INTRODUCTION

In recent years, the challenge of prioritizing orphan drugs within health care systems has received increasing attention. There are several features of orphan drugs that make them particularly interesting from a priority setting perspective. First, many rare conditions, for which orphan drugs are designated, are severe and highly debilitating conditions with few if any alternative treatments. Hence, there are strong expectations from patients and professionals to be able to use new treatments. Second, orphan drugs generally come at a very high cost and annual costs per patient in the order of €300,000-500,000 are not uncommon, implying that they rarely meet accepted cost-effectiveness criteria. In a broad sense we define cost-effectiveness to mean that the cost per health outcome of a treatment of interest is below a threshold value indicating an acceptable cost per health outcome. This general definition may, however, carry rather different implications depending on how the threshold is determined and interpreted (see Brouwer, W., van Baal, P., van Exel, J., & Versteegh, M. (2019). When is it too expensive? Cost-effectiveness thresholds and health care decision-making. European Journal of Health Economics, 20(2), 175-180). We return to this issue below.
of patients in need of orphan drugs and patients in need of other health care interventions. Third, over the last few years there has been a rapid increase of new orphan drugs on the market, with more in the pipeline. In the EU, about 140 new orphan drugs have reached the market in the last 15 years, and in the next 7 years another 120 are expected to reach the market. This is partly due to incentivizing measures in the EU regulations, including protocol assistance to a reduced charge to navigate through the regulatory process, access to centralized authorization procedures, and 10 years of market exclusivity. Furthermore, designated research grants are available from the European Commission to support development of orphan drugs.

Orphan drugs, their pricing, and prioritization, are thus likely to remain high on the health policy agenda for a considerable time. A number of arguments for and against a higher cost per health improvement for orphan drugs compared to treatment for more common conditions have been put forward in the literature.

In countries where cost-effectiveness is a relevant consideration for distribution of scarce health care resources, and where explicit or implicit cost-effectiveness thresholds are used as a decision-making criterion (normally among others) for whether a drug should be reimbursed or not, the question arises whether we should accept a higher cost for orphan drugs compared to drugs targeting common conditions. Some health care systems, like the Swedish and the English have accepted higher explicit thresholds for costs per health improvement for orphan drugs under certain conditions. In other systems, e.g. the Norwegian, it seems as if cost-effectiveness criteria have not been applied to orphan drugs and instead other criteria have been applied to allow for exceptions. In a comprehensive review by Paulden et al., they identify a large number of arguments and considerations to take into account when considering reimbursement of orphan drugs. However, it is difficult to see that most of them would support treating orphan and common drugs differently in the sense that a higher cost should be accepted. The most promising approach are the considerations they subsume under the heading of ‘value-propositions’, where we find broadly egalitarian considerations. In the article by Paulden et al. these arguments are simply presented. In this article, we present a more comprehensive analysis of egalitarian considerations for and against accepting a higher threshold for cost per health improvement for orphan drugs, where arguments that one should reasonably set aside are disentangled and where arguments needing further explorations are identified. As we will argue, even in potentially promising arguments put forward there are unresolved issues of both normative and empirical kinds. Hence, the aim of this article is to normatively analyse egalitarian arguments for supporting a higher threshold for cost per health improvement for orphan drugs.

Our analysis will start by looking at three substantial egalitarian theories: sufficientarianism, prioritarianism and outcome egalitarianism, showing that these do not support different thresholds for rare and common diseases. We will then turn to the question of whether orphan drugs are disadvantaged in a system applying similar cost-effectiveness thresholds for orphan and common drugs, showing this needs further empirical exploration. Assuming there is such a disadvantage in some cases, we will then explore the arguments from formal equality and opportunity egalitarianism, pointing to strengths and weaknesses of these arguments, and where further empirical and normative research is needed focusing on opportunity costs and systemic effects. The article ends with a short concluding section.

2 | SUBSTANTIAL EGALITARIAN CONSIDERATIONS

By egalitarian considerations, we mean considerations that presuppose some principle of distribution of goods claiming or implying that we should, to some extent, prioritize the worse off, even if this leads to a net loss of goods totally. There are different versions of egalitarian considerations in this sense. However, none of these versions buttresses the claim that orphan drugs should be prioritized (with one possible exception to which we will return), as will be elaborated soon. That egalitarian principles do not imply priority for orphan drugs is perhaps evident, since a condition making someone bad off and a condition being rare are two different things: there are

---


3In this article we will use the commonly used quality adjusted life years (QALY) as a representation of health in some examples. This is for the sake of convenience, and as far as we can see our arguments are valid for other representations as well. Also, whenever we write ‘higher cost for orphan drugs’ we mean ‘higher cost per health improvement’.


5The criteria in Sweden are that the condition has a very high severity, the treatment is not available in the market, the market will accept higher explicit thresholds for costs per health improvement for orphan drugs under certain conditions. In other systems, e.g. the Norwegian, it seems as if cost-effectiveness criteria have not been applied to orphan drugs and instead other criteria have been applied to allow for exceptions. In a comprehensive review by Paulden et al., they identify a large number of arguments and considerations to take into account when considering reimbursement of orphan drugs. However, it is difficult to see that most of them would support treating orphan and common drugs differently in the sense that a higher cost should be accepted. The most promising approach are the considerations they subsume under the heading of ‘value-propositions’, where we find broadly egalitarian considerations. In the article by Paulden et al. these arguments are simply presented. In this article, we present a more comprehensive analysis of egalitarian considerations for and against accepting a higher threshold for cost per health improvement for orphan drugs, where arguments that one should reasonably set aside are disentangled and where arguments needing further explorations are identified. As we will argue, even in potentially promising arguments put forward there are unresolved issues of both normative and empirical kinds. Hence, the aim of this article is to normatively analyse egalitarian arguments for supporting a higher threshold for cost per health improvement for orphan drugs.

Our analysis will start by looking at three substantial egalitarian theories: sufficientarianism, prioritarianism and outcome egalitarianism, showing that these do not support different thresholds for rare and common diseases. We will then turn to the question of whether orphan drugs are disadvantaged in a system applying similar cost-effectiveness thresholds for orphan and common drugs, showing this needs further empirical exploration. Assuming there is such a disadvantage in some cases, we will then explore the arguments from formal equality and opportunity egalitarianism, pointing to strengths and weaknesses of these arguments, and where further empirical and normative research is needed focusing on opportunity costs and systemic effects. The article ends with a short concluding section.

---

7Paulden et al., op. cit. note 4.

8Unlike utilitarian principles that favour the maximizing of goods and increased priority to the worse off only if that would be conducive to the goal of maximization. See Hirose, I. (2013). Egalitarianism. New York, NY: Routledge, pp. 1–6.
severe common conditions, and there are rare conditions that are relatively mild.9

Nonetheless, since it has been claimed that egalitarian considerations may favour the prioritization of orphan drugs,10 it is worthwhile to briefly demonstrate why versions of egalitarianism do not imply priority for orphan drugs. Let us start with three different types of egalitarian theories of the above defined kind: sufficiency, prioritarianism, and outcome egalitarianism.11 These theories cannot be used to justify accepting a higher cost for orphan drugs (although they can, of course, be used to support such justification for treatments targeting severe diseases).12 First, on sufficiency, justified claims on having access to treatment are related to the distance from a stipulated threshold of sufficiency. Patients with common diseases may be as far away from the stipulated threshold of sufficiency as patients with rare disease.

Second, on prioritarianism, treatment of more severe conditions is given more moral weight, since these conditions make patients worse off. Arneson has described prioritarianism as a combination of two claims: maximizing outcomes and priority to the worse off.13 However, prioritarianism will not support distinguishing between common conditions over rare equally severe conditions, all things being equal, since these conditions might be equally severe and treatment equally effective. Furthermore, if we want to maximize outcomes we have reason to focus on more common conditions, at every level of severity and effectiveness.

Third, on outcome egalitarianism, we should strive towards an as equal outcome of value (e.g. health) as possible in a population. Common severe conditions are likely to affect health outcomes more than equally severe rare conditions, simply since more people in the population will then be better off than before: prioritizing treatment of common diseases may therefore reduce total inequalities more than prioritizing rare ones. Hence, none of these three rationales supports accepting a higher cost for rare conditions; to some extent rather the contrary.


10Pauden et al., op. cit. note 4, p. 262.

11We ignore lexical egalitarianism, saying that we should give absolute priority to the worst off, since it should be self-evident that it is an open question if the worst off belong to a common or rare condition.


A reason for why egalitarian considerations could be relevant to apply, is if orphan drugs are disadvantaged in an illegitimate way by applying common health economic thresholds. So, are they thus disadvantaged?

First, the idea cannot be that all with rare and common diseases should have exactly equal access to all existing care in order not to be disadvantaged. The only way to guarantee that would be to always reimburse treatment—then everyone has access to all existing care. But then we are simply abstaining from making priorities within the health care system, an obvious non-starter. The suggestion must, more plausibly and modestly, be to level out, or equalize, the opportunity of getting access to treatment: the possibility to get access to treatment should not be worse only because one is suffering from a rare(r) disease. Indeed, this seems to be the view that has been proposed:

Whether or not a patient group is small or large is such an irrelevant group property and the groups’ size or the rarity of the condition should therefore not affect the groups possibilities to treatment... compared to other larger groups...14

Furthermore, possibilities to get treatment should be understood in probability of getting treatment: that it is unjust or unfair that individuals with rare diseases have lower probability of getting treatment than equally severe common diseases only because they are rare, since, again, rarity is morally irrelevant. The italicized clause is important here, since the argument focuses on equalizing opportunity to receive treatment for conditions that are alike on morally relevant grounds. More specifically, the argument focuses on to what extent accepting similar costs per health improvement disadvantage rare conditions. Hence, in the following during this section we will focus on the following question: Are orphan drugs (systematically) disadvantaged in comparison with equally severe drugs for common conditions if applying the same cost-effectiveness threshold?15

It was said in the Introduction that, given the high price often set for orphan drugs, they will seldom de facto reach accepted cost-effectiveness thresholds. This raises three questions. Is this unavoidable? If it is, is it a problem from an egalitarian perspective? If it is, can some form of egalitarian consideration support a higher threshold for orphan drugs to accommodate for this? Starting with the first

14Carlsson et al., op. cit. note 9, p. 906 (our italics and translation).

15Here we focus on orphan drugs with market approval. A related question is what would incentivize the development of orphan drugs, a question we will ignore in this analysis. In relation to this aspect, there have been incentives implemented in all OECD countries for decades, for instance tax cuts and extended monopolies. The resulting strong development of new orphan drugs in recent years indicates that the development of new treatments for rare diseases is far from disadvantaged. Carlsson et al., op. cit., note 9, pp. 862–865.
question, is it unavoidable that orphan drugs do not meet accepted cost-effectiveness thresholds?

A common argument from the pharmaceutical industry is that the research and development (R&D) cost requires the high pricing per patient, since basically the R&D cost should be recuperated from a smaller number of patients, and thereby may make it impossible to recuperate investment costs if pricing should be set to reach accepted cost-effectiveness thresholds. First, however, costs for developing orphan drugs may be lower, in general, than the cost of developing treatments for more common diseases, related to the fact that proper randomized controlled trials (RCT) usually cannot be done for orphan drugs since the patient group is too small, while being a requirement for marketing treatments for common diseases. The cost of an RCT is considerable. Furthermore, again, in all OECD countries, the cost for R&D of orphan drugs has been subject to economically advantageous regulation for decades already. Third, orphan drug status, in itself, has been shown to affect pricing, compared to other drugs with similar characteristics.

On the other hand, the market for rare conditions in relation to common conditions is obviously different. For instance, looking at Swedish sales figures for a drug for a common condition, Zytiga for prostate cancer, this amounts to about 900 patients being treated with Zytiga during 2018. Comparing this with the population of those with spinal muscular atrophy (SMA), for which Spinraza has recently been introduced in Sweden, best estimates show the population of those with SMA I–III to be 250–300 patients totally. According to national recommendation, only a fraction of these patients should be treated. This indicates that the markets for common and rare conditions are different and to the extent that there are similar expectations on return of investment for shareholders and owners in both cases, the differences in population size needs to be compensated by lower development cost if pricing should be in the same range. In other words, is it possible that the pharmaceutical industry will, with price reductions, still be able to recuperate R&D costs at a reasonable profit? Given, for instance, the general confidentiality as to how pricing relates to R&D costs this is difficult to assess, but also due to the complexity in allocating specific R&D investments to specific drugs. There are indications in the literature that some orphan drugs are doing very well, with revenues in the order of 10–12 times the R&D cost and cost of very invested capital over 7–8 years. Hence, price reductions are obviously possible in some cases without seriously affecting profitability of these drugs. Whether these reductions would be sufficient to meet accepted costs per health improvement is impossible for us to assess here and requires further empirical analysis.

However, in the following we will assume (for the sake of argument) that there are cases in which population size will not be compensated by lower development costs, and hence requires higher pricing of such orphan drugs. In such a case, the orphan drugs are less likely to reach accepted levels of cost per health improvement for more common drugs and, in this sense, are really disadvantaged.

4 | Egalitarian Considerations: Formal Equality and Opportunity Egalitarianism

A recent equity argument for accepting a higher cost for orphan drugs is the argument from formal equality. Still, it is debated and controversial and it is difficult to settle what position it supports regarding the aforementioned question. We will initially present an outline of the argument without taking a stand on its plausibility. We will then briefly present the debate on its plausibility so far. We will then, in some detail, investigate which issues have to be settled in order to take a stand in the debate.

The argument, as its name reveal, rests on the principle of formal justice or formal equality (FE): equal cases should be treated equally. Or, put negatively: if there is no morally relevant difference between two cases, they should not be treated differently. So, FE is a ban against making morally arbitrary differences between persons, patients, situations, or whatever. It should be noted that the formal principle of equality is just that: formal. FE says nothing in itself about what should be considered as morally relevant factors or differences. Therefore, it cannot follow from FE whether or not we should accept a higher cost for orphan drugs without additional premises. The most promising such additional premise would be to claim that the sheer number of individuals that happens to have a disease cannot be relevant in itself (for how they should be prioritized). This seems reasonable—we do not know of anyone who has claimed the opposite and can think of no grounds for doing so. So, it follows, one should not be down-prioritized or made worse off only because one has a rare disease. This is, in essence, the argument of FE for accepting a higher cost for orphan drugs.

---


23 See also Paulden et al., op. cit. note 4.

24 Carlsson et al., op. cit. note 9, p. 906.
However, against this it has been claimed that it also follows that one should not be down-prioritized or made worse off only because one has a common disease. In other words, it seems as if this line of reasoning implies that since rarity or commonness of a disease is morally irrelevant it should not be allowed to make a difference. From this the following conclusion seems straightforward: we should not accept a higher cost for rare (or common) diseases, at least not by and for itself.\(^{25}\)

However, the line of reasoning in the previous paragraph has been questioned.\(^{26}\) Remember the above assumption as a point of departure for this discussion: that patients with rare diseases are assumed to have an elevated cost for treatments compared to treatments for more common diseases. This is a result of the treatments being offered to patient groups consisting of fewer individuals, i.e. fewer individuals must share the cost for research and development. So, rarity together with applying commonly accepted levels of cost per health improvement, will disadvantage those with rarer diseases in such cases. Expressed in other words, comparing a common severe condition where cost-effectiveness is just below the accepted level of cost per health improvement, with an equally severe rare condition and with a similar treatment effect, the cost per health improvement for the latter will be higher, and is less likely to pass this level. Hence, from a formal equality perspective, patients that are equal in relevant respects will then be treated un-equally, which seems counter to the FE. This is due to an irrelevant factor, i.e. the rarity of the patient group.

Accepting a higher cost for orphan drugs is then only to level out or compensate for this morally irrelevant factor: rarity. Actually, we see this kind of willingness to accept higher costs in other areas of medicine and health care where FE otherwise might be compromised, e.g. by accepting higher costs (and thereby worse cost-effectiveness) in involving interpreters for patients from a non-dominating language group to compensate for a language barrier, despite having the same kind of condition as native speakers.\(^{27}\) Of course, comparing an intervention with an intervention with an interpreter is comparing different interventions and both these measures may be deemed cost-effective enough. But the reason to accept the cost of the interpreter, we would claim, is precisely of the formal equality-kind: to level out a morally irrelevant difference (language skills). And at least to some extent, one would be prepared to accept the added cost even if it would be large enough to make the cost-effectiveness of the combined intervention and interpreter worse than usual thresholds.

We will elaborate on the argument in the previous paragraph in detail in the following. Before that, there is a general presumption in this argument that we would like to bring out and make explicit that we accept: FE can have substantial implications about what ought to be done. This is so, since FE at least lays the burden of proof on those claiming that different groups, individuals, or situations should be treated differently: they have to demonstrate what relevant difference there is between the groups, individuals, or situations in question. Unless such a difference can be presented, they should be treated equally (at least if possible, otherwise they should have equal probability of benefiting—see below). Treated equally does not necessarily refer to performing the same act (i.e. applying the same level of cost per health improvement) but might refer to the consequences of the act (i.e. access to existing treatment). By extrapolating this line of reasoning, it could also be claimed that when there is (or we can find) no relevant difference but a difference is actually made or follows from what is done, those who are disadvantaged by the difference have an entitlement to be compensated (so as to restore or at least increase equality or equal probability). This is the fundamental point of the argument from FE for accepting a higher cost for orphan drugs.\(^{28}\)

However, such a conclusion first rests on the assumption that the orphan drug in question will not be able to reach accepted levels of cost per health improvement for common drugs under existing market conditions (see the former section for a discussion on this). Still, even if disadvantaged, the following questions need to be sorted out:

1. To what extent should we accept a higher cost and thereby the opportunity cost in terms of loss of health for other patients to compensate for irrelevant disadvantages (i.e. to equalize opportunity to access treatment)?
2. Even if acceptable just looking at orphan drugs, would adjusting to account for FE concerns result in systemic adverse side-effects to the health care system?

We acknowledge that these questions are not settled presently. More research, both of a normative and empirical kind, is needed to shed light on them. In the following, we will clarify the questions and highlight the relevant features of future investigations.

### 4.1 How much should achieving FE be allowed to cost in terms of foregone health?

Even if there is a disadvantage for orphan drugs and thereby a problem from an FE perspective, to what extent should we allow the opportunity cost of a higher cost for rare conditions, implying a loss of health in the health care system, if at all?

This hinges on how the value of FE in terms of equal opportunity to get access to existing treatment is valued against other justice considerations. This, in turn, is both dependent on the size of the opportunity cost and its distribution. If equally high or higher prioritized patients (given other justice considerations) will bear the opportunity cost in terms of foregone health, it is more problematic than if the cost is borne by lower prioritized patients.


\(^{26}\)Sandman & Gustavsson. op. cit. note 21, pp. 22–33.

\(^{27}\)Ibid.

\(^{28}\)Ibid.
Two ideas worth exploring in more detail are:

- Could we apply a two-level threshold idea as to whom should bear the opportunity cost—implying that the opportunity cost is only acceptable if it affects patients two levels away? For example, the cost of FE for highly severely ill patients should not be borne by patients moderately severely ill, but by patient with mild conditions—if we accept different costs per health improvement for mild/moderate and highly severe conditions. The rationale would be that, in general, considerations of equality favour improving the situation of the worse off over the situation of the better off. This supports, it seems, having the better off (mildly ill) bearing the opportunity costs of promoting FE rather than the worse off (severely ill).29

- Could a 'needs to have' approach be applied where the burden of proof lies on the pharmaceutical industry that higher costs per health improvement for orphan drugs are needed in individual cases, or generally given a representative set of orphan drugs? One of the preconditions for accepting a higher cost per health improvement for orphan drugs, is that return on investment requires a higher price per treatment. However, this is dependent both on the size of the investment and on the size of the market. We could, in principle, require that the pharmaceutical industry has to show that the higher pricing is needed given this. This would also imply that with larger indications, this need disappears gradually as the size of the market increases.

### 4.2 How does dealing with certain injustices affect the justice of the system as a whole?

If we have settled that orphan drugs are disadvantaged (the empirical questions) and we have settled the extent to which this supports compensation (the normative questions) there is one remaining kind of query: the extent to which addressing one disadvantage from an FE perspective should have us address also other disadvantages that may affect costs and health improvements. It would seem arbitrary to only address some disadvantages if we cannot find relevant differences among these. At the same time, the more disadvantages we try to compensate for, the greater the opportunity cost.

There are a great number of factors that affect the cost of treatment that all reasonably must be considered as irrelevant, at least from the point of view of FE of opportunity to get access to treatment: how difficult it is to develop new treatments, the body’s ability to metabolize drugs, the interest in the medical community of the therapeutic field in question etc. Generally, this seems to be what FE would require.

Moreover, we should be careful not to compensate for certain irrelevant differences in such a way that we increase other irrelevant differences. Accepting a higher cost for orphan drugs in a system generally implies that rare conditions of high severity get somewhat better access to existing treatment, but at the cost of a greater degree of foregone health in the system as a whole. Following the prioritarian approach, it should primarily be patients at the lower end of the priority setting spectrum that should suffer this opportunity cost—i.e. generally patients with milder conditions, if benefits are comparable. However, in a complex health care system, we usually have limited control over who will bear the opportunity costs or where rationing takes place in order to free resources for new treatments,20 although we probably could do more to achieve such control. Looking at the Swedish system, vulnerable patient groups where access to treatment or care is not primarily industry driven, e.g. dementia, or older patients with moderately to severe conditions primarily affecting quality of life are likely to be losing out. Hence, there is a definite risk that the opportunity cost and displacement effects of allowing a higher cost to compensate for disadvantages from an FE perspective, will result in overall unwanted consequences from a justice or equality perspective.

This being said, we should not discard out of hand the possibility of accepting different levels of opportunity costs for disadvantaged patient groups. We need to remember that we already do compensate for extra costs in order to uphold FE.31 Even so, such adjustments would increase the opportunity cost of FE, and more research is needed to investigate effects on the system as a whole, both as to total health impact and distribution of health depending on who bears the opportunity costs. Moreover, and perhaps more importantly, we need normative research about who should bear the opportunity costs, if anyone.

### 5 MAKING OPPORTUNITY COSTS EXPLICIT

Although assessing the overall consequences of a mix of push and pull measures to incentivize research and development of orphan drugs is very difficult, the implications of accepting a higher cost for orphan drugs in order to prioritize rarity are possible to assess. In a world with scarce resources, any health care system must ask the key question of how much we can, and should, pay for medical interventions. There is no easy answer to this question although paying a high price to compensate for disadvantages from rarity (or other disadvantages) means that resources will be withheld elsewhere in the health care sector.32 The vital point to keep in mind is that when resources are withheld within the health care sector, the opportunity costs must be considered in terms of health.33

---


31Sandman & Gustavsson, op. cit. note 21, p. 27.


Prioritization decisions in Sweden suggest that a cost per health improvement in terms of QALY of 2 million SEK (approximately €200,000) could under certain circumstances be considered acceptable for the reimbursement of orphan drugs. The trade-offs and considerations of opportunity costs involved in such decision are not entirely clear, however. Evidence is emerging that the health care system in Sweden may produce QALYs at a cost of around 150,000–250,000 SEK, figures that are in line with estimates from similar health care systems. These estimates suggest that the opportunity cost of paying 2 million SEK for a QALY is approximately 8 to 10 QALYs forgone when one QALY is gained. This is perhaps one of the most important pieces of evidence in making the trade-offs explicit between prioritizing rarity and the cost of doing so in terms of forgone health. For example, McCabe et al. (2005) provided arguments that the opportunity cost of prioritizing rarity had to be considered, although estimates of the productivity of the health care sector were lacking at the time.

Hence, the implications of using pull measures such as accepting higher prices for orphan drugs can, and should, be made explicit. The price paid by current generations (by health forgone due to high prices) can be counted in longevity and quality of life forgone. This may then be balanced with the estimated benefits in future generations (potentially better health as research and development are incentivized). Similar arguments apply if we pay high prices for mediocre drugs (for example based on the argument that there are no other treatment options available). The key argument here is that these trade-offs now can be made explicit.

Making the opportunity cost explicit, is also important for the discussion around budget impact. Some authors have downplayed the importance of high prices as they claim that overall budget impact is low. In a recent study, orphan drugs spending amount to 0.7–7.8% of the total pharmaceutical budget in different European countries, and projections about the future end up at different plateaus of spending depending on assumptions. At the same time, just looking at Sweden, it is suggested that between 2–8% of the total population suffer from a rare disease (somewhat depending on how this is defined), which might indicate a potential for even greater budget impact in the future if research and development continue to prove successful. The proportion of overall resources that will be spent on orphan drugs may not necessarily be small in the future, emphasizing the importance of making trade-offs between overall health and health in patients with rare diseases explicit.

6 | CONCLUDING REMARKS: FUTURE RESEARCH NEEDS

In this paper we have discussed arguments grounded in considerations of justice for and against accepting a higher cost for orphan drugs. Based on this analysis we conclude that some arguments may be set aside, and some require further analysis.

Substantial egalitarian considerations in general do not seem to support accepting a higher cost per health improvement for treatments of rare disease. Whereas egalitarian considerations do support giving priority to severe conditions, none of the three specifications of need supports giving priority to rare diseases.

The most promising argument for giving priority to orphan drugs seems to be the argument drawing on formal equality. However, this idea needs to be explored in more detail. In this paper we have pointed to three crucial parts of this question.

First, there is an empirical question that needs to be explored: the extent to which it is true that people suffering from rare diseases have a lower probability of getting access to treatment in systems applying the same level of costs per health improvement for common and rare conditions. If orphan drugs are not systematically disadvantaged, there is no real ethical question at play here.

Second, if it is true that orphan drugs are disadvantaged there is still a normative question that needs to be explored: the extent to which considerations of irrelevant disadvantages should be given compensation, since such compensation has an opportunity cost in terms of forgone health for other patients.

Third, if there are convincing justice-based arguments for giving priority to rarity, we still need to carefully consider how such policies affect the health care system as a whole. As egalitarian considerations point in the direction of giving priority to severe conditions the opportunity cost of taking rarity into account should primarily affect patients among the best off. Although there are several methodological challenges related to such studies there are strong reasons to investigate which patients will bear the opportunity cost of taking justice-based arguments into account.

Hence, while some considerations of an egalitarian kind may be put aside, arguments based on considerations of formal equality and opportunity cost should be explored in more detail.

ACKNOWLEDGEMENTS
Financial support from the Swedish Research Council and from the Swedish Research Council for Health, Working Life and Welfare is gratefully acknowledged (2014-4024).

CONFLICT OF INTEREST
The authors declare no conflict of interest.
AUTHOR BIOGRAPHIES

Niklas Juth is a senior associate professor in medical ethics. His main research interests are in ethics and bioethics, genethics, and the intersection between political philosophy and medical ethics, e.g. autonomy and justice in health care.

Martin Henriksson is an associate professor in health economics with a special focus on economic evaluation. His research focuses on applied economic evaluation and the appropriate role of economic evaluation in health care decision making.

Erik Gustavsson is a senior lecturer in applied ethics with a special focus on medical ethics. His research focuses on medical ethics, especially ethical issues that arise in health care priority setting.

Lars Sandman is professor of healthcare ethics and director of the National Centre for Priorities in Health, Linköping University, Sweden. His research focuses on priority setting ethics and ethics in health technology assessment.

How to cite this article: Juth N, Henriksson M, Gustavsson E, Sandman L. Should we accept a higher cost per health improvement for orphan drugs? A review and analysis of egalitarian arguments. Bioethics. 2020;00:1–8. https://doi.org/10.1111/bioe.12786