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Establishing a Reasonable Price for an Orphan Drug

July 2018

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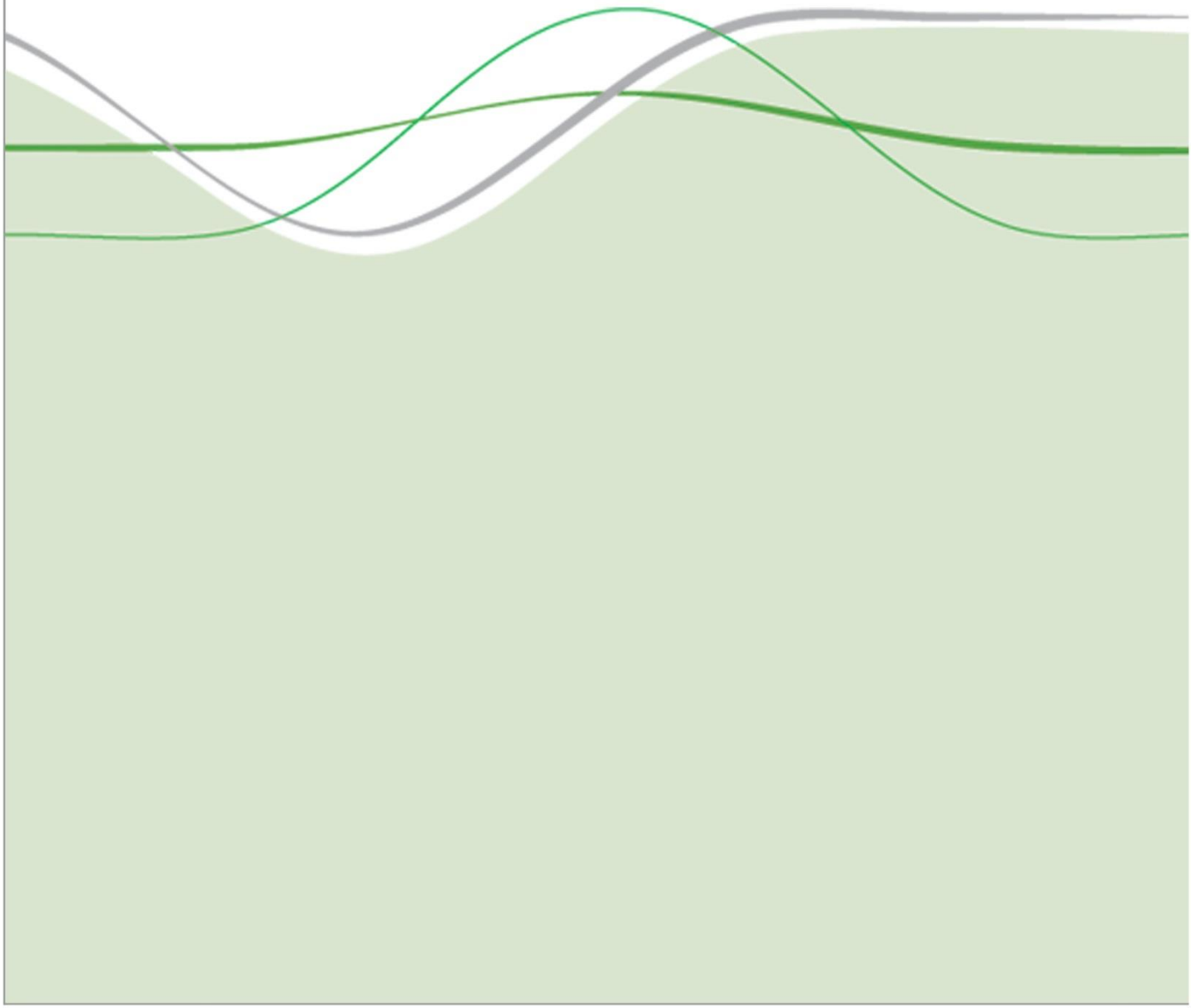

Establishing a Reasonable Price for an Orphan Drug

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ABSTRACT

Objective: The high cost of drugs for rare diseases ('orphan drugs') has generated considerable debate. While there is debate in the economic literature over whether a premium should be paid for 'rarity', these drugs are reimbursed in many countries with high prices. Therefore, the question then arises as to what should be a reasonable price for an orphan drug. This paper addresses that question based on the proposition that, although society may be willing to sacrifice some health gain overall to make treatments for orphan diseases available, it would not accept a situation whereby manufacturers of these drugs make higher profits than those manufacturers of drugs for non-orphan conditions. We propose a way to adjust an established payer/HTA body incremental cost-effectiveness threshold (CET) to take account of differences in patient populations and costs of research and development (R&D) in order to sustain sustain prices that generate rates of return from investments in developing orphan drugs that are no greater than the industry average.

Methods: We investigated the cost of conducting research for orphan drugs as compared to non-orphan drugs, as well as patient population sizes targeted by orphans and non-orphans. We split all novel drug approvals of the FDA between 2011-2015 (N=182) into those receiving orphan drug designation (n=71) and the remainder (n=111). We then collected the numbers of patients involved in clinical trials for those novel drugs approvals issued in 2015 from *ClinicalTrials.gov*. To estimate differences in revenues, we reviewed all appraisals conducted by NICE (England) and SMC (Scotland) regarding novel drugs approvals in our sample, to collect data on patient population sizes.

Results: On average, the estimated research and development (R&D) cost of an orphan drug is around the 27% of the cost of a non-orphan. However, potential market revenue is also lower for orphan drugs compared to non-orphans, as the average non-orphan patient populations were around 80 and 100 patients per 50,000 people for SMC and NICE appraised drugs respectively, which are higher than the cut-off population size (25 patients per 50,000 people) for orphan designation in the EMA's definition of rare diseases. Using the NICE incremental cost-effectiveness threshold (£20K per QALY) as an anchor and adjusting by R&D costs and expected market revenue, in the base case scenario we estimated the adjusted reasonable CET for orphan drugs to be £39.3K per QALY at the orphan population cut-off and £78.5K per QALY at the orphan population mid-point. For ultra-orphan drugs (with a patient population size of 1 in 50,000 or lower) the adjusted CET resulted in £938.4K.

Conclusions: Our research proposes one general method for establishing a reasonable price for an orphan drug, based on the proposition that rates of return for investments in developing orphan drugs should not be greater than the industry average. We establish that in order to secure such a reasonable price for an orphan drug, the cost-effectiveness threshold for orphans would need to be higher. The threshold would also need to increase as the targeted patient population size decreases. Further research is required to improve the estimates of key parameters, including non-orphan drugs average populations and the relative costs of the manufacture and distribution of orphan and non-orphan drugs. Our analysis does not indicate what society *should* be prepared to pay for an orphan drug, since this involves important societal judgments about whether some population health in total should be forgone in order to provide funding for treatments for rare conditions and, if so, how much. Rather, our approach could be viewed as one way of determining the *maximum allowable price* society should be willing to pay, based on allowing a reasonable rate of return.

1. INTRODUCTION

The high cost of drugs for rare diseases (often known as orphan drugs) has generated considerable debate. Many health economists argue that there is no justification for a premium for 'rarity' and that, in terms of reimbursement decisions (i.e. public subsidy), orphan drugs should not be judged any differently from drugs for common diseases. Given the current trend towards value-based pricing, this would mean orphan drugs should demonstrate that they represent good value for money when judged by conventional criteria. Otherwise, society would be sacrificing overall health gain in order to make these therapies available (McCabe et al, 2005). However, in practice this policy would lead to most orphan drugs being denied reimbursement (Clarke, 2006).

Other economists have argued that there may be characteristics of orphan drugs that might justify departing from the standard value for money criteria (Drummond et al, 2007). These additional characteristics could relate to the severity of the health condition and the absence of alternative effective therapies (Sussex et al, 2013). However, surveys of the general public mostly suggest that there is no willingness to pay a premium for rarity although there may be a case for paying more for drugs to treat severe conditions, or where there is unmet need (Desser et al, 2010; Linley et al, 2013).

Although the question of whether society should allow the reimbursement of orphan drugs is an important issue, the reality is that orphan drugs are currently being reimbursed in many jurisdictions. (Zamora et al., 2017.) The question then arises as to what should be a reasonable price for an orphan drug. Coté and Keating (2012) argue that there is a risk that manufacturers are exploiting society's willingness to pay for therapy in situations where individuals have no other effective therapy. They argue that many orphan drugs appear to be very profitable to manufacturers, that manufacturers may deliberately create situations whereby their drug could be designated 'orphan' and that many orphan drugs are marketed for multiple indications, which taken in their totality would not lead the drug to be designated orphan. In support of these arguments, Hughes and Polleti-Hughes (2016) estimate that companies holding orphan drug market authorizations generate a higher return on assets.

While health care decision-makers may be willing to provide funding for orphan drugs, they require reassurance that the prices being charged by manufacturers are not 'excessive'. In its technology appraisal of eculizumab for atypical haemolytic uraemic syndrome, the National Institute for Health and Care Excellence (NICE) acknowledged that treatment would produce a substantial health gain (greater than 10 quality-adjusted life-years) but felt that there was insufficient justification of the drug's price (of £330,000 for a year's therapy). This implied an incremental cost per QALY gained greater than £300,000, more than 10 times NICE's normal threshold range of £20,000-£30,000 per QALY. In approving the drug for use in the UK National Health Service, it referenced the annual cost of other specialized services and suggested that there should be further negotiation regarding the drug's price (NICE, 2015).

Therefore, if it is difficult to apply value-based pricing in the case of orphan drugs, how could one determine a reasonable price for these therapies? This paper addresses that issue, based on the proposition that, although society may be willing to sacrifice some health gain overall in order to make treatments for some orphan diseases available, it would not accept situation whereby the manufacturers of these drugs made substantially higher profits than manufacturers of drugs for non-orphan conditions. That is, the rates of return from investments in developing orphan drugs should be no greater than the

pharmaceutical industry average, after adjustments for risk and any other relevant factors.

2. METHODS

The two major differences between orphan and non-orphan drugs are that (i) the costs of research and development are likely to be lower for orphan drugs, as the clinical development programme is less extensive, and (ii) the treatment population for orphan drugs is likely to be smaller, given the rarity of disease. Therefore, in order to explore what should be a reasonable price for an orphan drug, we investigated the cost of conducting research into rare diseases, as compared with non-orphan conditions. We then investigated the adjustment that would need to be made to a payer's "normal" cost-effectiveness threshold (CET) for non-orphan drugs in order to achieve the industry-wide rate of return, in relation to the expected size of the treatment population. For illustrative purposes we use the UK threshold used by NICE in England and Wales and the Scottish Medicines Consortium (SMC) in Scotland.

2.1. A reasonable price for an orphan drug

We based our proposed approach for calculating a reasonable price for orphan drugs on the assumption that, as the target population size of a medicine goes down, the revenue generated also goes down unless the drug price increases to counter the effect of lower sales volumes. On the other hand, it is also likely that the R&D cost of a drug for a rare disease, and possibly other cost components including commercialization, marketing and manufacturing costs, are lower than for a non-orphan drug, because smaller numbers of patients are available for recruitment to clinical trials

We propose a reasonable price as one generated by these two opposing effects, affecting, on the one hand, revenue, and, on the other hand, the cost of drug development and commercialisation, in a way that its rate of return is approximately equal to the rate of return of a drug for a common disease.

Rather than just estimating how much higher or lower the price of an orphan drug should be because of these opposing adjustments, we have expressed the reasonable price in terms of the change that might be required in the CET which determines the maximum allowable price for a drug. The reason for this approach is that one would expect all drugs to produce health-related gains, whether designated orphan or not, but the 'acceptable' level of that threshold may vary depending on the designation. For simplicity we assume that all of the benefits of drugs can be expressed in QALYs.

For a formal development of our approach consider the following notation:

$t = 0$: research starts

P_D: patent or other form of exclusivity duration in number of years

$t = T_P$: point of patenting

$t = T_L$: point of market launch

$t = T_{Ex} = T_P + P_D$: point of patent expiration or other form of exclusivity

$t = 0, \dots, T_{P,} \dots, T_L, \dots, T_{Ex}$: drug's life-cycle

δ: discount factor

P_{no}: price non-orphan

P_o: price orphan

$P_{no/c}$: price non-orphan comparator

$P_{o/c}$: price orphan comparator

$P_{no} = P_{no/c} = P_o = P_{o/c} = 0, \forall t \in [0, T_L)$

q_{no}^t: quantity non-orphan (equal to comparator) in period t

q_o^t: quantity orphan (equal to comparator) in period t

$q_{no}^t = q_o^t = 0, \forall t \in [0, T_L)$

R_{no}^t: R&D cost of a non-orphan in period t

R_o^t: R&D cost of an orphan in period t

$R_{no}^t = R_o^t = 0, \forall t \in (T_L, T_E]$

C_{no}^t: other components of the cost of a non-orphan (marketing, manufacturing, distribution) in period t

C_o^t: other components of the cost of an orphan (marketing, manufacturing, distribution) in period t

$C_{no}^t = C_o^t = 0, \forall t \in [0, T_L)$

π_{no}: return for a non-orphan developer (current value at t=0)

π_o: return for an orphan developer (current value at t=0)

B_{no}: per patient health gain non-orphan

B_o: per patient health gain orphan

$B_{no/c}$: per patient health gain alternative (therapy) to non-orphan

$B_{o/c}$: per patient health gain alternative (therapy) to orphan

CET: cost effectiveness threshold

Let the Incremental Cost Effectiveness Ratio (ICER) for a non-orphan be:

$$ICER = \frac{(P_{no} - P_{no/c})}{(B_{no} - B_{no/c})}$$

Payers and/or HTA agencies fix the CET which ICER must not overcome for a reimbursement recommendation. Substituting the ICER by the CET, then we have that,

$$CET = \frac{(P_{no} - P_{no/c})}{(B_{no} - B_{no/c})}$$

Assuming value-based prices, a non-orphan drug developer will set the price as follows:

$$P_{no} = CET(B_{no} - B_{no/c}) + P_{no/c} \qquad (1)$$

Analogously an orphan developer will set the price as follows:

$$P_o = CET(B_o - B_{o/c}) + P_{o/c} \qquad (2)$$

Let the return for a non-orphan drug developer be:

$$\pi_{no} = \sum_{t=0}^{t=T_{Ex}} \delta^t \left(P_{no} q_{no}^t - C_{no}^t - R_{no}^t\right)$$

Analogously the return for an orphan drug developer will be:

$$\pi_o = \sum_{t=-0}^{t=T_{Ex}} \delta^t \left(P_o q_o^t - C_o^t - R_o^t\right)$$

Following our approach for a reasonable price of an orphan drug, both returns should be equal and therefore we have that,

$$\sum_{t=0}^{t=T_{Ex}} \delta^t \left(P_o q_o^t - C_o^t - R_o^t\right) = \sum_{t=0}^{t=T_{Ex}} \delta^t \left(P_{no} q_{no}^t - C_{no}^t - R_{no}^t\right) \quad (3)$$

Using (1) and (2) into (3) and assuming that the cost effectiveness threshold for an orphan CET_o must be different from the CET as our reasonable pricing approach establishes, we have that,

$$\sum_{t=0}^{t=T_{Ex}} \delta^t \left(\left(CET_o\left(B_o - B_{o/c}\right) + P_{o/c}\right) q_o^t - C_o^t - R_o^t\right) = \sum_{t=0}^{t=T_{Ex}} \delta^t \left(\left(CET\left(B_{no} - B_{no/c}\right) + P_{no/c}\right) q_{no}^t - C_{no}^t - R_{no}^t\right)$$

Rearranging we have that,

$$CET_o = \frac{\sum_{t=T_P}^{t=T_{Ex}} \delta^t \left(CET\left(B_{no} - B_{no/c}\right) q_{no}^t + \left(P_{o/c} q_o^t - P_{no/c} q_{no}^t\right) - \left(C_{no}^t - C_o^t\right) - \left(R_{no}^t - R_o^t\right)\right)}{\sum_{t=T_P}^{t=T_{Ex}} \delta^t \left(CET\left(B_o - B_{o/c}\right) q_o^t\right)} \quad (4)$$

where CET_O represents the adjusted cost effectiveness threshold for an orphan drug. Under perfect information about health benefits, prices and quantities of new orphan and non-orphan drugs and their comparators, as well as for R&D costs and other components of the cost for orphans and non-orphans, CET could be adjusted by applying (4) to calculate a reasonable value-based price for each new orphan drug. However, collecting accurate data for all variables involved in (4) is beyond the scope of this work[1]. Therefore, in order to apply our proposed approach to the data we have been able to collect (i.e. population sizes and R&D costs), it is necessary to make assumptions about several components of (4). We set out our assumptions below:

- Cost and health benefits for both comparators, orphan and non-orphan drugs, are equal to zero: $P_{o/c} = P_{no/c} = 0$ and $B_{o/c} = B_{no/c} = 0$
- Equal variable costs (manufacturing, distribution, etc.) of orphans and non-orphans: $C_{no}^t = C_o^t$
- Average health gain per patient for non-orphan drugs equal to one: $B_{no} = 1$
- Equal average health gain per patient for orphans and non-orphans: $B_o = B_{no}$

Applying the above list of assumptions, we can simplify (4) into:

[1] Perfect knowledge of costs and of numbers of patients would still require judgements around (i) failure rates and the costs associated with failures and (ii) the allocation of global fixed costs across individual country markets. Our view is that it makes more sense to use industry-wide evidence on relative costs and failure rates rather than seek to establish the costs associated with a particular drug. The latter approach raises efficiency issues (it risks becoming a cost-plus system) as well as putting requiring cost information which may not be forthcoming, and judgements about shares of global cost burden which may be disputed.

$$CET_o = \frac{\sum_0^{T_{EX}} \delta^t \left(CET q_{no}^t - (R_{no}^t - R_o^t) \right)}{\sum_0^{T_{EX}} \delta^t q_o^t} \qquad (5)$$

Where CET is th Cost Effectiveness Threshold; q_{no} is the average population of non-orphan, q_o is the cut-off (alternatively the average) population of orphan; R_{no} is the R&D cost of a non-orphan; and R_o is the R&D cost of an orphan.

Additionally, for the adjustment of the CET we also want to differentiate between orphan[2] - from now on noted by the subscript *o* - and ultra-orphan drugs[3] - from now on noted with the subscript *uo*. For this purpose, we want to make a specific assumption for ultra-orphans:

- Variable costs (manufacturing, distribution, etc.) of ultra-orphans are lower than variable costs of non-orphans, in the same proportion as the R&D costs: $C_{no}^t > C_{uo}^t$

Applying this additional specific assumption for ultra-orphans to (4) and keeping all other assumptions for orphan drugs constant we have that:

$$CET_{uo} = \frac{\sum_0^{T_{EX}} \delta^t \left(CET q_{no}^t - (C_{no}^t - C_{uo}^t) - (R_{no}^t - R_{uo}^t) \right)}{\sum_0^{T_{EX}} \delta^t q_{uo}^t} \qquad (6)$$

Where, in addition to (5), q_{uo}^t is the cut-off (alternatively the average) population of ultra-orphan in period t; C_{no} is the variable cost of a non-orphan; C_{uo}^t is the variable cost of an ultra-orphan in period t; and R_{uo}^t is the R&D cost of an ultra-orphan in period t.

Finally, it should be noted that the general approach considers global figures of both costs and revenues for non-orphan and orphan developers. In applying the approach to a particular country or market, these estimates will need to be appropriately adjusted by its weight of the global market. We make additional assumptions to implement the general approach to a particular country or market. We assume that (i) the CET in any given country has been appropriately determined[4] (ii) the ratios of patient numbers for a typical orphan or ultra-orphan drug, as compared to a non-orphan in a particular country are the relevant ratios and (iii) the share of the total global pharmaceutical market for all products represented by a country's market is the relevant share of global R&D that should be charged to that market[5].

2.2. Novel drug approvals by designation

[2] According to the European Medicines Agency's (EMA), rare diseases are defined as life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the EU (25 in 50,000 people). Orphan designations are granted by EMA to medicines that target to treat rare diseases. See: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac0580b18a41

[3] SMC and NICE additionally define ultra-orphan drugs as medicines that have been granted by the EMA with the orphan status and target to treat conditions with a prevalence of 1 in 50,000 people in England and/or Scotland. See: https://www.scottishmedicines.org.uk/media/2782/pace-overview-document.pdf.

[4] For a discussion of the issues involved in setting the CET in any individual jurisdiction in order to signal the optimal amount of R&D see Danzon, Towse and Mestre-Ferrandiz, 2015.

[5] There is always the possibility that the size of a country's market is not driven by the appropriate CET, but by a desire to free-ride on paying for R&D costs. Of course, it is possible that a country is overpaying for drugs, given the underlying willingness to pay for health gain.

All novel drug approvals completed by the Food and Drug Administration (FDA) in the period 2011-2015 were considered for the study (n=182)[6]. The sample was divided into two groups: those approved under the orphan designation, and those approved under non-orphan designations. Within the orphan and non-orphan drug groups, the sample was also divided into oncology and non-oncology drugs, since in many jurisdictions oncology drugs indicated for small patient populations (possibly because of targeted therapy), are not treated differently for reimbursement, even though they are technically 'orphan'.

2.3. Research and development cost

In order to estimate any difference between the cost of developing an orphan and a non-orphan drug, we investigated the cost of conducting research for all novel drug approvals issued in 2015. For this subsample, data on the number of patients involved in clinical trials was collected from *ClinicalTrials.gov*[7]. For each drug, we identified the number of patients in clinical trials involved at the different phases of development (e.g. phases I, II and III). Within medicines designated as orphan and non-orphan, we also distinguished between medicines approved for oncology and non-oncology indications.

For the estimation of the cost of developing a drug we followed the methodology of Mestre-Ferrandiz et al. (2012). They estimate the R&D cost of a new drug based on the impact of four cost drivers: out-of-pocket costs, time of development, cost of capital, and failure rates of development.

We searched the literature for estimates of the per-patient cost in clinical trials. We found a per-patient trial cost – only trial site related costs – in the report by Battelle (2015) for Pharmaceutical Research and Manufacturers of America (PhRMA). We estimated the out-of-pocket cost by multiplying average number of patients in clinical trials and per-patient costs. We also found estimates of failure rates by development phases, broken down by orphan and non-orphan indications (Hay et al., 2014). Finally, we kept unchanged the cost-of-capital from the original modelling of Mestre-Ferrandiz et al. (2012) and updated the model with the most recent estimates of the time of development for development phases 1, 2 and 3 (DiMasi et al., 2016). As times for clinical development between orphan drugs and non-orphan drugs for are not considered to be significantly different (Orfali et al., 2012), we have used the same estimates for both.

Although very important, the costs of R&D are only one component of the cost of bringing a new drug to market. In addition, there are costs in manufacturing, marketing and distribution. It is not known whether these other costs are also lower for orphan drugs, or whether they are the same as for non-orphan products. Therefore, different assumptions were made about the potential reduction in these other costs for orphans and ultra-orphans and their impact explored in a sensitivity analysis.

2.4. Patient population size

In order to estimate the sales volume for companies, we searched for data on target patient populations and annual drug cost per patient[8]. To gather this information, we consulted Scottish Medicines Consortium (SMC) and National Institute for Health and

[6] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm430302.htm
[7] https://clinicaltrials.gov/
[8] We take the drug cost per course of treatment when the whole medicine treatment course per patient lasts less than one year.

Care Excellence (NICE) appraisals, which often give estimates of the potential treatment population for the technologies being appraised. We considered all technology appraisals conducted during the period January 2011-March 2017.

At the time of the study, some drugs for rare conditions were being appraised by the Advisory Group for National Specialised Services (AGNSS), (see https://www.nice.org.uk/news/article/nice-to-assess-high-cost-drugs-for-rare-conditions). NICE was, however, appraising some cancer drugs for small patient populations that were designated 'orphan'. We found data for patient populations from a total number of 48 SMC appraisals (24 orphans and 24 non-orphans) and 33 NICE appraisals (11 orphans and 22 non-orphans). Drugs appraised by both SMC and NICE, amounted to a total number of 21 drugs (7 orphans and 14 non-orphans).

In order to make the patient population data from both sources comparable we standardised by dividing by the total population of England[9] and Scotland[10], and then multiplying by 50,000 to make the resulting rates per 50,000 comparable with the European Union orphan designation.

2.5. Cost-effectiveness estimates and appraisal decisions

We also obtained data on the incremental cost effectiveness ratios (ICERs) of appraised medicines included in our sample, along with the appraisal decisions (recommended or not recommended). The main purpose of collecting actual ICERs and decisions was to understand what NICE and SMC had actually decided and discuss these decisions in relation to our adjusted CET reflecting a proposed reasonable price for an orphan drug.

Health technology appraisals of NICE often present more than one ICER. In such cases we followed the algorithm developed by Drummond et al. (2014) for the selection of the most plausible ICER. This method is a rank-based selection process which selects the ICER in the following order:

1. The ICER clearly adopted by NICE for decision making purposes;
2. The estimate given by NICE's Decision Support Unit (in cases where the DSU was consulted);
3. The estimate given by the Evidence Review Group (ERG) report;
4. The estimate provided by the manufacturer.

The SMC also often presents more than one ICER in appraisals (i.e. sensitivity analyses, changes in the modelling). However, since the decision is taken based on a detailed discussion of the estimate provided by the manufacturer, rather than an estimate produced by an independent review group, we selected that estimate. For both NICE and the SMC, the ICERs in appraisals take into account confidential discounts offered through 'Patient Access Schemes'.

The purpose of considering ICERs from both SMC and NICE was not to make comparisons of ICERs between the two organisations, but to make comparisons between the ICERs for orphan and non-orphan drugs based on each data source. The use of data

[9] 'Mid-2013 Population Estimates for Clinical Commissioning Groups (CCGs) and NHS area teams in England by Single Year of Age and Sex (experimental statistics) and NHS Area teams' for the total population of England: http://www.ons.gov.uk/ons/search/index.html?newquery=01currccg

[10] Mid-year 2016 estimate from National Records of Scotland (NRS): https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population/population-estimates/mid-year-population-estimates/mid-2016

from two different sources provides a better indication of whether there is a consistent pattern between the ICERs of orphan and non-orphan drugs. However, the estimated average ICERs for orphan and non-orphans of NICE and SMC are based on different samples. To solve this problem, we also estimated average ICERs for orphans and non-orphans based only on technologies that had been appraised by both organisations.

3. RESULTS

3.1. Novel drug approvals by designation and indication

Table 1 gives details of the NDAs made by the FDA for the period 2011-2015. It can be seen that around 40% of all approvals were for orphan drugs and that around 50% of all approvals were oncology products.

Table 1. Distribution of novel drug approvals by designation and indication

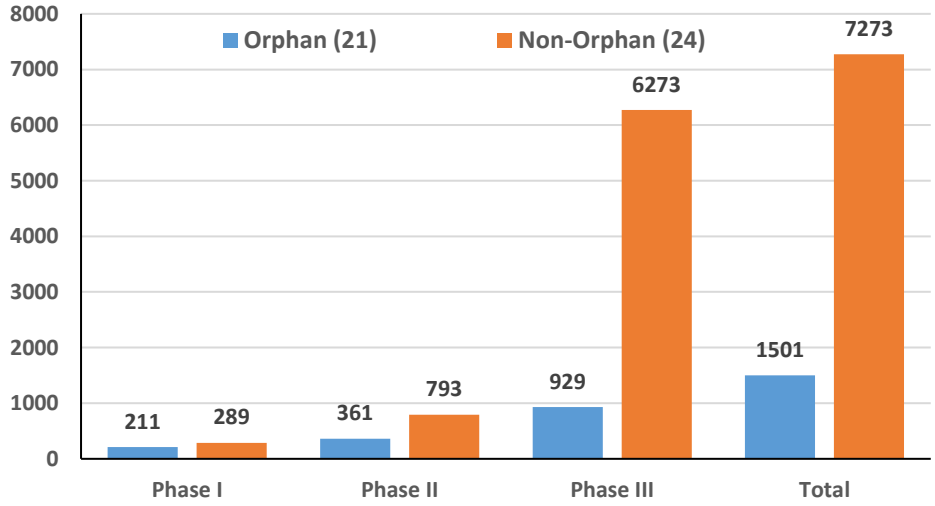
	Non-oncology	Oncology	Total
Orphan Drugs	36	35	71
Non-orphan drugs	58	53	111
Total	94	88	182

Source: FDA, Novel Drugs Approvals 2011-2015

3.2. Research and development cost

Based on the data for 2015 novel drug approvals, a significantly greater number of patients were enrolled in clinical trials for non-orphan drugs as compared to orphan drugs. This is as expected; orphan drugs target rare diseases, so the size of the treatment populations must be lower. Therefore, the average sample size for the clinical trials is also likely to be lower, because of the challenges of recruiting patients. The main difference occurs in Phase 3 trials, where the effectiveness of the drug is typically tested on larger samples of patients in order to demonstrate a statistically significant difference in relative treatment effect. Figure 1 shows differences both by development phase and in total.

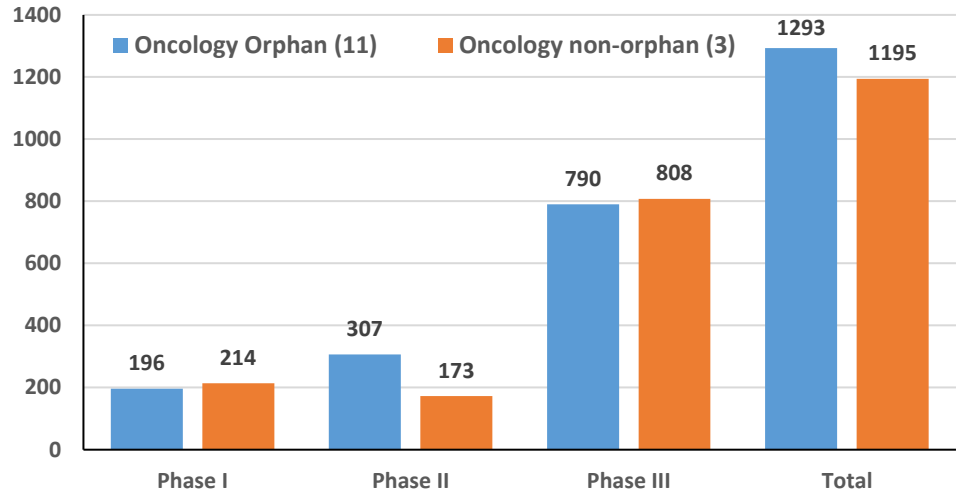
Figure 1. Average number of patients by orphan and non-orphan designation for all indications



Sources: FDA, Novel Drug Approvals 2015; ClinicalTrials.gov
Notes: oncology drugs are included in all indications

However, for oncology products no significant differences in patient numbers were observed between medicines designated orphan or non-orphan, suggesting that the evidentiary standards are similar across all cancer indications. See Figure 2.

Figure 2. Average number of patients by orphan and non-orphan designation for oncology medicines



Source: ClinicalTrials.gov

The size of clinical trials is one of the main determinants of the out-of-pocket cost of developing a drug and therefore the R&D cost of developing an orphan drug must be lower than that of a non-orphan drug.

The other factor we take into account is the difference in the overall development success rate (defined in terms of the proportion of drugs obtaining a market authorization from FDA), which is a key driver of overall R&D cost. Evidence in the literature suggests this was 32.9% for orphans and 10.4% for non-orphans. Focusing only on oncology indications, the orphans' cumulative success rate was 23%, but only 5.4% for oncology non-orphan drugs (Hay et al., 2014). One can only speculate why this might be the case. One possibility is that targeting smaller patient populations, often based on a gene expression test, increases the chances of success.

Using our estimates of out-of-pocket costs and success rates from the literature, we estimated the R&D costs based on the model developed Mestre-Ferrandiz et al. (2012). These estimates, set out in Table 2, should be viewed with caution as they are based on a small sample. However, they do suggest possible differences in the R&D costs for orphan and non-orphan drugs.

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 novel drug approvals of FDA; Estimates for all indications include oncology products.

One point to note when considering the results in Table 2 is that the R&D cost of a non-orphan drug for oncology indications is double the R&D cost of an orphan drug for oncology, despite the number of patients in clinical trials being similar (Figure 2). This reflects the lower probability of success, so more non-orphan oncology projects need to be started to achieve one successful licensed product. For all indications, however, the difference arises mainly from the different number of patients involved in trials.

Overall, we estimated the R&D cost of an orphan to be around the 27% of the cost of a non-orphan, which is in line with what Coté and Keating (2012) argued, and also with an EvaluatePharma Orphan Drug Report (2014) which estimated the phase III cost of an orphan to be 24.7% of the phase III cost of a non-orphan. However the corresponding figure for an oncology orphan drug is around 50%. In order to estimate the relative lifecycle costs of producing orphan and non-orphan drugs it is necessary to determine whether all the other costs (in manufacturing, marketing and distribution) are reduced by a corresponding amount. If that is not the case, it would be necessary to estimate what proportion R&D costs are of the total.

Danzon (1997) estimated that R&D costs represent 30% of total lifecycle costs. This is the only estimate we have found in the literature. Therefore, for the base case estimate we produced adjustments of cost-effectiveness thresholds by applying equations (5) and (6) based on two alternative assumptions:(i) for ultra-orphans we assume that *all* drug lifecycle costs were reduced by the same proportion as R&D costs, and (ii) for regular orphans only 30% of lifecycle costs were reduced by 26.9% (or 55.1% for oncology drugs), the remainder being equivalent for regular orphan and non-orphan drugs. The first approach produces more conservative estimates, as the greater adjustment to the drug lifecycle cost cancels out a greater proportion of the revenue adjustment in our formula, thereby resulting in a higher adjusted CET. However, because we are not sure which assumption is more appropriate, we present the adjusted CETs for orphan and ultra-orphan drugs resulting from both approaches in a sensitivity analysis.

Table 3 shows estimates of average patient populations for the drugs appraised by NICE and the SMC. The average patient population per 50,000 inhabitants for an orphan drug is quite similar in both the SMC and NICE appraisals. However, the same figure for non-orphans is 25% higher in England than in Scotland. This may be due to the small sample size, the different subsets of drugs appraised by the two organisations, or other country-specific demographic or epidemiologic factors. However, for both SMC and NICE, the average patient population is much lower for orphan drugs. Assuming that potential revenues are related to patient populations, a reasonable price for orphans would need to take account of these differences.

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

	SMC	**NICE**
	Average number of patients	**Average number of patients**
Orphan	2.54	2.61
Non-orphan	82.8	102.57

Source: SMC and NICE

3.3. Estimating the reasonable price for an orphan drug

Using our estimates of differences in R&D costs and treatment populations for orphan and non-orphans and applying our proposal of a reasonable price as set out in equations (5) and (6), we can estimate adjusted CETs corresponding to orphan and ultra-orphan drugs. Although estimates of orphan and non-orphan population sizes presented in Table 3 show some degree of variability between SMC and NICE, for the base case we use the NICE estimate of non-orphan patient population size for the adjustments, rounded to 100 per 50,000 inhabitants. In a sensitivity analysis we explore the impact of different assumptions about the size of the non-orphan patient population.

Adjustments of the CET have been made both orphan designation and 'ultra-orphan' drugs. For the adjustment of the revenue for orphans and ultra-orphans, we have calculated the average adjusted CETs taking the 'cut-off' point populations of orphan and ultra-orphan drugs as well as the mid-point cut-off orphan population and average non-orphan population used in NICE appraisals. These population sizes are set out in Table 4 below, standardised by population and in absolute numbers.

Table 4. Non-orphan, orphan and ultra-orphan population sizes

	Standardised per 50,000	**Absolute[a]**
Orphan cut-off population	25	26,932
Orphan mid-point population	12.5	13,462
Ultra-orphan cut-off population	1	1,077
Non-orphan average[b]	100	107,732

Sources: EMA, NICE and Authors calculations

Notes: [a]To estimate the absolute populations we first multiply standardised numbers by the UK population (less Scotland) in NICE technology appraisals and, second, we divide the resulting number by 50,000; [b]Non-orphan average population is the average population of the non-orphan drugs appraised by the NICE rounded to 100 per 50,000 people.

To estimate the adjusted CET applying (5) and (6) we have made several assumptions which enable us to estimate the adjustment for the UK:

1. The £20,000/QALY threshold currently used by NICE is the appropriate starting point
2. The corresponding weights of global R&D cost and operational variable cost relevant to the UK market are proportional to the UK's market share of global pharmaceutical sales[11]
3. Patent expiration time is ten years after market launch time ($T_{Ex} = T_L + 10$)[12]
4. Non-orphan drugs only achieve 50% of the potential sales due to in-class competition[13]

[11] Data of 2015 market share of the UK has been taken from the IMS World Review Executive™ 2016.

[12] We assume ten years following EMA's market exclusivity regulation for orphan drugs. See: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001927.jsp&mid=WC0b01ac0580d71fbd

[13] We assume same length for patent for non-orphan drugs but without market exclusivity

5. A discount rate of 11% is used for the revenues (same as used for the estimation of R&D cost)

R&D costs, other costs and revenues (populations) have been discounted to the present value at the time period ($t = 0$) when research starts.

Table 6 shows our base case estimates of the adjusted CETs that would sustain reasonable prices for orphans and ultra-orphans according our formulae (5) and (6).

Table 6. Adjusted cost effectiveness thresholds for orphan and ultra-orphan drugs – base case

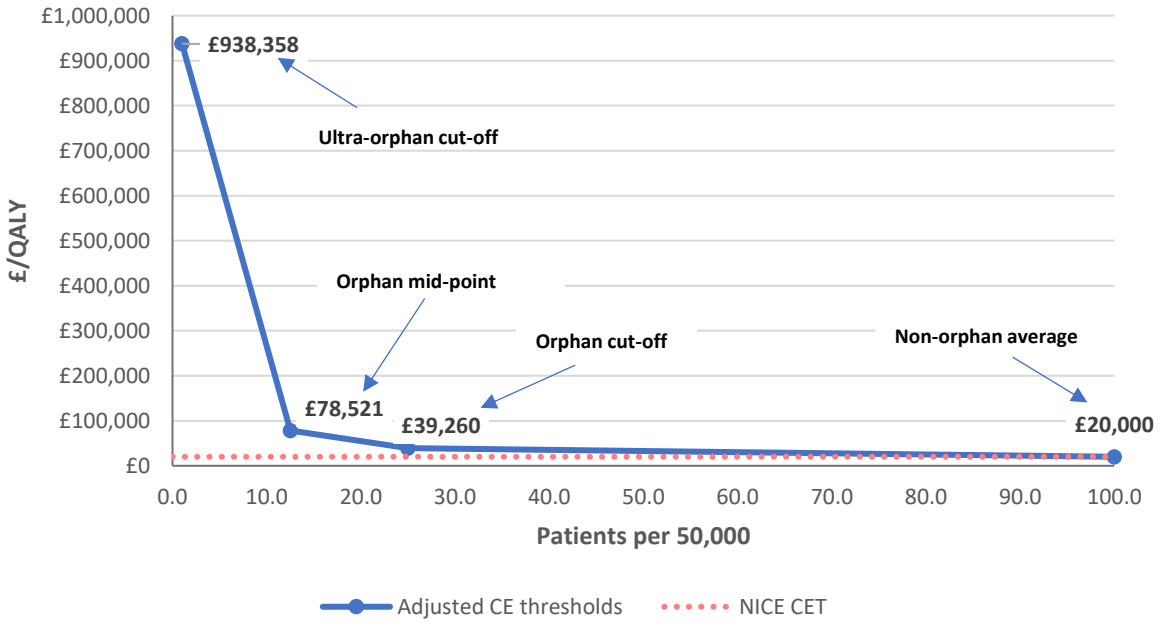
	Adjusted CET
Orphan cut-off population	£39.3k
Orphan mid-point population[a]	£78.5k
Ultra-orphan cut-off population[b]	£938.4k

Source: Authors calculations

Notes: [a]Orphan mid-point population is represented by the median point between orphan cut-off population and zero. [b]Ultra-orphan cut-off point adjusted CETs are calculated assuming that operational costs (e.g. manufacturing, marketing, commercialisation) decrease in the same proportion as R&D costs.

By connecting estimates of the adjusted cost effectiveness thresholds given in Table 6, Figure 3 shows how adjusted cost effectiveness thresholds and population sizes relate to each other.

Figure 3. Adjusted cost effectiveness thresholds



Source: Authors calculations

3.4. Actual decisions made by NICE and SMC

Table 7 shows the average ICERs of the orphan and non-orphan drugs appraised by both, NICE and SMC, irrespective of whether the technologies were recommended.

Table 7. Average ICER of orphan and non-orphan drugs (all drugs appraised)

	SMC	NICE
Orphan drugs	£68,064	£73,530
Non-orphan drugs	£24,090	£25,051

Sources: SMC https://www.scottishmedicines.org.uk/; NICE https://www.nice.org.uk/

In general, the ICERs for orphan drugs are higher than the ICERs for non-orphans. As Table 7 shows, average ICERs for orphans are almost 3 times higher than average ICERs for non-orphans in both, NICE and SMC appraisals.

Considering only the recommended technologies, the same pattern emerges, but with a smaller difference in the ICERs for orphans and non-orphans. For recommended technologies the ICERs of orphans are almost 2 times higher for orphans than for non-orphans (See Table 8).

Table 8. Average ICER of orphan and non-orphan drugs (drug with positive recommendations only)

	SMC	NICE
Orphan drugs	£46,211	£43,918
Non-orphan drugs	£24,090	£25,051

Sources: SMC https://www.scottishmedicines.org.uk/; NICE https://www.nice.org.uk/

These data suggest that both organizations may be implicitly adjusting their willingness to pay for medicines that target rare diseases, although in the case of NICE the decisions made on oncology drugs (orphan and non-orphan) will also be influenced by application of the End-of-Life (EoL) guidance. In line with which the actual pattern of orphan and non-orphan ICERs of recommended technologies by the NICE and the SMC seem to reflect, a higher CET for drugs for rare diseases has recently been proposed in the NICE and NHS England public consultation on proposals to change the arrangements for evaluating and funding highly specialized technologies (mostly ultra-orphan drugs)[14]. The original proposal was to increase the cost effectiveness threshold for highly specialized technologies up to £100,000 per QALY. After responses were received, the proposal was changed to allow a modified cost effectiveness threshold of £100,000 per QALY that can be increased up to £300,000 per QALY depending on the absolute QALY gain offered by the appraised technology[15].

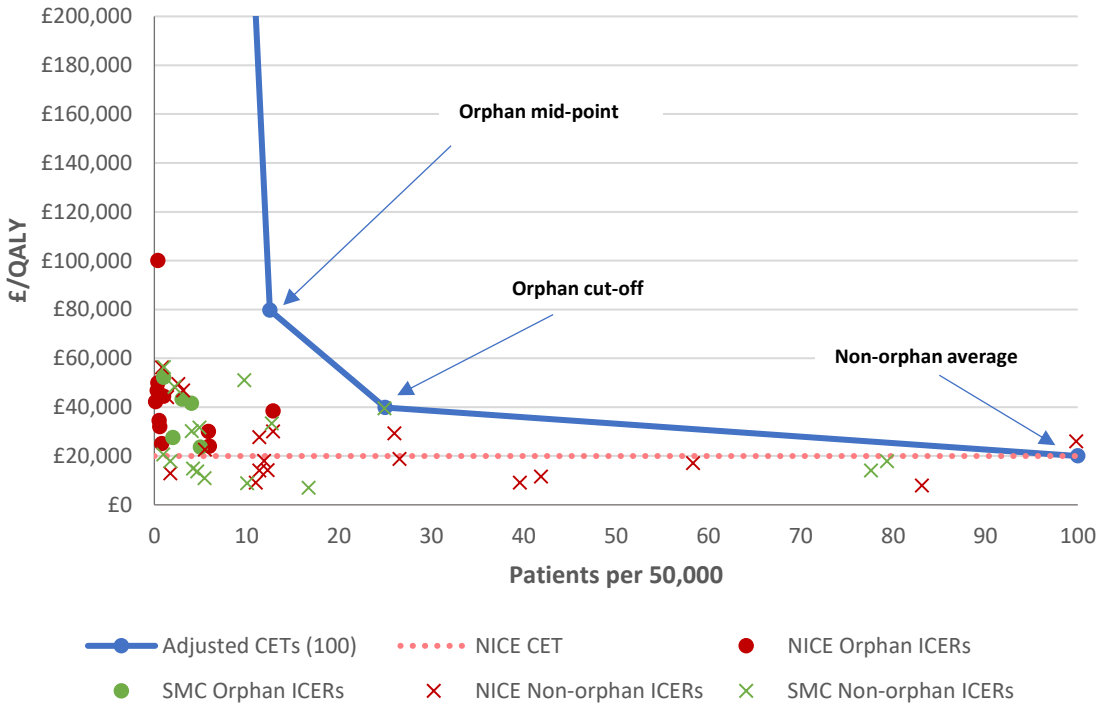
We have superimposed our adjusted cost-effectiveness thresholds on the actual decisions by the SMC and by NICE in Figure 4 to see how the proposed adjusted thresholds from our approach compare with SMC's and NICE's decisions. In Figure 5 the adjusted ICERs for orphan drugs based on two different orphan population sizes (e.g. cut-off and midpoint populations) are superimposed on ICERs of recommended orphan and non-orphan technologies by SMC and NICE. All observations for non-orphans whose populations exceed the orphan population cut-off point, present ICERs below (or quite close to) the standard cost effectiveness threshold. Below the orphan population cut-off point, Figure 4 shows a mix of orphans and non-orphans.

[14] For more details about the consultation see:https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/consultation-on-changes-to-technology-appraisals-and-highly-specialised-technologies

[15] See: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/board-paper-TA-HST-consultation-mar-17-HST-only.pdf

There are three non-orphan drugs (out of 17) appraised by the SMC, two oncology drugs and one for hepatitis C, targeting small populations, with ICERs considerably above the standard cost-effectiveness threshold. Looking at drugs recommended by NICE there are also three (out of 12), all oncology drugs, targeting populations below the orphan cut-off population, for which ICERs are considerably above the standard cost-effectiveness threshold. All but one of the orphan drugs recommended by the SMC have ICERs higher the standard cost effectiveness threshold. This shows that drugs targeting rare diseases, or with population sizes close to orphan drugs, are granted cost-effectiveness thresholds implying higher prices than those that would be implied by the standard threshold. This may reflect the higher willingness to pay for End of Life (EoL) treatments, which are mostly oncology products for highly stratified patient populations. However, all actual ICERs fall below our proposed adjusted cost-effectiveness threshold.

Figure 4. Adjusted cost-effectiveness thresholds and NICE-SMC decisions to recommend



Sources: NICE (*https://www.nice.org.uk/*), SMC (*https://www.scottishmedicines.org.uk/*) and authors' calculations.

Notes: The line that relates population sizes to adjusted CET by connecting our adjusted CETs of Table 6 goes to the point of the ultra-orphan CET (£983k/QALY). Outlier observations showing either too large populations (all non-orphans) or too large ICERs (all ultra-orphans) have been excluded from the graph in order to keep a comparable scale. Five outliers have been excluded.

3.5. Adjusted ICERs for oncology orphan drugs

We have also calculated adjusted ICERs for oncology products separately. The main reason to treat oncology drugs separately in our analysis is the existing differences between oncology and non-oncology drugs with regards to the cost of R&D. We have calculated the adjusted ICER thresholds for oncology orphans and ultra-orphans, proceeding in the same way as for all indications but adjusting for the oncology products' specific differences in R&D costs for oncology orphan drugs (see Table 2). Apart from this variation we apply the same set assumptions used for all drugs. Table 9 shows the adjusted CETs for several population sizes of oncology orphans and non-

orphans. Adjusting the CET for orphan sample average population size, we have applied the same specific assumptions used for ultra-orphans for all indications because the average oncology orphan population is smaller than ultra-orphan cut-off population. Therefore, the adjusted CET for orphan sample average population for oncology drugs results higher than the adjusted CET for ultra-orphan as Table 9 shows.

Table 9. Adjusted cost-effectiveness thresholds for orphan and ultra-orphan oncology drugs

	Adjusted CET
Oncology Orphan cut-off population.	£39.8k
Oncology Orphan mid-point population[a]	£79.6k
Oncology Ultra-orphan cut-off population[b]	£982.4k

Source: Authors calculations

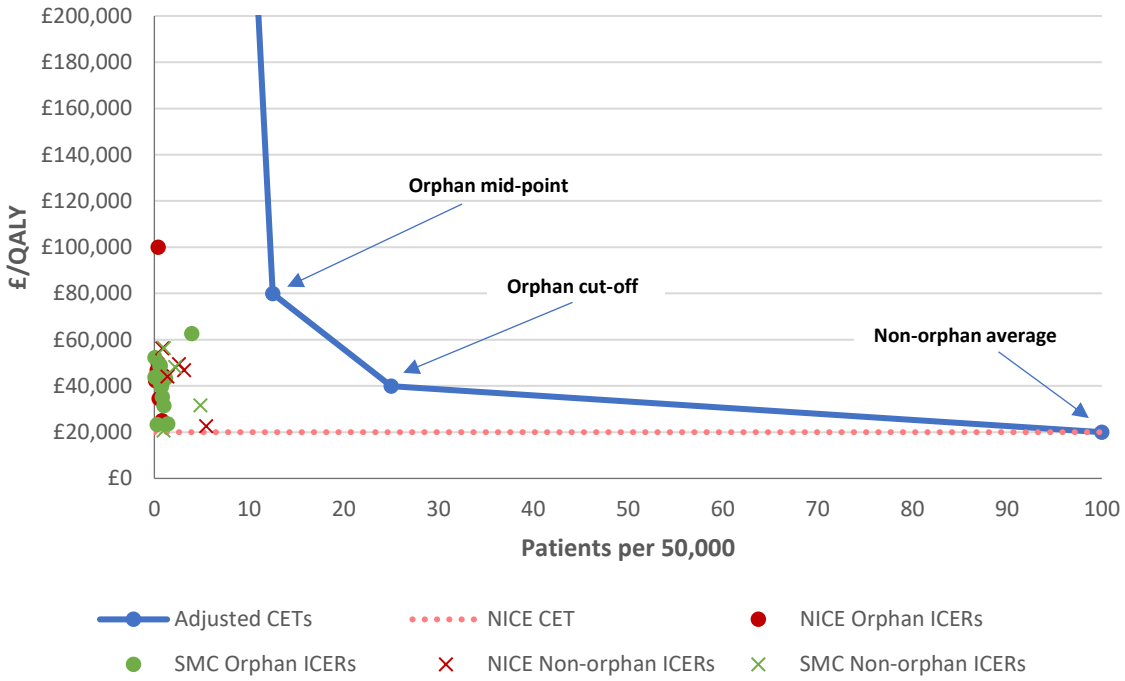
Notes: [a]Orphan mid-point population is represented by the median point between orphan cut-off population and zero.

[b]Ultra-orphan cut-off point adjusted CETs are calculated assuming operational costs (e.g. manufacturing, marketing, commercialisation) decrease in the same proportion as R&D costs.

Figure 5 shows the adjusted cost effectiveness thresholds for oncology orphans superposed with SMC and NICE actual decisions on oncology products. All drugs included in Figure 5 are oncology medicines recommended by either the NICE or the SMC.

As stated before, all patient populations for oncology drugs appraised and recommended by NICE and SMC fall below the orphan population cut-off point regardless of whether these drugs are designated orphan or not. This suggests that stratification and personalized medicine is becoming routine in innovation in oncology. All ICERs of appraised and recommended orphan and non-orphans in oncology are higher than the standard cost effectiveness threshold. Furthermore, there are no significant differences between the orphan' and non-orphan' populations, despite the fact that orphans have smaller patient populations. Finally, all actual ICERs are far below the line connecting the adjusted cost-effectiveness thresholds calculated as per our formula for the reasonable CET.

Figure 5. Adjusted cost-effectiveness thresholds and NICE-SMC actual decisions for oncology orphan and non-orphan drugs



Sources: NICE (*https://www.nice.org.uk/*), SMC (*https://www.scottishmedicines.org.uk/*) and authors' calculations.
Note: The line that relates population sizes to adjusted CETs by connecting our estimates of adjusted CETs of Table 9 goes to adjusted CETs corresponding to ultra-orphan cut-off point and orphan oncology sample average.

4. SENSITIVITY ANALYSIS

To assess the impact of the several assumptions made to estimate the adjusted CETs, a sensitivity analysis was conducted. Additional to the impact of the assumptions made on the different population sizes of non-orphans, orphans and ultra-orphans, we also explored the impact on the results of other assumptions applied, in particular, those regarding the market exclusivity period for orphan drugs and the degree of in-class competition.

One feature of orphan drugs is the absence of competitors during the patent period. This is due firstly because of rarity, which hinders the development of treatments and therefore the likelihood of other competitors for the same disease[16], and secondly because of the market exclusivity period new orphan drugs are granted in the US (7 years)[17] and the EU (10 years)[18]. This is a different context than the one characterising non-orphan drugs developed to treat common diseases, where competition is common place and drugs have to compete for market share with other in-class competitors.

For the estimation of the base case CETs we assumed a length of 10 years of market exclusivity for orphan drugs and a 50% of market share for non-orphans. Additionally,

[16] See Milne et al. (2018), the recently published report of the Tufts Center for Drug Development.
[17] See: https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm239698.htm
[18] See: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000392.jsp

for the estimation of the CETs we assumed the populations in Table 4 of this paper. Therefore, we conducted a sensitivity analysis of the impact of these assumptions on the adjusted CET, using the ranges shown in Table 10.

Table 10. Assumptions and variations for sensitivities

Sensitivity	-20%	Base case	+20%
Non-orphan population size[a]	80	100	120
Competition in non-orphan markets[b]	40%	50%	60%
Market exclusivity of orphans	8 years	10 years	12 years

Notes: [a]Values standardised per 50,000 inhabitants; [b]Values of market share.

The sensitiveness of CETs to the six assumptions assessed is presented in Figure 6 in absolute terms.

As Figure 6 shows, the impact of assuming different lengths for the market exclusivity period for orphans is the lowest. This is because the way in which our algebraic approach works minimises the impact of the market exclusivity assumption[19]. The sensitivity of the CETs to the rest of the assumptions seems to be proportional, and constant across for each CETs (orphan cut-off, mid-point of the orphan cut-off, ultra-orphan cut-off). Changes of equal measure and sign around the assumptions of non-orphan average populations and in-class competition for non-orphans also produce equivalent variations as Figure 6 shows. This is because both have the same impact on the final aggregate non-orphan treatment populations.

Additionally, we assess the sensitivity of the adjusted CET for ultra-orphan drugs to the assumption that other components of the life-cycle cost of ultra-orphans (e.g. commercialisation, manufacturing, distribution) go down in the same proportion than the R&D cost. Table 11 compares the adjusted CETs for both, orphan and ultra-orphan drugs, under the two different assumptions applied to lifecycle costs other than the R&D. Estimates in the table show that the assumption represents a minimum impact. For orphans, assuming all costs decrease in the same proportion reduces the adjusted CET by 4.4% (£1,726). For ultra-orphans, assuming that only the R&D costs decrease while other life-cycle cost components remain constant increases the adjusted CET by 4.4% (£43,149).

Table 11. Sensitivity of the adjusted CET for ultra-orphans to the R&D and other life-cycle costs assumption

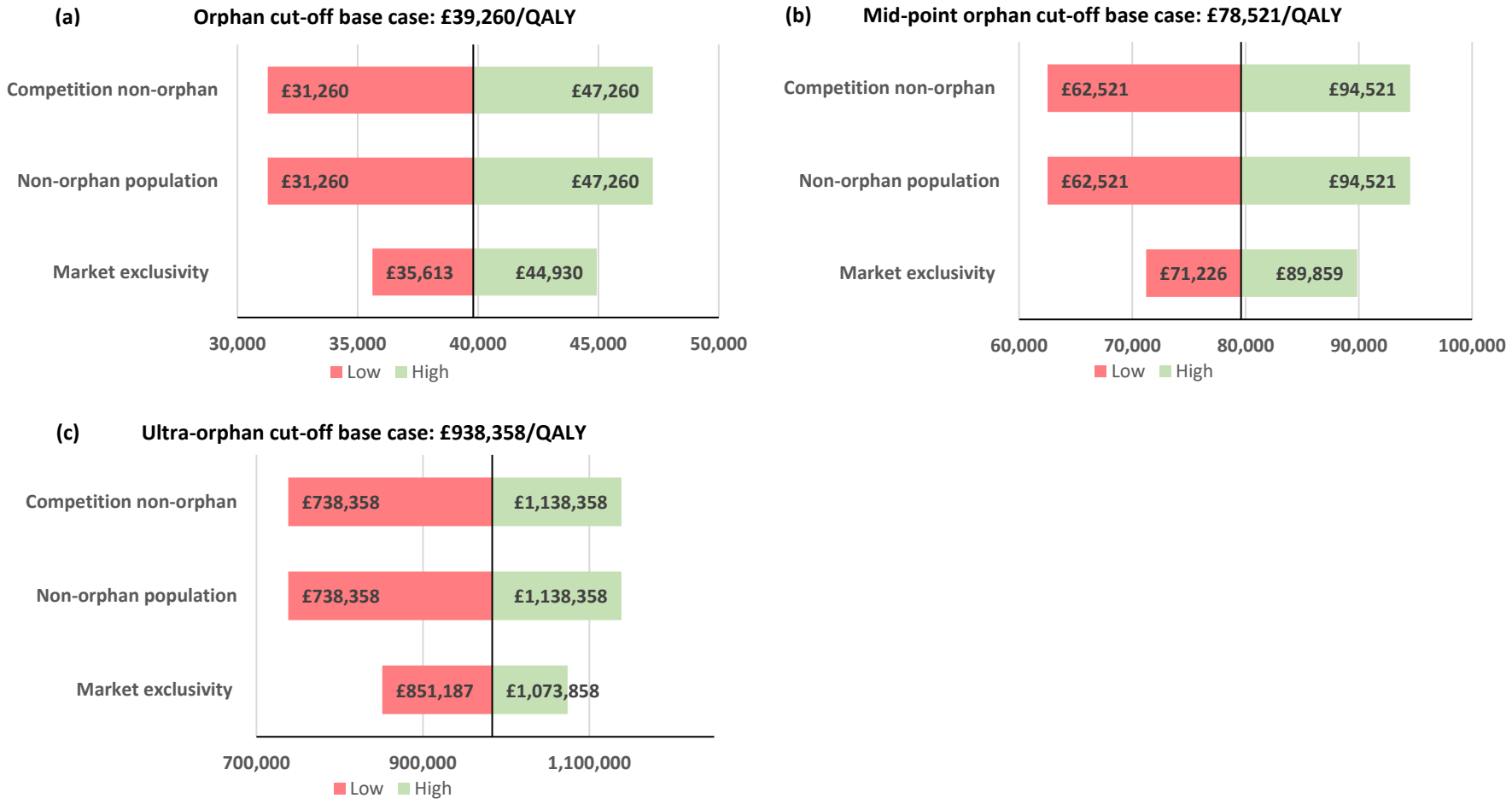
	All costs decrease in the same proportion than the R&D cost	Only R&D costs decrease for ultra-orphan drugs
Orphan cut-off point	£37,534	*£39,260*
Ultra-orphan cut-off point	*£938,358*	£981,507

Source: authors' calculations

Note: base case estimates are shown in italics

[19] Adding/reducing two years the market exclusivity for orphan and ultra-orphan drugs, increases/reduces the profit of orphan drug's developer during farthest periods. The impact over the CET adjustment then results minimised as their value is time-discounted several periods from $t = T_{Ex}$ to $t = 0$.

Figure 6. Sensitivity analyses: variations in absolute values



Source: Authors calculations

Notes: (a) variance on the adjusted CET for orphan cut-off; (b) variance on the adjusted CET for mid-point of the orphan cut-off; (c) variance on the adjusted CET for ultra-orphan cut-off

5. DISCUSSION

In this paper we propose a method for establishing a reasonable price for an orphan drug in situations where a value-based price is deemed inappropriate. The method rests on the proposition that, although society may be willing to sacrifice some health gain overall to make treatments for some orphan diseases available, it would not accept a situation whereby manufacturers of these drugs made higher profits than manufacturers of drugs for non-orphan conditions. In order to establish a price based on this proposition, we have examined, for illustrative purposes, how the standard incremental cost-per-QALY cost-effectiveness threshold (CET) in the UK would need to be adjusted to reflect typical differences between orphan and non-orphan products in both (i) the costs of R&D and (ii) in the size of the expected treatment population. Whilst we recognize that there may be issues as to how well the QALY captures health gain for some rare conditions, we regard the (cost-per-QALY) CET as an effective tool for illustrating our reasonable price approach.

It is important to note that our analysis does not indicate what society *should* be prepared to pay for an orphan drug, since this involves important societal judgments about whether some population health in total should be forgone in order to provide funding for treatments for rare conditions and, if so, how much. Rather, our approach could be viewed as one way of determining the *maximum allowable price* society should be willing to pay, based on allowing a reasonable rate of return. Awarding a lower price would send a signal to manufacturers about the level of priority being assigned to the treatment of orphan conditions. We return to this point later.

While we believe our proposed method has some merit, it is evident that further research is required in order to improve the estimates produced. First, in estimating the costs of R&D, we only sampled novel drugs approved by the FDA in 2015. A larger sample, covering more years, might have generated different estimates of the relative research costs for orphans and non-orphans. However, our estimates, showing a lower R&D cost for orphan products, are consistent with those in earlier studies (e.g. Coté and Keating, 2012). In addition, we show that the difference in the research cost between orphans and non-orphans is smaller for oncology products. This is consistent with our expectations, given that the research requirements for all oncology drugs are similar, with both orphan and non-orphan products being eligible for the FDA's 'fast track' programmes for innovative drugs, both 'Accelerated Approval' and 'Breakthrough Therapy' (FDA, 2015). These programmes often grant market approval based on less mature clinical data.

Secondly, we made assumptions about the differences in drug lifecycle costs other than R&D. Our simplest assumption was that only R&D costs, representing 30% of the total drug lifecycle costs, would be lower, with all other costs being the same for both orphan and non-orphan drugs. An alternative approach is to assume that the costs of manufacturing, marketing or distribution differed in the same proportion as R&D costs as orphans and non-orphans. This is the most conservative approach and produces slightly lower estimates of the adjusted CETs. Marketing and distributing an orphan drug to a small group of identified individuals, may be lower per patient than for a non-orphan drug. The truth is probably somewhere between these two extremes. However, since the assumption concerning the level of reduction (if any) in non-R&D costs makes a substantial difference to the adjusted CETs, these estimates should be verified by further research.

Thirdly, we haven't included the tax credit of the 50% of the phase III clinical testing costs for orphan drugs included in the US Orphan Drug Act of 1983[20] and which remained unchanged until 2018, when reduced to 27.5%[21]. Although in principle it could have an impact on our estimates of R&D cost for an orphan drug and consequently could reduce the adjusted CET for an orphan, the numerical impact is minor, since we are apportioning global R&D costs to the UK by the global market share of pharmaceutical sales. Furthermore, the tax credit will not be applicable for developers based in Europe and Asia.

Fourthly, the estimates of the costs of R&D are highly sensitive to the success rates in the development of new products. In our sample of oncology drugs, the numbers of patients in the different phases of clinical research were similar for orphans and non-orphans. However, applying different estimates of the success rate from the literature (5.4% for non-orphans and 23% for orphans) led to differences in overall R&D cost (Hay et al., 2014). While there might be reasons to expect a higher success rate for orphans, given the more precise targeting of therapy, this issue requires further investigation.

Fifthly, we used estimates of target patient populations given in technology appraisals performed by the SMC and NICE in the UK. These may not reflect typical patient populations for the drugs studied for two reasons. First, in the case of orphan drugs, it is possible that some would also be indicated for larger, non-orphan populations, negating the argument for an adjusted threshold to compensate for a smaller treatment population (Coté and Keeting, 2012). In the case of the non-orphan drugs studied, the appraisal conducted by NICE or the SMC may have focused on a sub-set of the total population for the licensed indication for the drug concerned. For example, for oncology products in particular, it is common for a technology appraisal to focus on a given stage of disease, even if the product is licensed for other stages.

This issue was harder to investigate, but we did note that a small number (10) of the non-orphan oncology drugs in our sample had estimated patient populations in the appraisals that were lower than those for many orphan drugs in the sample[22]. Therefore, if patient population sizes were to be used as part of an argument to allow an adjusted threshold for orphan drugs, such a policy would require increased accuracy in the estimation of target patient populations and an understanding that the eligibility of an orphan drug for an adjusted threshold could be lost if the total patient population size were to increase beyond that typically designated 'orphan'. Additionally, the policy should be designed to prevent potential perverse incentives to strategically narrow/stratify the scope of patients licenced in order to obtain higher prices.

Sixthly, we have used patient population sizes as a predictor of the likely revenue generated from the sales of the various products in the sample, at the price implied by the adjusted threshold in each case. However, it could be the case that the market exclusivity granted to orphan products means that revenue generation could be maintained for a given patient population for a longer period than that non-orphan drugs, since the latter would be more vulnerable to the entry of new, competitor products, including generics. Therefore, in the base case we assumed that a non-orphan

[20] See: https://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/howtoapplyfororphanproductdesignation/ucm364750.htm

[21] See page 805 in the document available at: https://docs.house.gov/billsthisweek/20171218/CRPT-115HRPT-466.pdf

[22] A table with the 10 oncology products is shown in the Appendix.

product would only be used in 50% of the total patient population, due to the emergence of competitors.

The use of so many assumptions means that there is considerable uncertainty around the estimates of the adjusted CETs our method has produced. This uncertainty is explored in the sensitivity analysis. However, if our method were applied in practice, it may be feasible to obtain more accurate data for many of the parameters. Whilst recognising that manufacturers are often reluctant to release information concerning the costs of developing and manufacturing drugs, our proposed method outlines some of the key data that, in principle, could be part of a more informed price negotiation. A drug by drug analysis would be possible in most jurisdictions, since there are relatively few drugs meeting orphan designation, especially those drugs for ultra-orphan diseases. However, we feel that proposing adjusted CETs by bands of patient population sizes is still the better approach, since it avoids a complete 'cost-plus' pricing policy which would give no incentives for efficiencies in research and development.

Also, although we have suggested potential adjustments to the threshold ICER for orphan drugs, we have retained the standard cost per QALY rubric. Despite orphan status, it seems reasonable to expect products to show evidence of QALY gains, thereby maintaining the principle of assessing cost-effectiveness. However, some would argue that it is unreasonable to require orphan drugs to meet the same evidential standards as non-orphans, given their smaller patient populations and likely lower level of understanding of the disease process (Winquist et al., 2012). This may be the case for many ultra-orphan products, but our research shows that oncology orphans often have trial population sizes equivalent to non-orphan cancer drugs. Furthermore, the trend for the FDA and EMA to offer various 'accelerated approval' programmes means that many oncology products, both orphan and non-orphan, will be licensed based on less extensive clinical data.

Finally, adopting this approach for establishing a reasonable price for an orphan drug does not tackle the broader issue of determining appropriate research priorities for the development of orphan drugs, or drugs in general. A value-based pricing policy not only ensures that the therapies adopted by the health care system are good value for money; it also encourages a shift in manufacturer research strategy towards delivering products that produce high added value in population health terms. Determining a reasonable price for the orphan drugs based on allowing a reasonable rate of return does not, of itself, appropriately drive the direction of future research. One could argue that the approach in England of allowing a higher threshold ICER for specialized services, but to limit this to £300,000 per QALY, is one way of sending such a signal to manufacturers. Namely, society may be willing to offer a reward to manufacturers for developing drugs for rare conditions, but this reward may not be as high as that to manufacturers developing drugs that have a major impact on population health.

This is a societal value judgment that we are not qualified to make. However, according to our data, the currently proposed CET for ultra-orphans in the UK would guarantee the average industry rate of return for most orphan drugs with patient populations as low as 3.2 per 50,000, but not for the target populations for drugs designated 'ultra-orphan' (i.e. 1 per 50,000 individuals). Therefore, there remains a case for having more discussion of priorities for research into rare diseases, given the large number of very rare diseases for which drugs could potentially be developed.

6. CONCLUSION

Our research proposes one method for establishing the reasonable price for an orphan drug, based on the proposition that the expected return for developing an orphan should be no greater than the industry average. Assuming prices for drugs are set according to value added, the method proposes the adjustment that would need to be made to a payer's "normal" cost-effectiveness threshold (CET) for non-orphan drugs in order to ensure that orphan drug developers achieve the industry-wide rate of return.

Our estimates of adjusted CETs – by the R&D cost and expected revenues – establish that in order to secure a price for orphan drugs that enables the manufacturer to achieve a rate of return equivalent to that from non-orphan drugs, the cost-effectiveness threshold for orphans would need to be higher. Furthermore, the threshold would also need to increase as the targeted patient population size decreases.

Further research is required, to improve the estimates and assumptions of key parameters (i.e. other relative operational costs, treatment populations sizes, average health gains, relative direct cost savings, degree of in-class competition for orphan and non-orphan drugs, etc.). In addition, society still needs to tackle the broader issue of determining appropriate research priorities for the development of orphan drugs.

Finally, results do not indicate what society should be prepared to pay for an orphan drug, since this involves societal judgments about whether some population health in total should be forgone in order to provide funding for treatments for rare conditions. Our research should be viewed as one way of determining the maximum price society should be willing to pay to ensure a reasonable rate of return.

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APPENDIX

Table A.1. Non-orphan oncology drugs and indications

Name	Indication
Lonsurf	To treat patients with an advanced form of colorectal cancer who are no longer responding to other therapies
Kadcyla	For patients with HER2-positive, late-stage (metastatic) breast cancer.
Xofigo	To treat men with symptomatic late-stage (metastatic) castration-resistant prostate cancer that has spread to bones but not to other organs.
Inlyta	To treat patients with advanced kidney cancer (renal cell carcinoma) who have not responded to another drug for this type of cancer.
Perjeta	To treat patients with HER2-positive late-stage (metastatic) breast cancer.
Xtandi	To treat men with late-stage (metastatic) castration-resistant prostate cancer that has spread or recurred, even with medical or surgical therapy to minimize testosterone.
Zytiga	In combination with prednisone (a steroid) to treat patients with late-stage (metastatic) castration-resistant prostate cancer who have received prior docetaxel (chemotherapy).