Establishing a Reasonable Price for an Orphan Drug

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The 'Problem' with Orphan Drugs

- Current orphan drug policies are unsatisfactory when viewed from almost all perspectives
- Patients find that access to care is sometimes restricted, because of affordability concerns
- Manufacturers, having responded strongly to incentives to conduct research into rare diseases, find that payers are reluctant to pay for the therapies, once developed
- Payers find that most orphan drugs do not justify funding, based on standard value for money criteria, but face political problems if they fail to provide funding

Differing Academic Perspectives

- On a utilitarian basis, the opportunity cost of treating rare diseases is too high (McCabe *et al, British Medical Journal 2005)*
- The notion of ‘social benefit embodied in current health technology assessment processes is too narrow (Drummond *et al, Int. J Tech Assess Health Care* 2007)
- Manufacturers make ‘excessive profits’ and there are several examples of ‘orphan drug creep’ (Côté and Keating, *Value in Health* 2012)

One Possible Solution

- Set the threshold of maximum willingness-to-pay for improved health (ie a QALY) in the jurisdiction concerned
- Do not reimburse any health technologies that exceed that threshold
- If manufacturers do not reduce their prices by a substantial amount (around 80%), no orphan drugs will be reimbursed

How Could we Estimate a Reasonable Price for an Orphan Drug?

- If a value-based price is not feasible, on what basis could a 'reasonable' price be established?
- A ***initial proposition*** could be that:
  - although society may be willing to sacrifice some health gain overall, in order to make orphan drugs available;
  - it would not tolerate a situation whereby the manufacturers of orphan drugs make higher profits than the manufacturers of drugs for non-orphan conditions

How Do Orphans Differ from Non-Orphans?

- R&D costs are likely to be lower, as the cost of the Phase III programme is likely to be lower
- Revenues will be lower, since patient numbers are lower
- Financial risk may differ, although it's hard to say whether it would be higher or lower

Study Methods

(Berdud, Drummond and Towse, 2017*)

Differences in R&D cost:

•We estimated the R&D cost of developing an orphan/non-orphan drug applying updated and specific versions of the model in Mestre-Ferrandiz et al. (2012)

Differences in sales volumes:

•We calculated the average size of target patient population of non-orphans and orphans in NICE and SMC appraisals

Therapeutic areas:

•We calculated differences separately for both oncology and non-oncology products

Normative Cost-effectiveness Threshold – the 'Reasonable Price':

•We adjusted NICE's Cost Effectiveness Threshold of £20k/QALY for an orphan drug by differences in the R&D cost and population ratios

** In draft*

Calculation of Normative ICERs

We propose the following formula to adjust NICE's CET in a way that lower costs of R&D and lower sales volumes of orphans are addressed in the Adjusted CET (ACET):

$$ACET = \frac{\dot{y}}{x_i} CET$$

•$i = \{O, UO\}$ where *O* means orphan and *UO* means ultra-orphan

•x_i : orphan (or ultra-orphan) drugs' treatment population sizes to non-orphan drugs' treatment population size ratio

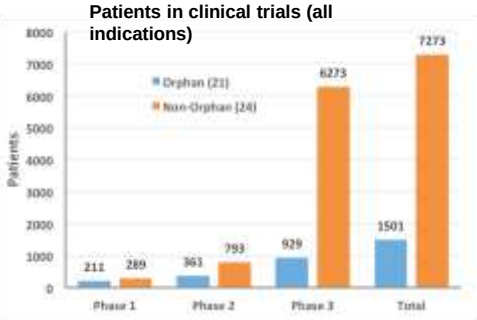
- Based on EMA's and NICE's definitions, 2 different treatment population size options have been used for orphan and for ultra-orphan

•y: orphan drugs' cost or R&D to non-orphan drugs' cost of R&D ratio

- We assumed that the total lifecycle cost of an orphan is reduced proportionally in all its components as it does for the R&D (most conservative approach)

Results – R&D costs

Patients in clinical trials (all indications)



Patients in clinical trials (oncology)

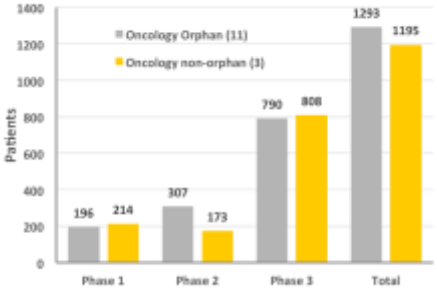


Table 2. Estimated R&D cost of a new drug FDA (US$ millions)

	Orphan drugs	Non-orphan drugs	% of orphans to non-orphans
All indications	521.2	1,939.7	26.9%
Oncology	492.7	893.5	55.1%

Source: Authors' calculations based on Mestre-Ferrandiz et al. (2012) methodology
Notes: Estimates have been calculated using data from 2015 NDAs of FDA; Estimates for all indications also include oncology products.

Orphan/non-orphan cost of R&D adjustment factor for the ACET: $\gamma = 0.269$

Results – Target Populations

Table 3. Estimates of average patients per 50,000 inhabitants

	SMC	NICE
	Average annual number of patients	Average annual number of patients per drug
Orphan	2.54	2.61
Non-orphan	82.8	102.57

Source: SMC and NICE

Non-orphan drugs' average treatment populations

Based on the average non-orphan population size of the NICE TAs, we take 100 per 50,000 people to calculate the adjustment factor for revenue

Cut-off patient sizes of orphan and ultra-orphan by definition:

- Orphan drugs (EMA): 25 patients in 50,000 people
- Ultra-orphan drugs (SMC-NICE): 1 patient in 50,000 people

Additionally to cut-off points in definitions, we also take12.5 patients and 0.5 patients per 50,000 people as midpoints to calculate different ACETs

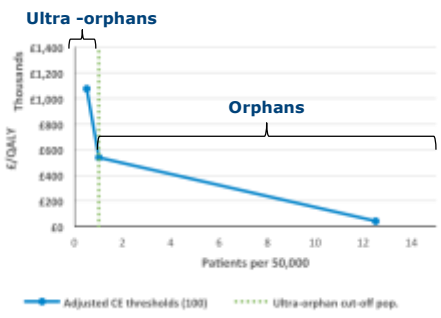
Revenue adjustment factor: x_i in proposed ACET formula

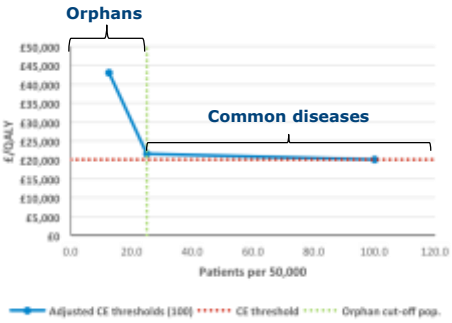
	Non-orphan population (100/50,000)
Orphan (cut-off)	0.25
Orphan (midpoint)	0.125
Ultra-orphan (cut-off)	0.01
Ultra-orphan (midpoint)	0.005

Results – Normative ICERs

Normative ACETs for orphan and ultra-orphan drugs calculated as per our formula

	Non-orphan population (100/50,000)
Orphan (cut-off: 25/50,000)	£21,520
Orphan (midpoint: 12.5/50,000)	£43,040
Ultra-orphan (cut-off: 1/50,000)	£538,000
Ultra-orphan (midpoint: 0.5/50,000)	£1,076,000





Unresolved Issues

- Could a better estimate of R&D costs be obtained by using a larger sample of NDAs?
- Are non-R&D costs lower for orphans and by how much?
- Does market exclusivity give orphans a longer revenue-generating period than non-orphans?
- What is the impact on revenue of multiple indications for both orphans and non-orphans?
- ACET formula is under revision: a more general approach which implies less assumptions is being developed
- Should the adjusted of the ICER be made on a ‘bespoke’ basis for each orphan drug, rather than in population bands?

Benefits and Inadequacies of this Approach

- Would give society some control over orphan drug prices (ie gives a *maximum* price)
- Would benchmark to overall industry rate of return, which will increasingly be determined by value for money assessments
- Gives an incentive to generate QALYs, but ***not*** necessarily ensure that manufacturers undertake research that will deliver the highest total social gains

Ways of Dealing with the Inadequacies of 'Rate of Return' Pricing Policies

- Be more explicit about priorities for treatments among the various untreated orphan diseases
- Consider the use of prizes for research, with the drug then supplied at marginal cost
- Consider new funding mechanisms for orphan disease research (on the national and international level)

  eg vaccines, antibiotics

Conclusions

- Revisions to orphan drugs policies are required
- We need more public debate about priorities for treatment of rare diseases
- If we do decide that we wish to make these treatments available, we need a ways of:

  (i) establishing a reasonable price and;

  (ii) setting priorities for research

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When playing as a slideshow, this slide will display live content

Poll: Do you agree that there should be a higher cost effectiveness threshold for orphan drugs compared to that used to appraise treatments for common conditions?

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Pre/Post Comparison: Do you agree that there should be a higher cost effectiveness threshold for orphan drugs compared to that used to appraise treatments for common conditions?

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Poll: If you agree, on which basis the threshold should be adjusted?

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