Ultra-orphan Medicinal Products Assessment: Comparison of the National Institute for Health and Care Excellence (NICE) and the Institute of Clinical and Economic Review (ICER) HTA Frameworks

Dusza M[1], Kloc K[1], Rémuzat C[2], François C[2], Toumi M[3]

[1]Creativ-Ceutical, Krakow, Poland, [2]Creativ-Ceutical, Paris, France, [3]Aix-Marseille University, Marseille, France

BACKGROUND

- Ultra-rare disease is a distinct subcategory of rare diseases, that affects very small numbers of patients being often life-threatening or chronically debilitating diseases [1].
- There is no universal definition for ultra-rare diseases. HTA bodies, like the National Institute for Health and Care Excellence (NICE) and the Institute of Clinical and Economic Review (ICER) adopt definitions for ultra-rare diseases, which slightly vary in terms of prevalence [2].
  - NICE follows the European Commission's definition which indicates the prevalence of ultra-rare disease as less than 2/100,000 population [3]. For the UK it should be less than 1,000 of patients [4].
  - ICER defines ultra-rare disease as affecting less than 10,000 Americans, which translates into ~3/100,000 [14].
- Examples of conditions classified as ultra-rare are presented in Figure 1 with corresponding prevalence rates in the EU and US.

Figure 1. Prevalence rates of selected ultra-orphan diseases in Europe and United States

Ultra-rare disease	Prevalence (per 100,000)	
	EU	US
Cryopyrin-associated periodic syndromes	0.1-0.2 [10]	0.1-0.2 [8]
Fabry disease	0.22 [5]	2.0 [6]
Paroxysmal nocturnal haemoglobinuria	0.3 [5]	0.1-0.5 [9]
Mucopolysaccharidosis type I	1.0 [5]	0.2-1.0 [9]
Pompe disease	1.75 [5]	3.6 [7]

- Due to the low number of patients and difficult achievement of investment return, ultra-orphan drugs are usually priced higher than drugs for common conditions.
  - In the UK, between 2013 and 2016, the average annual cost per patient for high-cost therapies (with annual cost per patient >£2,500) used in ultra-rare diseases (<1,000 patients) was nearly 3.5 times higher than the average annual cost of other high-cost therapies used in common conditions (>32,000 patients) [3]. (Fig. 2)
- Consequently, because of their high prices, ultra-orphan drugs are less likely to meet the cost-effectiveness thresholds established by HTA bodies.

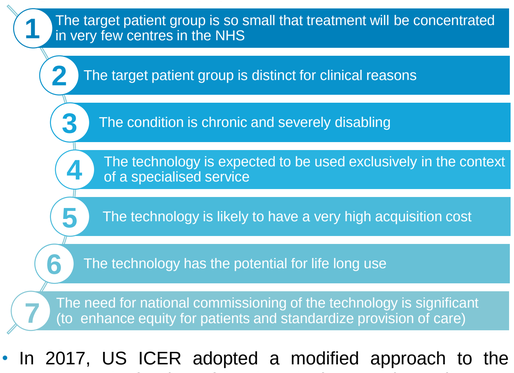
Figure 2. Average cost of high-cost therapies in the UK according on the target population size [4]

Target population size	Average annual cost of high-cost therapy (>£2,500) per patient
>32,000 patients per year	£8,877
1,000-32,000 patients per year	£24,397
<1,000 patients per year	£30,637

DISCUSSION

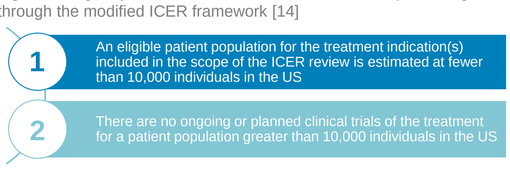
- ICER and NICE have developed assessment frameworks for ultra-orphan medicines, but the approaches differ in terms of inclusion and decision-making criteria.
- In 2013, NICE has developed Highly Specialised Technology (HST) programme to assess novel drugs for very rare diseases.
  - HST approach is applicable to treatments intended for small populations with chronic and severely disabling conditions. The acquisition cost is expected to be very high and the therapy is expected to be life-long [12].
  - There are 7 qualification criteria to be met to be eligible for this process (Fig. 3).

Figure 3. Eligibility criteria for the assessment of ultra-orphan drugs through the HST approach [12]



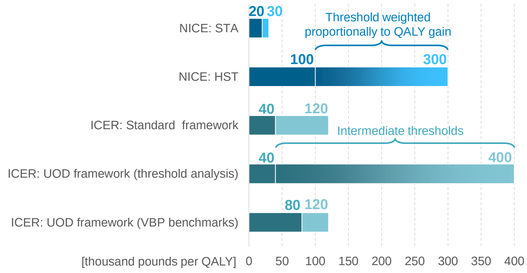
- In 2017, US ICER adopted a modified approach to the assessment of value of treatments for a serious ultra-rare condition. There are two qualification criteria for drugs to be included in this approach [14]. (Fig. 4)

Figure 4. Eligibility criteria for the assessment of ultra-orphan drugs through the modified ICER framework [14]



- The key adaptation of the NICE approach under HST compared to the single technology appraisal (STA) is significantly increased cost-effectiveness threshold, which is used by the Evaluation Committee to determine recommendations. (Fig. 5)
  - For the standard STA, the acceptable cost-effectiveness threshold is usually £20,000, or £30,000 under certain conditions (inability to appropriately capture utility gain, innovative nature of the technology, "life-extending" criteria) [11].
  - The threshold for HST ranges from £100,000 to £300,000, depending on the expected number of QALYs gained over the patient's lifetime. The lower threshold applies if the new therapy is expected to provide 10 or less QALYs through the whole patient's lifetime horizon, while the higher if the treatment provides 30 or more QALYs. For therapies giving 11-29 QALYs, the threshold is weighted proportionally to the expected QALY gain [12].
- Increased range of willingness-to-pay thresholds was also adopted in the ICER value framework intended for ultra-orphan drugs. When conducting threshold analysis, ICER calculates unit prices to achieve a range of thresholds from $50,000 (~£40,000) to $500,000 (~£400,000), which is wider than the range used under standard approach ($50,000 /~£40,000 to $150,000/~£120,000). Oppositely to NICE, in the ICER framework there is no special quantitative weighting system applied to different magnitudes of QALY gains nor to baseline severity of the condition [13,14]. (Fig. 5)
  - Despite the use of much higher thresholds in the threshold analysis for ultra-orphan drugs, the thresholds used for determining value-based price (VBP) benchmarks and calculating rebates remain the same as in the standard approach ($100,000/~£80,000 and $150,000/~£120,000). However, ICER indicates that decision-makers often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and higher cost-effectiveness ratios [14].
  - Another adaptation of the ICER value framework for ultra-orphan drugs is the inclusion of additional, societal perspective in the economic modelling and VBP benchmark calculations, if the technology significantly impacts productivity, education, disability, or nursing costs [14].

Figure 5. Willingness to pay thresholds (thousand pounds per QALY) adopted in NICE and ICER frameworks ($10,000 = ~£8,000)



STA – Single Technology Appraisal, HST - Highly Specialised Technology programme, UOD – ultra-orphan drug, VBP – value-based price

CONCLUSIONS

- NICE and ICER frameworks for ultra-orphan drugs adopt different eligibility and assessment criteria, which may result in different outcomes for the same drug.
- Extensive criteria for HST, which all need to be met, may cause less drugs to be eligible for this path. In such cases, demonstration of cost-effectiveness under less flexible Single Technology Appraisal will be required.
- Eligibility criteria in ICER could allow more drugs to be assessed under the framework, which adopts higher willingness-to-pay threshold in the economic assessment. While this higher willingness-to-pay threshold together with the additional societal perspective of the evaluation may provide wider context for potential decision-makers, the VBP benchmarks and rebates for ultra-orphan drugs are still calculated using standard thresholds of $100-150 thousand.
  - Considering that ultra-orphan drugs are not likely to reach the benchmarks, the final acceptance will depend on how the estimates for additional thresholds and perspective are considered by the individual payers using the report.

REFERENCES

1. Richter T. et al. Rare Disease Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. Value Health. 2015;18(6): 906-14.
2. The Definition of Ultra Rare. Available from: https://haystackproject.org/the-issue [accessed: 9th October 2019]
3. Regulation (EU) no 536/2014 of the European Parliament and of the Council of 16 April 2014.
4. Jørgensen J. and Kefalas P. A price comparison of recently launched proprietary pharmaceuticals in the UK and the US. Journal of Market Access & Health Policy 2016, 4: 32754
5. Kanters T.A. et al. International differences in patient access to ultra-orphan drugs. Health Policy and Technology Volume 7, Issue 1, March 2018, Pages 57-64.
6. The National Fabry Disease Foundation website. Available from: https://www.fabrydisease.org/index.php [accessed: 9th October 2019]
7. Dasouki M. et al. Pompe Disease: Literature Review and Case Series. Neurol Clin. 2014;32(3):751-76.
8. Kümmerle-Deschner JB. Cryopyrin-associated periodic syndrome. Z Rheumatol. 2012;71(3):199-208.
9. NIH Genetics Home Reference website. Available from: https://ghr.nlm.nih.gov/ [accessed: 9th October 2019]
10. Sibley C. Does this patient have a cryopyrin-associated periodic syndrome (CAPS)? Available from: https://www.rheumatologyadvisor.com/home/decision-support-in-medicine/rheumatology/cryopyrin-associated-periodic-syndrome-caps/ [accessed: 9th October 2019]
11. NICE. Guide to the methods of technology appraisal 2013. April 2013.
12. NICE. Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes. April 2017.
13. ICER. Overview of the ICER value assessment framework and update for 2017-2019.
14. ICER. Modifications to the ICER value assessment framework for treatments for ultra-rare diseases. Final Version. November 2017.

ISPOR 2019, Copenhagen, Europe, November 2-6 2019. PRO98.