvement in early multi-stakeholder early dialogues
21 and early scientific advice to better align across HTA bodies and agree on what QoL evidence would
22 be accepted, and a greater acceptance of registry data to leverage early on data on natural history on
23 the disease.
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36 **Second, our results enable a better understanding of whether the QoL evidence actually**
37 **considered was impactful.** Results point to a limited influence of PRO evidence in general. In the
38 NICE appraisals, this was because QoL is mainly measured by HSUVs used in the economic models.
39 PRO evidence was considered to support the interpretation of HSUVs included in the model in one
40 case, and potentially in a few other cases; but overall, its influence was fairly limited. Just over 1/3 of
41 the HSUVs were accepted, even if, in some cases, they were recognised as not ideal. In the
42 remaining cases, the HSUVs were highly uncertain and in most cases the relevant committee
43 recognized that all benefits were not captured. In these cases, interpretation was informed by
44 information from patient and clinicians in four cases, and a patient survey in one case.
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50 Only three disease-specific PROMs were reported, but their consideration had a limited influence on
51 the decision and in only one case, it was mapped to were included in only one case to derive HSUVs.
52 This confirms the issue of a lack of validated disease-specific (~~preference-based~~) PROMs and their
53 conversion into HSUVs through mapping [8, 45, 46][45][8][46]. Disease-group PROMs were more
54 frequently used and may constitute a suitable alternative for rare diseases; however, their influence
55 was also limited. A similar situation was seen around the use of symptom-specific PROMs. By
56 contrast, there were a number of cases where the relevant committees recognized that the QoL
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1 evidence did not capture the full range of dimensions important to patients. These related to
2 improvements in QoL, such as the ability to return to work, to perform daily activities, to have a social
3 life, to maintain independence and dignity, improving in walking, better tolerability profile, reduced
4 dosing frequency, or improved patient choice, as well as decrements in QoL, such as the impact from
5 relying on wheelchairs, or adverse events not captured. However, considering that many of these
6 domains are typically covered in PROMs, the issue may be more around the lack of sensitivity of
7 these measures rather than domains not being captured.
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11 In Germany and France, most of the PRO evidence was considered inconclusive due to the frequent
12 lack of a statistically significant improvement and/or ~~as~~ they did not meet the country-specific
13 evidentiary requirements. In Germany, ~~the~~ PROMs need to be validated and ~~the~~ PRO evidence
14 clinically relevant (based on a minimally important difference (MID)). However, a treatment failing to
15 meet the MID criterion does not imply lack of improvement across all patients, where there may be
16 some patients improving above the MID and others under [47]. This may be more frequent in
17 heterogeneous and small patient populations [48]. In France, the PRO endpoint should be a
18 significant one (e.g., primary endpoint). In only one case in France and two cases in Germany was
19 QoL considered improved, and this concerned different treatments. Similarly in the Netherlands, the
20 PRO evidence was generally inconclusive and the HSUVs reported in three cases were considered
21 very uncertain.
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28 Overall, findings suggest that a big proportion of the PRO evidence and HSUVs appraised are either
29 not considered or provide inconclusive uncertain outcomes. The main contrast between NICE and the
30 other countries is their willingness to account for other forms of evidence, such as patient surveys or
31 expert input to provide additional and complementary information on QoL impact. They also appear to
32 be more flexible when interpreting ~~the~~ QoL evidence, e.g., in recognising that all benefits are not
33 captured by the measures used, and account for that when making their decisions.
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38 **We then tried to understand whether the issues highlighted by the relevant committees related**
39 **to nature of rare disease treatments.** One main distinction seen in NICE's HST Programme is a
40 greater likelihood of treatments targeting children/infants, or treating heterogeneous and/or multi-
41 systemic conditions. In the 15 NICE appraisals affecting children, only three considered children-
42 specific PROMs (PedsQL) and none considered any proxy-reported PRO evidence. This confirms the
43 frequent lack of validated measures in children [10], but does not reflect the common reliance on
44 proxy-reported data [9]. In only one case was the PedsQL mapped to EQ-5D, but results were limited
45 and the challenges in collecting data from children recognised (together with another case).
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51 The extent to which it may be more difficult to capture meaningful and generalisable outcomes in
52 heterogenous populations and conditions affecting multiple organs [9, 10, 49] was not entirely clear
53 from the results. There were, however, cases where evidence on QoL was lacking to estimate the
54 HSUVs required by the model (ataluren), to capture all relevant symptoms (asfotase alfa), or to deal
55 with multiple co-morbidities (mannitol).
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58 Patient numbers for three HST treatments were small (an incidence of 1-7 patients/year in England),
59 possibly resulting in uncertain aggregated results [9]. In one case (cerliponase), the HST Committee
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1 recognised an initial improvement in QoL based on PRO evidence. However, vignettes were used to
2 derive HSUVs due to the lack of correspondence of PRO evidence with health states. The other two
3 cases either did not report (asfotase alfa), nor collect (strimvelis) any PRO evidence, and published
4 literature was used to derive HSUVs.
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6 No existing treatments were available for almost 60% of the 12 HST and 17% of the 12 TA treatments
7 (in total, 9 of 24 treatments). Current standards of care for these diseases require multi-disciplinary
8 specialised services and are considered burdensome for patients and their carers. They generally
9 entail monitoring of disease, management of symptoms, complications or disability, and/or supportive
10 care (e.g. counselling, occupational therapy, physiotherapy, social care, palliative care, etc.). This
11 may create additional challenges in identifying the relevant domains of QoL to measure in the
12 comparative arm [50].
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17 Three quarters of the conditions appraised affect QoL of families and carers, and the treatments were
18 considered to improve their QoL. None of the PRO evidence collected and reported related to carer
19 burden. However, the NICE Committees did account for the impact on carers either qualitatively or in
20 cases where impact on carer's QoL was collected within a patient and carer survey (eculizumab). On
21 the other hand, carer HSUVs were estimated in only eight cases for which more than half the data
22 were uncertain or inconclusive. This further emphasises the tendency for inconsistent inclusion of
23 carer HSUVs and the variety of approaches used for their measurement [51]. There is a need for
24 methodological guidance on when and how to include carer HSUVs in QALY and non-QALY
25 approaches to HTA [52]. Considering that 80% of rare diseases affect children, and are often severe
26 and disabling, including carer QoL is crucial in determining the added benefit of a new treatment.
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35 **Limitations**

36 This study is not without limitations. First, it relies on information from a small number of appraisals,
37 which is unavoidable given the small number of RDTs (excluding oncology treatments) considered
38 each year. Secondly, it relies on official reports, which may not comprehensively depict the full
39 appraisal process. This was more pronounced for some study countries that do not provide detail of
40 their appraisal of the evidence. Based on expectations around transparency, we considered that the
41 items documented in the HTA reports included the most important determinants of decisions. Further,
42 there may have been some limitations relating to language barriers given the use of google translator
43 for some of the countries. However, no inconsistencies across countries were identified that could
44 indicate missing or misinterpreted information. Additionally, our document analysis was qualitative
45 and as a result, we may have missed or misinterpreted some aspects leading to the decision. Given
46 the complexity of some of these appraisals, it was challenging to identify explanations for some of the
47 limitations highlighted, and how they related to the nature of rare diseases. However, we attempted to
48 identify some possible explanations and examples on some of the implications. Finally, this study
49 highlights some of the nuances in considering QoL evidence in rare diseases. It is possible that some
50 of the same issues could arise in the HTA of more common diseases. Further research would be
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needed, ~~comparing~~ to compare the results from this analysis with those from a similar analysis of HTAs for common non-cancer treatments.

Conclusions

This study highlights some of the limitations and challenges in ~~using~~ appraising PRO evidence and HSUVs ~~to understand the impacts of a rare condition and treatments on QoL, and the influence of these aspects on determination of value in appraising rare disease treatments.~~ In many cases, PRO evidence ~~did not failed to~~ have a major influence in HTA ~~decisions~~, as ~~it they~~ often ~~failed to did not~~ demonstrate meaningful change or ~~evidence~~ was inconclusive. The HSUVs were often very uncertain due to ~~various numerous~~ reasons, such as ~~being~~ insensitive to change, ceiling effects, limited face validity, ~~failed to capture not capturing~~ all domains important to patients, lack of long-term data or methodological issues. This emphasises the need for improved development, testing, use and reporting of PRO evidence, and ~~use~~ of HSUVs ~~that are~~ better adapted to rare disease specificities, ~~such as e.g.~~ small sample sizes. HTA bodies would also benefit from greater flexibility in accepting ~~use of~~ less conventional techniques to derive ~~QoL evidence, such as HSUVs, for example, using vignettes, but there is a need to develop methodologies that support their robust development and use application. vignettes or patient surveys, which are currently often not accepted. However, there is a need to better understand how to develop methodologically sound vignettes and other less conventional evidence.~~ Additionally, ~~patient patient based evidence, including patient surveys, focus groups, interviews, and and expert testimony, etc and patient and clinical and clinical input~~ have shown to be crucial ~~in for~~ providing information about the burden of illness, treatment benefits including ~~outcomes these~~ that matter most, and in ~~helping in supporting~~ the interpretation of uncertain aspects ~~of~~ the QoL evidence considered important for the decision. ~~Patients should be better informed about the different types of evidence and input that could be useful for decision making and be involved throughout the process. Future research could compare the techniques used to derive HSUVs in the HTA appraisals with those available in the published research to identify any additional learnings from the application of these techniques in specific disease areas.~~

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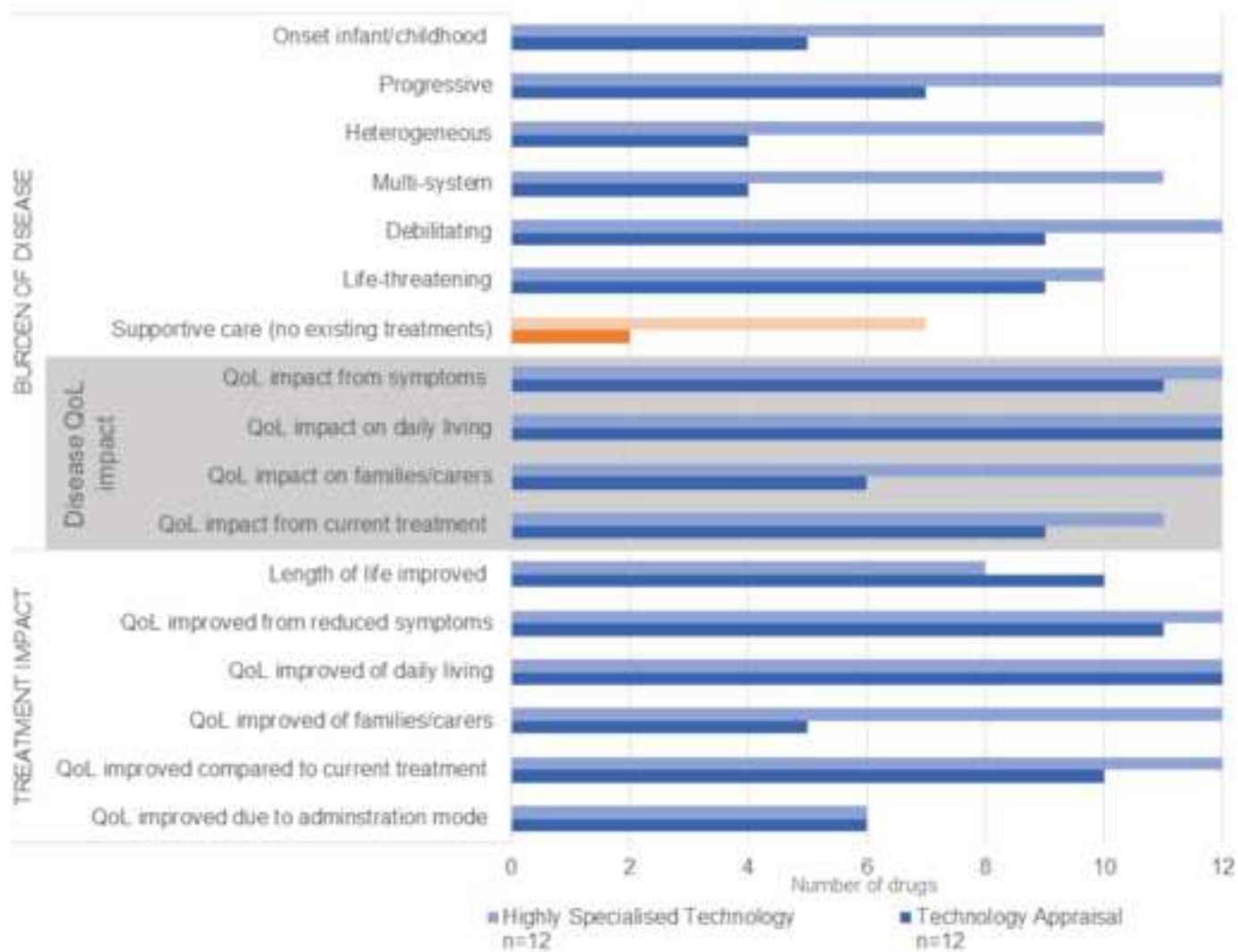


Table 1. Types and influence of PRO data and patient evidence considered in NICE TA and HST appraisals of non-oncology rare disease treatments (n=24)

| | | PRO data considered in NICE appraisals by PROM type and level of influence | | | | Patient evidence |
|---------------------------------------|---|---|-------------------|----------------------|----------------------|---------------------|
| | | Generic | Disease- group | Disease- specific | Symptom- specific | |
| NICE Highly Specialised Technology | Asfotase alfa | ++ | NR | | | |
| | Eculizumab | HSUV | | | | +++ |
| | Patisiran | HSUV | | | +++ | +++ |
| | Voretigene | | NR | | | |
| | Cerliponase | ++ | | ++ | | |
| | Elosulfase alfa* | | | | | +++ |
| | Ataluren | ++ | ++ | | | |
| | Migalastat | ≈ | | | ≈ | +++ |
| | Eliglustat | HSUV | | | ++ | +++ |
| | Strimvelis** | | | | | |
| | Burosumab** | | | | | |
| NICE Technology Appraisal | Inotersen | | | | ≈ | |
| | Mannitol | HSUV | | ++ | | |
| | Colistimethate sodium and tobramycin dry powders for inhalation (DPI) [=antibiotics] | | | HSUV | | +++ |
| | Nintedanib | HSUV | NR | | NR | ++ |
| | Lumacaftor–ivacaftor | HSUV | | ++ | | |
| | Mepolizumab | HSUV | HSUV | | NR | |
| | Obeticholic acid** | | | | | |
| | Holoclax * | | | | | |
| | Pirfenidone*** | | | | | |
| | Darvadstrocel | | NR | | | |
| | Nusinersen | HSUV | | | | |
| | Letemovir | ≈ | ≈ | | | +++ |
| | Lanadelumab | ≈ | | ≈ | NR | |

Legend: HSUV: Health State Utility Value; NICE: National Institute for Health and Care Excellent; PRO: Patient Reported Outcome; PROM: Patient Reported Outcome Measure

*No PRO data was provided, but patient based evidence or PRO data from the literature was used instead

** No PRO data was provided, QoL evidence was derived from HSUVs from vignettes or published literature

*** No PRO data was included in the appraisal report as this is a re-assessment and no new QoL evidence was presented

| | |
|-----|---|
| +++ | Influence – PRO results / patient evidence were influential in the final decision |
| ++ | Possible influence - PRO results / patient evidence were reported and suggested some type of benefit, but no discussion about these results was reported |

| | |
|------|--|
| ≈ | No influence - PRO results were reported, but did not show any benefit and no discussion about these results was reported |
| NR | Not reported / no influence - PRO results not reported, but the report listed the PROM as having been collected |
| HSUV | Used to derive HSUVs – PRO results was used to derive HSUVs (further discussed in Table X) |

Table 1. Use and influence of PRO evidence in NICE TA and HST appraisals of non-oncology rare disease treatments (n=24)

| MEDICINE Generic name - indication | PROM (by type) Instrument (source) | PRO EVIDENCE Description of results | APPRAISAL Influence of PRO evidence on decision |
|--|--|--|--|
| Asfotase alfa Paediatric-onset hypophosphatasia | G - EQ-5D (EU patient survey) G - CHAQ, LEFS (small trials) | EQ-5D - children 0.76 treatment arm vs 0.43 no treatment - adults 0.39 no treatment - scores varied depending on walking ability [-0.24 to 0.73 in children, -0.01 to 0.51 in adults] Other trial PRO data in academic confidence | EQ-5D results not used to derive HSUVs but may have been considered by clinicians when developing the vignette's health states based on 6MWT severity levels. Specifically, mental health and pain domains |
| Eculizumab Atypical haemolytic uraemic syndrome (aHUS) | G - EQ-5D (2 phase II prospective, open-label, non-randomised, single arm trials, n=37) P - Survey (patient submission, n=37) | EQ-5D: mean improvement = 0.208 Survey: burden of disease and of current treatment on patients, carers/families | EQ-5D used to derive HSUVs. Survey shows greatly impaired QoL of patients and carers from living with aHUS |
| Patisiran Hereditary transthyretin amyloidosis | G - EQ-5D-5L (RCT, n=255) D - NIS, Norfolk-DN (RCT, n=255) P - <u>Patient and clinical</u> input | All PRO evidence significantly improved. NIS was trial's primary endpoint <u>Patient input: factors not captured in model important for patients, e.g. ability to walk</u> | EQ-5D-5L used to derive HSUVs. Effective based on significantly improved outcomes. PRO evidence captures most relevant treatment impacts, except for ability to return to work, daily activities, social life, impact on carers and families. Higher ICER accepted given effect size and aspects not captured. |
| Voretigene Inherited retinal dystrophies | D - VFQ (patient survey) | Results not reported as confidential | The committee highlighted preference for QoL ↓ collected from trials |

| MEDICINE Generic name - indication | PROM (by type) Instrument (source) | PRO EVIDENCE Description of results | APPRAISAL Influence of PRO evidence on decision |
|---|---|---|---|
| Cerliponase Neuronal ceroid lipofuscinosis type 2 | G - EQ-5D 5L, PedsQL, PedsQL-FM (pivotal trial, single-arm, open-label, n=23, children 3-16 years) D - CLN2-QoL (pivotal trial) | QoL evidence: improvement in initial treatment phase (only short term data) | Recognition of limited QoL evidence due to short term data. Unclear if PRO data influenced committee discussions |
| Elosulfase alfa Mucopolysaccharidosis type IVa | P - e Cross-sectional survey from patient and family, company submission, 63 patients + 56 families O - Observational study on natural history (n = 325 people, up to 10 years) | No PROMs collected in trials Surveys: QoL impact related to reliance on wheelchair, endurance, pulmonary function and height. Impact on carers up to 15 hours/day Observational study: decline in endurance, restricted growth, limitations in daily living | Survey used to derive HSUVs Observational study: supported interpretation of impact on QoL and HSUVs, including aspects not captured in HSUV |
| Ataluren Duchenne muscular dystrophy | G - PedsQL (phase IIb) G - PODCI, ADLQ (RCT, confirmatory trial) P - Survey of carers (company submission) | PRO results not reported. PODCI, ADLQ confidential Survey: impact on multiple aspects of life, e.g. emotional wellbeing, mental health, personal care, ability to maintain relationships. Caregivers felt tired, depressed, anxious. In many cases, at least another family member in addition to both parents were involved in giving care (for example, siblings and grandparents) | QoL data (all): underestimate due to short trial duration (48 weeks too short to capture impact on ability to walk) PedsQL: results not aligned with patient statements on meaningful stabilisation or improvement in walking, or ability to conduct daily activities Survey: unclear influence, possibly considered in estimating extent of impact on caregivers, but not reported |

| MEDICINE Generic name - indication | PROM (by type) Instrument (source) | PRO EVIDENCE Description of results | APPRAISAL Influence of PRO evidence on decision |
|--|---|--|---|
| Migalastat Fabry disease | G - SF-36 physical and mental health components (open-label, non-inferiority RCT (ATTRACT) and RCT (FACETS)) D - BPI, GSRS (ATTRACT, FACETS) P - P atient and clinical input (oral administration) | QoL data: inconclusive (no change), except for change in GSRS <u>Input: benefits of oral administration</u> | Patient input confirmed benefit of oral administration over infusion PRO data not discussed in report, nor used to derive HSUVs |
| Eliglustat Gaucher disease | G - SF-36 general health, physical and mental components (open-label trial (ENCORE) and RCT (ENGAGE)) D - FSS, BPI (ENCORE and ENGAGE) P - p atient survey and patient submission (oral administration) | QoL: maintained with treatment FSS: fatigue > placebo (not statistically significant) SF-36, BPI: no change Patient input: preference for oral administration | SF-36 used to derive HSUV Unclear influence of PRO evidence. Adverse event HSUVs included, not clear if influenced by FSS or BPI Advantage of oral administration as key driver for decision (patient survey) |
| Strimvelis Adenosine deaminase deficiency–severe combined immunodeficiency | None | No QoL evidence presented. Data being collected within trial (not reported) | Not reported |
| Burosumab for X-linked hypophosphataemia | None | No QoL evidence presented. Data being collected within trial (not reported) | Not reported |

| MEDICINE Generic name - indication | PROM (by type) Instrument (source) | PRO EVIDENCE Description of results | APPRAISAL Influence of PRO evidence on decision |
|--|--|--|---|
| Inotersen Hereditary transthyretin amyloidosis | D – Norfolk QoL-DN (RCT) | Norfolk QoL-DN: no change in treatment arm, decrease in placebo arm | Not reported |
| Mannitol for cystic fibrosis | G - HUI2 (RCT, trial 301) D - CFQ-R (RCT, trial 302) | HUI2: no significant change CFQ-R: no significant change, improvement in respiratory, physical and vitality domains, but not significant | HUI2 used to derive HSUVs. No ideal measures to capture the QoL impact, including adverse events from current treatments, e.g. unpleasant taste or sensations, as reported by patients |
| Colistimethate sodium and tobramycin dry powders for inhalation (DPI) [=antibiotics] Pseudomonas lung infection in cystic fibrosis | D - CFQ-R (open-label RCT) P - Treatment satisfaction questionnaire: administration mode, manufacturer submission P - Patient input | Colistimethate sodium DPI CFQ-R from non-inferiority trial Tobramycin DPI No QoL data collected in trial, relied on treatment satisfaction questionnaire and patient input | Colistimethate sodium DPI CFQ-R: no improvement since non-inferiority trial Tobramycin DPI Questionnaire: higher values for DPI over nebuliser Limited influence of QoL data on decision and interpretation of economic model. Recognition of improved speed and adherence with DPI based on patient input <u>and questionnaire</u> |
| Nintedanib Idiopathic pulmonary fibrosis | G - EQ-5D, PGI-C (RCT) D - SQRQ, SOBQ, CASA-Q P - p Patient input (tolerability) | PRO data: not reported Patient input: better tolerability profile impacting <u>QoL</u> , ability to go outdoors due to less photosensitivity | EQ-5D used to derive HSUVs |

| MEDICINE Generic name - indication | PROM (by type) Instrument (source) | PRO EVIDENCE Description of results | APPRAISAL Influence of PRO evidence on decision |
|---|---|--|---|
| Lumacaftor–ivacaftor Cystic fibrosis | G - EQ-5D (RCTs TRAFFIC and TRANSPORT) D - CFQ-R (TRAFFIC and TRANSPORT) | EQ-5D: high baseline values due to patients perception of life as "normal", difficult to capture improved QoL (ceiling effect, common in cystic fibrosis). No significant difference [mean difference 0.0095 (TRAFFIC) and -0.0009 (TRANSPORT)] CFQ-R: mean difference of 2.2 < 4 MID | CFQ-R: other studies with similar severity levels showed greater changes compared to trial results EQ-5D: no evidence on reasons for being inappropriate. EQ-5D usually captures most important aspects in cystic fibrosis based on expert input |
| Mepolizumab Severe refractory eosinophilic asthma | G - EQ-5D (RCT DREAM) D - SGRQ, ASQ (RCTs MENA and SIRIUS) | SGRQ: QoL increase due to fewer exacerbations AND improved symptom control and lung function | EQ-5D used to derive HSUVs SGRQ: possible confounding (exacerbation reduction ~ fewer symptoms). Improved symptoms recognised (beyond those from fewer exacerbations). SGRQ also mapped to derive HSUVs |
| Obeticholic acid for primary biliary cholangitis | None | No PRO data collected in trial | |
| Holoclax for limbal stem cell deficiency after eye burns | None | No PRO data collected in trial | HSUVs derived from impact on visual acuity |
| Pirfenidone Idiopathic pulmonary fibrosis | None | Re-submission to extend indication to patients >80% FVC. Quality of life data not discussed (as did not change from initial submission, for which the report was no longer available) | No PROMs reported, no impact on decision (apart from QoL data captured in model). |
| Darvadstrocel Crohn's disease | D - PDAI (RCT ADMIRE) | PDAI results not reported | PDAI does not capture QoL impact (only symptoms) => preference for EQ-5D trial data |

| MEDICINE Generic name - indication | PROM (by type) Instrument (source) | PRO EVIDENCE Description of results | APPRAISAL Influence of PRO evidence on decision |
|--|---|---|--|
| Nusinersen Spinal muscular atrophy | G - PedsQL (RCT CHERISH) | PedsQL results not reported in appraisal report, only in committee papers. Data kept confidential, likely due to the challenges to collect data from babies and children for SMA | PedsQL mapped to EQ-5D |
| Letermovir Cytomegalovirus | G - EQ-5D (RCT PN001) D - FACT-BMT (PN001) P – Patient and clinical input (on QoL from preventing CMV) | PN001 trial: not powered to show changes QoL, no improvements Results confounded by mix of patients who have had CMV reactivation and started pre-emptive therapy and those who have not | Trial limitations and challenges to capture change recognized Patient and clinical experts input on QoL impact from preventing CMV accounted for in decision (ICER likely to be lower due to this, which lead to a positive decision) |
| Lanadelumab for hereditary angioedema | G - EQ-5D-5L, SF12, WPAI:GH (RCT HELP-03, open-extension HELP-04) D - AE-QoL _L , HADS (HELP-03 + 04) | EQ-5D-5L: no change due to lack of sensitivity in condition (timing of response - only two responses during attacks captured) AE-QoL _L : statistically improved Other PROMs not reported in appraisal report or committee papers | EQ-5D-5L data used to derive HSUVs Other results not commented |

Legend: G: generic patient reported outcome measure; D: disease, disease-group or symptom-specific patient reported outcome measure; P: patient-based evidence; NA: no report available; MID: minimal important difference; CHAQ: childhood health assessment questionnaire; LEFS: lower extremity functional scale; NIS: neuropathy impairment score; Norfolk-DN: Norfolk quality of life-diabetic neuropathy; VFQ: visual function questionnaire; PedsQL: Paediatric Quality of Life Inventory - Parent Report for Toddlers; PedsQL-FM: PedsQL family impact module; CLN2-QoL: CLN2 quality of life instrument; PODCI: paediatric outcomes data collection instrument; ADLQ: activities of daily living questionnaire; FSS: fatigue severity scale; BPI: brief pain inventory; CFQ-R: cystic fibrosis questionnaire revised; HUI2: Health Utility Index Mark 2; SGRQ: St George Respiratory Questionnaire; SOBQ: University of California San Diego shortness of breath questionnaire; CASA-Q: cough and sputum assessment questionnaire; PGI-C: patient global impression of change; ASQ: asthma control questionnaire; PDAI: perianal disease activity index; FACT-BMT: functional assessment of cancer therapy; AE-QoL: angioedema quality of life questionnaire; WPAI:GH: work productivity and activity impairment questionnaire - general health; HADS: hospital anxiety and depression scale; EQ-5D-5L: EuroQol-5 Dimension-5 Level

Sources: [16-39]

Table 3. Types and influence of HSUVs and patient evidence considered in NICE TA and HST appraisals of non-oncology rare disease treatments (n=24)

| | | Techniques to derive HSUVs considered in NICE appraisals | | | | Patient evidence |
|------------------------------------|--|--|---------|-----------|----------------------|------------------|
| | | by HSUV technique and level of influence | | | | |
| | | Generic PROMs | Mapping | Vignettes | Published literature | Various |
| NICE Highly Specialised Technology | Asfotase alfa | | | ≈ | | |
| | Eculizumab | ≈ | | | | +++ |
| | Patisiran | ≈ | | | | +++ |
| | Voretigene | | | ≈ | | |
| | Cerliponase | | | ≈ | | |
| | Elosulfase alfa | | | | | +++ |
| | Ataluren | | | | ++ | |
| | Migalastat | ≈ | | | | +++ |
| | Eliglustat | | ++ | | | +++ |
| | Strimvelis | | | | ++ | |
| | Burosumab | | | ≈ | | |
| NICE Technology Appraisal | Inotersen | ≈ | | | | |
| | Mannitol | +++ | | | | |
| | Colistimethate sodium and tobramycin dry powders for inhalation (DPI) [=antibiotics] | | ≈ | | | +++ |
| | Nintedanib | ≈ | | | | ++ |
| | Lumacaftor–ivacaftor | | ≈ | | | |
| | Mepolizumab | | +++ | | | |
| | Obeticholic acid | | | | ++ | |
| | Holoclax | | ++ | | | |
| | Pirfenidone* | | | | | |
| | Darvadstrocel | | | ≈ | | |
| | Nusinersen | | ≈ | | | |
| | Letermovir | ≈ | | | | +++ |
| | Lanadelumab | +++ | | | | |

Legend: HSUV: Health State Utility Value; NICE: National Institute for Health and Care Excellent; PRO: Patient Reported Outcome; PROM: Patient Reported Outcome Measure

*No HSUV results were considered as this is a re-assessment and no new QoL evidence was provided

| | |
|-----|--|
| +++ | Accepted – HSUV results / patient evidence were influential in the final decision |
| ++ | Not commented - HSUV results / patient evidence were reported and suggested some type of benefit, but no discussion about these results was reported – assumption is that they are likely to have influenced the decision |
| ≈ | Uncertain - HSUV results were reported, but were considered uncertain |

Table 42. Use and influence of HSUVs in NICE TA and HST appraisals of non-oncology rare disease treatments (n=23)*

| MEDICINE Generic name, indication | HSUV Technique, appraisal | DECISION ICER, reasons |
|---|--|--|
| Eculizumab Atypical haemolytic uraemic syndrome | EQ-5D - all benefits not captured due to lack of data - ERG's HSUV lower than manufacturers (10 versus 25 QALYs) => in both cases, substantial increase in QoL recognised | Restrict - monitoring and stopping rules Cost-consequence model ~10-25 QALYs => QoL underestimated due to lack of data => magnitude of benefit substantial despite uncertainty |
| Patisiran Hereditary transthyretin amyloidosis | EQ-5D: 5L mapped to 3L => uncertain assumptions around HSUV, duration of treatment benefit HSUV after stopping treatment - uncertain evolution after stopping => little effect on ICER HSUV carer - estimates revised to align with inotersen => considered acceptable HSUV adverse events (gastro-intestinal, GI) - possible overlap with impact captured in EQ-5D => value between manufacturer's estimate and no disutility => scenario analysis using pessimistic GI disutilities ~£125k/QALY Benefits not captured: ability to work, carry out daily activities, more active family and social life, maintain independence and dignity | List - commercial agreement ~£80-125k/QALY => no QALY weighing (~9.16 QALYs) => ICER acceptable due to additional factors (severity, rarity, size of health benefits, benefits not captured, innovativeness, impact on carers) |

| MEDICINE Generic name, indication | HSUV Technique, appraisal | DECISION ICER, reasons |
|--|--|--|
| Voretigene Inherited retinal dystrophies (caused by RPE65-mediated IRD) | Vignettes - implausible lowest health state [worse than death (-0.04)] given patients confirmed adapting to disease - few clinicians involved in development - focus of clinicians focus on vision loss rather than QoL => possible underestimation of QoL => EQ-5D more appropriate due to focus on QoL (and not vision loss) TTO (published literature) - not robust, good complement to vignettes => HSUV to fall between vignettes (company) and TTO (ERG) HSUV adverse events => suitable, small effect on ICER HSUVs carers (published literature) => only children included (adults excluded) | List - commercial agreement ICER range £114,956 (company)--£155,750 (ERG) => 1.2 QALY weight (QALY gains 12.1-17.7) |
| Cerliponase Neuronal ceroid lipofuscinosis type 2 | PedsQL - Trial QoL data not used as HSUVs unavailable for all model health states => preference for trial data, but recognition that possibility of negative values excluded, unrealistic given the severity of disability Vignettes/EQ-5D (5L mapped to 3L) - validation of vignettes and completion of EQ-5D 5L by clinical experts. 5L mapped to 3L - issues with robustness: additional elements such as pain and frequency of seizures included, but their association to motor and language scales defining health states unclear => neither source of data sufficiently robust, suggesting lack of correspondence between vignette and model health states => EQ-5D 3L mapped to HSUVs using vignettes considered, given no alternative data HSUV carers/siblings => disutilities included, but 30 years considered to better reflect real life compared to life long | List - Managed Access Agreement ICER not specified, 3.0 QALY weight |

| MEDICINE Generic name, indication | HSUV Technique, appraisal | DECISION ICER, reasons |
|--|--|--|
| Elosulfase alfa Mucopolysaccharidosis type IVa | Various approaches and sources Issues around capturing QoL: - QOL rarely collected in trials, as challenging particularly for children (e.g. recollection of how they felt before treatment) - potential issue around questions: it's not about the activities they can do post-treatment, but about how they feel => EQ-5D not collected in trial, limited evidence on QOL => lack of developed/validated methods => impact of adverse effects on QoL not included => treatment improves QOL and HSUV increment considered appropriate => uncertainty remains in HSUV modelled | List - Managed Access Agreement + commercial agreement Cost-consequence model: limited impact on incremental QALYs QoL not appropriately captured due to challenges in measuring relevant effects and collecting data from children. No QoL measures collected in trials |
| Ataluren Duchenne muscular dystrophy | HSUV scoliosis and carers (published literature) - uncertainty around scoliosis not occurring after puberty (model assumption), or applying different HSUVs after loss of walking. Company's assumption: QOL linked to ability to walk greater since loss of walking would occur later. Clinical experts commented plausibility if loss is in upper limb muscle strength when ability to walk is lost, for which no evidence was presented => unreasonable to assume different HSUVs across treatment group once ability to walk is lost given no evidence | List - Managed Access Agreement Managed Access Agreement to capture carer HSUV using EQ-5D and Child Health Utility 9D Cost-consequence model ~2.389-8.562 QALY gains Wider benefits: indirect costs/benefits (ability to work of carers, decrease in out-of-pocket costs) |

| MEDICINE Generic name, indication | HSUV Technique, appraisal | DECISION ICER, reasons |
|---|---|---|
| Migalastat Fabry disease | <p>EQ-5D (questionnaire, Dutch cohort study with UK tariff) - enzyme replacement therapy and complications (comparator)</p> <ul style="list-style-type: none"> - to measure disutility of patients undergoing enzyme replacement therapy - similar HSUV as for end-stage renal disease, stroke, heart complications - patients/clinicians emphasised major impact on QoL <p>=> uncertain disutility values</p> <p>HSUV infusion (DCE)</p> <ul style="list-style-type: none"> - 506 people from UK general population - HSUV infusion > HSUV complications <p>=> not comparable since different methods used (uncertain face validity)</p> <p>=> patient input: recognition of added benefit of migalastat over ERT infusion (convenience from oral administration)</p> <p>=> decreasing infusion-disutility by 50% decreased QALY gains (from 0.98 to 0.34 incremental QALYs)</p> | <p>Restrict - if ERT + patient access scheme</p> <p>Confidential cost-consequence model</p> <p>Migalastat considered to have similar benefits compared to ERT, with the main advantage of oral administration (patient input). Main concern about adherence with oral administration. Main driver of model infusion disutility</p> |
| Eliglustat Gaucher disease | <p>SF36 mapped to EQ-5D (published algorithm)</p> <p>HSUV adverse events</p> <ul style="list-style-type: none"> - HSUV decrements applied <p>HSUV oral administration</p> <ul style="list-style-type: none"> - HSUV increment (0.12) based on preference for oral administration (vignette commissions by manufacturer) <p>=> too high, ERG's estimate of 0.05 more plausible</p> | <p>List - Patient Access Scheme</p> <p>Cost-consequence model</p> <p>Model driven by QoL (mode of administration)</p> |

| MEDICINE Generic name, indication | HSUV Technique, appraisal | DECISION ICER, reasons |
|--|---|--|
| Asfotase alfa Paediatric-onset hypophosphatasia | Vignettes - 9 clinical experts completing EQ-5D for each level of severity (6MWT) => reasonable face validity (suitability of measure in capturing concept of interest) => not collected in trials - health states in the Markov model defined based on severity levels of 6MWT that, however, may not capture all the relevant symptoms => measure accepted due to lack of available evidence => HSUV for most severe health state very low (0.23), potentially overestimating benefits (more space for HSUV gain) => lack of correspondence between vignettes and model health states EQ-5D (European patient survey) => aligned with values in vignette study | List - Managed Access Agreement + commercial agreement Cost-consequence model ~14-25 QALYs HSUV considered to reasonably capture impact on QoL, risk of underestimation compensated by carer disutility not included in model |
| Strimvelis Adenosine deaminase deficiency–severe combined immunodeficiency | Trial QoL data not included in model because limited HSUV QoL (published literature - no detail) - Full health HSUV from general population => since no data on long term effect, these were explored within sensitivity and scenario analyses. The committee agreed lower values should be used HSUV intravenous immunoglobulin (IVIG) or severe infections - ERG: 0.75 HSUV included - plausibility confirmed by clinical experts HSUV carer - improved fast after treatment - no approach to measure - to be considered qualitatively during deliberations | List £12-120K/QALY (14.0-19.6 QALY gained) Impact of changes of QoL on model not reported |

| MEDICINE Generic name, indication | HSUV Technique, appraisal | DECISION ICER, reasons |
|--|--|---|
| Burosumab X-linked hypophosphataemia | Vignettes - 6 clinicians value QoL of patients with XLH aged 18, 40 and 60 years using EQ-5D 5L - some missing data, company inferred 1 for healed health states - scored by clinicians not patients, not from trials => approach deemed appropriate (in absence of alternatives), but highly uncertain HSUV carer (literature) - published literature on people with limited mobility => acceptable, not robust | List - Managed Access Agreement + commercial agreement £113-£150K/QALY (5.52-15.99 QALYs gained) Most/less conservative assumptions included/excluded carer disutility (and different stopping ages) resulting in ICERS ranging from £112-149k/QALY. Unclear to what extent variation due to inclusion/exclusion of carer disutility |
| Inotersen Hereditary transthyretin amyloidosis | EQ-5D (Brazilian registry converted with UK tariffs, source model HSUVs) - modelling of values from dataset with a number of assumptions, e.g. cap to ensure HSUVs do not exceed the general population => model could generate implausible health state classifications => not ideal, but acceptable, considered uncertain HSUV carer - 1 in stages 1-2, 2 in stage 3 | List - commercial agreement £96,697-£150,636/QALY (no QALY weighing) HSUV values did have some effect on model, but generally uncertain => unclear if driving the model => time-dependent HSUVs used within each health state |
| Mannitol Cystic fibrosis | HUI2 (trial) - mean disutility at baseline (0.988), average change at each timepoint added to baseline to calculation HSUV for each health state => HUI2 baseline considered high given multiple comorbidities => EQ-5D measure preferred => difficulty to value health states in chronic conditions. Standard method of using general population's valuation of QoL descriptions to generate HSUVs appropriate HSUV lung transplant and pulmonary exacerbations (literature) | Restrict - clinical parameters, 2nd line ICER<£30K Model changes with extension of life, little with changes in QoL - patients confirmed treatment improved QoL, considered important => HSUVs values very uncertain |

| MEDICINE Generic name, indication | HSUV Technique, appraisal | DECISION ICER, reasons |
|--|---|---|
| <p>Colistimethate sodium and tobramycin dry powders for inhalation (DPI) [=antibiotics] Pseudomonas lung infection in cystic fibrosis</p> | <p>HSUV Colistimethate sodium DPI CFQ-R mapped to EQ-5D => no preference-based model considered a methodological limitation Health utility study linking EQ-5D responses to FEV% health states => issue around establishing relationship, but considered more appropriate compared to manufacturer's model (mapping)</p> <p>HSUV Tobramycin DPI (patient input) => DPI to improve QoL in terms of speed and adherence compared to nebuliser</p> | <p>List - Patient Access Scheme</p> <p>Drivers of cost-effectiveness model: cost of interventions and their comparators, QALY gains/losses</p> <p>Colistimethate sodium DPI: small QALY loss (based on HSUV/QoL evidence) but substantial cost savings over nebuliser</p> <p>Tobramycin DPI: dominant - small QALY gain (no HSUV/QoL evidence, based on patient input) and cost saving (DPI dominated nebuliser)</p> |
| <p>Nintedanib Idiopathic pulmonary fibrosis</p> | <p>EQ-5D (trial) - model based on predicted FVC changes and rate of exacerbations</p> <p>HSUV adverse events - serious gastro-intestinal events, rash related events => model did not include diarrheadiarrhoea-adverse events as not severe and affected a small proportion of patients => committee did not agree, and considered it to affect QoL</p> <p>HSUV exacerbations => possible gains in QOL not captured in QALY (tolerability profile, reduced dosing frequency) => lack of sensitivity to change</p> | <p>Restrict - clinical parameters + Patient Access Scheme</p> <p>Dominant over pirfenidone (survival equal, differences in QALYs)</p> <p>Committee recognised that additional impact on QoL not captured in model</p> |

| MEDICINE Generic name, indication | HSUV Technique, appraisal | DECISION ICER, reasons |
|---|---|---|
| Lumacaftor–ivacaftor Cystic fibrosis | <p>HSUV QoL (multivariate mixed model)</p> <ul style="list-style-type: none"> - repeated regression analysis to model relationship between EQ-5D, lung function and pulmonary exacerbations in trials - no change in EQ-5D + little opportunity to demonstrate improved QoL due to ceiling effect - clinical experts state that EQ-5D capture most important effects in cystic fibrosis - committee tested model with values from another study (Lancaster) that better captured changes in QOL using EQ-5D in patients with similar levels of severity, resulting in increased ICER by ~65K/QALY <p>=> HSUV not captured adequately, uncertainty in model => however, trial data used, which is the biggest trials conducted in cystic fibrosis to date</p> <p>HSUV lung transplant (literature)</p> | <p>Reject</p> <p>~-218-349K/QALY</p> <p>Model mostly driven by changes in life years gained</p> <p>When HSUVs from other study were used (Lancaster), ICER increased by 65K</p> |
| Mepolizumab Severe refractory eosinophilic asthma | <p>SGRQ (MENSA trial) mapped to EQ-5D</p> <ul style="list-style-type: none"> - mapping algorithm based on population with chronic obstructive pulmonary disease - used as baseline value, adjusted due to differences between treatment arms and ages <p>=> considered acceptable</p> <p>EQ-5D (DREAM trial)</p> <ul style="list-style-type: none"> - <u>values adjusted for differences in baseline utilities values</u> <p>=> <u>baseline adjustment considered appropriate</u></p> <p>HSUV exacerbation</p> <ul style="list-style-type: none"> - mid-point between trial data and published value <p>=> little change when using different disutility values, approach acceptable</p> | <p>List - Patient Access Scheme</p> <p>~£29k/QALY</p> <p>Little effect of QoL on ICER. <u>EQ-5D mapped from SGRQ considered in model, EQ-5D values from DREAM trial accounted for in the interpretation of QoL impact.</u></p> <p>Drivers included exacerbation rates, age-related mortality estimates and attrition rates</p> |

| MEDICINE Generic name, indication | HSUV Technique, appraisal | DECISION ICER, reasons |
|--|--|--|
| Obeticholic acid Primary biliary cholangitis | No HSUVs data collected in trials Published literature and expert assessment - Chronic Hepatitis C and previous Technology Appraisal reports => some issues raised, but accepted | List - Patient Access Scheme ~£33K/QALY, additional factors considered: ICER underestimated in trial due to lack of adjustment up to recommended dose in some patients + innovative nature + potential to return to normal life + opportunity cost of liver transplant on other patients needing it |
| Holoclax Limbal stem cell deficiency after eye burns | Mapping (HSUV visual acuity) - combination of visual acuity in both best and worst seeing eyes - published mapping algorithm => model did not capture: negative effect on donor eye => if donor disutility captured, ICER likely to decrease HSUV from pain, burning, photophobia - base case value attached to presence of moderate or severe pain/burning/ photophobia derived from EQ-5D 3L tariff and uses the level 2 and 3 decrements of -0.123 and -0.386 respectively. Alternative values of no decrement and that derived from the general population SG method of -0.291 for both moderate and severe were used Disfigurement HSUV - Bespoke standard gamble exercise performed by 520 UK participants who were presented with various clinical scenarios describing moderate to severe limbal stem cell deficiency, including an image of a patient's eye with this condition showing the extent of the disfigurement typically present - estimated at 0.308 => applied from non-reference case methods and likely to be exaggerated => patients with one eye may prioritise impact of disfigurement over visual acuity, and those with two eyes affected may prioritise visual acuity over disfigurement => cataract disutilities considered more appropriate estimate of impact on QoL | Restrict - subgroups and 1 eye + Patient Access Scheme £6,948-£30,415-£42,139/QALY (lower values with 1 eye) Best plausible ICER was above £20K/QALY (includes ERG's estimate of disfigurement decrement). The committee accepted that if the model had considered a negative impact on donors, it would most likely be cost-effective => accepted for reimbursement |

| MEDICINE Generic name, indication | HSUV Technique, appraisal | DECISION ICER, reasons |
|---|---|--|
| | => HSUV of 0.840 as base case for visual acuity and HSUV decrement of 0.140 for disfigurement | |
| Pirfenidone Idiopathic pulmonary fibrosis | no info (resubmission, no new data) | Restrict - clinical parameters + Patient Access Scheme £32,643-£38,687/QALY |
| Darvadstrocel Crohn's disease | Vignette => considered robust given significant number of participants (n=835 general public and n=162 patients with Crohn's disease) => reliable estimates of HSUVs => vignettes used considered appropriate (even if EQ-5D not collected in trial), also aligns with values in literature => HSUVs in some health states might be too low, and that correctly derived HSUVs for these 3 health states could result in higher ICERs | Reject £143,131/QALY Very uncertain model. HSUVs may have some influence on ICER levels |

| MEDICINE Generic name, indication | HSUV Technique, appraisal | DECISION ICER, reasons |
|--|---|---|
| Nusinersen Spinal muscular atrophy | <p>HSUV expert elicitation</p> <ul style="list-style-type: none"> => not based on formal elicitation methods (may differ if other clinicians were to redo exercise) => questions asked to clinicians not available, making it difficult to interpret => health states based on motor function may not have captured QOL impact, differences in HSUVs between health states small <p>HSUV PedsQL mapped to EQ-5D</p> <ul style="list-style-type: none"> - published algorithm for later onset, and HSUVs adapted for the early onset model based on assumed correspondence of health states (values confidential) => limited face validity, not considered appropriate => challenge in babies and children => HSUV techniques not ideal, results highly uncertain <p>HSUV carer</p> <ul style="list-style-type: none"> - best health state based on general population HSUV, worse health state based on cross-sectional study of SMA patients, adjusted for each health state - equal transitions between these 2 points (values confidential) => based on assumptions and not on evidence => key driver in ICER (better ICER for later onset, worse for early onset due to carer disutility "saved" from early death - seen as "perverse" effect) => to be included, but highly uncertain <p>Disutility due to bereavement</p> <ul style="list-style-type: none"> - applied as -0.04 | <p>Restrict - Types 1,2,3 + Managed Access Agreements</p> <p>ICER not specified</p> <p>Key driver in models - may impact differently early and late onset models: carer disutility (highly uncertain, difficult to quantify), resource costs</p> |

| MEDICINE Generic name, indication | HSUV Technique, appraisal | DECISION ICER, reasons |
|---|---|--|
| Letermovir Cytomegalovirus | EQ-5D-3L (published literature) - Long term disutility associated with haematopoietic stem cell transplant derived from a mix of EQ-5D 5L and 3L values from two published studies - ERG proposed alternative approach based on difference between mean HSUVs of patients in trial (PN001, 48 weeks) and the general population from another study => ERG approach preferable | List - commercial agreement <£24,269/QALY likely <£20,000/QALY ICER likely to decrease due to QoL not captured in evidence (when considering PROM data) |
| Lanadelumab Hereditary angioedema | Published literature Committee accepted alternative approach to EQ-5D-5L (recognised as insufficiently sensitive). Published study used to derive HSUVs, which collected EQ-5D-5L about health state today and health state during last attack | Restrict - indication + commercial agreement <£20,000/QALY QALY gains small relatively to costs, ICER could change with different clinical scenarios |

*No HSUVs were reported for one treatment (pirfenidone) given it was a re-assessment; therefore, it was excluded from this analysis, which focuses on the 23 remaining treatments.

Legend: HSUV: health state utility values; QALY: quality-adjusted life years gained; ICER: incremental cost-effectiveness ratio; EQ-5D: EuroQoL-5 Dimension; EQ-5D-3L: EuroQoL-5 Dimension-3 Level; EQ-5D-5L: EuroQoL-5 Dimension-5 Level; GI: gastro-intestinal; QoL: quality of life; ERG: Evidence Review Group; IRD: Inherited retinal dystrophies ; TTO: time-trade off; PedsQL: Paediatric Quality of Life Inventory - Parent Report for Toddlers; DCE: discreet choice experiment; ERT: enzyme replacement therapy; 6MWT: 6-minute walk test; IVIG: intravenous immunoglobulin; HUI2: Health Utility Index Mark 2; DPI: tobramycin dry powders for inhalation; CFQ-R:cystic fibrosis questionnaire revised; FEV: Forced Expiratory Volume; SGRQ: St George Respiratory Questionnaire

Sources: [16-39]

Table 5. Use and influence of PRO evidence in HAS, G-BA and ZIN appraisals of non-oncology rare disease treatments

| MEDICINE Generic name - indication | PRO EVIDENCE AND APPRAISAL | | |
|--|---|--|---|
| | HAS (France) | G-BA (Germany) | ZIN (Netherlands) |
| Asfotase alfa Paediatric-onset hypophosphatasia | no details provided | no trial QoL data, no conclusion | no details provided |
| Eculizumab Atypical haemolytic uraemic syndrome (aHUS) | no details provided | NA | no details provided |
| Patisiran Hereditary transthyretin amyloidosis | no details provided | Norfolk QoL-DN: statistically improved; validity and reliability confirmed; possible bias from higher missing values after 18 months in control group; no MID, effect size's hedges calculated for dossier; clinically relevant difference | NA |
| Voretigene Inherited retinal dystrophies | VFQ: not demonstrated. Secondary judgment criterion, no hierarchical test | VFQ: unsuitable. Transferability and MID from NEI VFQ-25 to new VFQ inappropriate | Vignettes, EQ-5D-5L, HUI3: not adequately collected |
| Cerliponase Nuronal ceroid lipofuscinosis type 2 | PedsQL, CLN2-QoL, EQ-5D 5L: exploratory consideration of QoL, stabilisation in treatment group versus degradation in natural history data | PedsQL: no benefit in QoL recognised due to lack of comparative data and clinical relevance of change CLN2-QoL: not considered as no data on its development (by company) and validation provided | NA |
| Elosulfase alfa Mucopolysaccharidosis type IVa | no details provided | no details provided | no PROM data collected in trial |
| Ataluren Duchenne muscular dystrophy | no details provided | PODCI: not statistically significant. Quality and patient relevance not demonstrated due to lack of information | PedsQL, PODCI: not statistically significant |
| Migalastat Fabry disease | no details provided | SF-36: inconclusive | SF-36: inconclusive |
| Eliglustat Gaucher disease | no details provided | BPI, FSS, SF-36: no significant differences | SF-36, BPI, FSS, DS3: clinically relevant and crucial, no significant differences |

| MEDICINE Generic name - indication | PRO EVIDENCE AND APPRAISAL | | |
|--|---|--|--|
| | HAS (France) | G-BA (Germany) | ZIN (Netherlands) |
| Strimvelis Adenosine deaminase deficiency–severe combined immunodeficiency | NA | NA | NA |
| Burosumab for X-linked hypophosphataemia | SF-36, PROMIS: exploratory, not usable | SF-10: lack of information on questionnaire development, restrictions in content validity, reliability and validity. Results not accounted for | NA |
| Inotersen Hereditary transthyretin amyloidosis | Norfolk QoL-DN: modest improvement as co-primary endpoint SF-36: not discussed | SF-36: biased due to missing values Norfolk-DN: no valid MID based on hedge's g, effects not clinically relevant. Statistically significant improvement, but not clinically relevant C-SSRS: not discussed | NA |
| Mannitol for cystic fibrosis | no details provided | NA | CFQ-R: no significant improvements. Overall effect around improving QoL and reducing pulmonary exacerbations |
| Colistimethate sodium and tobramycin dry powders for inhalation (DPI) [=antibiotics] Pseudomonas lung infection in cystic fibrosis | no details provided | NA | no details provided |
| Nintedanib Idiopathic pulmonary fibrosis | EQ-5D, EORTC QLQ-30, QLQ-LC13: no expected improvement | G-BA/IQWiG EQ-5D VAS: statistically improved, benefit not proven given hedge's g SGRQ: not discussed | SGRQ: not clinically relevant |
| Lumacaftor–ivacaftor Cystic fibrosis | no details provided | not collected in trial | EQ-5D: used to derive HSUVs |

| MEDICINE Generic name - indication | PRO EVIDENCE AND APPRAISAL | | |
|---|---|--|--|
| | HAS (France) | G-BA (Germany) | ZIN (Netherlands) |
| Mepolizumab Severe refractory eosinophilic asthma | NA | no details provided | no details provided |
| Obeticholic acid for primary biliary cholangitis | no details provided | PBC-40: validated measure. Responsiveness and MID not examined. Marginal change, but clinical relevance not determined | PBC-40: no improvement |
| Holoclax for limbal stem cell deficiency after eye burns | NA | no details provided | NA |
| Pirfenidone Idiopathic pulmonary fibrosis | no details provided | SGRQ, WHO QoL: no proof of added benefit | EQ-5D, SGRQ: from published paper. Unclear benefit as baseline values and validation difficult to verify |
| Darvadstrocel Crohn's disease | Van Assche Score, IBDQ: exploratory secondary endpoints, no change captured | IBDQ: not designed or validated for target population, no information on MID. Inconclusive QoL benefit | NA |
| Nusinersen Spinal muscular atrophy | PedsQL: not possible to quantify QoL benefit due to low response rates | PedsQL: QoL not demonstrated. Caregiver experience included | PedsQL mapped to EQ-5D |
| Letermovir Cytomegalovirus | EQ-5D-3L: unsuitable, used to derive HSUVs for different health states rather than change in QoL associated with an illness | EQ-5D, FACT-BMT FACT-BMT considered validated in patient population | not details provided |
| Lanadelumab for hereditary angioedema | AE-QoL: unusable as exploratory endpoint | AE-QoL: statistically improved, considered clinically relevant based on Hedge's g | NA |

Legend: NA: no report available; MID: minimal important difference; Norfolk-DN: Norfolk quality of life-diabetic neuropathy; VFQ: visual function questionnaire; PedsQL: Paediatric Quality of Life Inventory - Parent Report for Toddlers; CLN2-QoL: CLN2 quality of life instrument; PODCI: paediatric outcomes data collection instrument; FSS: fatigue severity scale; BPI: brief pain inventory; CFQ-R: cystic fibrosis questionnaire revised; HUI3: health utility index 3; SGRQ: St George Respiratory Questionnaire; FACT-BMT: functional assessment of cancer therapy; AE-QoL: angioedema quality of life questionnaire; SF-36: short form 36; DS3: Gaucher disease severity score; PROMIS:

patient reported outcome measurement information system; SF-10: short form 10; EORTC-QLQ 30: European Organisation for Research and Treatment of Cancer - Quality of life 30; QLQ-LC13: modular supplement to EORTC QLQ 30 for use in lung cancer; NEI: National Eye Institute; PBC-40: quality of life for primary biliary cirrhosis; WHO QOL: Quality of life - WHO; IBDQ: Inflammatory Bowel Disease Questionnaire