# A Comparative Review of NICE and SMC Decision-Making for Ultra-Orphan Medicines

Katherine Gibbs, PhD; Andrea Schmetz, MBA; Helena Emich, PhD; Katie Gardner, PhD

Evidera, London, UK

POSTER # PRO109

## Introduction

- The National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC) assess the clinical and cost-effectiveness of health technologies in the UK.
- Each organisation uses different criteria, methodologies and decision-making processes for appraising ultra-orphan medicines.
- These differences may lead to divergent appraisal outcomes and variations in access to ultra-orphan medicines across the UK.

### SMC assessment of ultra-orphan medicines

- In April 2014, the SMC introduced more flexible approaches for the assessment of medicines for end-of-life and very rare conditions, recognising that these medicines were unlikely to be accepted through the standard appraisal process.[1,2]
- Ultra-orphan medicines were defined as those used to treat a condition with a prevalence of 1 in 50,000 or less (~100 people in Scotland) and were assessed using a specialised decision-making framework.[3]
  - Key assessment criteria used by the SMC included the nature of the condition and the impact of the medicine, the impact of the medicine beyond direct health benefits and on specialist services, costs to the National Health Service (NHS) and Personal Services, and value for money, based on evidence provided in the manufacturer's submission.
  - A cost-effectiveness ratio was still requested but greater flexibility was shown, given the nature of ultra-orphan conditions and the sparsity of available data.
  - If the preliminary advice was 'not recommended', the applicant company could request a patient and clinician engagement (PACE) meeting and had the option to offer a new or revised patient access scheme (PAS).
- The first decisions made under the revised process were published in October 2014.[2]
- Following an independent review of access to new medicines in Scotland conducted in 2016, which reported that SMC acceptance of ultra-orphan medicines had not improved to the same extent as end-of-life or orphan medicines,[2] a new approach for the assessment of ultra-orphan medicines was introduced in Scotland in April 2019 with the aim of improving access (see Figure 4 for further information).[4]
- The current analysis is based on SMC ultra-orphan assessments conducted before the introduction of the new approach.

### NICE assessment of ultra-orphan medicines

- The NICE highly specialised technology (HST) programme, introduced in 2013 and revised in 2017, evaluates medicines for very rare conditions.[5,6]
- To be eligible for the HST programme, the treatment must meet all of the following criteria[6]:
  - The target patient group is so small that treatment will usually be concentrated in very few centres in the NHS. (Note: an exact prevalence threshold is not specified.)
  - The target patient group is distinct for clinical reasons.
  - The condition is chronic and severely disabling.
  - The technology is expected to be used exclusively in the context of a highly specialised service.
  - The technology is likely to have a very high acquisition cost.
  - The technology has the potential for lifelong use.
  - The need for national commissioning of the technology is significant.
- Medicines assessed via the HST programme with incremental cost-effectiveness ratios (ICERs) up to £100,000 per quality-adjusted life year (QALY) are funded from routine commissioning budgets, while medicines above this threshold are considered for funding through NHS England's Clinical Priorities Advisory Group (CPAG) relative prioritisation process.[7]
- Ultra-orphan medicines that do not meet the eligibility criteria for the HST programme are assessed via the standard technology appraisal process (if selected for appraisal).
- Additionally, ultra-orphan medicines for cancer indications which are not initially recommended for routine commissioning may be recommended for funding through the Cancer Drugs Fund (CDF), if additional data collection could reduce clinical uncertainty and the medicine has the potential to be cost-effective when end-of-life criteria are taken into account.[8]

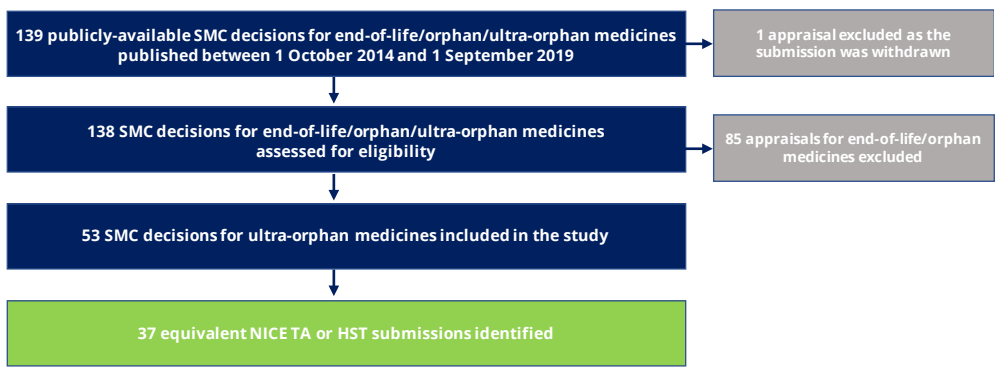
## Objective

- The objective of this study was to compare the outcomes of NICE and SMC appraisals for ultra-orphan medicines to understand whether the two bodies are aligned in their decision-making, how this has evolved over time, and the reasons behind any divergences.

## Methods

- SMC decisions published between 1 October 2014 and 1 September 2019 utilising the ultra-orphan decision-making framework were cross-referenced to equivalent NICE technology appraisal (TA) or HST guidance (Figure 1).[9,10] Withdrawn or terminated submissions were not included. Key data related to the submission process and outcome were extracted. Wholesale prices in the UK were acquired for each medicine from the IHS Markit 2019 pricing database.

**Figure 1. Identification of SMC and NICE appraisals included in the analysis**

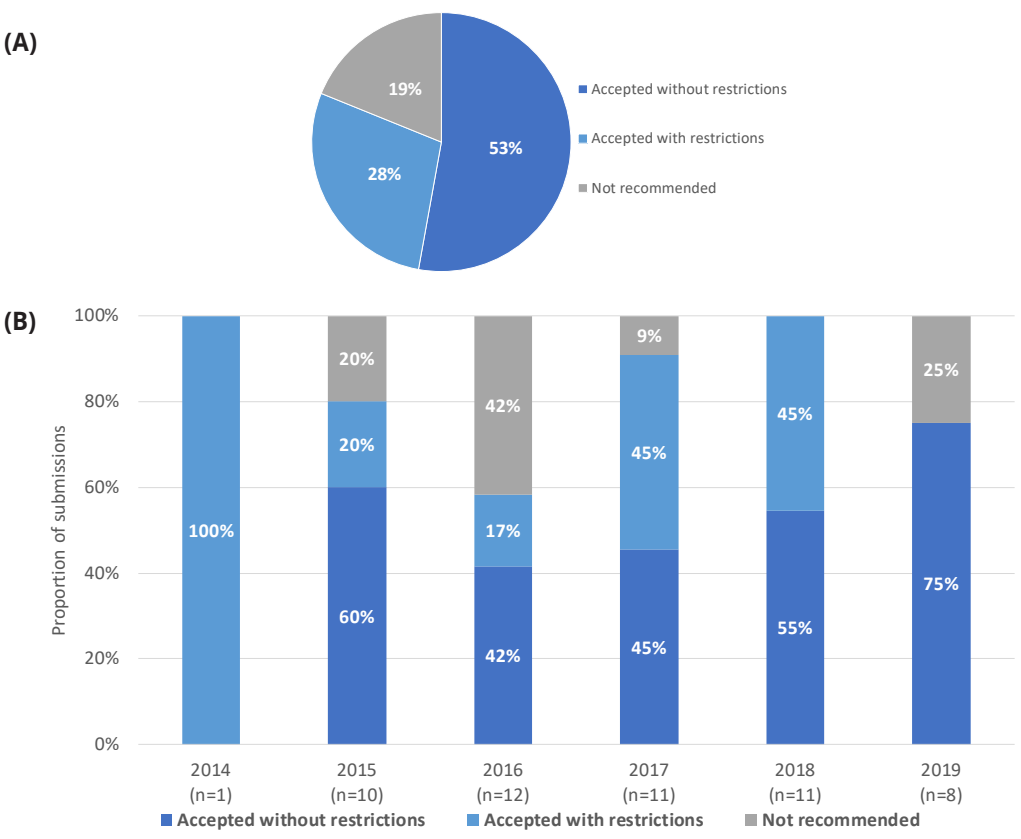



Abbreviations: HST = highly specialised technology; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium; TA = technology appraisal

## Results

- Between 1 October 2014 and 1 September 2019, 53 medicines were assessed using the SMC ultra-orphan decision-making framework.
- Overall, 43 (81%) ultra-orphan medicines were recommended for routine use within NHS Scotland; 28 (53%) were accepted without restrictions, while 15 (28%) were accepted with restrictions to their indication and/or use (Figure 2).
- The majority of accepted submissions took account of feedback from a PACE meeting (95%) and/or included a PAS to improve the cost-effectiveness of the medicine (86%).

**Figure 2. SMC decisions for ultra-orphan medicines (A) over the entire study period* and (B) by year**

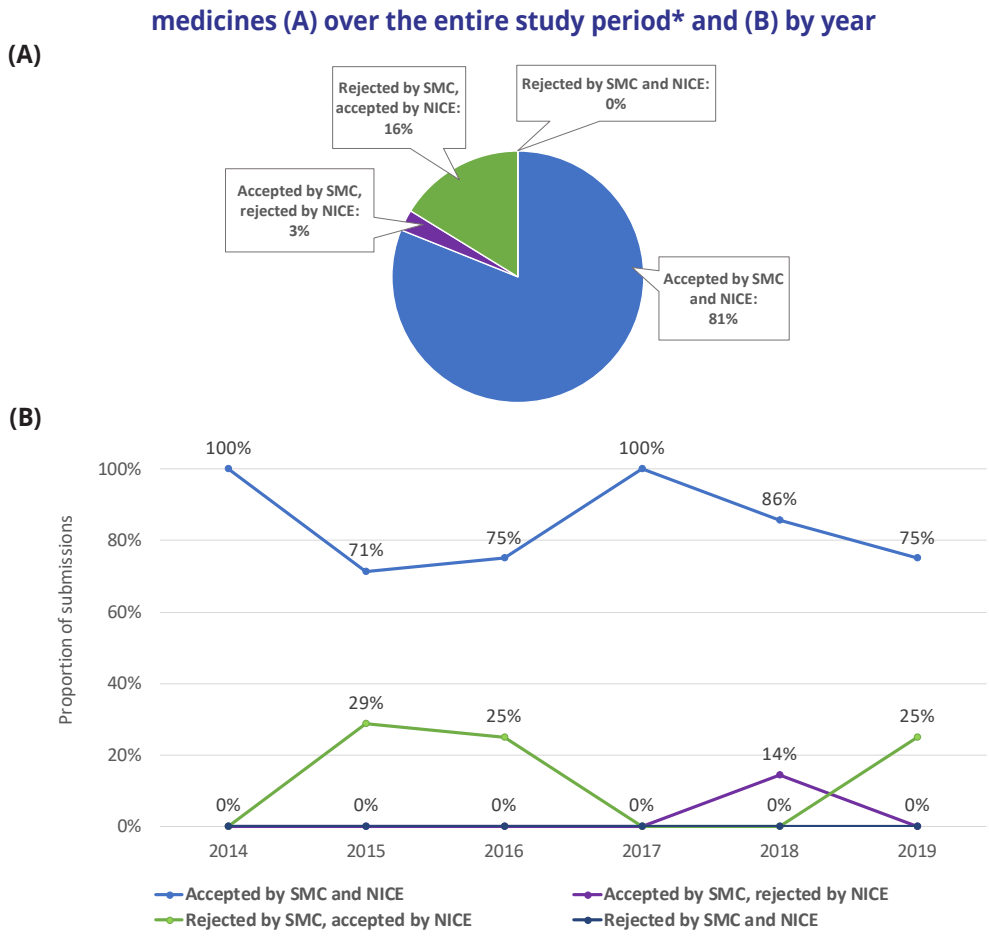



*1 October 2014 to 1 September 2019; Abbreviation: SMC = Scottish Medicines Consortium

- SMC decisions for ultra-orphan medicines were cross-referenced to equivalent NICE TA or HST guidance and 37 equivalent NICE submissions were identified.
- NICE and SMC decision-making for ultra-orphan medicines was aligned in the majority (30/37; 81%) of cases (Figure 3A).
- Concordance between the two agencies remained stable over the study period (2014 to 2019; Figure 3B).

## Results (cont.)

**Figure 3. Alignment between NICE and SMC decision-making for ultra-orphan medicines (A) over the entire study period* and (B) by year**




*1 October 2014 to 1 September 2019; Abbreviations: NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium

- Six of the seven ultra-orphan medicines with opposing decisions were accepted by NICE but not recommended by the SMC (Table 1). The SMC appraisals stated that "justification of the treatment's cost in relation to its health benefits was not sufficient" and "the submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC."
  - All six were approved by NICE under either the HST programme (three in total) or the CDF (three in total).
- For the one ultra-orphan medicine accepted by the SMC but not recommended by NICE (pembrolizumab for patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant [ASCT] and brentuximab vedotin), the NICE appraisal highlighted uncertainties over the cost-effectiveness and noted the availability of another immunotherapy (nivolumab) for the subpopulation in question.
  - Although nivolumab is also available in Scotland, the SMC concluded there was an unmet need for additional treatment options based on feedback from clinical experts and patient group representatives at the PACE meeting and noted that greater uncertainty over cost-effectiveness could be accepted for ultra-orphan medicines.

**Table 1. Ultra-orphan medicines with opposing decisions from NICE and SMC**

| Medicine | Indication | Key clinical evidence | QALY gains | Base-case ICER | NICE HST | NICE CDF | NICE decision | SMC decision |
|---|---|---|---|---|---|---|---|---|
| **Tisagenlecleucel (Kymriah®)** | Adult patients with R/R DLBCL after ≥2 lines of systemic therapy | Open-label, single-arm, phase II study (N=147) | NR | £49,975–£49,839 (with PAS) | No | Yes | ✓ | ✗ |
| **Axicabtagene ciloleucel (Yescarta®)** | Adult patients with R/R DLBCL or PMBCL, after ≥2 lines of systemic therapy | Open-label, single-arm, phase I/II study (N=111) | 4.1 | £57,943 (with PAS) | No | Yes | ✓ | ✗ |
| **Ataluren (Translarna®)** | Ambulatory patients aged ≥5 years with DMD resulting from a nonsense mutation in the dystrophin gene | Randomised, DB, placebo-controlled phase IIb study (N=114) | 6.089 | £793,498 (without PAS) | Yes | No | ✓ | ✗ |
| **Eculizumab (Soliris®)** | All patients with atypical haemolytic uraemic syndrome | Two open-label, single-arm, phase II studies (N=17 and N=20) | 15.3 | NR | Yes | No | ✓ | ✗ |
| **Elosulfase alfa (Vimizim®)** | All patients with mucopoly-saccharidosis, type IVA (Morquio A Syndrome, MPS IVA) | Randomised, DB, placebo-controlled phase III study (N=176) | 9.91 | £829,870 (with PAS) | Yes | No | ✓ | ✗ |
| **Cabozantinib (Cometriq®)** | Adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma | Randomised, DB, placebo-controlled phase III study (N=330) | 0.71 | £93,141 (without PAS) | No | Yes | ✓ | ✗ |
| **Pembrolizumab (Keytruda®)** | Adult patients with R/R classical Hodgkin lymphoma who have failed ASCT and brentuximab vedotin | Open-label, single-arm, phase II study (N=69) | 1.274 | £40,765 (with PAS) | No | No | ✗ | ✓ |

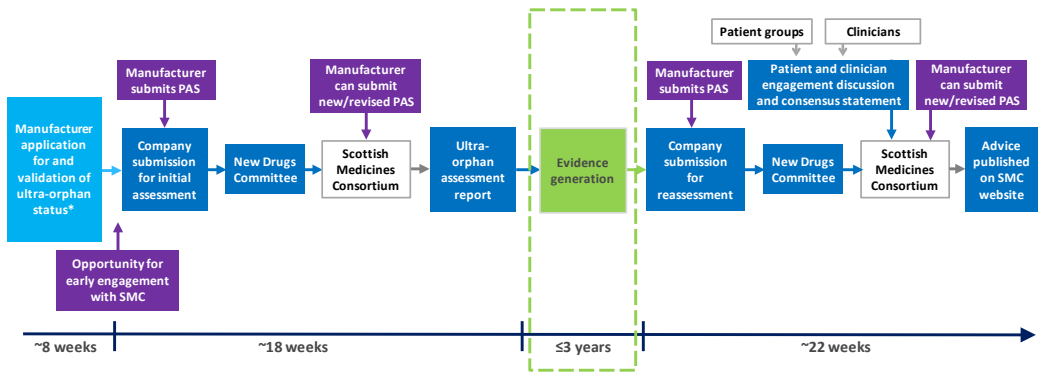
Green checkmark indicates medicine was recommended by NICE or SMC; red 'X' indicates medicine was not recommended; *As reported in SMC appraisal document; Medicines are ordered by date SMC advice was published; Abbreviations: ASCT = autologous stem cell transplant; CDF = Cancer Drugs Fund; DB= double-blind; DLBCL = diffuse large B-cell lymphoma; DMD = Duchenne muscular dystrophy; HST = highly specialised technology; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; NR = not reported; PAS = patient access scheme; PMBCL = primary mediastinal large B cell lymphoma; QALY = quality-adjusted life year; R/R = relapsed or refractory; SMC = Scottish Medicines Consortium

- Price level developments for ultra-orphan medicines with opposing decisions from NICE and the SMC were analysed on a case-by-case basis due to variability in mechanism of action and effect size.
- Price history data were available for all medicines except tisagenlecleucel (Kymriah®).
- Prices for all ultra-orphan medicines analysed remained at the level achieved at market introduction with no changes over time. (Note: prices researched were wholesale prices not accounting for any confidential discounts that may have been applied.)

## Conclusions

- NICE and SMC decision-making for ultra-orphan medicines is aligned in the majority of cases. Our research highlights the role of the NICE HST programme and CDF in ensuring access to ultra-orphan medicines in England. The HST programme allows greater flexibility when assessing the cost-effectiveness of ultra-orphan medicines, while the CDF provides an additional pathway to access for ultra-orphan medicines with oncology indications. On the other hand, the SMC's PACE process allows the patient and clinician voice to play a more prominent role in decision-making and may therefore impact appraisals in which there are questions over the unmet need for a treatment.
- In April 2019, the SMC introduced a new pathway for the assessment of ultra-orphan medicines (Figure 4).[4] The new SMC pathway as well as the success of the CDF in providing access to ultra-orphan medicines in England emphasise the rising importance of targeted and well-planned real-world evidence (RWE) generation, as this is a key requirement of both pathways. Particularly in the ultra-orphan space, RWE is a challenge which manufacturers should consider early in development to increase the probability of optimal HTA and pricing outcomes.
- Looking ahead, it will be interesting to see whether the new SMC pathway improves access to ultra-orphan medicines in Scotland and what impact this has on alignment between NICE and SMC appraisals in future.

**Figure 4. Revised SMC pathway for the assessment of ultra-orphan medicines[4]**




*All criteria must be met: condition has a prevalence of ≤1 in 50,000 in Scotland; medicine has EMA orphan designation which is maintained at time of marketing authorisation; condition is chronic and severely disabling; condition requires highly specialised management; Abbreviations: PAS = patient access scheme; SMC = Scottish Medicines Consortium

## Acknowledgments

The authors would like to thank Colleen Dumont, Janet Dooley and Sean Smith for their editorial and graphic design support and Roy Mootoosamy for critical reading of the poster.

## References

**1.** Task and Finish Group. Assessment of medicines for end of life care and very rare conditions (orphan and ultra-orphan medicines) in Scotland. Report for the Cabinet Secretary for Health and Wellbeing. 2013. **2.** Scottish Government. Review of Access to New Medicines. Independent review by Dr Brian Montgomery. December 2016. **3.** Scottish Medicines Consortium. Process for End of Life and Very Rare Conditions (orphan and ultra-orphan medicines). October 2016. **4.** Scottish Government. A Guide to the Ultra-Orphan Pathway. May 2019. **5.** National Institute for Health and Care Excellence. Interim Process and Methods of the Highly Specialised Technologies Programme. May 2013. **6.** National Institute for Health and Care Excellence. Interim Process and Methods of the Highly Specialised Technologies Programme - Updated to reflect 2017 changes. April 2017. **7.** National Institute for Health and Care Excellence. NICE and NHS England consultation on changes to the arrangements for evaluating and funding drugs and other health technologies assessed through NICE's technology appraisal and highly specialised technologies programmes. March 2017. **8.** NHS England. Appraisal and Funding of Cancer Drugs from July 2016 (including the new Cancer Drugs Fund). A new deal for patients, taxpayers and industry. 2016. **9.** Scottish Medicines Consortium. https://www.scottishmedicines.org.uk/medicines-advice/. Accessed 1 September, 2019. **10.** National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/published. Accessed 1 September, 2019.



Funding provided by Evidera